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SYNTHESIS OF OPTICALLY ACTIVE PHEROMONES

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1. INTRODUCTION

1.1. *Pheromones as semiochemicals*

Pheromones [pherein (Gr.) = to transfer + hormon (Gr.) = to excite] are substances that are secreted by an individual bio-organism and are received by a second individual of the same species, and produce a specific reaction, for example, a definite behavior or a developmental process.[1] In other words, pheromones are chemical substances used for intraspecific communication. Compounds used for interspecific communication are called allomones (favoring their producers) and kairomones

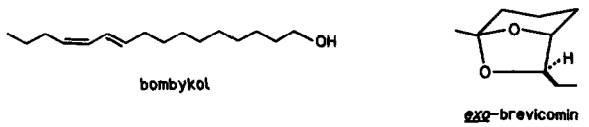

Fig. 1. Achiral and chiral pheromones.

(favoring their receivers). Pheromones, allomones and kairomones are the chemical substances that deliver messages. The term semiochemicals [semion (Gr.) = a mark or a signal] is used as a generic name for the signal substances such as pheromones, allomones and kairomones.[2]

The first isolation of a pheromone was announced in 1959 by Butenandt *et al.* from the silkworm moth, *Bombyx mori*.[3] The pheromone was named bombykol and was identified as an achiral olefinic alcohol as shown in Fig. 1. Most of the pheromones isolated from butterflies and moths are achiral aliphatic olefinic alcohols or their derivatives. In the late 1960s Silverstein *et al.* isolated several chiral pheromones from beetles. An example is *exo*-brevicomin, the aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*.[4] Since then over 100 chiral pheromones have been isolated and identified. In Figs 2–8 are listed 99 chiral pheromones which are of synthetic interest. The stereoformulae depicted in Figs 2–8 represent those of the natural and bioactive enantiomers. In this Report, the formula number assigned to each pheromone in Figs 2–8 will be used throughout. The producers of the pheromones are listed in the legends of Figs 2–8.

1.2. *Chemical significance of synthesizing optically active pheromones. Determination of absolute configuration*

In 1973 when we began our studies on pheromone synthesis, almost nothing was known about the absolute configuration of chiral insect pheromones. Difficulties are often encountered in stereochemical studies of natural pheromones because they are often obtained only in small amounts (several μg to several mg) as volatile oils in many cases. This is therefore beyond the scope of conventional methods of stereochemical assignment such as degradation to a simple compound of known absolute configuration or X-ray crystallographic analysis. The best way to circumvent this difficulty is to execute an enantioselective synthesis of the target pheromone starting from a compound of known absolute configuration. This approach generates the target molecule with known

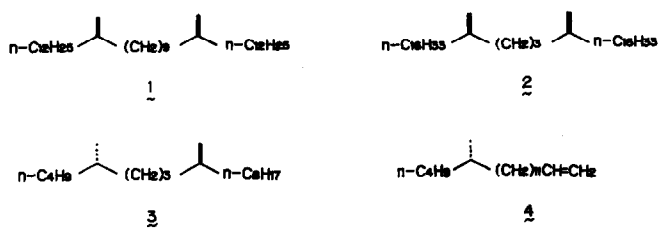

Fig. 2. Examples of pheromone hydrocarbons.
1: Female-produced sex pheromone of the tsetse fly, *Glossina palladipes* (H)*.[102,374]
2: Female-produced sex pheromone of the tsetse fly, *Glossina morsitans morsitans* (H)*.[262,375]
3: Female-produced sex pheromone of the moth *Leucoptera scitella* (A)*.[376]
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* Throughout Figs 2–8, these capital letters indicate the stereochemistry–bioactivity relationships. For details see pp. 3289–3292 and Fig. 88.

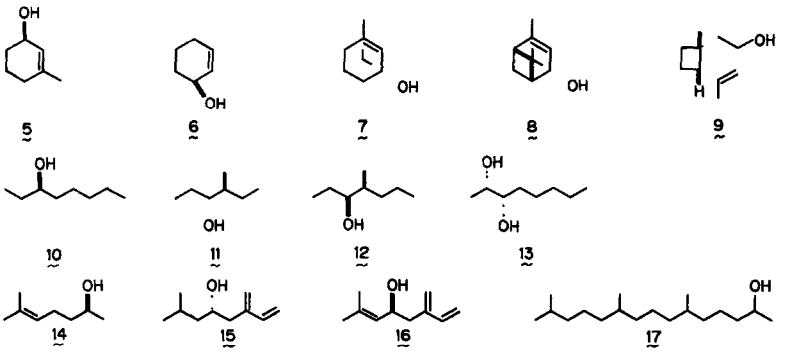

Fig. 3. Examples of pheromone alcohols.

5 (seudenol): Female-produced aggregation pheromone of the Douglas-fir beetle, *Dendroctonus pseudotsugae* (C).[180,377]
6: Female-produced aggregation pheromone of Douglas-fir beetle (C).[181]
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16 (ipsdienol): Male-produced aggregation pheromone of *Ips paraconfusus* (A).[65,371,382]
17: Female-produced sex pheromone of the rice moth, *Corcyra cephalonica* (U).[383]

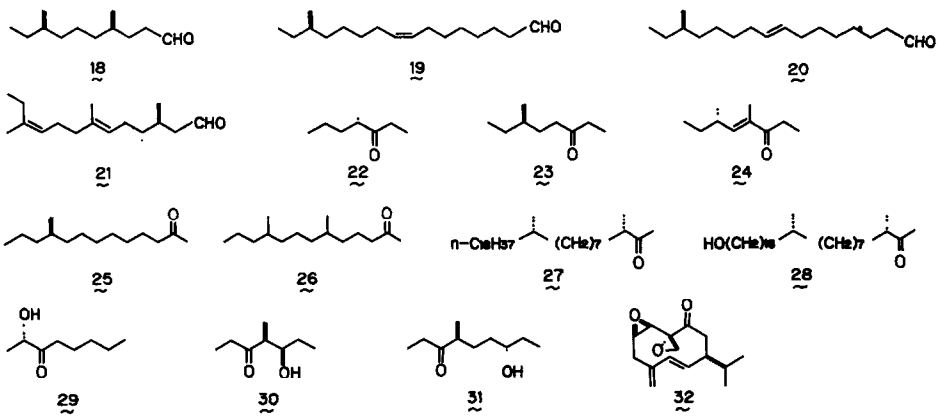

Fig. 4 Examples of pheromone aldehydes and ketones

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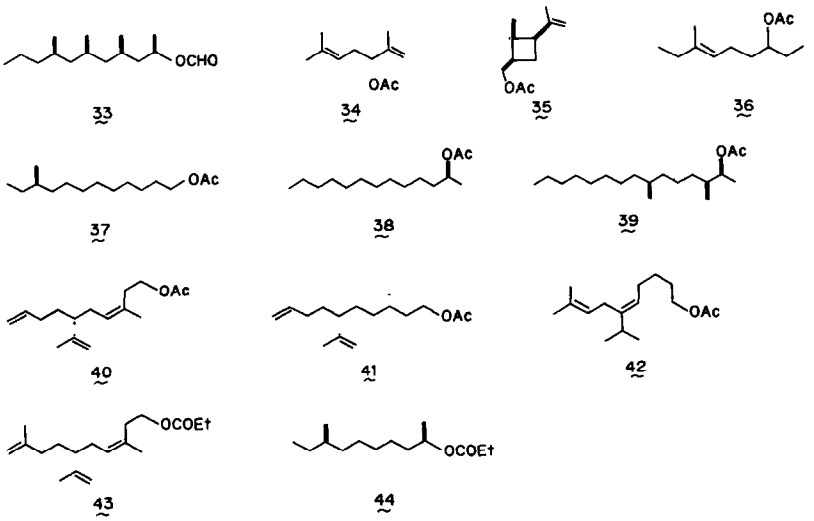
32 (periplanone-B): Female-produced sex pheromone of the American cockroach, *Periplaneta americana* (A) [134]



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35 Female-produced sex pheromone of the citrus mealybug, *Planococcus citri* (A).[49]

36 Male-produced aggregation pheromone of the square-necked grain beetle, *Cathartus quadricollis* (U) [298]

37 Sex pheromone (minor component) of the smaller tea tortrix moth, *Adoxophyes* sp (C) [96,390]

38 Aggregation pheromone of *Drosophila mulleri* (A) [51]

39 Female-produced sex pheromone of the pine sawfly, *Neodiprion lecontei* (A) [57,391]

40 and **41**: Female-produced sex pheromone of California red scale, *Aonidiella aurantii* (A).[107,276]

42. Female-produced sex pheromone of the yellow scale, *Aonidiella citrina* (A) [101 392]

43: Female-produced sex pheromone of the white peach scale, *Pseudoulacaspis pentagona* (A) [109]

44 Female-produced sex pheromone of the western corn rootworm, *Diabrotica virgifera virgifera* (A) [104,306]

absolute configuration. If chiroptical properties such as $[\alpha]_D$ value and ORD/CD spectrum of the natural pheromone are recorded, then we can compare these with corresponding data for the synthetic material. The absolute configuration of the natural pheromone will thus be clarified.

The usefulness of the above approach was first demonstrated by myself in 1973 as shown in Fig. 9. My synthesis of the (*S*)-enantiomer of 14-methyl-8-hexadecen-1-ol **9-2**, the dermestid beetle pheromone artefact,[5] from (*S*)-2-methyl-1-butanol **9-1** showed (*S*)-**9-2** to be dextrorotatory.[6,7] Because natural **9-2** isolated from the insect was laevorotatory, its absolute configuration was unambiguously shown to be *R*.[6,7] [Later, the genuine pheromone of the dermestid beetle (*Trogoderma inclusum*) was shown to be (*R*, *Z*)-14-methyl-8-hexadecenal **19**[8].] Since then, a synthesis starting from a compound of known absolute configuration has become the standard method for determining the absolute configuration of a chiral pheromone the chiroptical properties of which are known. Even in the absence of such chiroptical data, the absolute configuration of a pheromone may be clarified by combining a synthesis of the pure enantiomers of known stereochemistry with bioassay results. In general, the bioactive enantiomer is the natural pheromone.

1.3. *Biological significance of synthesizing optically active pheromones. Clarification of stereochemistry–pheromone activity relationships*

Among chiral compounds there are many cases in which only one enantiomer is bioactive. For examples, (*S*)-glutamic acid is tasty, while its (*R*)-isomer is not; (+)-Estrone is bioactive as a female sex hormone, but the (−)-isomer is inactive (See Fig. 10). However, in the case of odorous

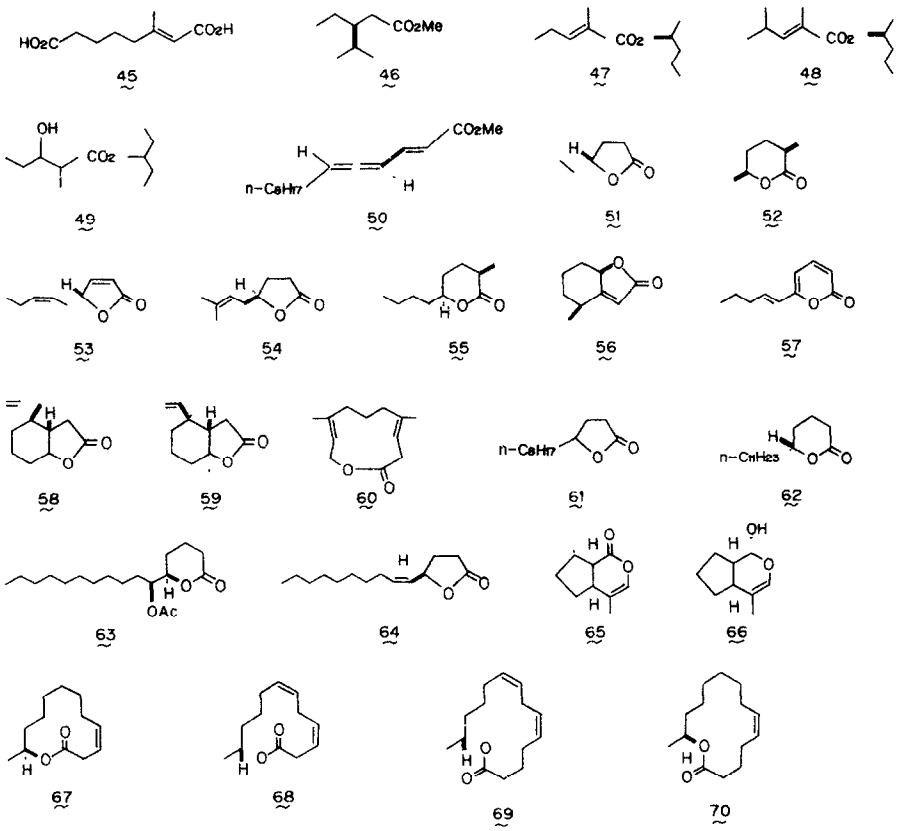


Fig 6 Examples of pheromone acid, esters and lactones

45 (callosobruchusic acid) Female-produced sex pheromone of the azuki bean weevil, *Callosobruchus chinensis* (**C**) [267]

46 Pheromone of *Formica* species of ants (**U**) [281]

47 (dominicalure 1) and **48** (dominicalure 2) Male-produced aggregation pheromone of lesser grain borer, *Phyzopertha dominica* (**C**) [393]

49 (sitophilate) · Male-produced aggregation pheromone of the granary weevil, *Sitophilus granarius* (**U**) [403]

50 Male-produced sex pheromone of the dried bean beetle, *Acanthoscelides obtectus* (**U**) [178,190]

51 Aggregation pheromone of *Trogoderma glabrum* (**U**) [346]

52 Male-produced sex pheromone of the carpenter bee, *Xylocopa hirutissima* (**U**) [46]

53 Male-produced pheromone of a pyralid moth, *Aphomia gularis* (**U**) [394]

54 (eldanolide) Male-produced pheromone of the African sugar-cane borer, *Eldana saccharina* (**A**) [8–]

55 (invictolide), **56** (dihydroactinidiolide) and **57** Queen-produced queen recognition pheromone of the red imported fire ant, *Solenopsis invicta* (**A**) [232,395]

58 (anastrephin), **59** (epianastrephin) and **60** (suspensolide) Male-produced sex pheromone of the Caribbean fruit fly, *Anastrepha suspensa* (**C**) [199,200]

61 Defensive secretion of rove beetles, *Bledius mandibularis* (**U**) [299]

62 Queen-produced pheromone of the oriental hornet, *Vespa orientalis* (**A**) [300]

63 Oviposition attractant pheromone from apical droplets on the egg of the mosquito, *Culex pipiens fatigans* (**A**) [2–8,396]

64 Female-produced sex pheromone of the Japanese beetle, *Popillia japonica* (**B**).[83,91]

65 (nepetalactone) and **66** (nepetalactol) Female-produced sex pheromone of the vetch aphid, *Megoura viciae* (**A**) [397]

67 (ferrulactone II) Aggregation pheromone of the rusty grain beetle, *Cryptolestes ferrugineus* (**A**) [398]

68 Aggregation pheromone of *Oryzaephilus mercator* (**A**) [398]

69 Aggregation pheromone of *Oryzaephilus surinamensis* (**A**) [398]

70 Aggregation pheromone of *Cryptolestes pusillus* (**A**) [398]

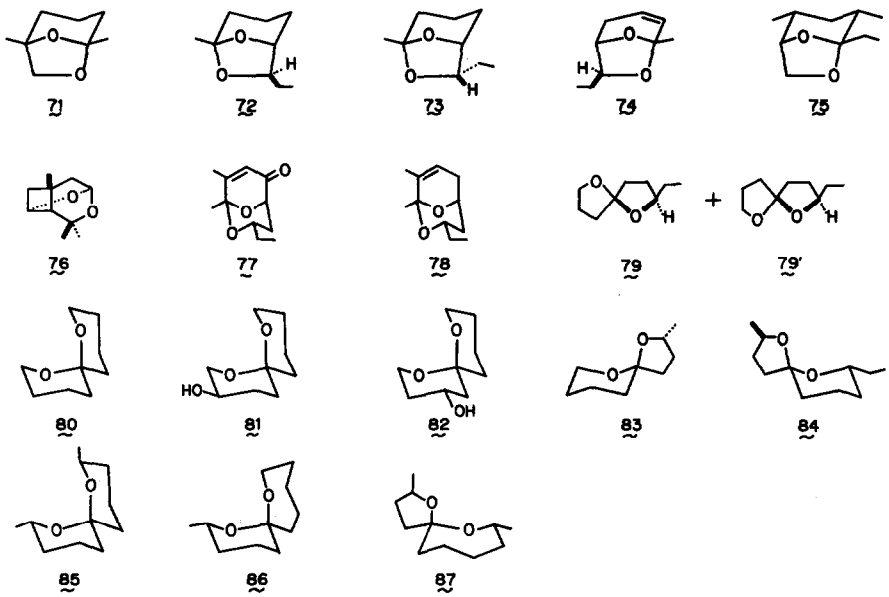


Fig. 7. Examples of pheromone acetals.

71 (frontalin): Female-produced aggregation pheromone of the southern pine beetle, *Dendroctonus frontalis* (A).[12,71]

72 (*exo*-brevicomin): Aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis* (A).[11,12]

73 (*endo*-brevicomin): Aggregation pheromone of *Dryocoetes autographus* (A).[219,399]

74: Male-produced pheromone of the house mouse, *Mus musculus* (U).[60]

75 (α-multistriatin): Female-produced aggregation pheromone of the smaller European elm bark beetle, *Scolytus multistriatus* (A).[170]

76 (lineatin): Female-produced aggregation pheromone of *Trypodendron lineatum* (A).[42,203]

77 and **78**: Male-produced pheromone of the swift moth, *Hepialus hecta* (A).[339,400]

79 and **79′** (chalcogran): Aggregation pheromone of *Pityogenes chalcographus* (U).[88]

80 (olean), **81** and **82**: Female-produced sex pheromone of the olive fruit fly, *Dacus oleae* (G).[67,373]

83: Pheromone of *Paravespula vulgaris* (U).[401]

84: Pheromone of *Andrena haemorrhoea* (U).[356]

85: Pheromone of *Andrena wilkella* (U).[336]

86: Pheromone of *Andrena haemorrhoa* (U).[342]

87: Pheromone of *Andrena haemorrhoa* and *Paravespura vulgaris* (U).[343]

substances, the situation is not always clear. For example, the enantiomers of carvone are both odorous, the (+)-isomer smells like caraway, whereas the (−)-isomer has a spearmint odour.[9,10] Both the enantiomers of camphor show the same odour which cannot be distinguished even by a perfumer.

What kind of relation exists between absolute configuration and bioactivity in the case of pheromones? The correct perception of pheromones is essential in the successful life of insects. Incorrect perception of communications mediated by pheromones will lead to the death of that insect. In the case of human beings, however, it is of little importance whether one can discriminate between (+)-carvone and (−)-carvone or not. In 1973 I thought that it was highly probable that pheromone perception is an enantioselective or enantiospecific process. To prove or disprove this, we had to synthesize pure enantiomers of pheromones so that we could have reliable bioassays. If we supply a sample (70% e.e.) to an entomologist, he may give us a confusing result due to contamination with the wrong enantiomer to the extent of 15%. Synthesis of optically pure pheromones certainly helps to clarify stereochemistry–pheromone activity relationships.

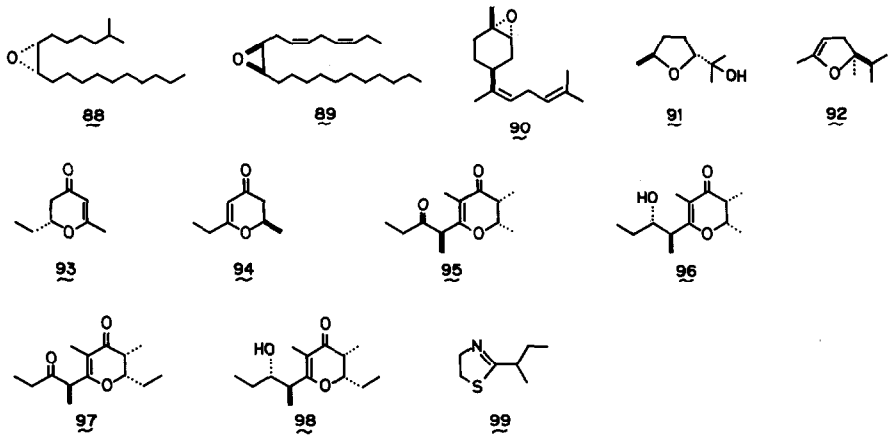


Fig. 8. Examples of heterocyclic pheromones other than acetals.

88 (disparlure): Female-produced sex pheromone of the gypsy moth, *Lymantria dispar* (**B**).[14]
89: Female-produced pheromone of the salt marsh caterpillar moth, *Estigmene acrea* and the fall webworm moth, *Hyphantria cunea* (**A**).[214]
90: Male-produced sex pheromone of the southern green stinkbug, *Nezara viridula* (**A**).[112]
91 (*trans*-pityol): Male specific attractant of the bark beetle, *Pityophthorus pityographus* (**A**).[334,402]
92: Sex-specific compound in females of *Hylecoetus dermestoides* (**U**).[115]
93: Male-produced sex-pheromonal component of the ghost moth, *Hepialus californicus* (**U**).[68,354]
94: Male-produced pheromone of the swift moth, *Hepialus hecta* (**A**).[339,400]
95 (stegobinone) (**B**) and **96** (stegobiol) (**A**): Female-produced sex pheromone of the drugstore beetle, *Stegobium paniceum*.[340,341]
97 (serricorone) and **98** (serricorole): Female-produced sex pheromone of the cigarette beetle, *Lasioderma serricorne* (**U**).[355]
99: Male-produced pheromone of the house mouse, *Mus musculus* (**U**).[404]

The first work of mine in this area appeared in 1974 when I synthesized the pure enantiomers of *exo*-brevicomin **72** starting from the enantiomers of tartaric acid (Fig. 11).[11] Only the (+)-enantiomer of **72** was bioactive.[12] Pheromone perception in this case was highly enantioselective. Quite independently in 1974, two other groups were also successful in synthesizing pheromone enantiomers. Silverstein *et al.* synthesized the enantiomers of 4-methyl-3-heptanone **22**, the principal alarm pheromone of the leaf-cutting ant (*Atta texana*), and found (*S*)-**22** to be bioactive.[13] Marumo *et al.*, worked on the synthesis of the enantiomers of disparlure **88**, the pheromone of the gypsy moth, and found (7*R*, 8*S*)-(+)-**88** to be bioactive.[14]

Since then many pheromone enantiomers have been synthesized and their chiroptical and biological properties examined. This established the absolute configuration of the natural products and clarified their stereochemistry–pheromone activity relationships. In this Report, I will summarize

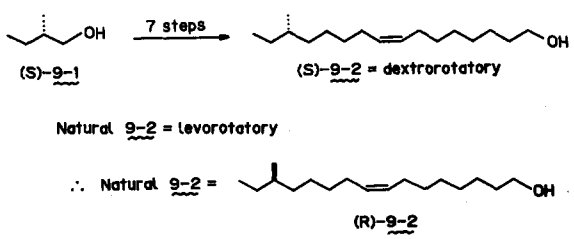


Fig. 9. Determination of the absolute configuration of the dermestid beetle pheromone artefact.

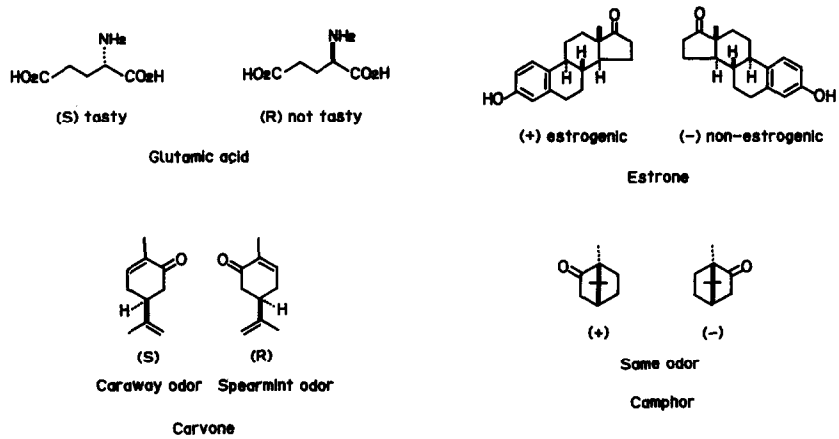


Fig. 10. Enantiomerism and bioactivity.

the present status of the synthesis of pheromone enantiomers with a brief survey of the stereochemistry–bioactivity relationships. The early phase of the synthesis of chiral pheromones was reviewed by Rossi[15] and by myself.[16,17]

2. GENERAL SYNTHETIC AND ANALYTICAL METHODOLOGIES

2.1. *General synthetic methodologies*

Synthesis of pheromone enantiomers can be achieved by one of the following three methods: (i) derivation from optically active natural products such as α-amino acids, hydroxy-acids, terpenes and carbohydrates, (ii) optical resolution of an intermediate or final product, and (iii) chemical or biochemical asymmetric synthesis. Each method will be discussed with several examples.

2.2. *Analytical techniques for the determination of enantiomeric purity*

In order to examine an enantioselective synthesis, one must be familiar with current methods for the determination of enantiomeric purity. This subject was recently reviewed by Morrison,[18] by myself[19] and by Schurig.[20]

Enantiomeric purity is defined as follows and in almost all cases equals the optical purity.

$$\% \text{ Enantiomeric Purity} = \% \text{ enantiomeric excess} = \% \text{ e.e.} = \frac{M_+ - M_-}{M_+ + M_-} \times 100$$

where M_+ is the mole fraction of the dextrorotatory enantiomer (here the predominant one), and M_- is the mole fraction of the laevorotatory one.

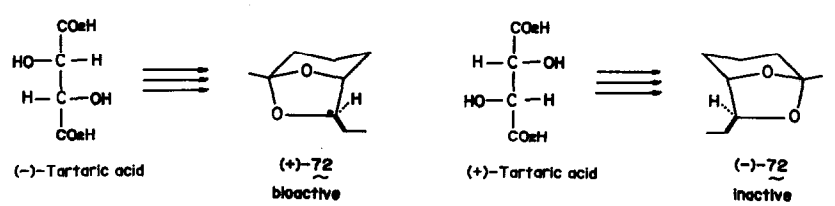


Fig. 11. Bioactivity of the enantiomers of *exo*-brevicomin.

2.2.1. *Problems in the determination of the enantiomeric purity of pheromones based upon the magnitude of specific rotations.* The definition of optical purity as found in textbooks is based upon classical polarimetric methods

$$\% \text{ Optical Purity} = \frac{[\alpha]^{*}_{\text{mixture}}}{[\alpha]_{\text{a pure enantiomer}}} \times 100.$$

* Specific rotatory power $[\alpha] = \alpha/(c \times l)$, where α is the measured angle of rotation of plane-polarized light in degrees, l is the length of the cell (dm) containing the sample, and c is the concentration of the sample (in g/ml). c can be the density in the case of a neat liquid. To record $[\alpha]_D$ value of a neat liquid, one should not forget to measure the density of that liquid.[21] The measurement of density demands a considerable amount of the pure liquid.

In those cases where the specific rotation of a pure enantiomer is exactly known and the value is large then polarimetric determination of the optical purity leads to a simple determination of the enantiomeric purity. However, the following three points are noted.

(i) The magnitude of the specific rotation of different samples of the same compound must be compared using the same solvent. (1*S*, 4*S*, 5*S*)-*cis*-Verbenol **7**, a component of the aggregation pheromone of a bark beetle *Ips paraconfusus*, is laevorotatory in chloroform and dextrorotatory in acetone or in methanol.[22]

(ii) In the case of a compound with a small $[\alpha]_D$ value then a trace amount of an impurity with a large $[\alpha]_D$ value can cause an error in polarimetrically determined optical purity with misleading consequences. Indeed, the $[\alpha]_D$ value of (+)-disparlure **88**, the gypsy moth pheromone, is too small to be measured correctly ($+0.48° \sim +0.8°$ in carbon tetrachloride).

(iii) It is sometimes difficult to know whether the reported $[\alpha]_D$ values are reliable or not. For example in the case of *exo*-brevicomin **72**, even after the publication of 17 different syntheses of the enantiomers, it is still difficult to determine its exact $[\alpha]_D$ value. When ether was used as the solvent, the $[\alpha]_D$ values of the enantiomers of **72** were recorded as $+50.3°$,[23] $-60.6°$,[24] $-66°$,[25] $-66.5°$,[26] $-67.5°$,[27] $+69.3°$,[28] $-69.7°$,[28] $+70°$,[25] $+72.4°$,[29] $-73°$,[30] $-73.4°$,[31] $-73.6°$,[29] $+74°$,[32] $-80.0°$,[7] $+80.9°$,[33] $+81.1°$,[34] $+81.5°$,[35] $+81.6°$,[36] $+82.4°$[37] and $+84.1°$.[7] In our work,[29] the enantiomeric purity of (+)- and (−)-**72** was as high as 99.8% as checked by Schurig's complexation GLC.[38] Similarly, Mulzer's (+)- and (−)-**72** was of >99% e.e. as checked by Schurig.[28] However, Mulzer's $[\alpha]_D$ values were $+69.3°$ and $-69.7°$, while ours were $+72.4°$ and $-73.6°$. If chloroform was used as the solvent, the $[\alpha]_D$ values of the enantiomers of **72** were reported to be $+59.0°$,[39] $+60.3°$,[40] $-60.6°$,[39] $+64.8°$,[41] $+72.1°$[29] and $-73.2°$.[29] By Schurig's complexation GLC, Oehlschlager's (+)-**72** was shown to be of 95% e.e., but its $[\alpha]_D$ value was only $[\alpha]_D^{27} +59.0°$.[39]

The above data indicates the difficulty in estimating the enantiomeric purity of a sample only on the basis of its specific rotatory power. Trace amounts of impurities in the sample and/or in the solvent may alter the rotation value considerably. The rotation value should be regarded as a rough measure of the enantiomeric purity.

2.2.2. *NMR methods for the determination of the enantiomeric purity of pheromones.* Three NMR methods are available: (i) Measurement of the spectrum in the presence of chiral shift reagents such as $Eu(tfc)_3$ = $Eu(facam)_3$ or $Eu(hfc)_3$ = $Eu(hfbc)_3$. This method is suitable for acetal pheromones which have no functionality which can be used for derivatization. For the use of this method in the case of lineatin **76**, see ref. 42; (ii) Measurement of the spectrum of the total sample after derivatization giving a diastereomeric mixture. This method can be used for pheromones with derivatizable functional groups. The most popular derivatizing reagent is Mosher's acid [α-methoxy-α-trifluoromethylphenylacetic acid (MTPA)].[43] For the use of this method in the case of sulcatol **14**, see ref. 44; (iii) Measurement of the spectrum in the presence of chiral solvating agents such as (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[45] For the use of this method in the case of *cis*-2-methyl-5-hexanolide **52**, see ref. 46.

2.2.3. *Chromatographic methods for the determination of the enantiomeric purity of pheromones.* Under achiral conditions the two enantiomers of a chiral compound cannot be separated by chromatographic methods such as GLC or HPLC. Separation is possible, however, either by employing a chiral stationary phase or by converting the enantiomers into diastereomers followed by chromatographic fractionation on an achiral stationary phase. (i) Chromatographic analysis by employing a chiral stationary phase. Advent of GLC chiral stationary phases as developed by Schurig and others has enabled the direct measurement of e.e. of various acetal pheromones such as *exo*-brevicomin **72**[38] and lineatin **76**.[42] Microcrystalline cellulose triacetate was successfully employed in the resolution of (±)-**85** (*Andrena wilkella* pheromone) by HPLC.[47] Lactone enantiomers of **51** were separable on a preparative-scale column of microcrystalline cellulose triacetate.[48] (ii) Chromatographic analysis after conversion into a diastereomeric mixture. The conventional practice for the analysis of pheromones with a hydroxyl group is to derivatize it with MTPA and then submit the resulting MTPA ester to GLC or HPLC analysis. The pheromone **34** of the comstock mealybug was shown to be enantiomerically pure by this method after exchanging the acetate with MTPA.[49] Enantiomerically pure acetyl lactate can be used for the derivatization of pheromone alcohols.[50] The derived ester diastereomers are to be analyzed by capillary GLC. (*S*)-2-Tridecanol acetate **38**, a component of the aggregation pheromone of *Drosophila mulleri* was found to be enantiomerically pure by the acetyl lactate method.[51]

3. SYNTHESIS STARTING FROM OPTICALLY ACTIVE NATURAL PRODUCTS

There are so many chiral natural products that their use as starting materials for enantioselective synthesis is a common practice since the days of Emil Fischer. In planning a synthesis, knowledge is required regarding the stereochemistry of natural products.[52–54] The merit of this approach is the enantiomeric purity of natural products such as terpenes, amino acids and sugars. Therefore by carefully avoiding racemization in the course of the synthesis, an enantiomerically pure pheromone can be prepared from enantiomerically pure natural products. The structural limitations of natural products may, however, restrict the synthesis and sometimes necessitate a lengthy route to the target. Another snag is that natural products are seldom available in both enantiomeric forms. When we want to synthesize both enantiomers of a pheromone this may be difficult starting from a single available enantiomer of the natural product.

3.1. *Tartaric acid and other hydroxy acids as starting materials*

Tartaric acid is a versatile building block in synthesizing chiral pheromones as shown in Fig. 12. Both enantiomers of tartaric acid are available, and the presence of the C_2-axis in it is advantageous in many syntheses.[55] Other hydroxy-acids such as malic acid, citramalic acid and lactic acid are also employed as shown in Figs 13 and 14. Lactic acid is an important source of the enantiomers of propylene oxide, which is useful as a chiral building block.[56]

3.1.1. *Synthesis of* exo-*brevicomin from tartaric acid. exo*-Brevicomin **72** is a highly dissymmetric bicyclic acetal pheromone of the western pine beetle.[4] During its structure determination, natural **72** was initially reported to show no optical rotation between 350 and 250 nm.[4] Synthetic **72** was later found to have a high rotatory power. The misleading previous observation was an example of the difficulty encountered in manipulating small amounts of highly volatile materials.

The first synthesis of both enantiomers of *exo*-brevicomin **72** was achieved by myself in 1974 (Fig. 15).[11] The two asymmetric carbon atoms of tartaric acid were incorporated into **72** after a lengthy sequence of transformations. Three simpler syntheses of *exo*-brevicomin from tartaric acid appeared since then (Fig. 16). Meyer applied dithiane alkylation (**16-1** → **16-2**) to extend the carbon chain,[27] while we used a Grignard coupling followed by the Wacker oxidation (**16-3** → **16-4**).[29] A unique alternative as reported by Masaki *et al.* was to construct the acetal moiety before completing

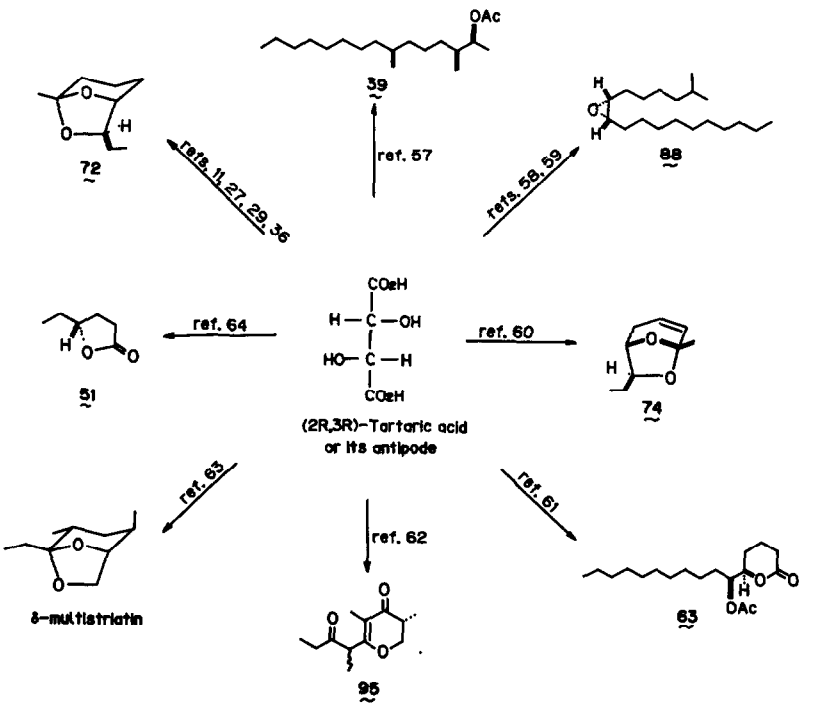


Fig. 12. Pheromones synthesized from tartaric acid.

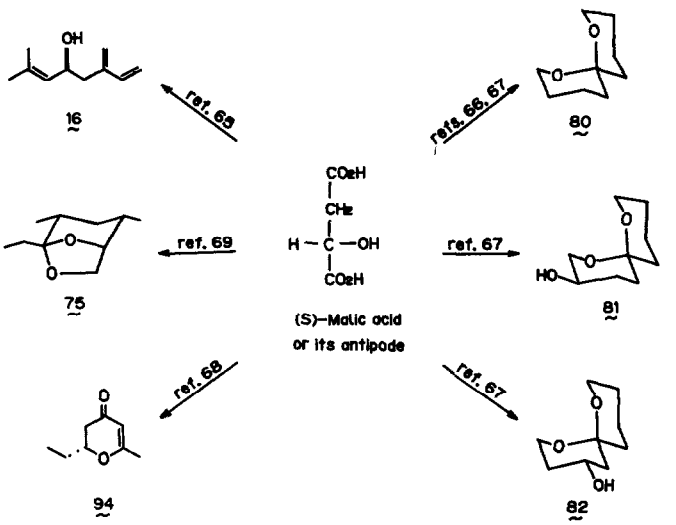


Fig. 13. Pheromones synthesized from malic acid.

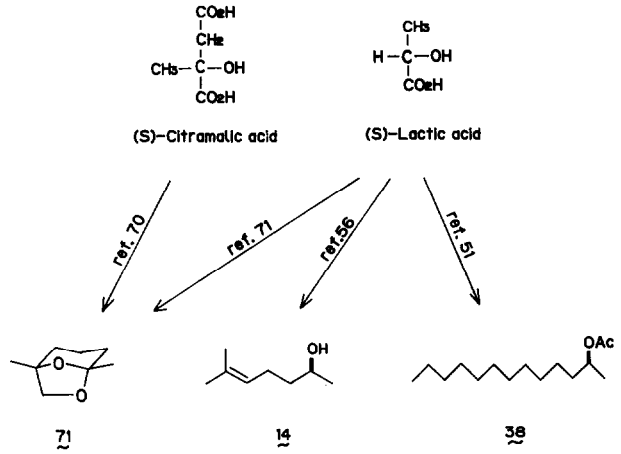
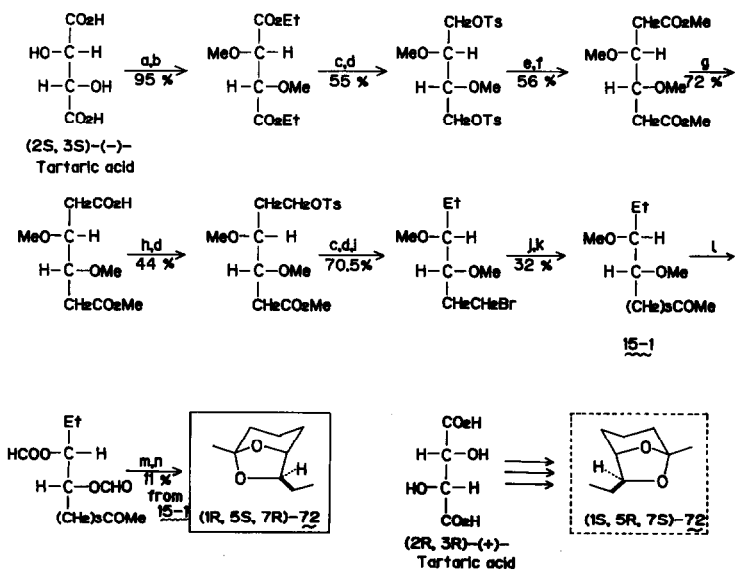


Fig. 14. Pheromones synthesized from citramalic and lactic acids.

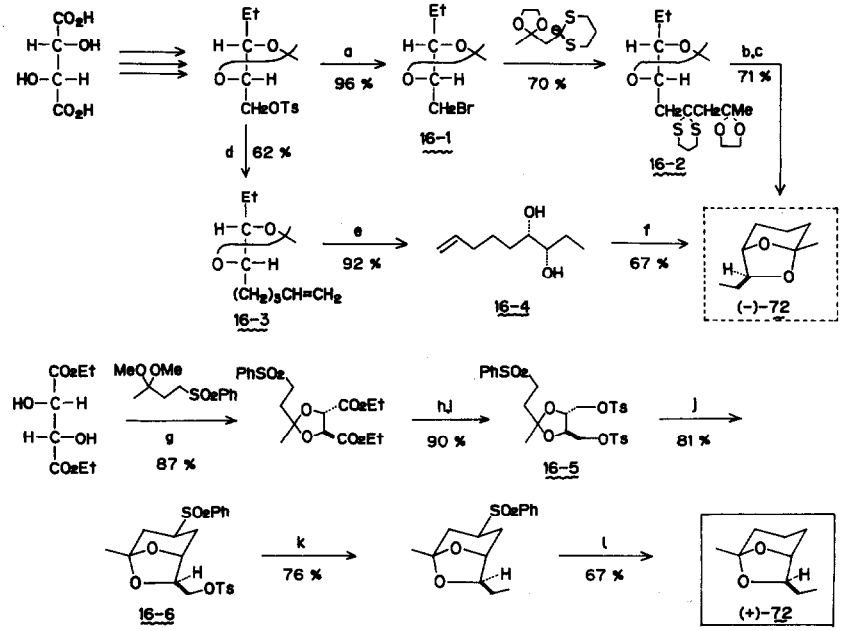
the construction of the carbon skeleton.[36] Intramolecular alkylation of the phenylsulfone **16-5** yielded **16-6** with the desired 6,8-dioxabicyclo[3.2.1]octane ring system. The overall yield in the Masaki synthesis was 32% in 6 steps from diethyl (−)-tartrate.

3.1.2. *Synthesis of disparlure from tartaric acid.* Disparlure **88** is the pheromone of the gypsy moth, *Lymantria dispar*.[72] The isolated amount of the natural pheromone was so small that its chiroptical properties could not be studied. Marumo's first synthesis of the enantiomers of disparlure in 1974 started from (*S*)-(+)-glutamic acid (see Section 3.2), and afforded important information



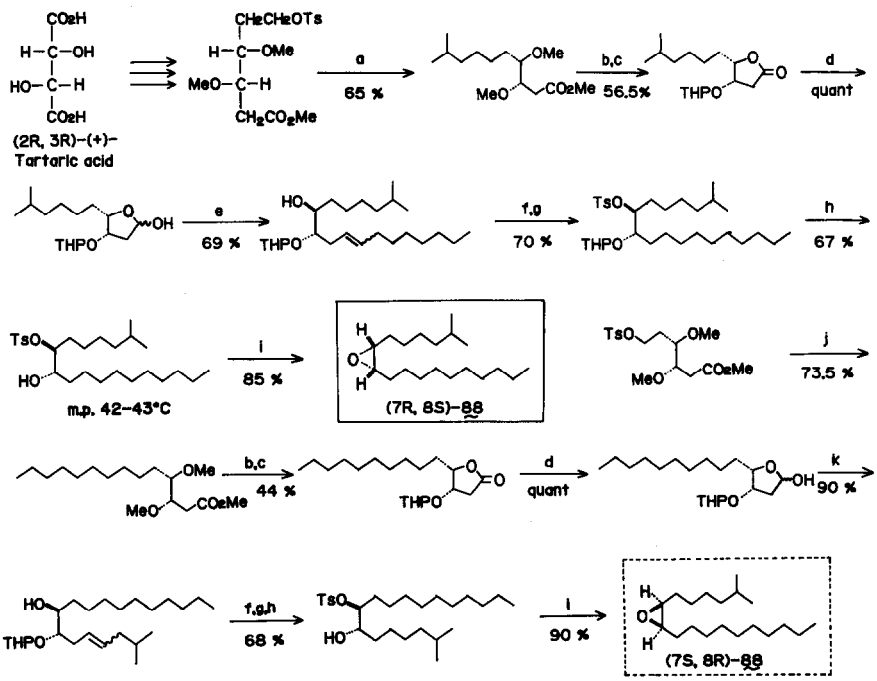
Reagents: (a) EtOH, H^+; (b) MeI, Ag_2O; (c) LAH; (d) $TsCl/C_5H_5N$; (e) NaCN/DMSO; (f) MeOH/HCl; (g) 1 eq KOH/MeOH; (h) B_2H_6/THF; (i) LiBr/Me_2CO; (j) $MeCOCH_2CO_2Et$, NaOEt; (k) $Ba(OH)_2$/EtOH aq; (l) CrO_3/AcOH; (m) NaOH; (n) dil HCl.

Fig. 15. Synthesis of *exo*-brevicomin from tartaric acid. The formula in the broken line shows the antipode of the natural pheromone.



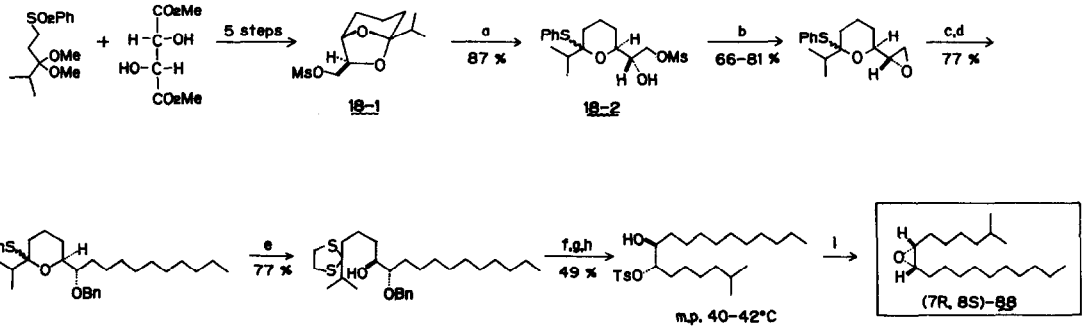
Reagents: (a) LiBr; (b) Raney-Ni/MeOH; (c) TsOH/MeOH aq; (d) $CH_2{=}CH(CH_2)_2MgBr$, Cu_2Br_2/THF; (e) 80% AcOH—Et_2O; (f) $PdCl_2$—$CuCl_2$/DME; (g) TsOH/C_6H_6; (h) $NaBH_4$/EtOH; (i) TsCl/C_5H_5N; (j) *n*-BuLi/THF; (k) Me_2CuLi/Et_2O, Me_2S; (l) Na/EtOH, THF.

Fig. 16. Later syntheses of *exo*-brevicomin from tartaric acid.



Reagents: (a) $[Me_2CH(CH_2)_2]_2CuLi/Et_2O$; (b) BCl_3/CH_2Cl_2; (c) DHP, TsOH; (d) $(i\text{-}Bu)_2AlH$/THF-toluene; (e) $n\text{-}C_7H_{15}CH{=}PPh_3$/THF; (f) H_2/Pd-C; (g) TsCl/C_5H_5N; (h) TsOH/MeOH; (i) KOH/MeOH; (j) $(n\text{-}C_8H_{17})_2CuLi/Et_2O$; (k) $Me_2CHCH_2CH{=}PPh_3$/THHF.

Fig. 17. Mori's synthesis of disparlure from tartaric acid.

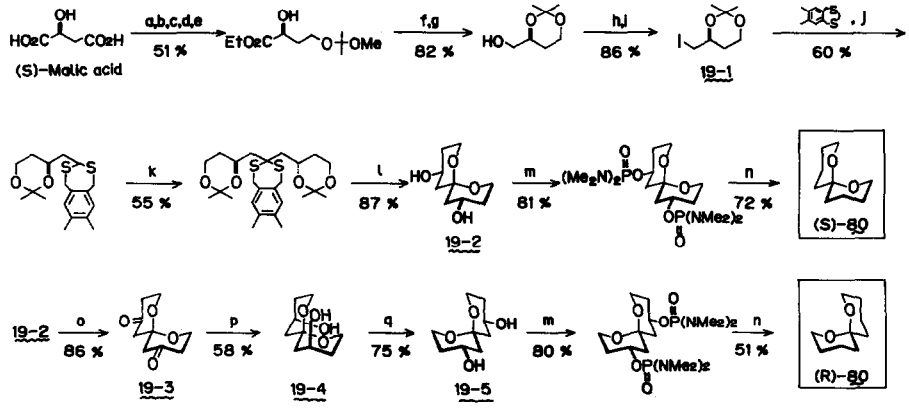


Reagents: (a) Et_2AlSPh/toluene ($-70 \sim -20°C$); (b) K_2CO_3/MeOH; (c) *n*-$C_9H_{19}MgBr$, Cu_2Br_2/THF; (d) BnCl; (e) $HS(CH_2)_2SH$, $AlCl_3/CH_2Cl_2$; (f) Raney-Ni; (g) $TsCl/C_5H_5N$; (h) H_2/Pd—C; (i) K_2CO_3/MeOH.

Fig. 18. Masaki's synthesis of disparlure from tartaric acid.

that (7*R*, 8*S*)-(+)-disparlure **88** is bioactive, whereas its antipode inhibits the pheromone action.[14] Our synthesis in 1976 started from the abundant (2*R*, 3*R*)-(+)-tartaric acid (Fig. 17) giving both enantiomers of disparlure in multi-gram quantities.[58] Later in 1986, Masaki *et al.* published a new synthesis of (+)-disparlure (Fig. 18).[59] The Masaki synthesis utilized a cleavage reaction of an intramolecular acetal **18-1** with an organoaluminum reagent giving **18-2**.

3.1.3. *Synthesis from malic acid of the major component of the olive fruit fly pheromone.* The olive fruit fly, *Dacus oleae*, is the major pest of olive in Mediterranean countries. Baker and Francke *et al.* identified the major component of the olive fruit fly pheromone as 1,7-dioxaspiro[5.5]undecane **80**, and confirmed the proposed structure by synthesizing (±)-**80**.[73,74] Two different syntheses of the enantiomers of **80** were accomplished by us starting from (*S*)-malic acid as shown in Figs 19 and 20.[66,67] The stereochemistry at the spiro center of **80** was controlled by attaching the hydroxyl group(s) to the tetrahydropyranyl ring as shown in **19-2** and **20-1** [= (4*S*, 6*S*)-**82**]. The hydroxyl



Reagents: (a) AcCl; (b) EtOH; (c) BH_3/THF; (d) $CH_2{=}C(OMe)Me$, PPTS; (e) NaOEt/EtOH; (f) $BF_3 \cdot Et_2O$; (g) LAH; (h) $TsCl/C_5H_5N$; (i) NaI, $NaHCO_3/Me_2CO$; (j) *n*-BuLi; (k) *n*-BuLi, **19-1**; (l) $CuCl_2 \cdot 2H_2O$, CuO/Me_2CO; (m) *n*-BuLi, $(Me_2N)_2POCl$/THF—TMEDA; (n) Li/$EtNH_2$–*t*-BuOH—THF; (o) PCC; (p) $LiB(s\text{-}Bu)_3H$; (q) dil HCl/THF.

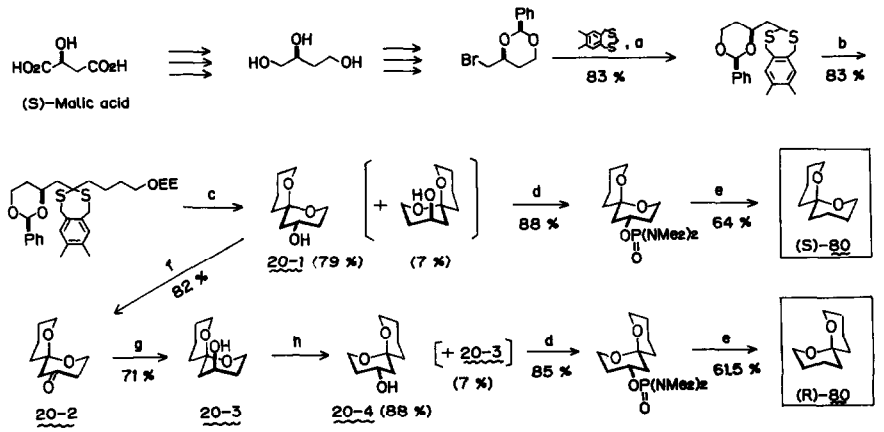
Fig. 19. Mori's first synthesis of the olive fruit fly pheromone from (*S*)-malic acid.

group(s) will adopt equatorial orientations and the absolute configuration of the carbon atom at the spiro center will be determined by the oxygen anomeric effect. Removal of the hydroxyl group(s) of **19-2** and **20-1** gave (*S*)-(+)-**80**. To prepare (*R*)-(−)-**80** from **19-2**, we converted **19-2** into a less stable diaxial compound **19-4** by the reduction of **19-3**. When **19-4** was treated with dilute hydrochloric acid, it furnished the more stable **19-5** with di-equatorial substituents. Deoxygenation of **19-5** yielded (*R*)-(−)-**80**. Similarly, **20-1** was converted into its antipode **20-4** [= (4*R*, 6*R*)-**82**] via **20-2** and **20-3** (Fig. 20). The direct determination of the enantiomeric purities of the enantiomers of **80** was executed by Schurig's complexation GLC method [(*R*)-**80** >99.5% e.e.; (*S*)-**80** = 92% e.e.].

3.1.4. *Synthesis of frontalin from lactic acid.* Frontalin **71** was isolated from the female southern pine beetle, *Dendroctonus frontalis*.[75] It was also isolated as a component of the aggregation pheromone of the male western pine beetle, *Dendroctonus brevicomis*.[76] Mori's synthesis[77] of the enantiomers of **71** was followed by their bioassay by Wood *et al.* against *D. brevicomis*. This demonstrated the bioactivity of (1*S*, 5*R*)-(−)-**71**.[12] The antipodal (1*R*, 5*S*)-(+)-frontalin was inactive. In the case of *D. frontalis*, the natural pheromone was later found to be a mixture of (1*S*, 5*R*)-**71** and (1*R*, 5*S*)-**71** in a ratio of 85:15 as revealed by the ^{1}H NMR-shift reagent analysis.[78] Olfactory receptor cells of *D. frontalis* were more responsive to (1*S*, 5*R*)-(−)-**71** than to (1*R*, 5*S*)-(+)-**71**.[79] In 1983 Naef and Seebach reported an interesting synthesis of the enantiomers of frontalin.[71] In their synthesis (Fig. 21) they used lactic acid to generate a quaternary chiral center in the acetal **21-1**. In the course of the alkylation of **21-1** with **21-2**, the chirality in the part of lactic acid was once lost by the enolate formation to give **21-3**. However, it was regenerated after the alkylation giving **21-4**. The bulky *t*-butyl group of **21-3** effectively controlled the course of the alkylation. All of the syntheses of frontalin enantiomers published prior to May 1983 were critically reviewed in that paper.[71]

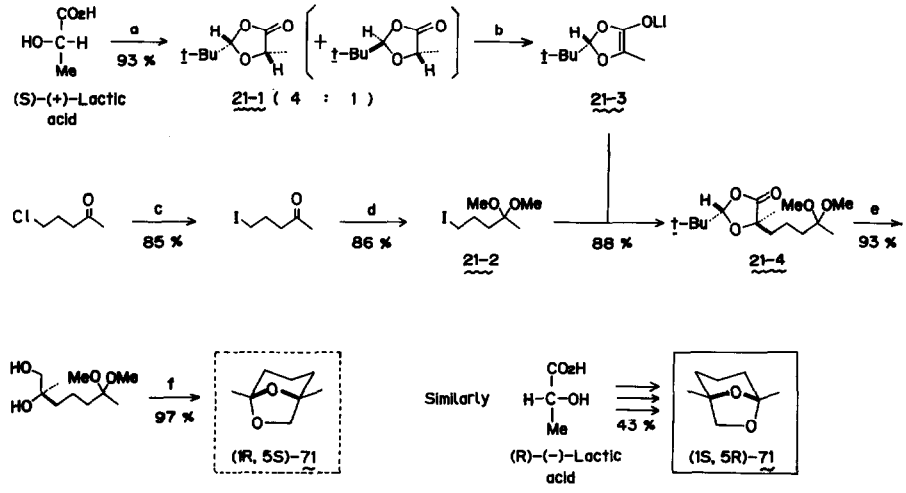
3.2. α-*Amino acids as starting materials*

α-Amino acids are useful starting materials in the synthesis of enantiomerically pure compounds.[80] In the field of pheromones, too, there are many examples of the utilization of α-amino acids. Utilization of glutamic acid in pheromone synthesis was initiated by Marumo in 1974



Reagents: (a) *n*-BuLi; (b) *n*-BuLi, $I(CH_2)_4OEE$; (c) $CuCl_2 \cdot 2H_2O$, CuO/Me_2CO, chromatog. (SiO_2); (d) *n*-BuLi, $(Me_2N)_2POCl$/THF—TMEDA; (e) Li/$EtNH_2$–*t*-BuOH—THF; (f) PCC; (g) LiB(*s*-Bu)$_3$H; (h) TsOH/MeOH.

Fig. 20. Mori's second synthesis of the olive fruit fly pheromone from (*S*)-malic acid.



Reagents: (a) *t*-BuCHO, H^+; (b) LDA/THF; (c) NaI/Me_2CO; (d) TsOH, $Me_2C(OMe)_2$; (e) LAH/Et_2O; (f) TsOH/Et_2O—H_2O.

Fig. 21. Synthesis of frontalin from lactic acid.

to obtain disparlure,[14] and this approach subsequently became quite popular (Fig. 22). α-Amino acids other than glutamic acid were also used in pheromone syntheses (Fig. 23).

3.2.1 *Synthesis of ipsenol from leucine.* (−)-Ipsenol **15** is a component of the aggregation pheromone isolated from the frass produced by male California five-spined ips (*Ips paraconfusus*).[89] By synthesizing (−)-ipsenol from (*S*)-leucine as shown in Fig. 24, the (*S*)-configuration was assigned.[65,86] The key intermediate was epoxide **24-1**, which gave (*S*)-(−)-**15** after the Grignard coupling with **24-2**. The five-spined engraver beetle, *Ips grandicollis*, aggregated only in response to (*S*)-(−)-**15**, while the (*R*)-isomer was nearly inactive.[90]

3.2.2. *Synthesis of the Japanese beetle pheromone from glutamic acid.* The pheromone isolated from the female Japanese beetle (*Popillia japonica*)[91] was shown to be (*R*, *Z*)-5-(1-decenyl)dihydro-2(3H)-furanone **64** by the synthesis of both the enantiomers of **64** (Fig. 25).[83] The (*S*, *Z*)-isomer

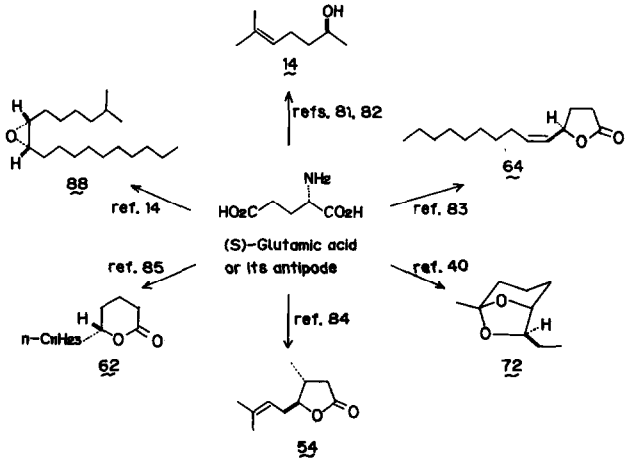


Fig. 22. Pheromones synthesized from glutamic acid.

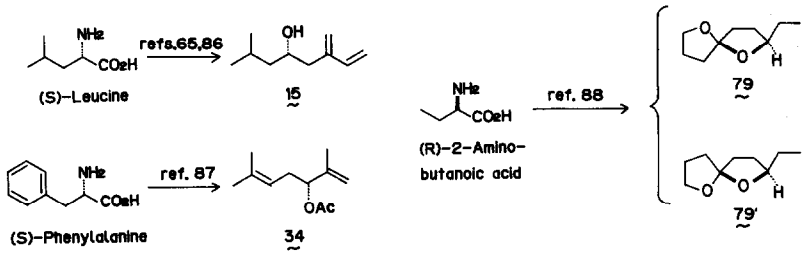
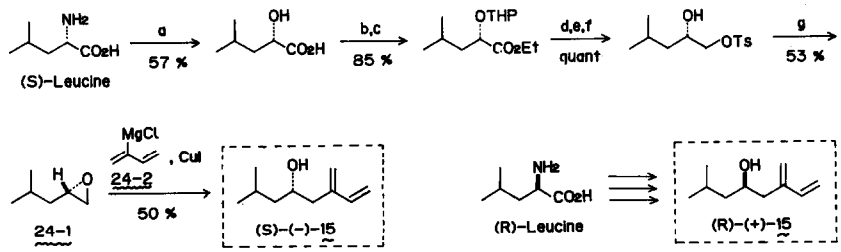
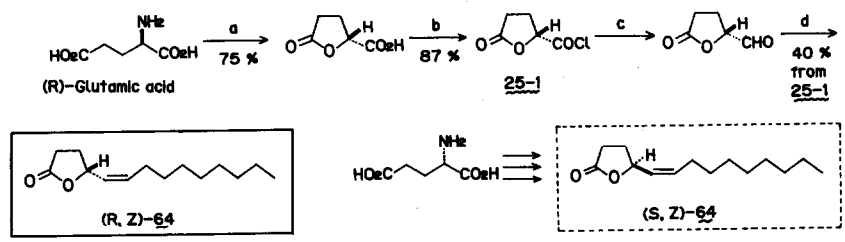


Fig. 23. Pheromones synthesized from other α-amino acids.



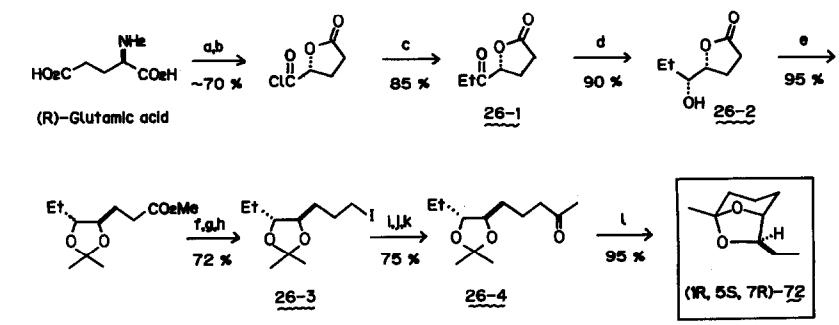
Reagents: (a) $NaNO_2$, dil H_2SO_4; (b) EtOH, H^+; (c) DHP, TsOH; (d) LAH; (e) $TsCl/C_5H_5N$; (f) AcOH—THF—H_2O; (g) KOH aq.

Fig. 24. Synthesis of ipsenol from leucine.



Reagents: (a) HNO_2; (b) $SOCl_2$; (c) $H_2/Pd—BaSO_4$, $(Me_2N)_2C=S$/toluene; (d) $Ph_3P=CH(CH_2)_7Me$/THF—HMPA, inverse addition.

Fig. 25. Synthesis of the Japanese beetle pheromone from glutamic acid.



Reagents: (a) HNO_2; (b) $(COCl)_2$; (c) EtMgBr, $Cu_2Br_2 \cdot Me_2S$/THF, −40°C; (d) Li(*s*-Bu)$_3$BH/THF, −80°C; (e) $Me_2C(OMe)_2$, MeOH, Amberlyst-15; (f) LAH; (g) $TsCl/C_5H_5N$; (h) NaI/Me_2CO; (i) LDA/THF—HMPA, −80°C, $MeCH(CN)NEt_2$; (j) NH_4Cl aq; (k) $SiO_2—H_2O/CH_2Cl_2$; (l) dil H_2SO_4.

Fig. 26. Synthesis of *exo*-brevicomin from glutamic acid.

was a strong inhibitor of the pheromone action so that the racemate was inactive as an attractant.[83,91]

3.2.3. *Synthesis of* (+)-exo-*brevicomin from* (−)-*glutamic acid.* Figure 26 shows Larchevêque's synthesis of (+)-*exo*-brevicomin **72**.[40] The key-steps of this synthesis were the selective reduction of **26-1** with L-selectride giving *syn*-**26-2** and the two-carbon elongation of **26-3** to **26-4** by employing $MeCH(CN)NEt_2$ as a novel building block.

3.3. *Citronellic acid and other terpenes as starting materials*

Chiral terpenes are popular starting materials for the synthesis of pheromones with substituents such as methyl, isopropyl and isopropenyl groups. As shown in Fig. 27, (*R*)-(+)-citronellic acid was extensively used to construct the carbon skeleton with methyl branching. The fact that (*R*)-citronellic acid of >99% e.e. is derivable from natural (*R*)-pulegone is a favorable situation for the synthesis of enantiomerically pure pheromones. (*S*)-Citronellal of ⩾96% e.e. is also available as the result of the industrialization of the asymmetric synthesis of menthol by Takasago. The bifunctional nature of citronellic acid allows the synthesis of both the enantiomers of a pheromone starting from (*R*)-citronellic acid. This will be described later in Sections 3.3.1. and 3.3.2.

In Fig. 28 the derivation of various terpenoidal pheromones from monoterpenes is shown. The drawback of this approach is that there are some monoterpenes, such as the α- and β-pinenes, the enantiomeric purities of which are not always over 99% e.e. It is therefore necessary to check the enantiomeric purity of the starting terpenes prior to the initiation of the work. A Russian review is available on the syntheses of mono- and sesqui-terpenoidal insect pheromones.[125]

3.3.1. *Synthesis of* 4,8-*dimethyldecanal from* (*R*)-*citronellic acid.* 4,8-Dimethyldecanal **18** was

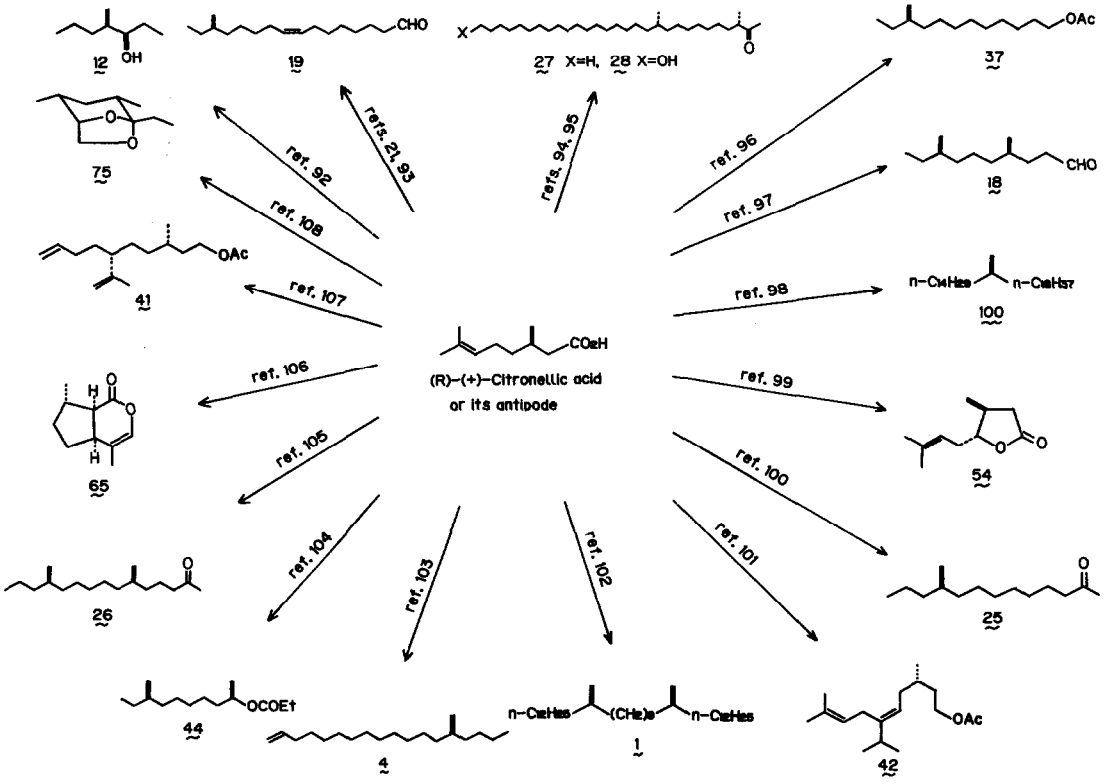


Fig. 27. Pheromones synthesized from citronellic acid.

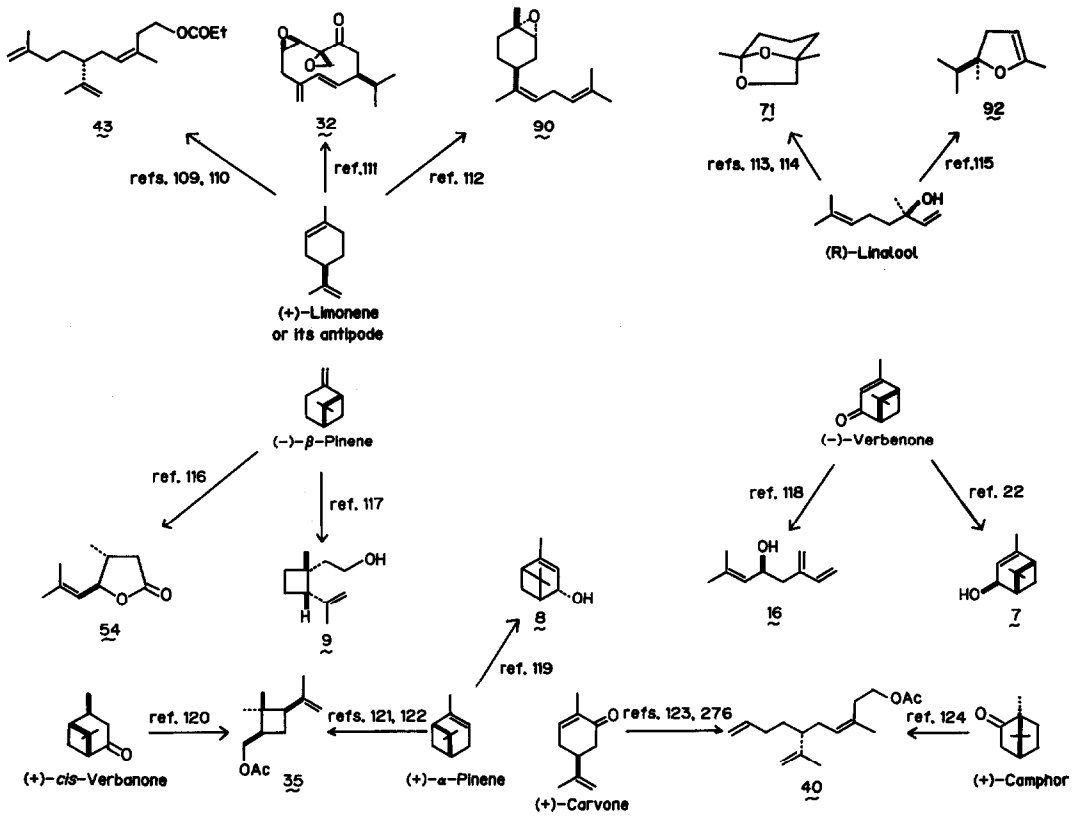
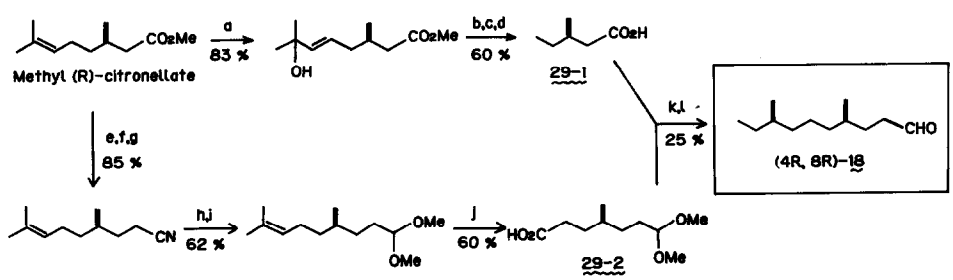


Fig. 28. Pheromones synthesized from various monoterpenes.

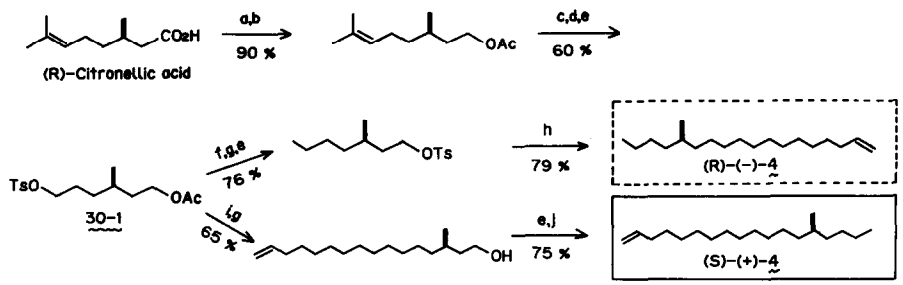
isolated by Suzuki as the aggregation pheromone of the red flour beetle, *Tribolium castaneum*.[126] We synthesized all of the four stereoisomers starting from (*R*)-citronellic acid.[97] Figure 29 illustrates the synthesis of (4*R*, 8*R*)-**18**. The key-step was the mixed Kolbe electrolysis between **29-1** and **29-2**. (4*R*, 8*R*)-**18** was active as the natural pheromone even at 1 ng/disc dose.[127,128]

3.3.2. *Synthesis of* 14-*methyl*-1-*octadecene from* (R)-*citronellic acid.* The peach leafminer moth



Reagents: (a) PhSeOH–*t*-BuOOH; (b) O_3, $NaHCO_3/CH_2Cl_2$—MeOH; Me_2S; (c) $N_2H_4 \cdot H_2O$, KOH, heat; (d) HCl; (e) LAH; (f) $TsCl/C_5H_5N$; (g) NaCN/DMSO; (h) $(i\text{-}Bu)_2AlH/n$-hexane; (i) $HC(OMe)_3$, MeOH, TsOH; (j) $RuCl_3$—$NaIO_4/CCl_4$—MeCN aq; (k) e^-, NaOMe/MeOH (Pt-electrode); (l) $HClO_4$ aq-THF.

Fig. 29. Synthesis of (4*R*, 8*R*)-4,8-dimethyldecanal from methyl (*R*)-citronellate.



Reagents: (a) LAH; (b) Ac_2O/C_5H_5N; (c) O_3, $NaHCO_3/CH_2Cl_2$—MeOH; (d) $NaBH_4$; (e) $TsCl/C_5H_5N$; (f) Me_2CuLi/Et_2O; (g) NaOH/MeOH aq; (h) $[CH_2{=}CH(CH_2)_9]_2CuLi/Et_2O$; (i) $[CH_2{=}CH(CH_2)_8]_2$-$CuLi/Et_2O$; (j) Et_2CuLi/Et_2O.

Fig. 30. Synthesis of the pheromone of the peach leafminer moth from (*R*)-citronellic acid.

(*Lyonetia clerkella*) is one of the notorious pests in peach orchards in Japan. Sugie *et al.* isolated and identified its sex pheromone as 14-methyl-1-octadecene **4**.[129] Both enantiomers of **4** were synthesized by us (Fig. 30).[103] Elongation of the carbon chain of **30-1** furnished the enantiomers of **4**. Only (*S*)-**4** was bioactive.[130]

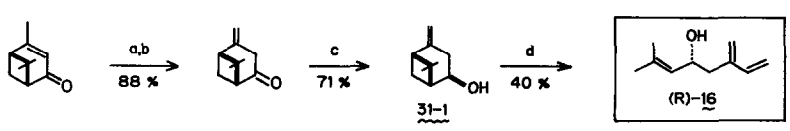
3.3.3. *Synthesis of ipsdienol from verbenone.* (+)-Ipsdienol **16** was isolated as a component of the aggregation pheromone of *Ips paraconfusus*.[89] Its absolute configuration was shown to be *S* by my synthesis of (*R*)-(−)-**16** from (*R*)-(+)-glyceraldehyde acetonide.[131] Ohloff and Giersch achieved the synthesis of both enantiomers of **16** starting from the enantiomers of verbenone.[118] Figure 31 shows the synthesis of (*R*)-(−)-**16**. The key-step was the thermolysis of **31-1** to **16**.

3.3.4. *Synthesis of the sex pheromone of the citrus mealybug from* (+)-*α-pinene via* (+)-*cis-verbanone*. The citrus mealybug, *Planococcus citri*, is an economic problem in citrus groves in the U.S.A. and Israel. Its females release a sex pheromone which was shown to be (1*R*, 3*R*)-(+)-**35**.[120] Its synthesis (Fig. 32) utilized the photolysis of (+)-*cis*-verbanone giving **32-1**.[120]

3.3.5. *Synthesis of* (−)-*periplanone-B from* (+)-*limonene*. Periplanone-B **32** is a component of the sex pheromone produced by female American cockroach, *Periplaneta americana*.[132] Still's stereoselective synthesis of (±)-**32**[133] was followed by optical resolution of his intermediate. This enabled the assignment of **32** as the absolute configuration of the natural and bioactive enantiomer.[134] An enantioselective synthesis of the natural and laevorotatory enantiomer of **32** was recently achieved by us starting from (+)-limonene (Fig. 33).[111] The key-steps were the cyclization of **33-1** to **33-2**, and the introduction of the diene system (**33-3** → **33-4**). The racemate of **33-4** was an intermediate of Schreiber's synthesis of (±)-**32**.[135] Two other syntheses of (±)-**32** have been reported.[136,137]

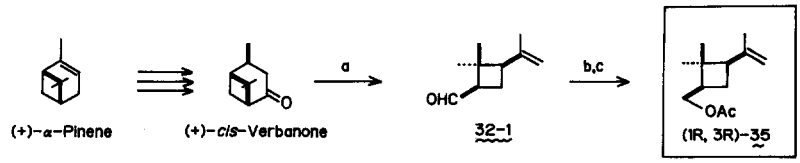
3.4. *Carbohydrates and related compounds as starting materials*

Carbohydrates are widely used as chiral building blocks.[138] They are employed in pheromone synthesis in which the construction of a chiral center with oxygen functionality is required. The rigid conformation of the pyranosides or anhydro sugars can be used to generate a chiral



Reagents: (a) NaH/THF; (b) H_3BO_3 aq; (c) LAH; (d) heat, 550°C/0.01 Torr, 1sec.

Fig. 31. Synthesis of ipsdienol from verbenone.

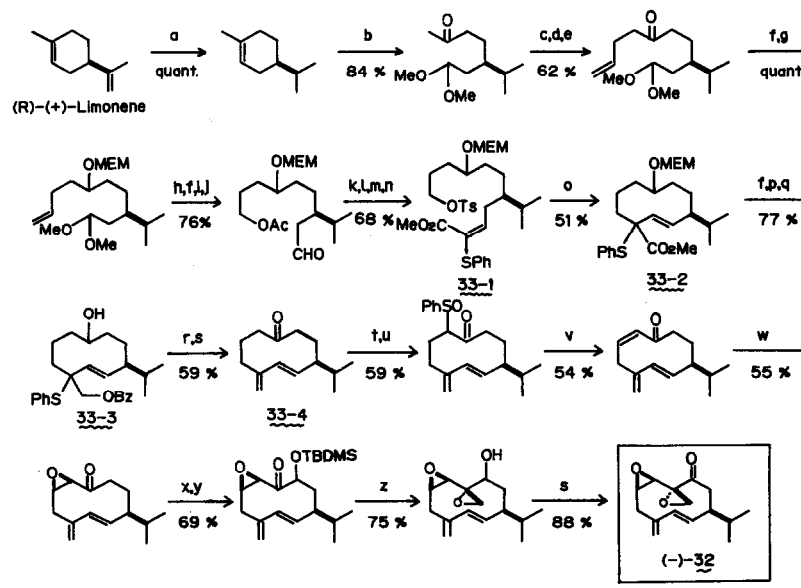


Reagents: (a) hν; (b) $NaBH_4$; (c) Ac_2O/C_5H_5N.
Fig. 32. Synthesis of the pheromone of the citrus mealybug from *cis*-verbanone.

center with a methyl substituent. A drawback to the use of carbohydrates is the fact that one must remove unwanted oxygen functionalities of the starting sugars to build rather simple molecule-like pheromones with a smaller number of chiral centers than those existing in sugars. Another shortcoming is that antipodal sugars of unnatural series are not easily secured.

In Fig. 34 are shown those pheromones synthesized from D-glucose. D-Glucose was employed in constructing pheromones with up to four chiral centers like (−)-α-multistriatin **75** and (+)-invictolide **55**.

Pheromones synthesized from carbohydrates other than D-glucose are shown in Fig. 35. As shown in Fig. 36, D-glyceraldehyde acetonide is a versatile chiral building block in pheromone synthesis. Conversion of D-mannitol to D-glyceraldehyde acetonide is used to prepare the latter.



Reagents: (a) H_2, PtO_2/MeOH; (b) (i) O_3/MeOH; (ii) Me_2S, TsOH/MeOH; (c) NaH—$CO(OMe)_2$/dioxane; (d) $CH_2{=}CHCH_2Br$; (e) KOH/MeOH; (f) LAH/Et_2O; (g) MEMCl, $(i\text{-}Pr)_2NEt/CH_2Cl_2$; (h) OsO_4—$NaIO_4/Et_2O$—H_2O; (i) Ac_2O/C_5H_5N; (j) 75% AcOH; (k) $PhSCH_2CO_2Me$, LDA/THF; (l) NaOAc/Ac_2O; (m) NaOMe/MeOH; (n) TsCl—DMAP—Et_3N/CH_2Cl_2; (o) $NaN(SiMe_3)_2$/DME; (p) BzCl—DMAP/THF—C_5H_5N; (q) Me_3SiI/MeCN; (r) Na, naphthalene/THF; (s) PCC—MS3A/CH_2Cl_2; (t) $LiN(SiMe_3)_2$, $PhSSO_2Ph$/THF; (u) $NaIO_4$/MeOH—H_2O; (v) $CaCO_3$/toluene, heat; (w) KH-*t*-BuOOH/THF; (x) $LiN(SiMe_3)_2$, $MoO_5\cdot HMPA\cdot C_5H_5N$/THF; (y) *t*-$BuSiMe_2Cl$ (TBDMSCl), imidazole/DMF; (z) (i) $Me_2S{=}CH_2$/DMSO—THF; (ii) $(n\text{-}Bu)_4NF$/THF.
Fig. 33. Synthesis of periplanone-B from limonene.

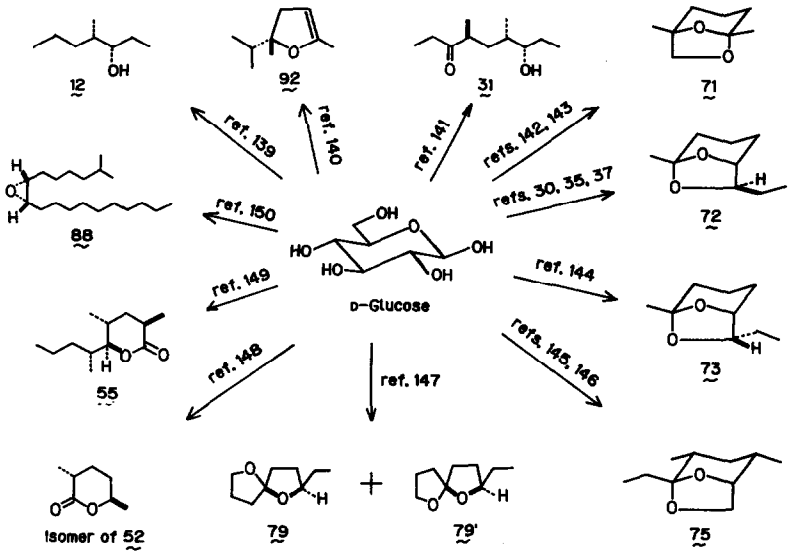


Fig. 34. Pheromones synthesized from D-glucose.

3.4.1. *Synthesis of* (−)-α-*multistriatin from* D-*glucose.* (−)-α-Multistriatin **75** is a component of the pheromone of the smaller European elm bark beetle, *Scolytus multistriatus.*[169] Its absolute configuration as depicted in **75** was assigned by two syntheses of enantiomerically impure (−)-**75**. Thus Silverstein *et al.* synthesized (−)-**75** starting from (*S*)-(+)-2-methyl-3-butenoic acid obtained by optical resolution.[170] My synthesis of (−)-**75** employed D-glyceraldehyde acetonide as the starting

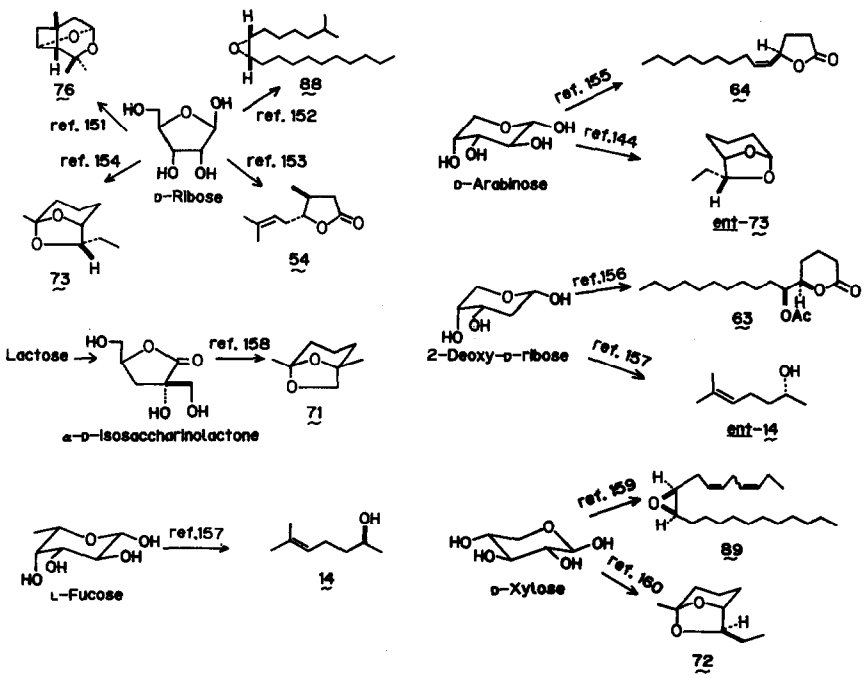


Fig. 35. Pheromones synthesized from carbohydrates other than D-glucose.

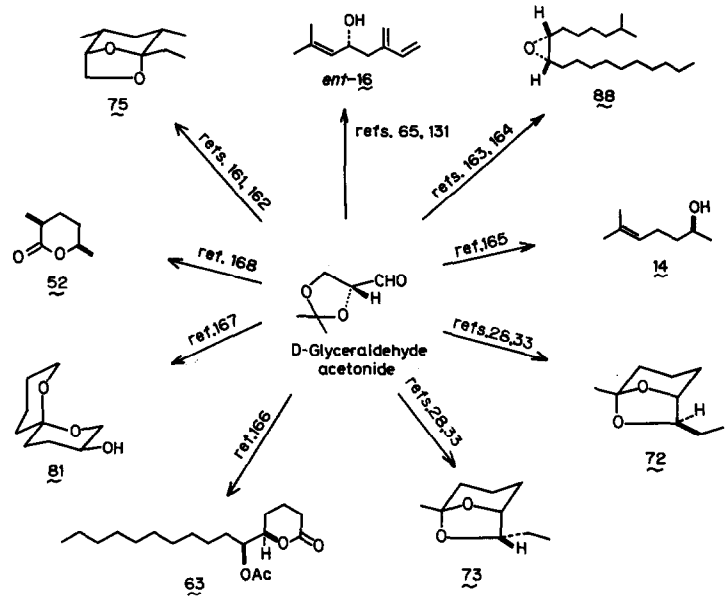
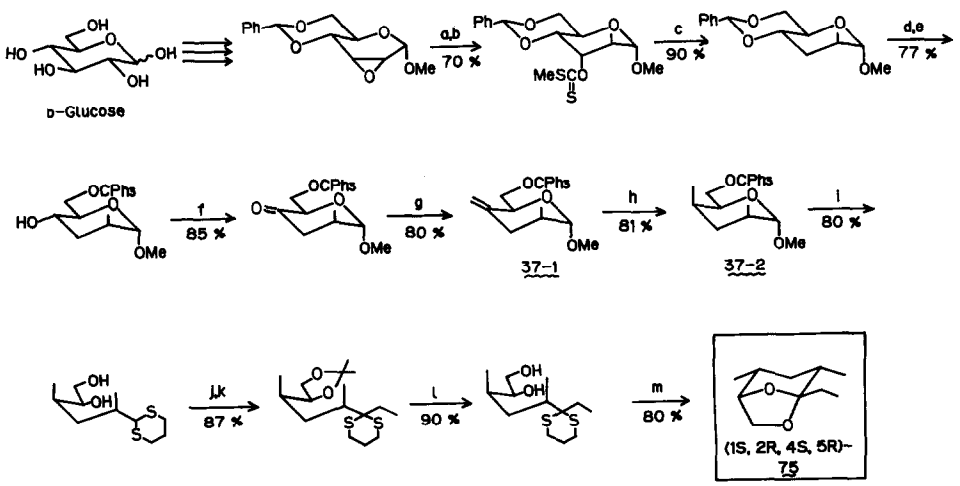


Fig. 36. Pheromones synthesized from D-glyceraldehyde acetonide.

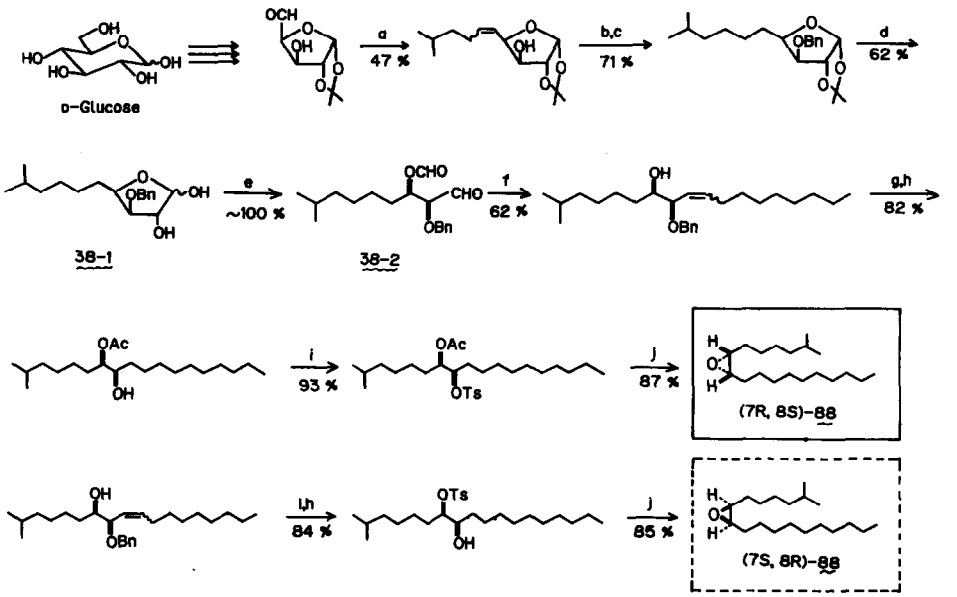
material.[161] A highly selective synthesis of (−)-**75** was achieved by Sum and Weiler starting from D-glucose (Fig. 37).[145] The crucial step was the construction of the 1,3-diaxial dimethyl substituents of **37-2** from **37-1** by stereoselective hydrogenation using the Wilkinson catalyst. The conformational rigidity of the pyranose system of **37-1** was the origin of the highly selective hydrogenation.

3.4.2. *Synthesis of disparlure from* D-*glucose.* Recently Achmatowicz *et al.* achieved a synthesis of disparlure **88** starting from D-glucose.[150] As shown in Fig. 38, two out of the four chiral centers



Reagents: (a) Me_2CuLi/Et_2O; (b) NaH, CS_2, MeI; (c) (n-Bu)$_3$SnH; (d) TsOH/MeOH; (e) Ph_3CCl/C_5H_5N; (f) $CrO_3 \cdot 2C_5H_5N/CH_2Cl_2$; (g) $Ph_3P{=}CH_2/Et_2O$; (h) H_2, $(Ph_3P)_3RhCl/C_6H_6$; (i) $HS(CH_2)_3SH$, BF_3/CH_2Cl_2; (j) $Me_2C(OMe)_2$, TsOH; (k) t-BuLi/n-hexane; EtI/HMPA; (l) TsOH/MeOH; (m) $HgCl_2$—HgO/MeCN.

Fig. 37. Synthesis of (−)-α-multistriatin from D-glucose.

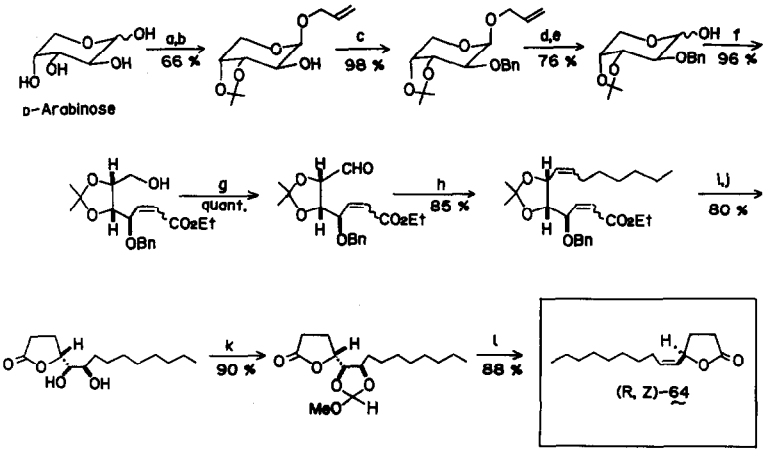


Reagents: (a) $Me_2CH(CH_2)_3PPh_3Br$, NaH/DMSO; (b) H_2/Pd—C; (c) NaH, BnCl/DMSO; (d) 85% CF_3CO_2H—H_2O/DME; (e) $Pb(OAc)_4/C_6H_6$; (f) $Me(CH_2)_8PPh_3Br$, *n*-BuLi/THF; MeOH; (g) Ac_2O/C_5H_5N; (h) H_2/Pd—C/AcOH; (i) $TsCl/C_5H_5N$; (j) KOH/MeOH.

Fig. 38. Synthesis of disparlure from D-glucose.

of D-glucose were utilized giving **88**. The unwanted two chiral centers were removed in the glycol cleavage reaction (**38-1** → **38-2**).

3.4.3. *Synthesis of the Japanese beetle pheromone from* D-*arabinose*. The Japanese beetle pheromone (+)-**64** was recently synthesized from D-arabinose.[155] The synthesis as shown in Fig. 39 furnished an enantiomerically pure sample of (+)-**64**. Two out of the three chiral centers of arabinose were removed in the final step.



Reagents: (a) CH_2=$CHCH_2OH$, HCl gas; (b) TsOH/Me_2CO; (c) BnBr, NaH/DMF; (d) *t*-BuOK/DMSO; (e) 0.1 N HCl—Me_2CO; (f) Ph_3P=$CHCO_2Et/CH_2Cl_2$; (g) PCC/CH_2Cl_2; (h) $Me(CH_2)_6PPh_3Br$, *n*-BuLi/THF; (i) H_2/Pd/AcOH—MeOH; (j) 90% CF_3CO_2H; (k) $HC(OMe)_3$, TsOH, CH_2Cl_2; (l) Ac_2O, heat, 140°C, 1.5 h.

Fig. 39. Synthesis of the Japanese beetle pheromone from D-arabinose.

4. SYNTHESIS BY OPTICAL RESOLUTION

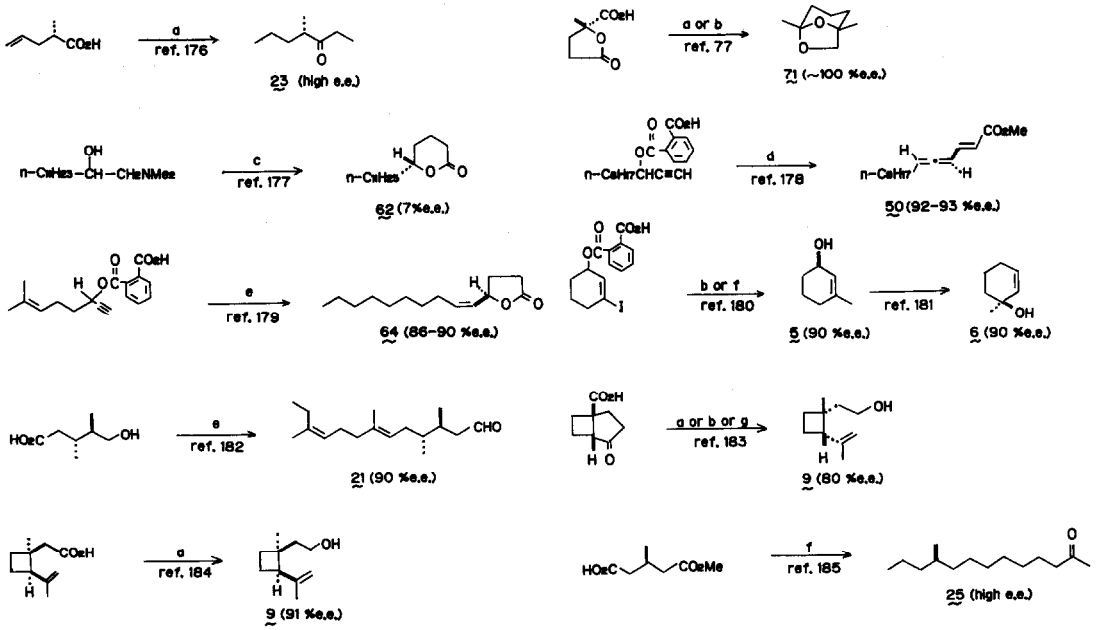
The art of optical resolution since the days of Pasteur was well-reviewed recently.[171-174] A full compilation of the experimental details of optical resolutions has been published.[175]

Because we can imagine any kind of suitable intermediates for resolution, the freedom of choice in the course of planning a synthesis is wider in this approach than that based upon derivation from natural products. However, the resolution is not always perfectly successful. Moreover, the absolute configuration and the enantiomeric purity of the resolved material must be carefully determined.

In addition to the classical fractional recrystallization procedure for optical resolution, chromatographic separation of diastereomers is now prevalent. In some instances, enantiomers can be separated on a small preparative scale by employing chiral stationary phase chromatography. As noted in Section 2.2.3., a spiroacetal (±)-**85** could be resolved by HPLC on microcrystalline cellulose triacetate.[47] This chiral stationary phase was found to be quite effective in separating lactone enantiomers.[48] For example, (±)-4-hexanolide **51** (2.47 g), when chromatographed on 800 g of cellulose triacetate, gave (*S*)-(−)-**51** (0.81 g; 96% e.e.) and (*R*)-(+)-**51** (0.78 g, 100% e.e.). This method could become convenient for routine resolution.

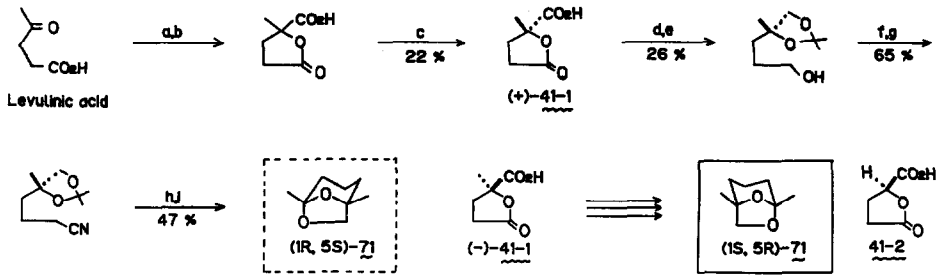
4.1. *Separation of diastereomeric mixtures by fractional recrystallization*

In Fig. 40 are listed pheromones synthesized by optical resolution of intermediates. In the synthesis of frontalin **71**, the resolution was highly successful.[77] However, in the synthesis of 5-hexadecanolide **62**, the material obtained by Coke and Richon was later estimated to be of only 7% e.e.[186] In many cases the yield of the resolved enantiomers was low and the optical purity of the resolved material did not reach >95% (Fig. 40). The low optical purity of the resolved intermediate



The compound shown at the left of the pheromone is the resolved intermediate. Resolving agent; (a) quinine; (b) cinchonine; (c) dibenzoyl (+)-tartaric acid; (d) (−)-1-(1-naphthyl)ethylamine; (e) (+)-1-phenylethylamine; (f) cinchonidine; (g) brucine.

Fig. 40. Pheromones synthesized by classical optical resolution of intermediates.

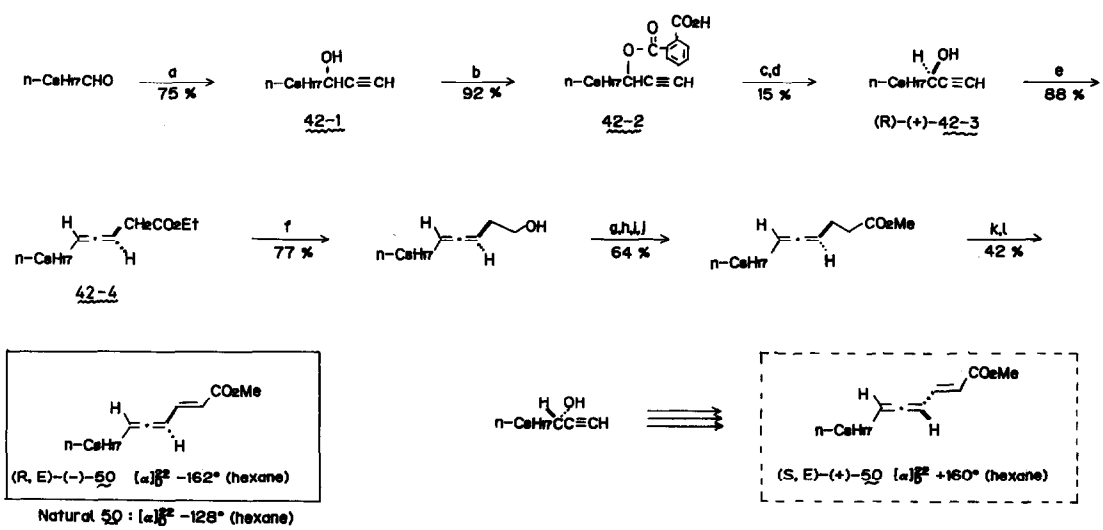


Reagents: (a) HCN; (b) HCl aq; (c) quinine; recrystallization; acidification; (d) LAH/Et_2O; (e) TsOH/Me_2CO; (f) TsCl/C_5H_5N; (g) NaCN/DMSO; (h) MeMgI/Et_2O; (i) dil HCl.
Fig. 41. Synthesis of frontalin by the classical optical resolution.

led to the production of the pheromone with an enantiomeric purity which was unsatisfactory for precise bioassay. In the case of grandisol **9**, the unnatural (−)-enantiomer obtained by resolution had been reported to be as active as the natural (+)-**9**.[184] When we synthesized[187] and bioassayed the enantiomerically pure (+)- and (−)-**9**, only the former was found to be active.[188] Because of this uncertainty in securing the enantiomerically pure material, the classical resolution procedure has gradually become less popular than the chromatographic resolution procedure.

4.1.1. *Synthesis of frontalin by optical resolution of a lactonic acid.* My first synthesis of the enantiomers of frontalin **71** was executed by the classical optical resolution of a lactonic acid (Fig. 41).[77] The absolute configuration of the resolved lactonic acids (+)-**41-1** and (−)-**41-1** was deduced by comparing their CD spectra with a known lactonic acid **41-2** derived from (*S*)-glutamic acid. Although the overall yield was modest, the synthesis was short and straightforward.

4.1.2. *Synthesis of methyl* (E)-2,4,5-*tetradecatrienoate by optical resolution of an acetylenic alcohol.* Our synthesis (Fig. 42)[178] of the enantiomers of chiral allenic ester **50** clarified the (*R*)-



Reagents: (a) HC≡CMgBr; (b) phthalic anhydride/C_5H_5N; (c) (*R*)-(+)-1-(1-naphthyl)ethylamine; recrystallization; (d) dil HCl; NaOH aq; (e) $MeC(OEt)_3$, $EtCO_2H$, heat; (f) $(i\text{-}Bu)_2AlH$; (g) TsCl/C_5H_5N; (h) NaCN/DMSO; (i) NaOH aq; HCl; (j) CH_2N_2; (k) LDA; PhSeSePh; (l) $NaIO_4$/THF/H_2O.
Fig. 42. Synthesis of the enantiomers of methyl (*E*)-2,4,5-tetradecatrienoate, the pheromone of the male dried bean beetle by classical optical resolution.

absolute configuration of the male-produced pheromone of the dried bean beetle, *Acanthoscelides obtectus*.[189] The synthesis was based on the classical method of optical resolution of the alcohol **42-1** via its phthalic half ester **42-2**. The absolute configuration of the resolved (+)-**42-3** was assigned as depicted by its hydrogenation to the known (*S*)-(+)-3-undecanol. The key-step of the synthesis was the transfer of the central chirality of (+)-**42-3** to the axial chirality of **42-4**. The synthetic (*R*, *E*)-**50** was laevorotatory. The natural and laevorotatory pheromone therefore had the (*R*)-configuration and was less enantiomerically pure than the synthetic pheromone. The synthetic **50** failed to attract the dried bean beetle.[190]

4.2. *Separation of diastereomeric mixtures by chromatography*

The task of optical resolution was facilitated very much by the advent of preparative HPLC and MPLC (medium pressure liquid chromatography) systems. These chromatographic techniques are quite efficient for the separation of the diastereomeric mixtures. The choice of chiral derivatization reagent is very important for successful resolution. In Fig. 43 are compiled the derivatized intermediates successfully used in pheromone syntheses. Carbamates derived from enantiomerically pure 1-(1-naphthyl)ethylamine and 1-phenylethylamine are most frequently used for the resolution of alcohols. A derivative of chrysanthemic acid [see our second lineatin (**76**) synthesis[42]] and MTPA ester were also used to resolve alcohols. For the resolution of acids, (*S*)-prolinol, (*R*)-phenylglycinol and (*S*)-1-phenylethylamine were used as the chiral derivatizing agents. Careful separation of the diastereomers followed by synthetic sequence designed to avoid racemization led to the syntheses of highly pure enantiomers of pheromones as in the cases of α-multistriatin **75**,[194] lineatin **76**,[42] anastrephin **58**,[199,200] lardolure **33**[198] and grandisol **9**.[201]

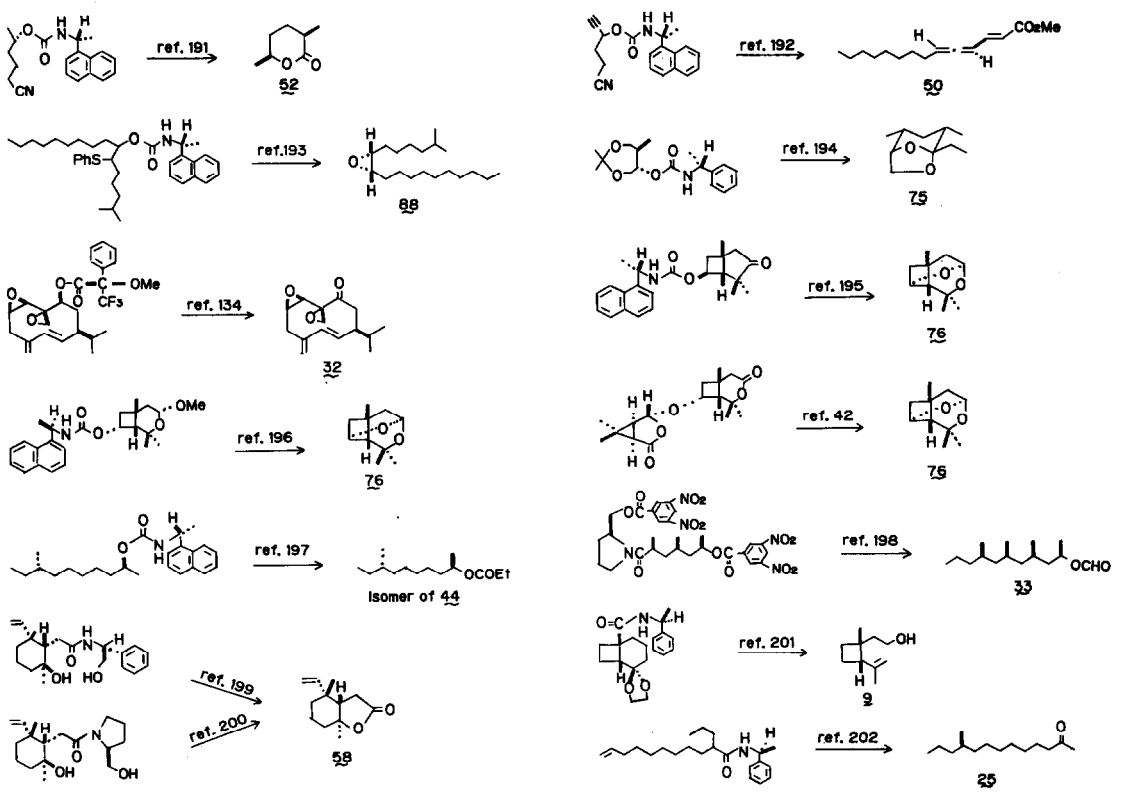
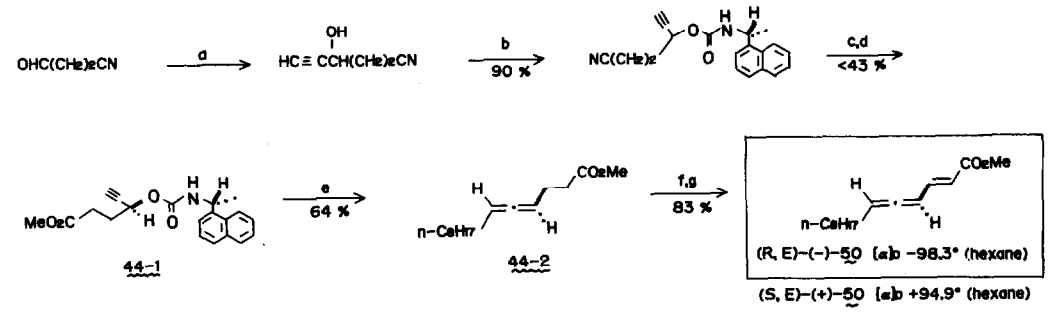


Fig. 43. Pheromones synthesized by the chromatographic optical resolution of the intermediates.

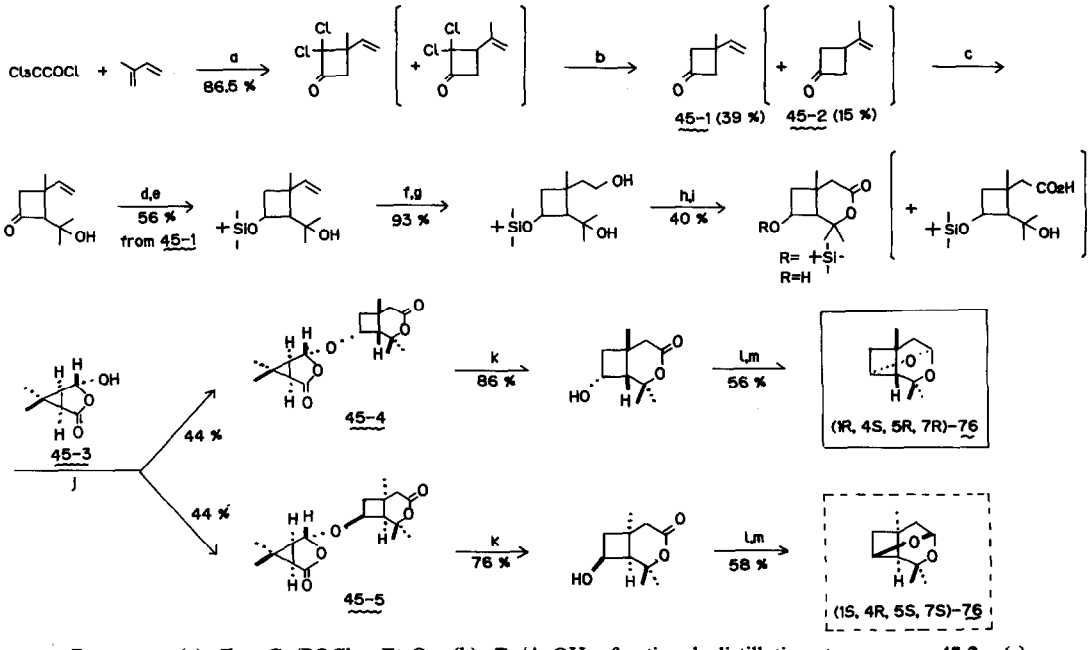


Reagents: (a) HC≡CMgBr; (b) (*R*)-1-(1-naphthyl)ethylisocyanate; (c) HCl/MeOH; (d) HPLC separation; (e) $(n\text{-}C_8H_{17})_2CuLi/Et_2O$ (inverse addition); (f) LDA, PhSeSePh; (g) $NaIO_4/THF—H_2O$.

Fig. 44. Synthesis of the enantiomers of methyl (*E*)-2,4,5-tetradecatrienoate by chromatographic optical resolution.

4.2.1. *Synthesis of methyl* (E)-2,4,5-*tetradecatrienoate by chromatographic separation of diastereomeric carbamates.* In 1978 Pirkle and Boeder synthesized the enantiomers of the pheromone of the dried bean beetle **50** (Fig. 44).[192] The carbamate **44-1** was obtained by HPLC separation, and its carbamate moiety functioned as a leaving group when it was treated with an organocopper reagent giving **44-2**. At this stage, however, partial racemization took place giving (*R*, *E*)-(−)-**50** of only 56% e.e. as judged by its $[\alpha]_D$ value. The use of an appropriate reaction to avoid partial racemization is very important in designing a synthesis of enantiomerically pure compounds.

4.2.2. *Synthesis of lineatin by chromatographic separation of diastereomeric acetals.* Lineatin **76** is the female produced pheromone of the striped ambrosia beetle, *Trypodendron lineatum*. Our synthesis of the enantiomers of **76** is shown in Fig. 45.[42] It started from dichloroketene and isoprene.



Reagents: (a) Zn—Cu/$POCl_3$—Et_2O; (b) Zn/AcOH; fractional distillation to remove **45-2**; (c) LDA/THF; Me_2CO; (d) Li(*s*-Bu)$_3$BH/THF; H_2O_2; (e) *t*-BuSiMe_2Cl, imidazole; (f) B_2H_6/THF; (g) H_2O_2, aq NaOH; (h) PDC/CH_2Cl_2; (i) (*n*-Bu)$_4$NF; (j) TsOH; MPLC separation; (k) HCl—MeOH; (l) (*i*-Bu)$_2$AlH; (m) dil HCl.

Fig. 45. Synthesis of the enantiomers of lineatin by chromatographic optical resolution.

The separation of the diastereomeric mixture of acetals **45-4** and **45-5** was effected by MPLC. The absolute configuration of **45-4** could be established by the X-ray analysis, because the resolving agent **45-3** was derived from (1*R*, 3*R*)-(+)-chrysanthemic acid. The natural pheromone was shown to be (1*R*, 4*S*, 5*R*, 7*R*)-(+)-**76** by bioassay of the enantiomers and by analysis of the natural pheromone by complexation GLC employing (+)-**76** as the reference sample.[203]

5. SYNTHESIS BY CHEMICAL ASYMMETRIC REACTIONS

In 1973 when our pheromone synthesis was initiated, chemical asymmetric synthesis was in its infant stage. It has now grown up to be a useful and versatile method for pheromone synthesis.[204–206] Chiral pheromones are simpler in their structures than macrolides or polyether antibiotics so those chemists in the field of asymmetric synthesis regarded chiral pheromones as good feasible targets to test the scope and limitations of their asymmetric reactions. Accumulation of the chiroptical data of chiral pheromones by other synthetic endeavours as reviewed already in this article greatly encouraged the people in the field of asymmetric synthesis. Such data facilitated the estimation of the optical yields of asymmetric reactions.

5.1. *Application of the Sharpless asymmetric epoxidation*

Discovery of the tartrate-mediated asymmetric epoxidation by Katsuki and Sharpless in 1980[207] dramatically facilitated the synthesis of optically active epoxides.[208–211] At the time of that discovery, a catalyst that was both selective and versatile was supposed to be impossible. How Sharpless solved the problem has been lucidly described.[212] By the Sharpless epoxidation reaction, either of the enantiomers of 2,3-epoxy alcohol can be prepared from the allylic alcohol by using either enantiomer of diethyl or diisopropyl tartrate as a chiral catalyst in the presence of *t*-butyl hydroperoxide and titanium tetraisopropoxide. The enantiomeric excess of the product is usually over 90%. This reaction is the most widely employed chemical asymmetric process in pheromone synthesis.

5.1.1. *Synthesis of pheromone epoxides, acetates, alcohols and keto alcohols by asymmetric epoxidation.* Various pheromones such as epoxides, acetates, alcohols and keto-alcohols (Fig. 46) were synthesized using asymmetric epoxidation. If highly enantiomerically pure (>99% e.e.)

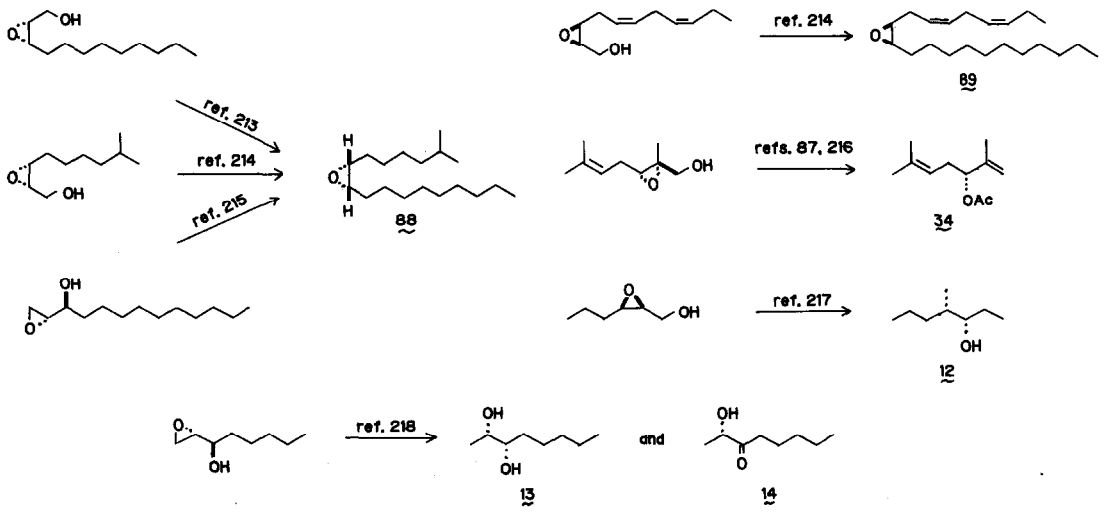
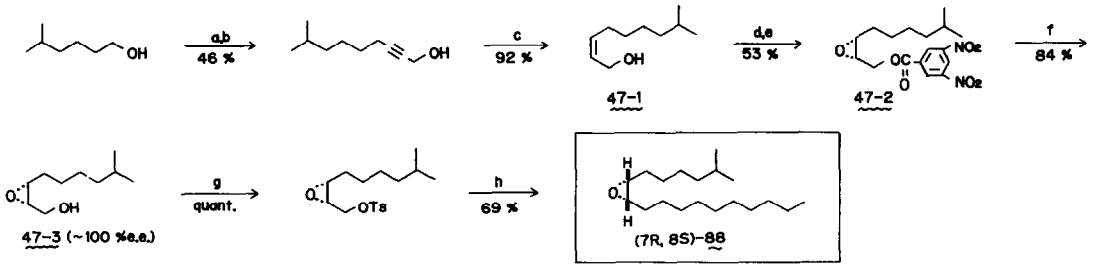


Fig. 46. Pheromone epoxides, acetate, alcohols and keto alcohol synthesized by employing the asymmetric epoxidation. Chiral epoxides served as intermediates are shown at the left of the target molecules.



Reagents: (a) PBr_3/Et_2O; (b) $LiC{\equiv}CCH_2OLi/THF—NH_3(liq)$; (c) $H_2/Pd—BaSO_4$, quinoline/MeOH; (d) $Ti(Oi\text{-}Pr)_4$, L-(+)-diethyl tartrate, t-BuOOH/CH_2Cl_2, −23°C; (e) 3,5-DNBCl/$Et_2O—C_5H_5N$; recrystallization; (f) K_2CO_3/THF—MeOH; (g) $TsCl/C_5H_5N$; (h) $(n\text{-}C_9H_{19})_2CuLi/Et_2O$-toluene.
Fig. 47. Synthesis of (+)-disparlure by the application of the asymmetric epoxidation.

pheromones are required then the epoxy-alcohols can be purified by recrystallizing their corresponding 3,5-dinitrobenzoates.[214] Figure 47 illustrates a synthesis of (+)-disparlure **88** via an epoxy alcohol **47-3**. This was obtained by asymmetric epoxidation of **47-1** followed by purification of the corresponding 3,5-dinitrobenzoate **47-2**.[214]

5.1.2. *Synthesis of pheromone acetals and lactones by asymmetric epoxidation.* Acetal pheromones have been synthesized (Fig. 48) by employing asymmetric epoxidation. Murahashi's synthesis of (1*S*, 5*R*)-(−)-frontalin **71** is shown in Fig. 49.[223] The synthesis was accomplished in only three steps (28% overall yield) giving (−)-**71** (92% e.e.). In Fig. 50 are listed pheromone lactones and others synthesized by asymmetric epoxidation.

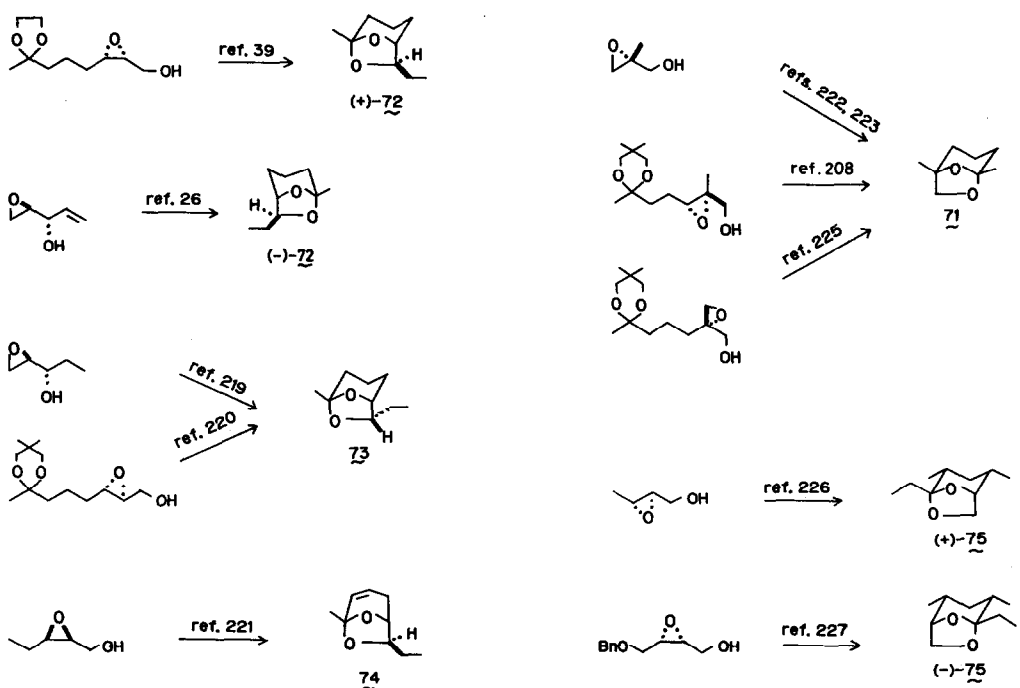
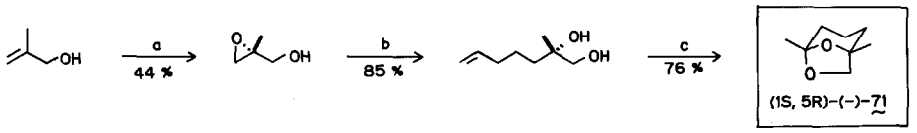


Fig. 48. Pheromone acetals synthesized by employing the asymmetric epoxidation. Chiral epoxides served as intermediates are shown at the left of the target molecules.



Reagents: (a) $Ti(Oi\text{-}Pr)_4$, D-(−)-diethyl tartrate, t-BuOOH/CH_2Cl_2, −20°C; (b) $CH_2{=}CH(CH_2)_2MgBr$, Li_2CuCl_4/THF, −78°C; (c) $PdCl_2$, CuCl, O_2/triglyme, 50°C.
Fig. 49. Synthesis of (−)-frontalin by the application of the asymmetric epoxidation.

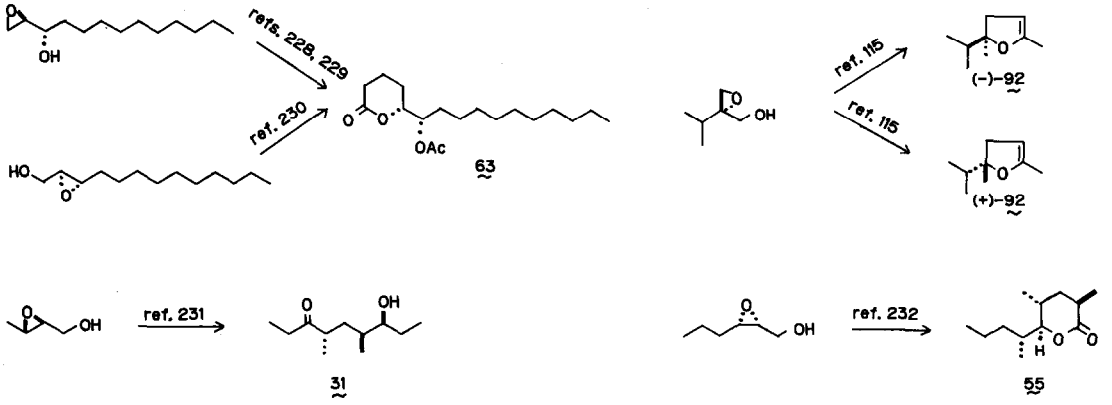


Fig. 50. Pheromone lactones and others synthesized by employing the asymmetric epoxidation.

5.2. *Application of asymmetric reductions*

Reduction of a prochiral ketone to a chiral alcohol is a well-investigated asymmetric process, and has been used frequently in pheromone synthesis. This reduction can be executed in three different ways: (i) catalytic asymmetric hydrogenation, (ii) treatment with a hydride reagent modified with a chiral auxiliary, and (iii) diastereoselective reduction of a ketone with a chiral auxiliary.

5.2.1. *Synthesis of pheromones by catalytic asymmetric hydrogenation.* Tai and his coworkers found that the nickel catalyst modified with tartaric acid could effect asymmetric hydrogenation of prochiral β-keto esters.[233] Applications of this finding in pheromone synthesis are shown in Fig. 51. The pine sawfly pheromone (2*S*, 3*R*, 7*R*)-**39** was synthesized from **51-2**, which in turn was synthesized by asymmetric hydrogenation of **51-1** over the nickel catalyst modified with D-tartaric acid.[234] Hydrogenation gave a mixture of the diastereomers (60% e.e.) which was further purified giving

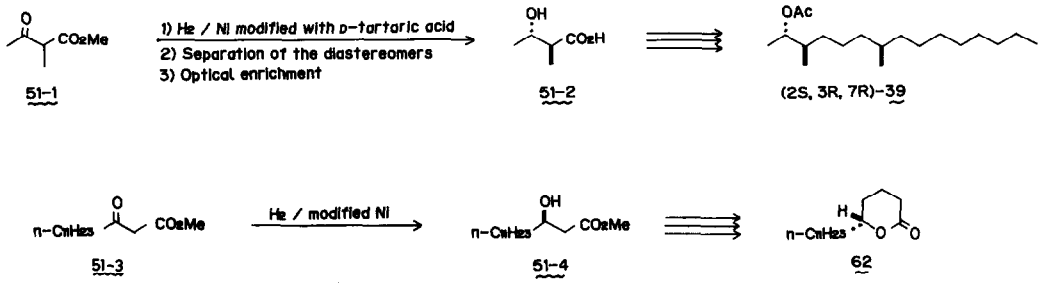


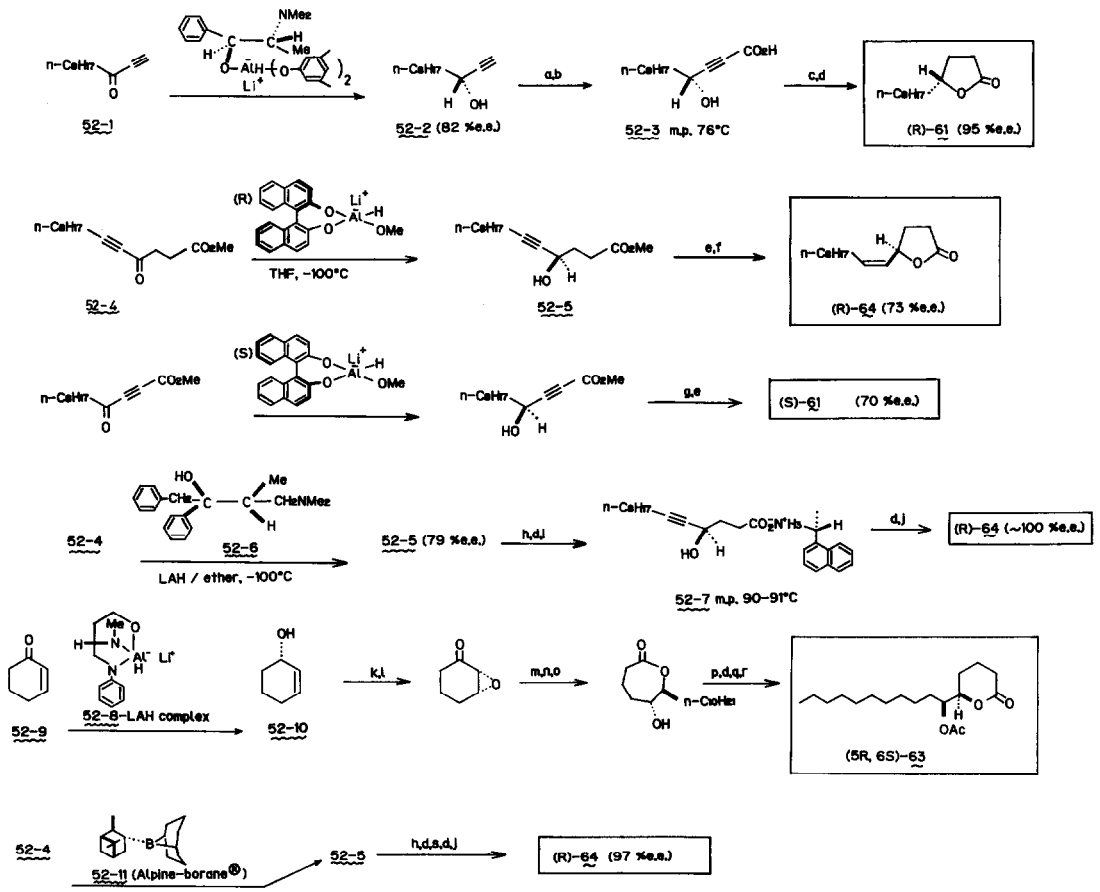
Fig. 51. Pheromones synthesized by asymmetric hydrogenation of β-keto esters.

51-2 (9% yield) from **51-1**. Asymmetric hydrogenation of a β-keto ester **51-3** gave **51-4**,[235] which furnished the pheromone of the oriental hornet **62**.[236]

Very recently, Noyori *et al.* have prepared β-hydroxy esters of high enantiomeric purities (98 ~ >99% e.e.) by asymmetric hydrogenation of β-keto esters over the 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-coordinated Ru(II) complex.[237]

5.2.2. *Synthesis of pheromones by reduction with hydride reagents modified with chiral auxiliaries.* Asymmetric reduction of α,β-acetylenic ketones with a chiral complex between lithium aluminum hydride, N-methylephedrine and 3,5-dimethylphenol was developed by Vigneron and Bloy and employed in pheromone synthesis (Fig. 52).[238] The dove beetle pheromone **61** was synthesized by reduction of **52-1** to **52-2** as the key-step. The product **52-2** (82% e.e.) was further purified as the corresponding acid **52-3** by its recrystallization, which eventually yielded (*R*)-**61** (95% e.e.). This asymmetric reduction was also used for the synthesis of (3*R*, 4*R*)-4-methyl-3-heptanol **12**, the antipode of the pheromone component of the smaller European elm bark beetle.[239]

Enantioselective reduction by binaphthol-modified lithium aluminum hydride reagents were applied to pheromone synthesis by Noyori *et al.*[240] Reduction of **52-4** with (*R*)-binaphthol-modified



Reagents: (a) 2 eq *n*-BuLi/THF; (b) CO_2; (c) H_2/Pd—C/EtOH; (d) H^+; (e) TsOH; (f) H_2/Lindlar Pd; (g) N_2H_2; (h) NaOH/MeOH aq; (i) (*R*)-1-(1-naphthyl)ethylamine; recrystallization; (j) H_2/Pd—$CaCO_3$; quinoline/*n*-pentane; (k) *t*-BuOOH, $VO(acac)_2$; (l) $CrO_3 \cdot 2C_5H_5N$; (m) LDA, Me_3SiCl; (n) *n*-$C_{10}H_{21}Li$; (o) MCPBA; (p) KOH/MeOH; (q) heat; (r) Ac_2O/C_5H_5N; (s) cyclohexylamine; recrystallization.

Fig. 52. Pheromones synthesized by employing modified hydride reagents.

lithium aluminum hydride reagent (BINAL-H) gave **52-5** (84% e.e.), which yielded the Japanese beetle pheromone (*R*)-**64** of 73% e.e.[240] Similarly, the defense substance **61** of the dove beetle was also synthesized.[240]

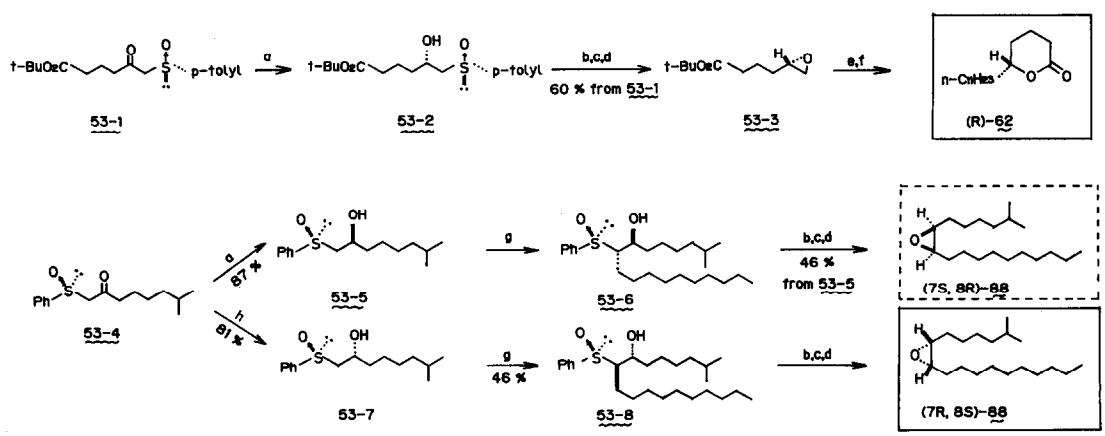
The Japanese beetle pheromone (*R*)-**64** was also prepared by us as shown in line 4 of Fig. 52.[241] Reduction of **52-4** with lithium aluminum hydride modified with (2*S*, 3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol **52-6** at $-100°C$[242] gave **52-5** (79% e.e.). This was purified by recrystallization of **52-7** giving pure (*R*)-**64**.

Fujisawa and his coworkers employed lithium aluminum hydride modified with (*S*)-4-anilino-3-methylamino-1-butanol **52-8** for the reduction of **52-9** to **52-10**.[243] The chiral auxiliary **52-8** was prepared from (*S*)-aspartic acid.[244] Starting from **52-10**, the mosquito oviposition pheromone (5*R*, 6*S*)-**63** was synthesized.[243]

Another synthesis of the Japanese beetle pheromone **64** was achieved by Midland *et al.* using B-3-pinanyl-9-borabicyclo[3.3.1]nonane **52-11** derived from (+)-α-pinene (Alpine-borane®) as the asymmetric reducing agent.[245] If the commercially available impure (+)-α-pinene was used, the e.e. of **52-5** was 78–88% e.e., which had to be purified as a crystalline derivative to yield the pheromone of high e.e. However, by using enantiomerically pure **52-11**, **52-5** of 97% e.e. was obtained.[245] Similarly Baker and Rao also synthesized the Japanese beetle pheromone (*R*)-**64** by employing **52-11**.[246]

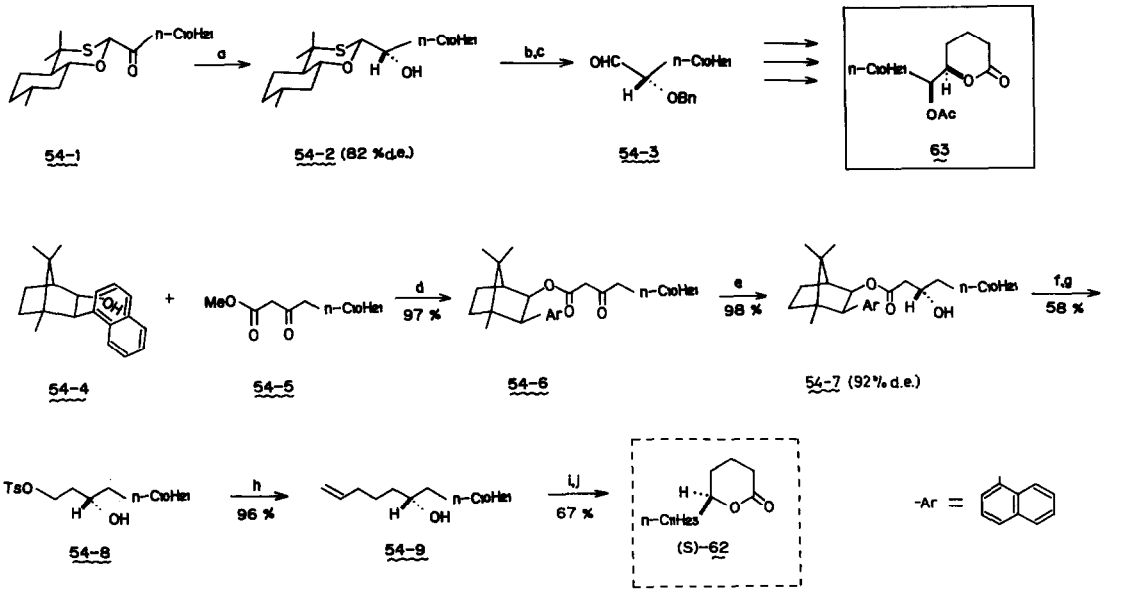
5.2.3. *Synthesis of pheromones by diastereoselective reduction of ketones modified with chiral auxiliaries.* Kosugi *et al.* found that the presence of zinc chloride in the reduction of chiral β-ketosulfoxides with diisobutylaluminum hydride effects highly diastereoselective reduction giving β-hydroxysulfoxides (Fig. 53).[247] Thus reduction of **53-1** yielded **53-2** which was converted to (*R*)-(+)-5-hexadecanolide **62**. Absence of zinc chloride resulted in the reversal of the stereochemical outcome of the reduction.[247] As an application of this diastereoselective reduction, Sato *et al.* accomplished the synthesis of both enantiomers of disparlure **88**.[248] α-Alkylation of the β-hydroxysulfoxide **53-5** was found to be diastereoselective. The product **53-6** afforded (7*S*, 8*R*)-(−)-disparlure **88**. By reducing **53-4** with diisobutylaluminum hydride alone, **53-7** was obtained, which gave (7*R*, 8*S*)-(+)-disparlure **88** via **53-8**. Due to the availability of enantiomerically pure chiral sulfoxides, the syntheses (Fig. 53) furnished the pure enantiomers, **62** and **88**.

Besides sulfoxides, two other chiral auxiliaries were used to effect diastereoselective reduction of ketones (Fig. 54). Reduction of oxathiane **54-1** with L-Selectride® yielded **54-2**, which was



Reagents: (a) $ZnCl_2$, $(i\text{-Bu})_2AlH/THF$; (b) Zn, Me_3SiCl/C_5H_5N—THF; (c) Me_3OBF_4/CH_2Cl_2; (d) 5% NaOH aq/CH_2Cl_2; (e) $n\text{-}C_{10}H_{21}MgBr$, CuI, Me_2S/THF; (f) $TsOH/C_6H_6$; (g) MeLi; $n\text{-}C_{10}H_{21}I$; (h) $(i\text{-Bu})_2AlH$.

Fig. 53. Pheromones synthesized by employing diastereoselective reduction of chiral β-ketosulfoxides.



Reagents: (a) LiBH(*s*-Bu)$_3$, LiI/toluene, −78°C, (b) BnBr, NaH/THF; (c) NCS, $AgNO_3$; (d) DMAP/toluene; (e) (*i*-Bu)$_2$AlH; 2,6-di-*t*-butyl-4-methylphenol/toluene, −65°C; (f) LAH/THF; (g) TsCl (1.1 eq), C_5H_5N; (h) CH_2=$CHCH_2MgCl$/THF; (i) O_3/MeOH; then Me_2S; (j) PCC, NaOAc, MS 4A/CH_2Cl_2.
Fig. 54. Pheromones synthesized by employing diastereoselective reduction of ketones with chiral auxiliaries.

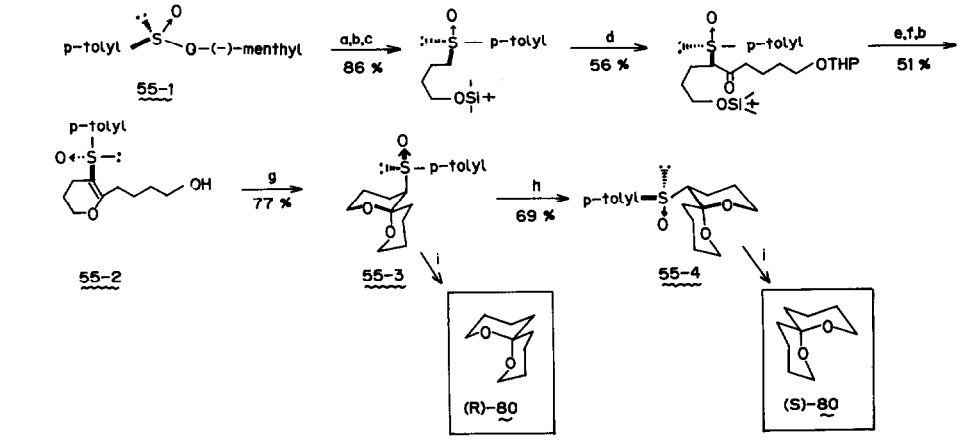
converted to the mosquito oviposition pheromone **63** via **54-3** through a lengthy route including inversion of configuration at C-5.[249] Taber's recent syntheses of (*S*)-(−)-5-hexadecanolide **62** proceeded in a highly selective and efficient manner.[250] The chiral auxiliary **54-4** was attached to *β*-keto ester **54-5** by ester exchange. The resulting *β*-keto ester **54-6** was reduced to **54-7** by the method of H. Yamamoto.[251] The chiral auxiliary **54-4** could be recovered unchanged after the reduction. The reduction product was monotosylated giving **54-8** which then yielded the lactone **62** via **54-9**.

5.3. *Application of intramolecular asymmetric carbon–oxygen bond formation*

Two different methods for the intramolecular diastereoselective formation of carbon–oxygen bonds were developed to synthesize chiral pheromones as detailed below.

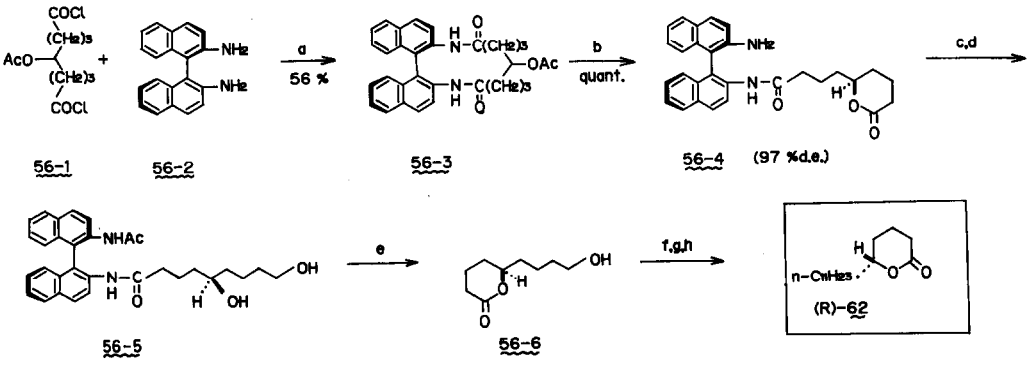
5.3.1. *Synthesis of the olive fruit fly pheromone by employing an intramolecular Michael addition of a hydroxyl group to the chiral vinyl sulfoxide moiety.* Iwata *et al.* synthesized the enantiomers of the olive fruit fly pheromone starting from (−)-menthyl (*S*)-*p*-toluenesulfinate **55-1** as shown in Fig. 55.[252] The key-step was the diastereoselective intramolecular Michael addition of the hydroxyl group of **55-2** giving the spiroacetal **55-3** as the kinetically controlled product with an axial sulfinyl group. Treatment of **55-3** with acid effected its isomerization to the more stable isomer **55-4**. Desulfurization of **55-3** and **55-4** afforded the pheromone enantiomers, (*R*)-**80** and (*S*)-**80**, respectively.

5.3.2. *Synthesis of* (R)-*5-hexadecanolide by asymmetric lactonization.* As shown in Fig. 56, derivatization of the prochiral **56-1** with the C_2-chiral auxiliary **56-2** yielded **56-3**. Oda and his coworkers found conditions suitable for the conversion of **56-3** diastereoselectively to **56-4**, which yielded a hydroxy lactone **56-6** via **56-5**.[253] This gave (*R*)-5-hexadecanolide **62** of high enantiomeric purity.



Reagents: (a) $THPO(CH_2)_4MgCl/THF$, $-10°C$; (b) H_3O^+; (c) *t*-$BuSiMe_2Cl$; (d) $LiNEt_2$, $THPO(CH_2)_4CO_2Me/THF$—HMPA, $-70°C$; (e) $(n\text{-}Bu)_4NF/THF$; (f) TsOH, $MgSO_4/CH_2Cl_2$; (g) NaH/THF; (h) TsOH/MeOH; (i) Raney-Ni/MeOH.

Fig. 55. Synthesis of the olive fruit fly pheromone by diastereoselective intramolecular Michael addition.



Reagents: (a) Et_3N/CH_2Cl_2 (high dilution); (b) 1% CF_3CO_2H/CH_2Cl_2, $-20°C$; (c) Ac_2O/C_5H_5N; (d) $LiBH_4$/EtOH; (e) $TsOH/CH_2Cl_2$; (f) $(COCl)_2$-DMSO—CH_2Cl_2; (g) $n\text{-}C_7H_{15}PPh_3Br$, *t*-BuOK/THF; (h) H_2/Pd—C.

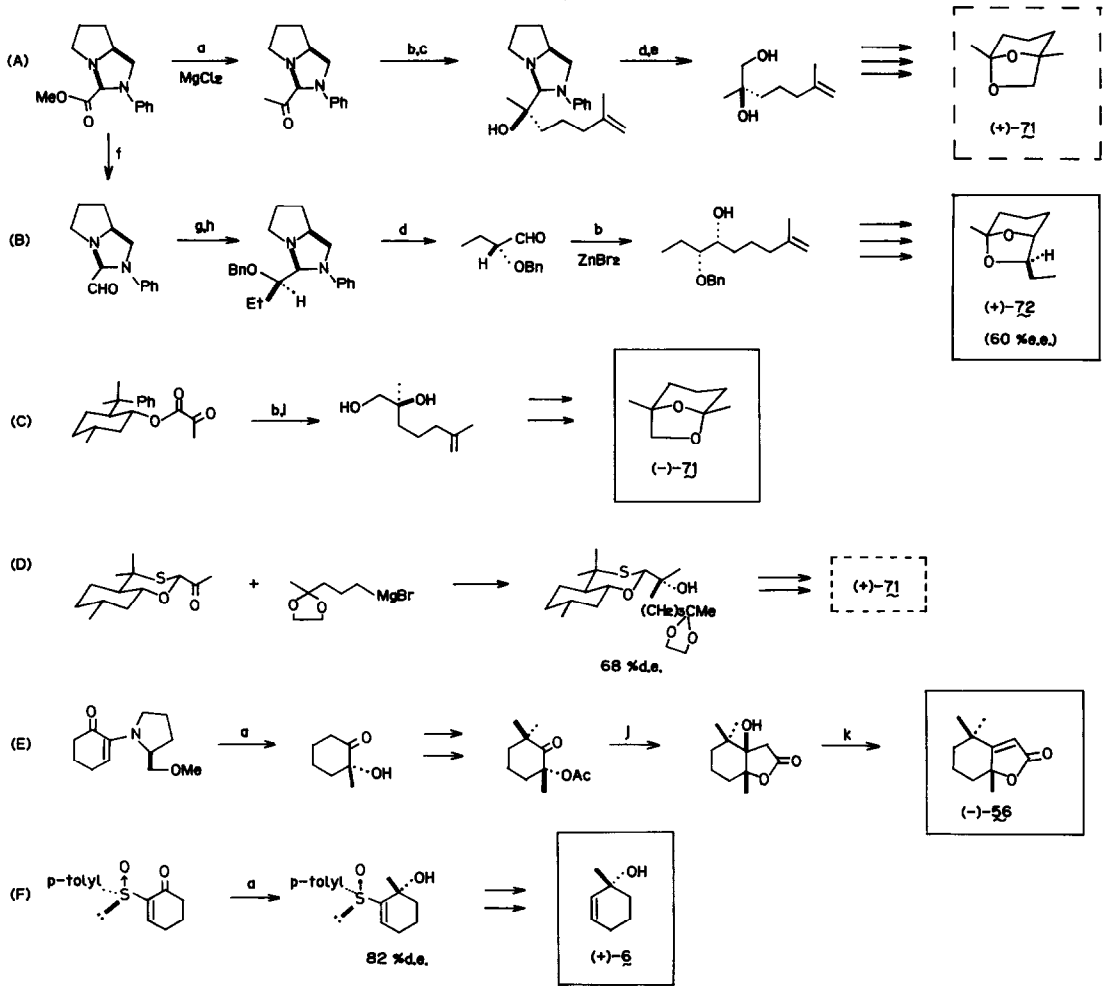
Fig. 56. Synthesis of (*R*)-5-hexadecanolide by asymmetric lactonization.

5.4. *Application of asymmetric carbon–carbon bond formation*

The rapid growth of efficient asymmetric carbon–carbon bond formation reactions in various syntheses of pheromones is summarized below.

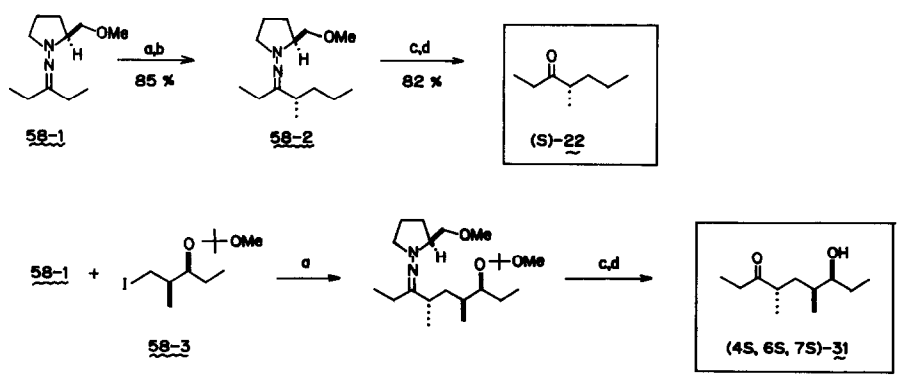
5.4.1. *Synthesis of pheromones by the addition of achiral nucleophiles to chiral substrates.* Examples of pheromone synthesis by the addition of Grignard reagents to chiral carbonyl compounds are listed in Fig. 57. Pheromones which have been synthesized are: the enantiomers of frontalin **71** by the routes (A),[254] (C),[255] and (D),[256] (+)-*exo*-brevicomin **72**,[33] (−)-dihydroactinidiolide **56**,[257] and (*R*)-1-methyl-2-cyclohexen-1-ol **6**.[258] Addition of the Grignard reagent was usually carried out at a low temperature to favour the conformation of one transition state by chelation control.

5.4.2. *Synthesis of pheromones by the addition of chiral nucleophiles to achiral substrates.* Enders *et al.* developed a useful method for enantioselective α-alkylation of acyclic ketones via metallated SAMP-hydrazones[SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine]. He applied it for the synthesis of the alarm pheromone of the leaf-cutting ant *Atta texana* [(*S*)-**22**] (Fig. 58).[259,260] Alkylation



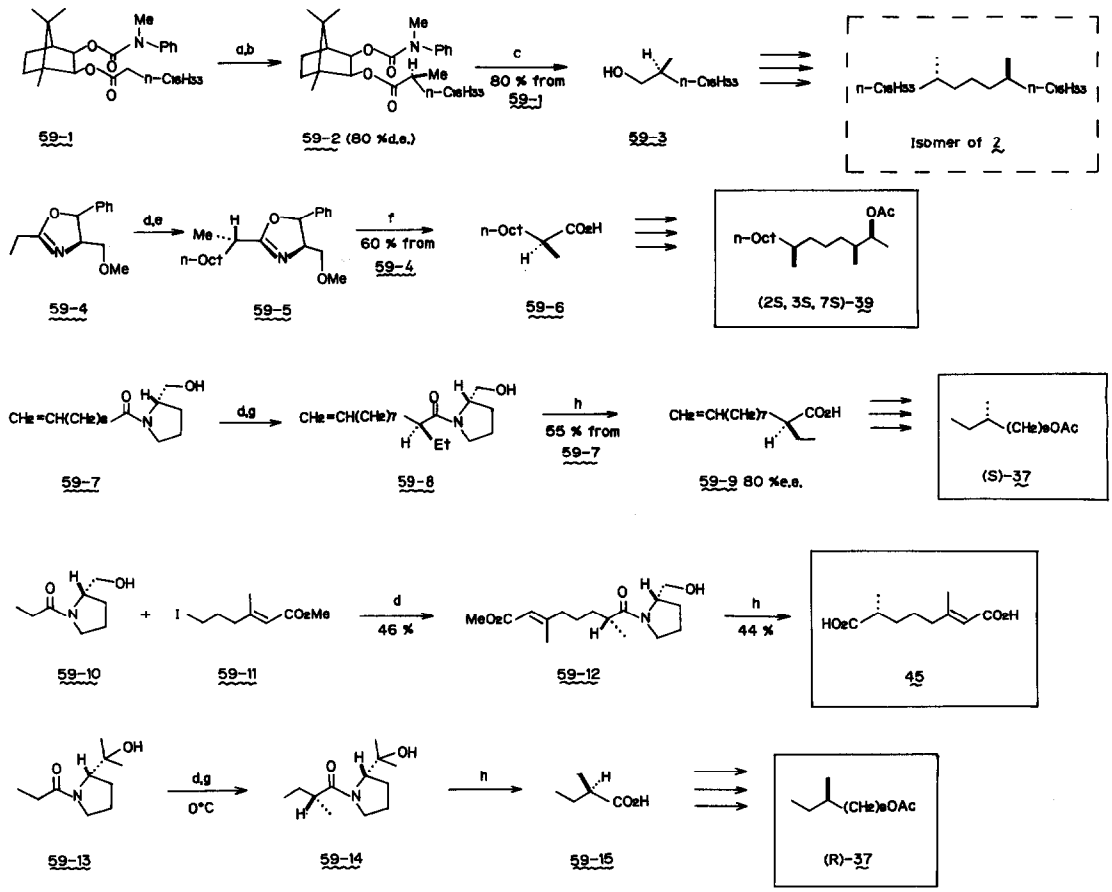
Reagents: (a) MeMgBr; (b) $CH_2{=}CMe(CH_2)_3MgBr$; (c) NH_4Cl aq; (d) 2% HCl aq; (e) $NaBH_4$; (f) $(i\text{-}Bu)_2AlH$; (g) EtMgBr; (h) BnBr/NaH; (i) LAH; (j) LDA; (k) $SOCl_2/C_5H_5N$.

Fig. 57. Pheromones synthesized by the addition of achiral Grignard reagents to carbonyl compounds with chiral auxiliaries.



Reagents: (a) LDA/Et_2O; (b) n-C_3H_7I, $-110°C$; (c) MeI; (d) dil HCl/n-pentane.

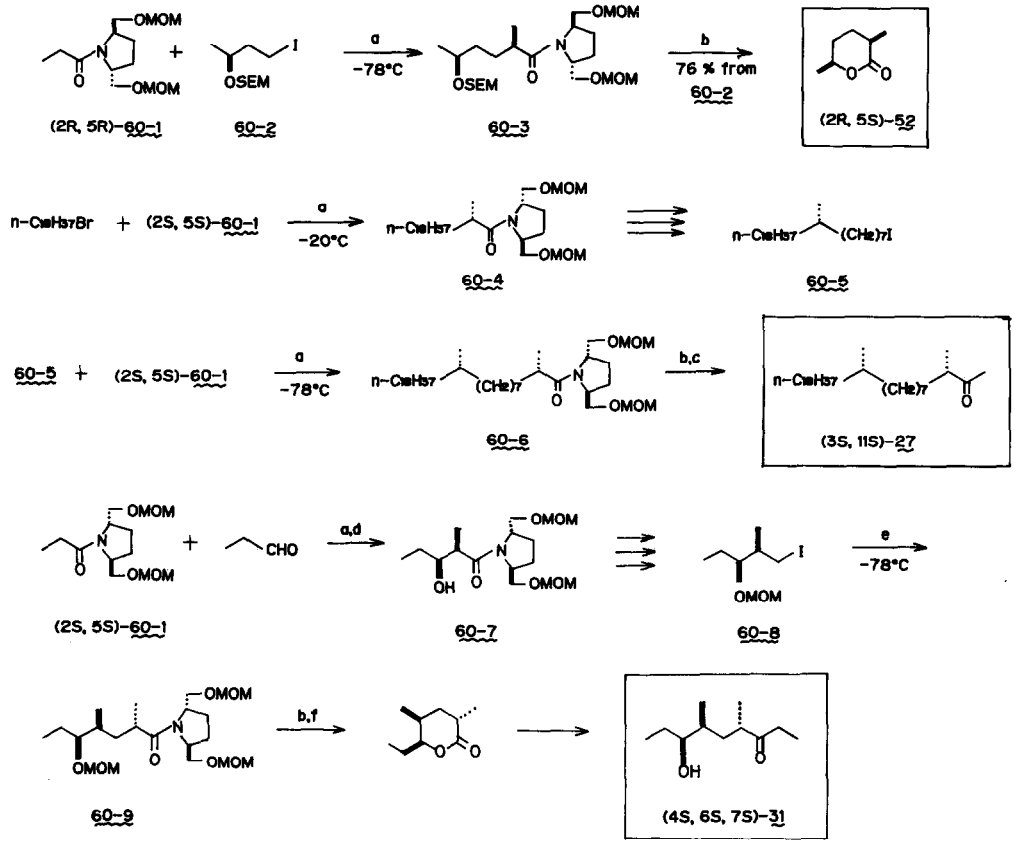
Fig. 58. Pheromones synthesized by the alkylation of the SAMP-hydrazone of diethyl ketone.



Reagents: (a) LiN(*i*-Pr)C_6H_{11}/THF, −80°C; (b) MeI/HMPA, −80 ~ −40°C; (c) LAH; (d) LDA/THF, −80 ~ −100°C; (e) *n*-$C_8H_{17}I$, −100°C; (f) dil H_2SO_4, heat; (g) EtI/HMPA, −100°C; (h) dil HCl, heat.
Fig. 59. Pheromones synthesized by alkylation of the chiral ester, oxazoline and amides.

of the SAMP-hydrazone **58-1** with *n*-propyl iodide and LDA gave **58-2**, the mild hydrolysis of which furnished (*S*)-**22**. Similarly, the cigarette beetle pheromone, serricornin **31**, was synthesized by us by alkylating **58-1** with **58-3**.[261]

Alkylation of esters, amides or oxazolines with chiral auxiliaries results in the asymmetric alkylation giving optically active acid derivatives (Fig. 59). Helmchen's asymmetric synthesis of all of the three possible stereoisomers of the pheromone **2** of the tsetse fly (*Glossina morsitans morsitans*) started from a chiral ester **59-1**.[262] This was alkylated giving **59-2**, which was finally converted to (17*S*, 21*S*)-**2** via **59-3**. Meyers's excellent method of synthesizing optically active dialkylacetic acids via chiral oxazolines[263] was used by Norin to achieve a synthesis of the pine sawfly pheromone **39**.[264] Thus alkylation of **59-4** yielded **59-5**. This then gave **59-6** which was employed as a building block of **39**. Diastereoselective alkylation of amides of prolinol as developed by Evans and Takacs[265] was used as follows. A chiral component **37** of the pheromone of the smaller tea tortrix moth (*Adoxophyes* sp.) was synthesized from amide **59-7** via **59-8** and **59-9**.[266] Alkylation of the amide **59-10** with **59-11** yielded **59-12**, which was hydrolyzed giving (*R*)-(−)-callosobruchusic acid **45**, a component of the copulation release pheromone of the azuki bean beetle, *Callosobruchus chinensis*.[267] By employing a modified amide **59-13**, (*R*)-2-methylbutanoic acid **59-15** of >98% e.e. was prepared via **59-14**.[268] The acid **59-15** was converted to the smaller tea tortrix moth pheromone (*R*)-**37**.[268]



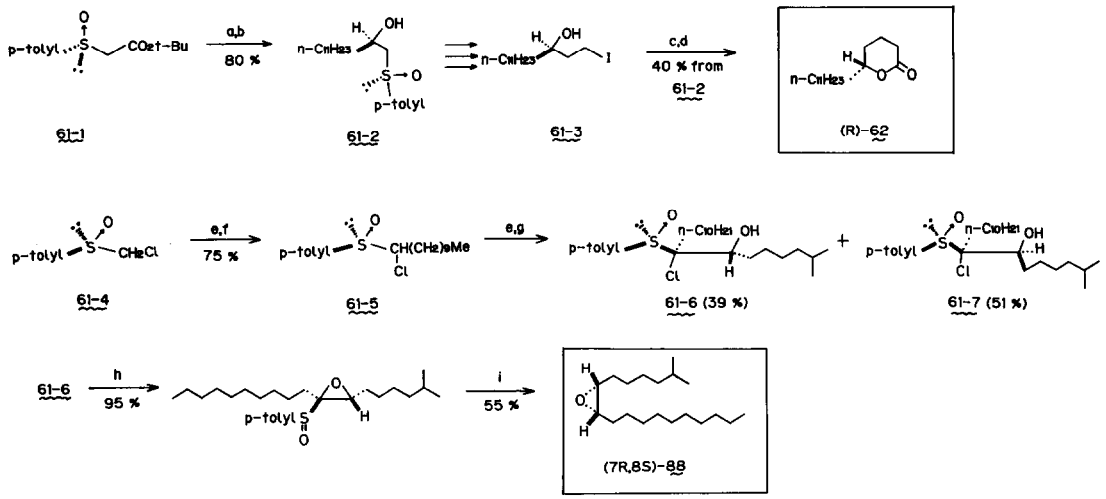
Reagents: (a) LDA/THF; (b) dil HCl, heat; (c) $MeLi/Et_2O$; (d) Cp_2ZrCl_2; (e) (2*S*, 5*S*)-**60-1**, LDA/THF; (f) $EtLi/Et_2O$, −100°C.

Fig. 60. Pheromones synthesized by using Katsuki's chiral amide.

Recently Katsuki and Yamaguchi employed their methods for the asymmetric synthesis of dialkylacetic acids and its β-hydroxy derivatives for the synthesis of three pheromones (Fig. 60).[269] The carpenter bee pheromone **52**, the German cockroach pheromone **27** and serricornin **31** were synthesized in optically pure state either by alkylation or by the aldol reaction of **60-1**. The C_2-chiral nature of **60-1** served to achieve high selectivity (>95% d.e.). The lithium enolate of **60-1** was employed for the alkylation to prepare **60-3**, **60-4**, **60-6** and **60-9**. For the aldol reaction giving **60-7** the zirconium enolate of **60-1** was used.

Aldol reaction with and alkylation of chiral sulfoxides were also employed in pheromone syntheses (Fig. 61). Solladié *et al.* executed the aldol reaction between **61-1** and dodecanal giving **61-2**.[270] This gave (*R*)-(+)-5-hexadecanolide **62** via **61-3**. Yamakawa's synthesis of (+)-disparlure **88** employed alkylation of **61-4** followed by aldol reaction of **61-5** with 6-methylheptanal as key-steps.[271] Although the latter step was not stereoselective, the resulting mixture could be separated. (+)-Disparlure **88** was prepared from **61-6**, while **61-7** furnished (−)-*trans*-disparlure.

5.4.3. *Synthesis of pheromones by asymmetric Michael addition.* Utilization of asymmetric Michael addition in pheromone synthesis was first reported by Oppolzer *et al.*[272] They employed a chiral auxiliary derived from camphor-10-sulfonic acid (Fig. 62). The Michael addition of an organo-copper reagent to **62-1** was found to be highly stereoselective giving **62-2** (>99% d.e.).[272] The addition product **62-2** was converted to the southern corn rootworm pheromone (*R*)-**25** via **62-3**.[272] Diastereoselective acetoxylation of **62-2′** by treatment of its silyl enol ether with lead tetraacetate



Reagents: (a) *t*-BuMgBr/THF; (b) n-$C_{11}H_{23}CHO$, −78°C; (c) $LiCH_2CO_2t$-Bu/THF-HMPA; (d) $TsOH/C_6H_6$; (e) LDA/THF; (f) n-$C_{10}H_{21}I$; (g) $Me_2CH(CH_2)_4CHO$; (h) *t*-BuOK/*t*-BuOH; (i) 1 eq n-BuLi/THF, −100°C.

Fig. 61. Pheromones synthesized by asymmetric carbon–carbon bond formation with chiral sulfoxides.

yielded **62-4**. This eventually gave the pheromone component (3*S*, 4*S*)-**12** of the smaller European elm bark beetle via **62-5**.[273]

Leznoff's syntheses[274] of the California red-scale pheromone (*R*)-**40** was based on Mukaiyama's asymmetric Michael addition using (−)-ephedrine as the chiral auxiliary.[275] Starting from **62-6**, the Michael adduct **62-7** was reduced giving the key-aldehyde **62-8** of not so high e.e. Conversion of **62-8** to the pheromone **40** was a known process.[276] Leznoff also tested Koga's method for the Michael addition[277] by employing the aldimine **62-9**.[274] In this case, the aldehyde **62-8** was obtained with satisfactory e.e. (>99%).

Oppolzer's asymmetric synthesis of the red-scale pheromone (*R*)-**40** was efficient using the camphor-derived chiral auxiliary.[278] Michael addition of isopropenylcopper to **62-10** gave the adduct **62-11**. Hydrolysis of **62-11** to **62-12** was followed by its conversion to the pheromone **40**. An excellent Tetrahedron Report is available on the use of camphor derivatives as chiral auxiliaries in asymmetric synthesis.[279]

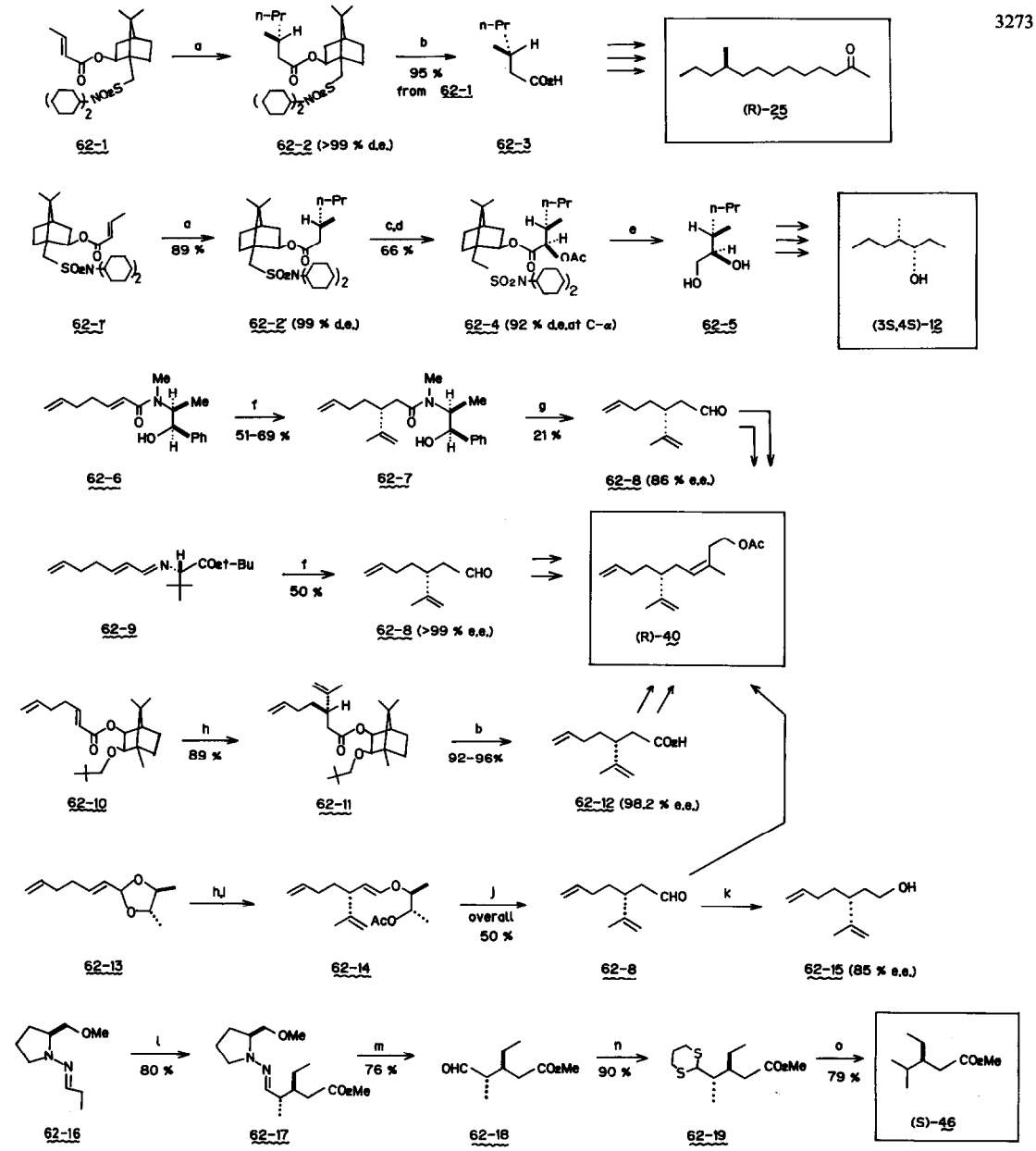
Normant and his coworkers reported another asymmetric synthesis of the red-scale pheromone **40** by employing an acetal **62-13** as the starting material. S_N2'-Type reaction of isopropenylcopper with **62-13** gave **62-14**, which furnished **62-15** of 85% e.e. via **62-8**.[280]

A pheromone component (*S*)-**46**, which showed a strong aggression inhibitory effect against the small forest ant and red wood ant, was synthesized by Enders *et al.* employing an asymmetric Michael addition via SAMP-hydrazone **62-16** giving **62-17**.[281] The pheromone **46** was prepared from **62-17** via **62-18** and **62-19**.

5.4.4. *Synthesis of pheromones by asymmetric reactions employing organoboranes.* The use of chiral organoboranes in organic synthesis was recently reviewed by Matteson.[282]

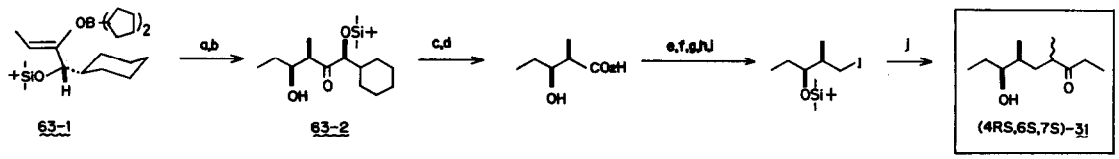
Baker and Devlin employed Masamune's asymmetric aldol reaction with the boron enolate **63-1**[283] in the synthesis of (4*RS*, 6*S*, 7*S*)-serricornin **31** (Fig. 63).[284] Aldol reaction of **63-1** with propanal gave **63-2**, which was converted to (4*RS*, 6*S*, 7*S*)-**31** in the conventional manner.

The reaction of chiral allylic boronic esters such as **64-1** and **64-3** with aldehydes leads to chiral homoallylic alcohols such as **64-2** and **64-4** as discovered by Hoffmann (Fig. 64). This method was used for the synthesis of the stereoisomers **95′** and **95″** of stegobinone **95**, the drugstore beetle pheromone,[285] and also for the synthesis of (−)-δ-multistriatin (δ-isomer of **75**).[286] (*R*)-Carvone



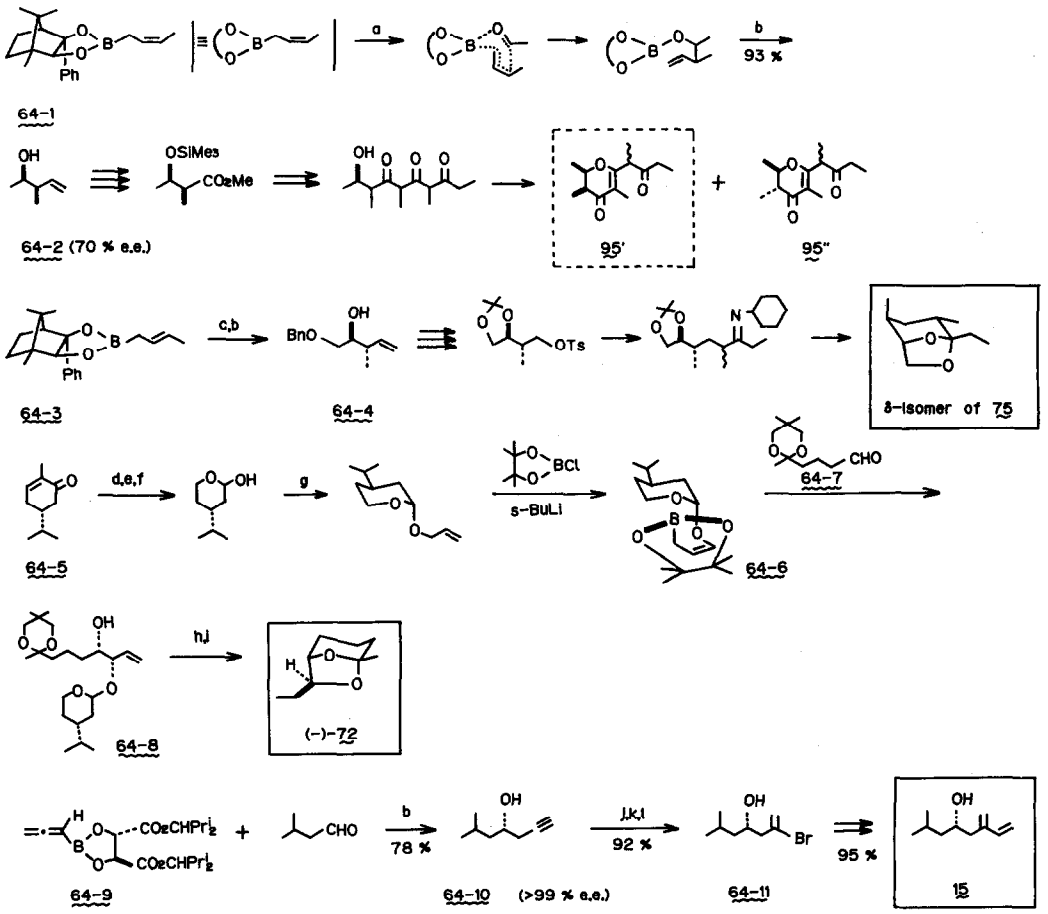
Reagents: (a) *n*-PrCu·BF_3, $(n\text{-Bu})_3P$; (b) NaOH; (c) LDA, Me_3SiCl; (d) $Pb(OAc)_4$; (e) LAH; (f) $CH_2{=}CMeMgBr$; (g) $(i\text{-Bu})_2AlH$; (h) $CH_2{=}CMeCu\cdot BF_3$, $(n\text{-Bu})_3P$; (i) Ac_2O/C_5H_5N, DMAP; (j) HCO_2H; (k) $NaBH_4$; (l) LDA, $EtCH{=}CHCO_2Me$; (m) O_3; (n) $HS(CH_2)_3SH$, $SnCl_4/CH_2Cl_2$; (o) Raney Ni.

Fig. 62. Pheromones synthesized by asymmetric Michael addition.



Reagents: (a) EtCHO; (b) H_2O_2; (c) $(n\text{-Bu})_4NF$; (d) IO_4^-; (e) CH_2N_2; (f) *t*-$BuSiMe_2Cl$; (g) $(i\text{-Bu})_2AlH$; (h) $TsCl/C_5H_5N$; (i) NaI; (j) Et_2CO, LDA; (k) $(n\text{-Bu})_4NF$.

Fig. 63. Serricornin synthesis by means of asymmetric aldol reaction.



Reagents: (a) MeCHO; (b) $N(CH_2CH_2OH)_3$; (c) $BnOCH_2CHO$; (d) O_3; (e) LAH; (f) $NaIO_4$; (g) $CH_2{=}CHCH_2OH$, TsOH; (h) H_2/Pd; (i) H_3O^+; (j) B-Br-9-BBN/CH_2Cl_2; (k) AcOH; (l) H_2O_2, NaOH.

Fig. 64. Pheromones synthesized by the reaction of chiral boronic esters with aldehydes.

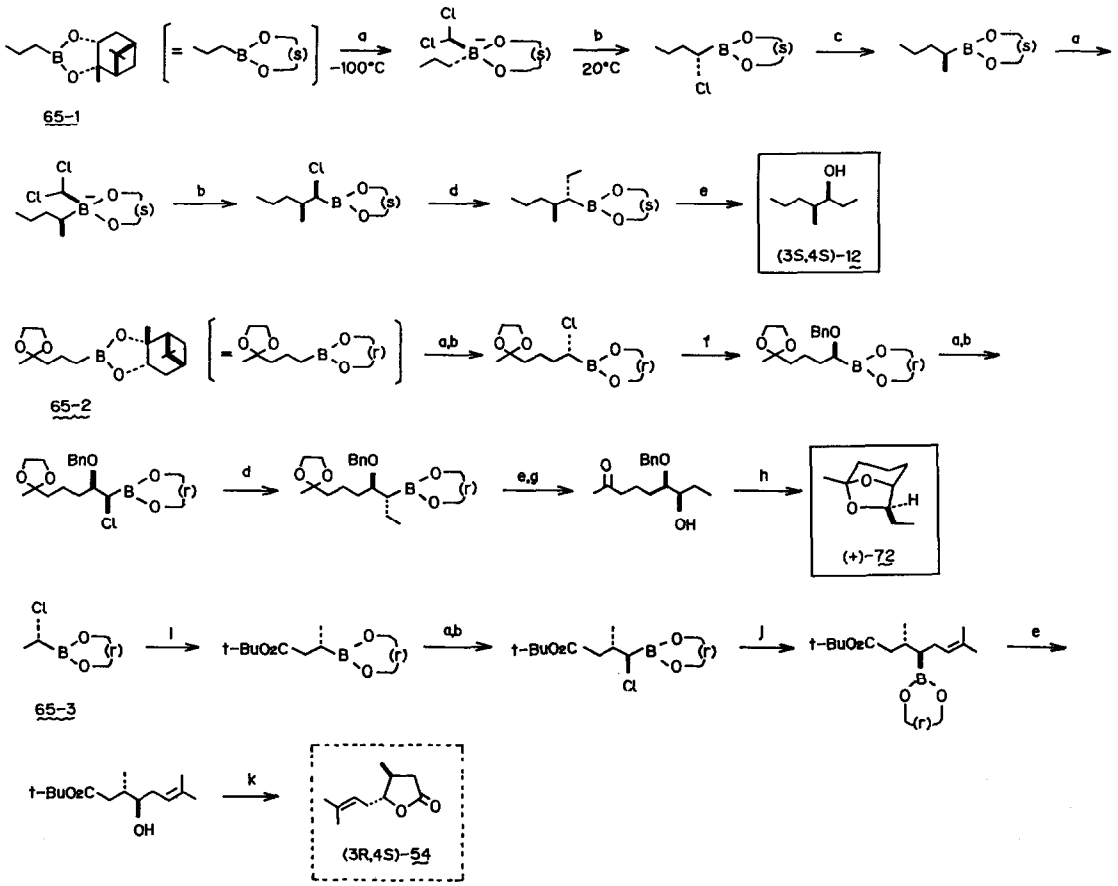
64-5 was used by Wuts *et al.* to prepare a chiral boronate **64-6**.[24] This was treated with the aldehyde **64-7** giving **64-8**, which finally yielded (−)-*exo*-brevicomin **72**.

The tartrate ester **64-9** of allenylboronic acid was found by H. Yamamoto *et al.* to react with 3-methylbutanal giving almost pure enantiomer of **64-10**. This gave (*S*)-(−)-ipsenol **15** via **64-11**.[287]

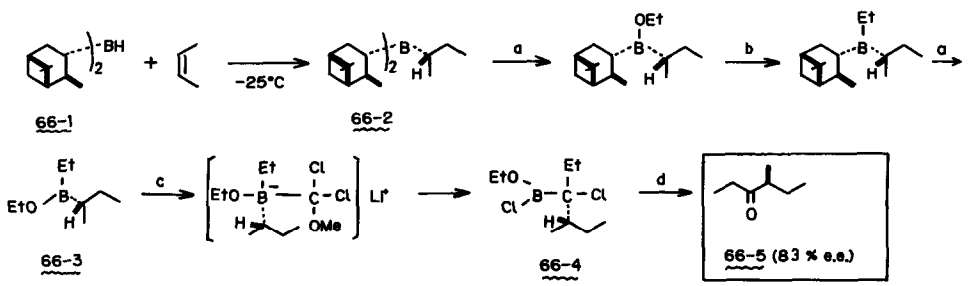
The homologation of chiral boronic esters with dichloromethyllithium was used efficiently by Matteson to synthesize chiral pheromones (Fig. 65).[282] As the chiral auxiliary, pinanediol was used. It is readily prepared from α-pinene. Synthesis of the pheromone component of the smaller European elm bark beetle (3*S*, 4*S*)-**12** from the chiral boronate **65-1** illustrates the steps required for establishing new chiral centers. In the similar manner the chiral boronate **65-2** yielded (+)-*exo*-brevicomin **72**, while **65-3** furnished (3*R*, 4*S*)-eldanolide **54**.[34]

Brown and coworkers executed carbenoidation of chiral borinic esters to acyclic ketones, and synthesized a component **66-5** of the alarm pheromone of the ant *Manica mutica* (Fig. 66).[288] Asymmetric hydroboration of (*Z*)-2-butene with diisopinocampheylborane **66-1** yielded **66-2**, which furnished a chiral borinic ester **66-3**. This when treated with the lithiate of α,α-dichloromethyl methyl ether gave **66-4**. Oxidation of **66-4** gave the pheromone **66-5**.

5.4.5. *Synthesis of pheromones by employing chiral acetals as intermediates.* As shown in Fig. 67, cleavage of the acetal **67-1** of nonanal and (2*R*, 4*R*)-2,4-pentanediol with allyltrimethylsilane in



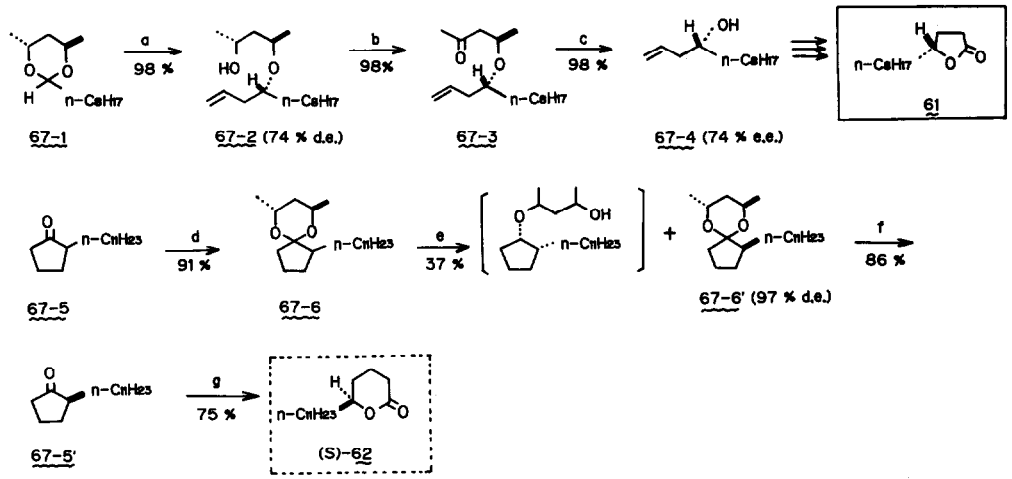
Reagents: (a) $LiCHCl_2$; (b) $ZnCl_2$; (c) MeMgBr; (d) EtMgBr; (e) OH^-, H_2O_2; (f) BnOLi; (g) H_2SO_4/SiO_2; (h) H_2/Pd; (i) $LiCH_2CO_2t\text{-}Bu$; (j) $Me_2C{=}CHCH_2MgCl$; (k) CF_3CO_2H/CH_2Cl_2.
Fig. 65. Pheromones synthesized by homologation of chiral boronic esters.



Reagents: (a) MeCHO; (b) LAH; (c) $LiCCl_2OMe$; (d) OH^-, H_2O_2.
Fig. 66. Synthesis of (*S*)-(+)-4-methyl-3-hexanone from a chiral borinic ester.

the presence of titanium tetrachloride was found to be diastereoselective giving **67-2**.[289] Oxidation of **67-2** to **67-3**, followed by retro-Michael cleavage of **67-3**, gave the homoallylic alcohol **67-4**. This alcohol **67-4** was converted to the defense substance **61** of the rove beetle.

Diastereoselective cleavage of a chiral acetal was useful in resolving the racemic ketone.[290] (±)-2-Undecylcyclopentanone **67-5** was converted to a diastereomeric mixture of acetals **67-6**. When



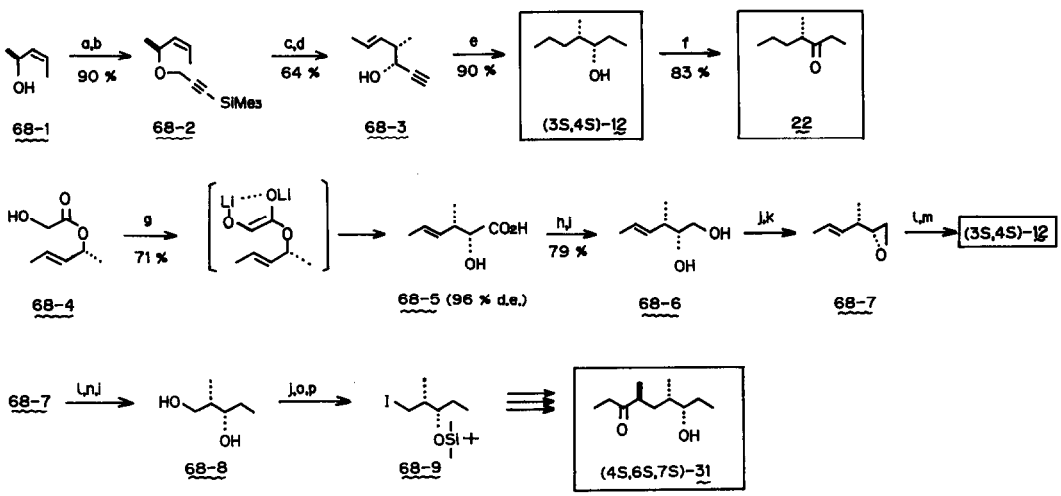
Reagents: (a) $TiCl_4$, $CH_2{=}CHCH_2SiMe_3/CH_2Cl_2$, −78°C; (b) PCC/CH_2Cl_2; (c) KOH/THF—MeOH aq; (d) (2*R*, 4*R*)-(−)-2,4-pentanediol, PPTS; (e) $(i\text{-Bu})_2AlH$; (f) 0.1 N—HCl/Me_2CO; (g) MCPBA/$CHCl_3$.

Fig. 67. Pheromones synthesized from chiral acetals.

this was treated with diisobutylaluminum hydride, only one diastereomer, **67-6′**, survived. Mild acid-hydrolysis of **67-6′** gave the (*S*)-ketone **67-5′**, which was oxidized under Baeyer-Villiger condition giving (*S*)-5-hexadecanolide **62**.

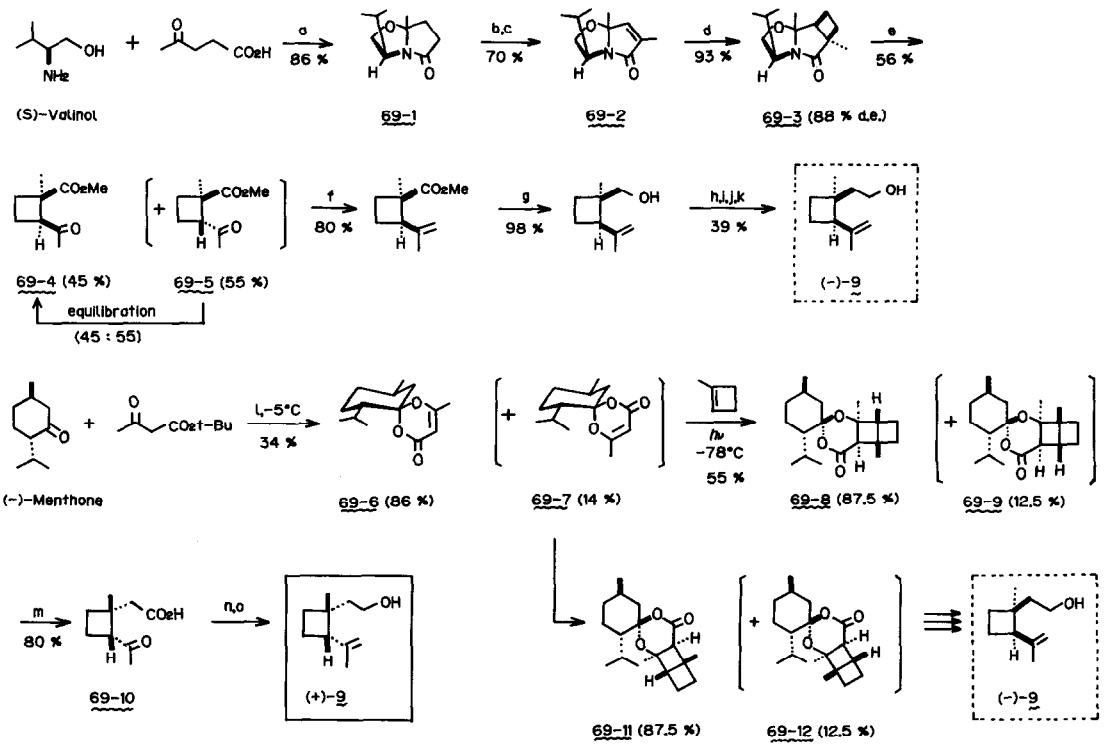
5.4.6. *Synthesis of pheromones by asymmetric sigmatropic rearrangements.* [2,3]-Wittig rearrangement and the Claisen rearrangement are two reactions useful in achieving asymmetric synthesis (Fig. 68).

Nakai explored acyclic stereocontrol via the asymmetric [2,3]-Wittig rearrangement,[291] and used it in pheromone synthesis.[292] The chiral ether **68-2** was prepared from **68-1**, and treated with



Reagents: (a) $HC{\equiv}CCH_2Br$, $(n\text{-Bu})_4NI$/75% NaOH aq; (b) EtMgBr, Me_3SiCl; (c) *n*-BuLi/THF, −85°C; (d) CsF/MeOH aq; (e) H_2/Raney Ni; (f) CrO_3/H_2SO_4; (g) $LiN(SiMe_3)_2$/THF, −78°C; then Me_3SiCl; (h) CH_2N_2; (i) LAH; (j) TsCl/C_5H_5N; (k) NaOH/MeOH; (l) Me_2CuLi; (m) H_2/PtO_2; (n) O_3; (o) NaI; (p) *t*-$BuSiMe_2Cl$.

Fig. 68. Pheromones synthesized by using asymmetric sigmatropic rearrangements.



Reagents: (a) toluene, TsOH, heat; (b) *s*-BuLi/THF; MeI; (c) *s*-BuLi/THF; Ph_2Se_2; H_2O_2/C_5H_5N; (d) $CH_2{=}CH_2$, PhCOMe/CH_2Cl_2; hν, −78°C; (e) H_2SO_4/MeOH; (f) $Ph_3P{=}CH_2$/THF; (g) LAH/THF; (h) TsCl/C_5H_5N; (i) NaCN/HMPA; (j) $(i\text{-Bu})_2AlH/CH_2Cl_2$; 5% H_2SO_4; (k) LAH/THF; (l) Ac_2O—H_2O; (m) HCO_2H, H_2O, Me_2CO; (n) Me_3SiCH_2MgCl/THF; $SOCl_2$; (o) LAH/Et_2O.

Fig. 69. Synthesis of grandisol by asymmetric photocycloaddition.

n-butyllithium to effect the rearrangement with chirality transmission giving **68-3** after deprotection. The unsaturated alcohol **68-3** furnished (3*S*, 4*S*)-4-methyl-3-heptanol **12**. Oxidation of **12** yielded **22**, the alarm pheromone of the leaf-cutting ant.

Fujisawa *et al.* used the ester enolate Claisen rearrangement of (*R*)-1-methyl-(*E*)-2-butenyl hydroxyacetate **68-4** to achieve chirality transfer.[293] By treatment with lithium hexamethyldisilazide, **68-4** gave **68-5**. This hydroxy acid **68-5** was converted into (3*S*, 4*S*)-**12** via **68-6** and **68-7**. Preparation of the key-alkylating agent **68-9** for serricornin (**31**) synthesis was also achieved starting from **68-7**.[293]

5.4.7. *Synthesis of pheromones by asymmetric photocycloaddition.* Asymmetric synthesis of cyclobutane compounds by photocycloaddition was recently used in two different syntheses of grandisol **9** (Fig. 69). Meyers and Fleming achieved asymmetric (2+2) photocycloaddition using the chiral α,β-unsaturated lactam **69-2** and ethylene.[294] The lactam **69-2** could be prepared from (*S*)-valinol and levulinic acid via **69-1**. The photo-adduct **69-3** (88% d.e.) was converted to unnatural (−)-grandisol **9** (88% e.e.).

Demuth *et al.* employed (−)-menthone as the chiral auxiliary and carried out the photoaddition of 1-methyl-1-cyclobutene to **69-6**.[295] The adduct was a mixture of **69-8** and **69-9**, from which pure **69-8** could be obtained by chromatographic fractionation. Acid hydrolysis of **69-8** gave the keto-acid **69-10**, from which enantiomerically pure (+)-grandisol **9** was prepared. Similarly, (−)-grandisol **9** can be obtained from **69-11**.

6. SYNTHESIS BY BIOCHEMICAL ASYMMETRIC REACTIONS

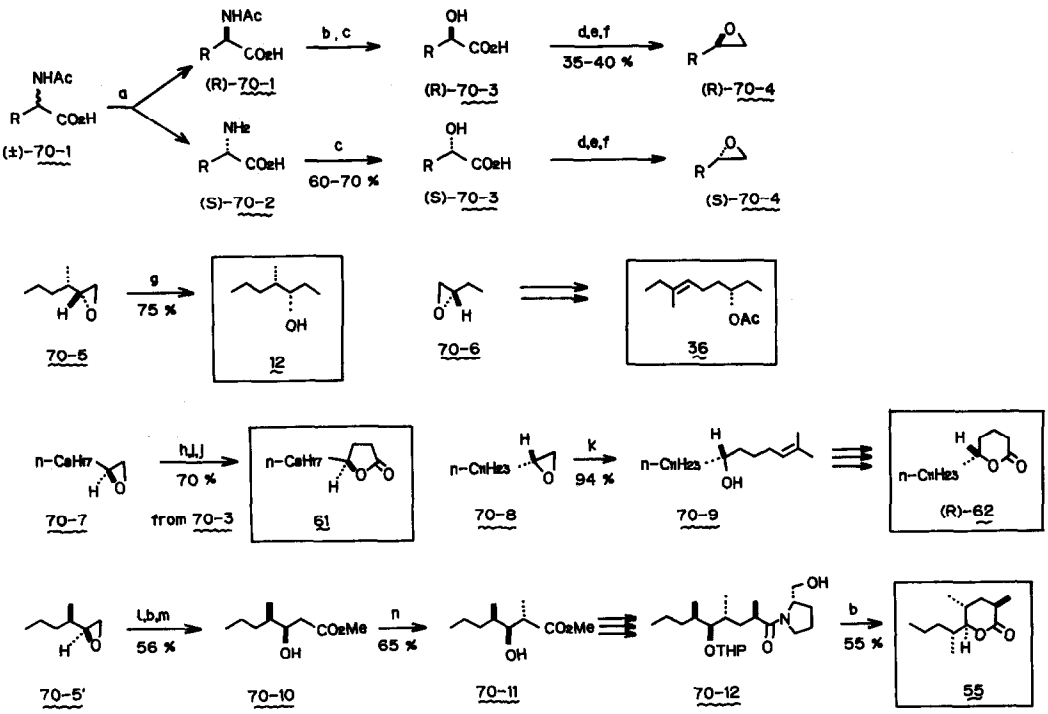
Biological systems such as microbes and enzymes can carry out asymmetric transformations which lead either to optical resolution or to asymmetric synthesis. Biological transformations can usually be executed at room temperature under almost neutral conditions. If the optical yield of the reaction is favorable it is advantageous to employ these transformations in the synthesis of enantiomerically pure pheromones. Work done on this subject in our group has been reviewed with representative experimental procedures.[296] In this Report, I will summarize all aspects of biochemical asymmetric reactions as applied (or as can be applied) to pheromone synthesis.

6.1. *Biochemical preparation of chiral epoxides and their use in pheromone synthesis*

Epoxides are versatile building blocks in organic synthesis and are used widely in pheromone synthesis.

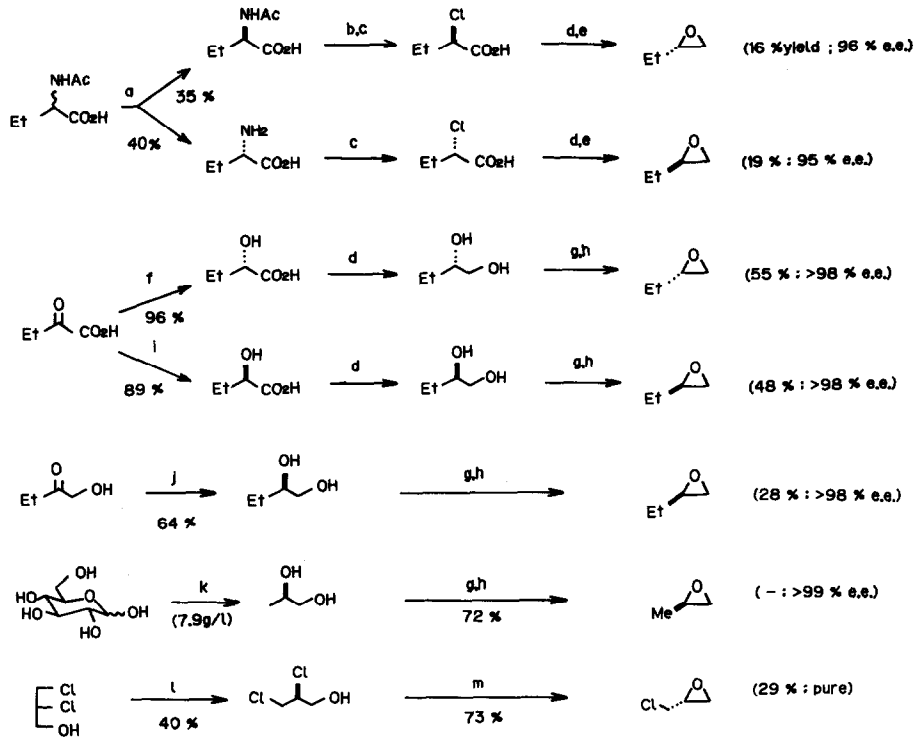
6.1.1. *Preparation of chiral epoxides from α-amino acids obtained by enzymatic resolution and their use in pheromone synthesis.* Chiral epoxides **70-4** can be prepared from chiral α-hydroxy acids **70-3**, which can be prepared from α-amino acids by deamination with nitrous acid.[297] Optically active α-amino acids **70-2**, which are not commercially available, can be prepared by enzymatic hydrolysis of racemic N-acetyl-α-amino acids (±)-**70-1** with amino acylase of *Aspergillus* origin.[297] Preparation and use of chiral epoxides are summarized in Fig. 70.

Treatment of the epoxide **70-5** with lithium dimethylcuprate gave (3*S*, 4*S*)-4-methyl-3-heptanol **12**.[297] For the synthesis of the aggregation pheromone **36** of the square-necked grain beetle, *Cathartus*



Reagents: (a) *Aspergillus* amino acylase; (b) dil HCl; (c) HNO_2; (d) LAH/Et_2O; (e) HBr/AcOH; (f) NaOMe/MeOH; (g) Me_2CuLi/Et_2O; (h) $CH_2(CO_2Et)_2$, NaOEt/EtOH; (i) NaOH aq; (j) dil H_2SO_4; (k) $Me_2C{=}CH(CH_2)_2MgBr$, CuBr; (l) NaCN/40% aq EtOH; (m) CH_2N_2/Et_2O; (n) LDA/THF—HMPA, MeI.

Fig. 70. Pheromones synthesized from epoxides prepared from α-amino acids.



Reagents: (a) amino acylase; (b) dil HCl, heat; (c) dil HCl, $NaNO_2$, $-10°C$; (d) $BH_3 \cdot THF$; (e) KOH; (f) L-lactate dehydrogenase, NADH; (g) HBr/AcOH; (h) $n\text{-}C_5H_{11}OK/n\text{-}C_5H_{11}OH$; (i) D-lactate dehydrogenase, NADH; (j) glycerol dehydrogenase, NADH; (k) *Clostridium thermosaccharolyticum*; (l) fermentation (patent not yet disclosed); (m) dil $NaOH/Et_2O$.

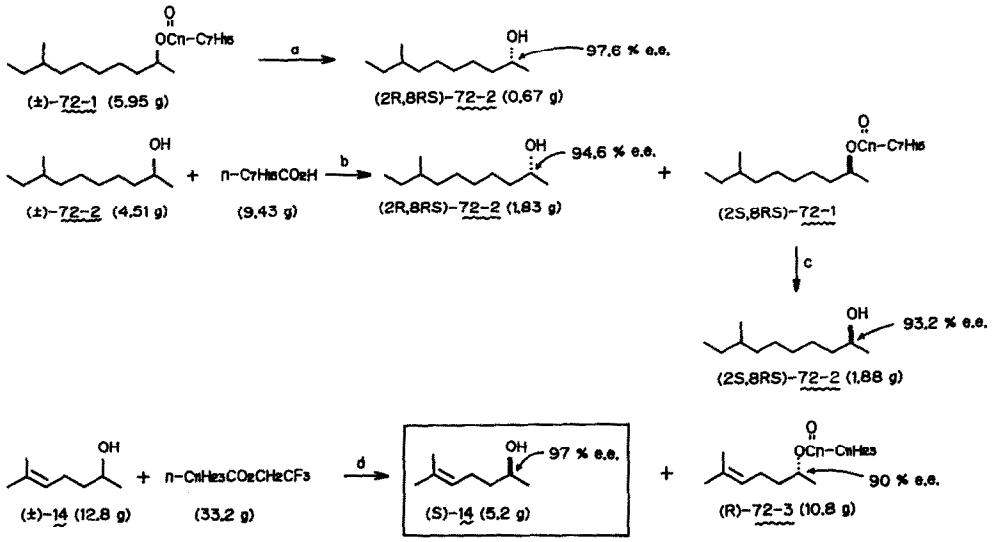
Fig. 71. Biochemical preparation of chiral epoxides.

quadricollis, 1,2-epoxybutane **70-6** was used as the starting material.[298] 1,2-Epoxydecane **70-7** was converted to 4-dodecanolide **61**.[299] (*R*)-(−)-5-Hexadecanolide **62** was synthesized from the epoxide **70-8** after its chain elongation giving **70-9**.[186] Only the (*R*)-enantiomer of this pheromone was bioactive as assayed by Ishay.[300] In a synthesis of (−)-invictolide **55**, the queen recognition pheromone of the red imported fire ant, the epoxide **70-5′** was converted to the β-hydroxy ester **70-10**, which finally yielded the pheromone **55** via **70-11** and **70-12**.[301]

6.1.2. *Other biochemical preparations of chiral epoxides.* Whitesides *et al.* have surveyed various biochemical routes to enantiomerically enriched 1,2-epoxybutane (Fig. 71).[302] An efficient biochemical method for the preparation of (*R*)-(+)-epoxypropane was also reported by Simon and Whitesides using D-glucose as the substrate to prepare (*R*)-1,2-propanediol.[303] Takano *et al.* found a microorganism to resolve (±)-2,3-dichloro-1-propanol giving its (*S*)-isomer, which was treated with base to yield (*R*)-epichlorohydrin.[304] Both the enantiomers of sulcatol **14** were synthesized from the (*R*)-epichlorohydrin.[305]

6.2. *Preparation of pheromone alcohols by asymmetric hydrolysis of the corresponding esters with lipases*

Asymmetric hydrolysis of pheromone esters or asymmetric esterification of pheromone alcohols can bring about kinetic resolution of pheromones. The propionate of the alcohol **72-2** (Fig. 72) is the sex pheromone **44** of rootworm (*Diabrotica*) species. Asymmetric hydrolysis of the octanoate (±)-**72-1** with lipase yielded (2*R*, 8*RS*)-**72-2**, while the asymmetric esterification of (±)-**72-2** with



Reagents: (a) *Mucor miehei* lipase (Novo-225), room temperature, pH 7.0 in water, 24 hr; (b) *Mucor miehei* lipase (Novo lipase 3A), 30°C, 6 weeks in hexane; (c) KOH/MeOH aq; (d) porcine pancreatic lipase (PPL, 40 g) in dry Et_2O (100 ml), room temperature, 3 days.
Fig. 72. Pheromone alcohols obtained by kinetic resolution with lipases.

octanoic acid in the presence of lipase yielded unesterified (2*R*, 8*RS*)-**72-2** and esterified (2*S*, 8*RS*)-**72-1**.[306]

Transesterification of (±)-sulcatol **14** with 2,2,2-trifluoroethyl dodecanoate catalyzed by porcine pancreatic lipase in dry ether gave (*S*)-sulcatol **14** and (*R*)-sulcatol dodecanoate **72-3**.[307]

6.3. *Preparation of pheromone alcohols and lactones by asymmetric reduction of ketones, keto esters and keto acids*

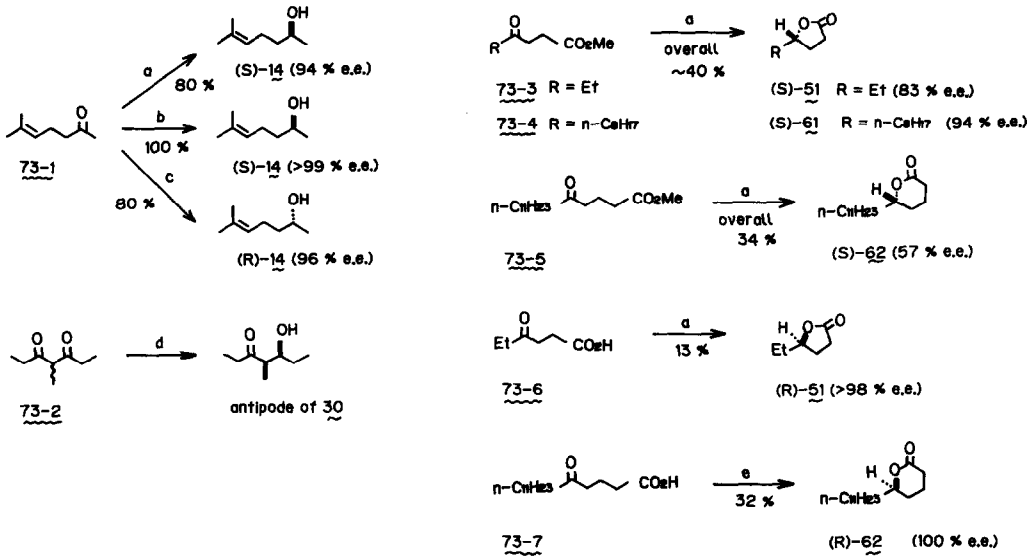
6.3.1. *Synthesis of pheromone alcohols by microbial reduction of ketones.* Veschambre and his coworkers reduced 6-methyl-5-hepten-2-one **73-1** with various microorganisms (Fig. 73). *Saccharomyces cerevisiae* and *Thermoanaerobium brockii* reduced **73-1** to (*S*)-sulcatol **14**, while *Aspergillus niger* gave (*R*)-**14**.[308] They also attempted the reduction of the diketone **73-2** with *Geotrichum candidum* under anaerobic conditions.[309] The product was the antipode (4*R*, 5*S*)-**30** of natural sitophilure **30**.

6.3.2. *Synthesis of pheromone lactones by microbial reduction of keto esters and keto acids.* Naoshima *et al.* was the first to prepare pheromone lactones such as (*S*)-**51**, (*S*)-**61** and (*S*)-**62** by the reduction of keto esters **73-3**, **73-4** and **73-5** with baker's yeast.[310] When the corresponding keto-acids **73-6** and **73-7** were reduced with baker's yeast, the products were found by Utaka *et al.* to be (*R*)-**51** and (*R*)-**62**.[311,312] The reduction of keto-acids took place with an enantioselectivity opposite to that in the case of keto-esters. Naoshima *et al.* used immobilized yeast cells for the reduction of the keto-acid **73-7** to (*R*)-5-hexadecanolide **62**.[313] Manzocchi *et al.* recently published the preparation of (*S*)-lactones by reduction of keto esters with baker's yeast.[314]

6.4. *Biochemical preparation of chiral lactones and their use in pheromone synthesis*

Chiral lactones can be prepared enzymatically by the employment of either oxido-reductases or hydrolytic enzymes. Chiral lactones are useful building blocks for pheromone synthesis.

6.4.1. *Synthesis of (+)-grandisol starting from a lactone prepared by enzymatic oxidation of a prochiral diol.* Jones *et al.* found that *meso*-diols such as **74-1** can be oxidized to chiral lactones like



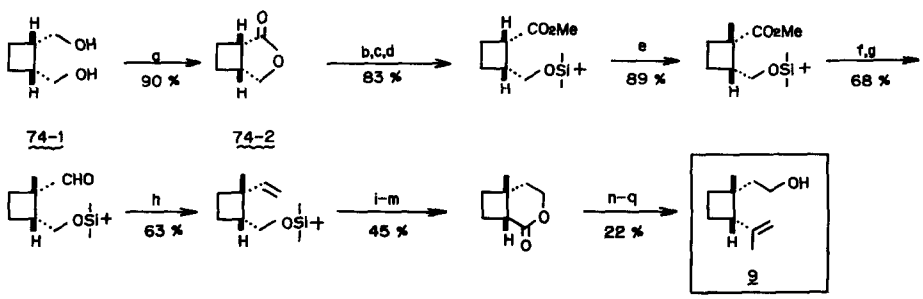
Reagents: (a) *Saccharomyces cerevisiae*, 6 days; (b) *Thermoanaerobium brockii* (growing), 24 hr; (c) *Aspergillus niger*, 24 hr; (d) *Geotrichum candidum* (anaerobic condition), 48 hr; (e) *Saccharomyces cerevisiae* immobilized in carageenan.

Fig. 73. Pheromones prepared by microbial reduction of carbonyl compounds.

74-2 by oxidation with horse liver alcohol dehydrogenase (HLADH) in the presence of NAD^+ and FMN.[315] The lactone **74-2** was converted to (+)-grandisol **9** (Fig. 74).[316]

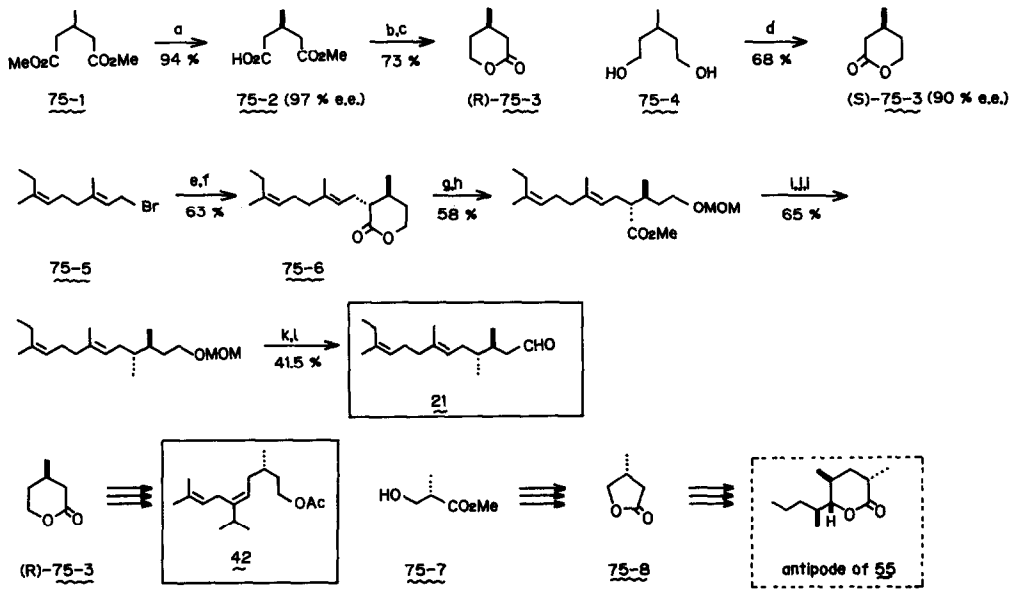
6.4.2. *Synthesis of (+)-faranal starting from a lactone prepared by biochemical methods.* Both enantiomers of 3-methyl-5-pentanolide **75-3** can be prepared by biochemical means (Fig. 75). Sih and his coworkers found that pig liver esterase (PLE) could convert dimethyl 3-methylglutarate **75-1** into the half ester (*R*)-**75-2** (69% e.e.).[317] Later Jones *et al.* was able to raise the enantiomeric purity of (*R*)-**75-2** to 97% e.e. by employing 20% methanol in water as the reaction medium instead of water alone.[318] This half ester, (*R*)-**75-2**, gave the lactone (*R*)-**75-3** after reduction and lactonization.[321] By oxidizing the diol **75-4** with HLADH, (*S*)-**75-3** could be obtained in a preparative scale (*ca.* 6 g in a batch).[319] The (*S*)-enantiomer of **75-3** is also available from **75-2** by preferential reduction of the ester group with lithium borohydride.[317]

(+)-Faranal **21**, the trail pheromone of Pharaoh's ant, has been synthesized from (*S*)-**75-3**.[320]



Reagents: (a) horse liver alcohol dehydrogenase (HLADH), NAD^+, FMN; (b) KOH/MeOH; HCl; (c) CH_2N_2/Et_2O; (d) *t*-BuSiMe$_2$Cl, imidazole; (e) LDA/THF/MeI; (f) (*i*-Bu)$_2$AlH/hexane; (g) $CrO_3 \cdot 2C_5H_5N/CH_2Cl_2$; (h) $Ph_3P{=}CH_2$/THF; (i) B_2H_6; H_2O_2—NaOH; (j) Ac_2O/C_5H_5N; (k) HF/MeCN aq; (l) Jones CrO_3; (m) 5% H_2SO_4 aq, heat; (n) MeLi/Et_2O; (o) Ac_2O; (p) LAH; (q) GLC separation

Fig. 74. Synthesis of (+)-grandisol from a prochiral diol.



Reagents: (a) pig liver esterase in 20% aq MeOH, pH 7 at −10°C; (b) $BH_3 \cdot Me_2S$/THF; (c) TsOH/C_6H_6; (d) HLADH, NAD^+, FMN, FMN reductase, catalase, pH 9, 14 days; (e) (*S*)-**75-3**; (f) $LiNEt_2$/THF; (g) MeOH/Et_3N; (h) MOMCl/Et_3N, Et_2O; (i) LAH/THF; (j) MsCl/Et_3N; (k) HCl/MeOH; (l) PDC/CH_2Cl_2.
Fig. 75. Pheromones synthesized from chiral lactones.

The key-step was the diastereoselective alkylation of (*S*)-**75-3** with **75-5** giving **75-6**. The yellow scale pheromone **42** was recently synthesized from (*R*)-**75-3**.[321] (*R*)-(+)-3-Methyl-4-butanolide **75-8** served as the starting material for the synthesis of (+)-invictolide **55**, the antipode of the pheromone of the red imported fire ant.[322] The lactone **75-8** could be prepared from the hydroxy-ester **75-7**.[323] Conversion of isobutyric acid into the enantiomers of **75-7** is a well-known microbial process, and the enantiomers are commercially available.

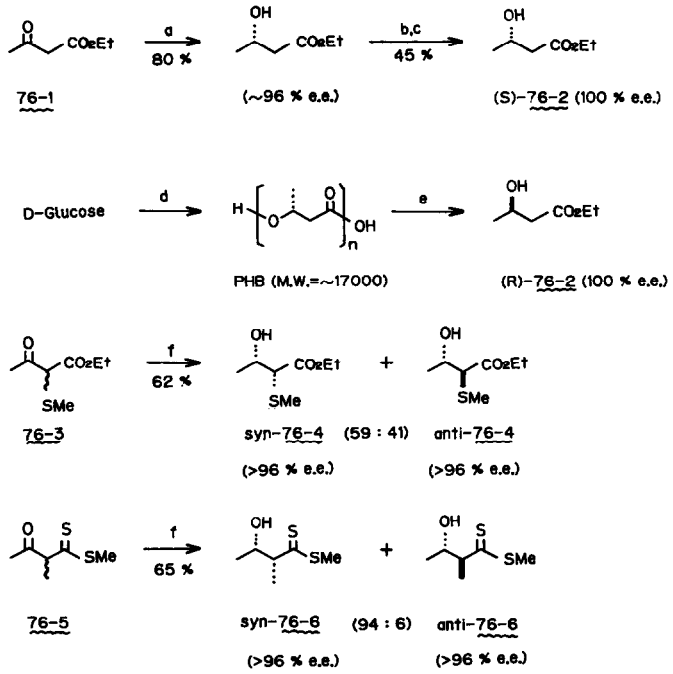
6.5. *Optically active ethyl 3-hydroxybutanoate and related compounds as building blocks*

6.5.1. *Preparation of optically active ethyl 3-hydroxybutanoate and its relatives.* Reduction of ethyl acetoacetate **76-1** with baker's yeast furnishes ethyl (*S*)-3-hydroxybutanoate **76-2** (83–97% e.e.) (Fig. 76).[324–330] Another yeast, *Saccharomyces bailii* KI 0116, can also be used to yield (*S*)-**76-2** (96% e.e.).[329] The hydroxy-ester (*S*)-**76-2** can be purified by recrystallizing the corresponding 3,5-dinitrobenzoate. Hydrolysis of the pure 3,5-dinitrobenzoate gives (*S*)-**76-2** (100% e.e.).[325,329]

Ethyl (*R*)-3-hydroxybutanoate (100% e.e.) is readily obtainable by ethanolysis of PHB (poly-3-hydroxybutanoate).[104,329,331] A wide variety of microorganisms generate granules which contain the polymeric ester of (*R*)-3-hydroxybutanoic acid as their intracellular reserve of organic carbon. Seebach *et al.* used PHB obtained from *Alcaligenes eutrophus*,[331] while we employed *Zoogloea ramigera* I-16-M for the production of PHB.[104,329] Starting from 50 g of *Z. ramigera* cells, 33 g of (*R*)-**76-2** was obtained.

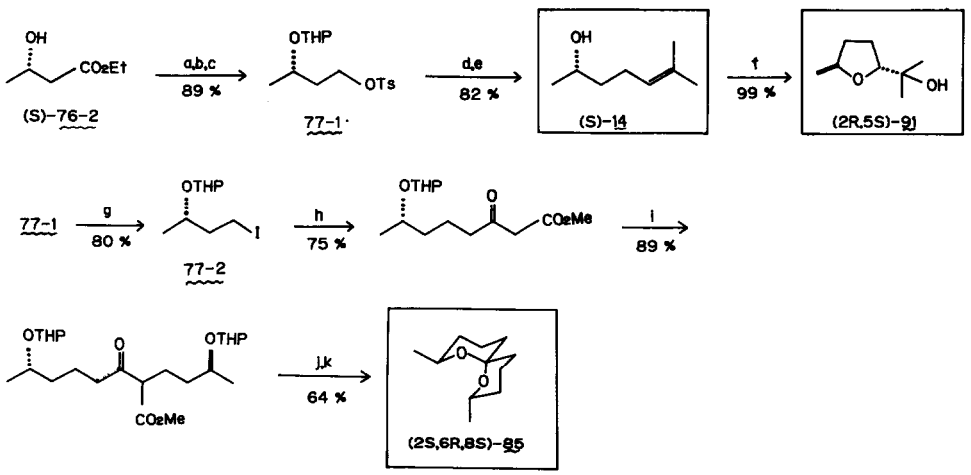
Fujisawa *et al.* reduced the α-methylthio-β-keto ester **76-3** with baker's yeast, and obtained (3*S*)-**76-4** (>96% e.e. at C-3).[332] They also studied the reduction of the β-keto-dithio-ester **76-5** with baker's yeast. The major product was *syn*-**76-6** (>96% e.e.).[333]

6.5.2. *Synthesis of sulcatol,* trans-*pityol and* 2,8-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecane from ethyl 3-hydroxybutanoate.* As shown in Fig. 77, (*S*)-sulcatol **14** was synthesized from ethyl (*S*)-3-hydroxybutanoate in 5 steps.[326] Treatment of (*S*)-sulcatol **14** with thallium (III) triacetate gave (2*R*, 5*S*)-pityol **91**.[334] 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane **85**, the main component of the mandibular



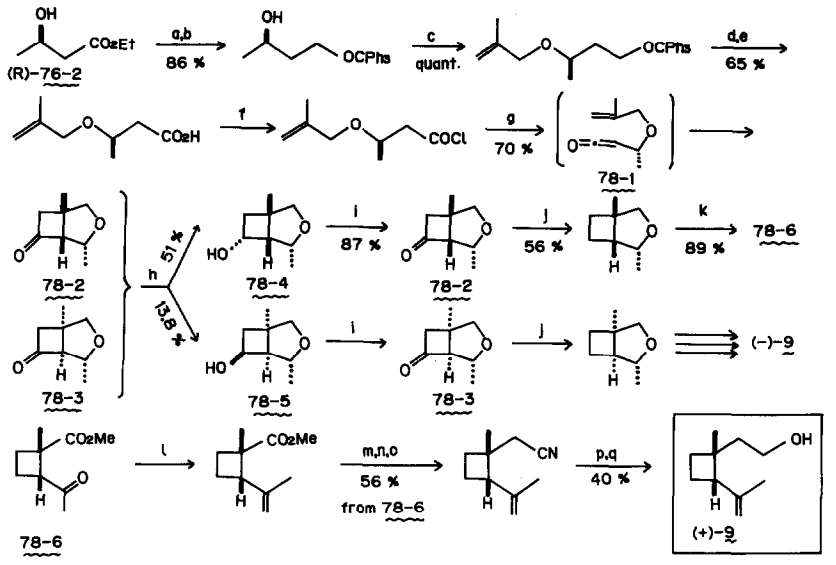
Reagents: (a) *Saccharomyces bailii* KI 0116; (b) $3,5\text{-}(O_2N)_2C_6H_3CO_2H$, DMAP, DCC/CH_2Cl_2; recrystallization; (c) KOH/THF—EtOH aq; (d) *Zoogloea ramigera*; (e) $EtOH—H_2SO_4/(CH_2Cl)_2$; (f) *Saccharomyces cerevisiae*.

Fig. 76. Preparation of optically active ethyl 3-hydroxybutanoate and its relatives.



Reagents: (a) DHP, TsOH; (b) LAH/Et_2O; (c) $TsCl/C_5H_5N$; (d) $Me_2C{=}CHMgBr$, CuI/THF; (e) $AcOH—THF—H_2O$, heat; (f) $Tl(OAc)_3/HBF_4—Me_2CO—H_2O$; (g) NaI, $NaHCO_3/Me_2CO$; (h) $MeCOCH_2CO_2Me$, NaH, *n*-BuLi/THF; (i) (*S*)-77-2, K_2CO_3/Me_2CO, DMF; (j) KOH/MeOH aq; (k) TsOH/MeOH.

Fig. 77. Synthesis of sulcatol, pityol and 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane from ethyl (*S*)-3-hydroxybutanoate.



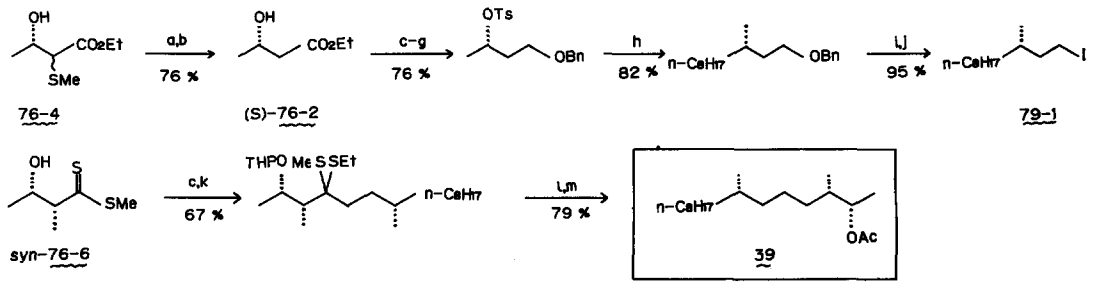
Reagents: (a) LAH/Et_2O; (b) Ph_3CCl/C_5H_5N; (c) $CH_2{=}CMeCH_2Cl$, NaH/DMF; (d) 80% AcOH; (e) Jones CrO_3/Me_2CO; (f) $(COCl)_2$; (g) Et_3N/CH_2Cl_2; (h) LiBH(*s*-Bu)$_3$/THF; $NaOAc/H_2O_2$; SiO_2 chromatog; (i) $(COCl)_2$, DMSO, Et_3N; (j) $N_2H_4 \cdot H_2O$, $KOH/HO(CH_2)_2O(CH_2)_2OH$; (k) RuO_2, $NaIO_4$/MeCN, phosphate buffer; CH_2N_2/Et_2O; (l) $Ph_3P{=}CH_2$; (m) LAH/Et_2O; (n) $TsCl/C_5H_5N$; (o) NaCN/aq HMPA; (p) $(i\text{-Bu})_2AlH/n$-pentane; (q) LAH/Et_2O.

Fig. 78. Synthesis of enantiomers of grandisol.

gland secretion of bees *Andrena wilkella*, was also synthesized from the β-hydroxy ester **76-2**[335,336] (Fig. 77). By employing (*R*)-**76-2**, the antipodes of these pheromones were also synthesized.

6.5.3. *Synthesis of grandisol from ethyl 3-hydroxybutanoate.* Starting from ethyl (*R*)-3-hydroxybutanoate **76-2**, both enantiomers of grandisol **9** were synthesized (Fig. 78).[187] The key-step was the intramolecular cycloaddition of olefinic ketene **78-1** giving a mixture of **78-2** and **78-3**. Although this mixture could not be fractionated, the corresponding alcohols, **78-4** and **78-5**, were separable. The alcohols, **78-4** and **78-5**, gave the ketones, **78-2** and **78-3**, respectively, after Swern oxidation. The ketone **78-2** yielded (+)-grandisol **9**, while the ketone **78-3** was converted to (−)-grandisol **9**. Bioassay with enantiomerically pure (+)- and (−)-grandisol **9** showed that only the (+)-isomer was bioactive.[188]

6.5.4. *Synthesis of the pine sawfly pheromone from hydroxy esters with sulfur-containing functional groups.* Fujisawa and his coworkers synthesized the sex pheromone **39** of the pine sawfly (*Neodiprion lecontei*) starting from the sulfur-containing hydroxy esters **76-4** and *syn*-**76-6** (Fig. 79).[333]



Reagents: (a) MCPBA; (b) Al—Hg; (c) DHP, PPTS/CH_2Cl_2; (d) LAH; (e) NaH; BnBr, $(n\text{-Bu})_4NI$; (f) TsOH/MeOH; (g) $TsCl/C_5H_5N$; (h) $(n\text{-}C_8H_{17})_2CuMgBr$/THF; (i) Li/NH_3; (j) HI aq; (k) EtMgI/THF; **79-1**/THF—HMPA; (l) Raney Ni/EtOH; H^+; (m) Ac_2O/C_5H_5N.

Fig. 79. Synthesis of the pine sawfly pheromone.

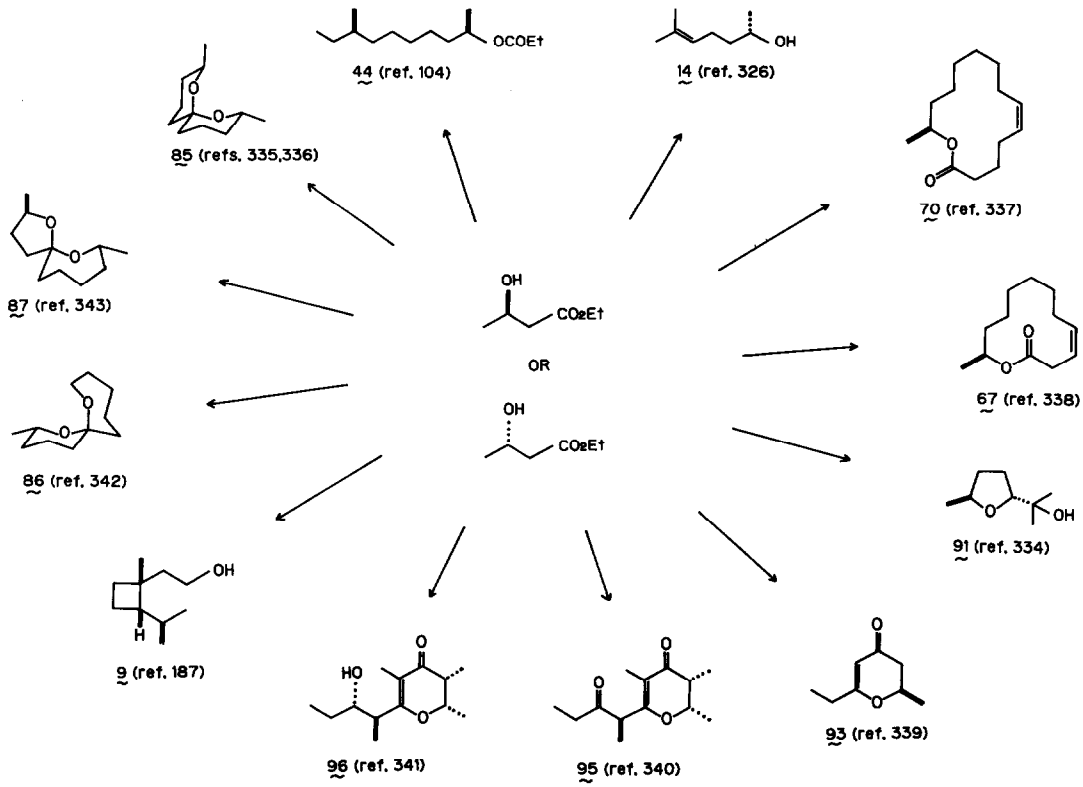


Fig. 80. Pheromones synthesized from ethyl 3-hydroxybutanoate.

Ethyl 3-hydroxybutanoate has been extensively used in pheromone synthesis. Figure 80 shows the pheromones which have been synthesized by us from both enantiomers of ethyl 3-hydroxybutanoate.

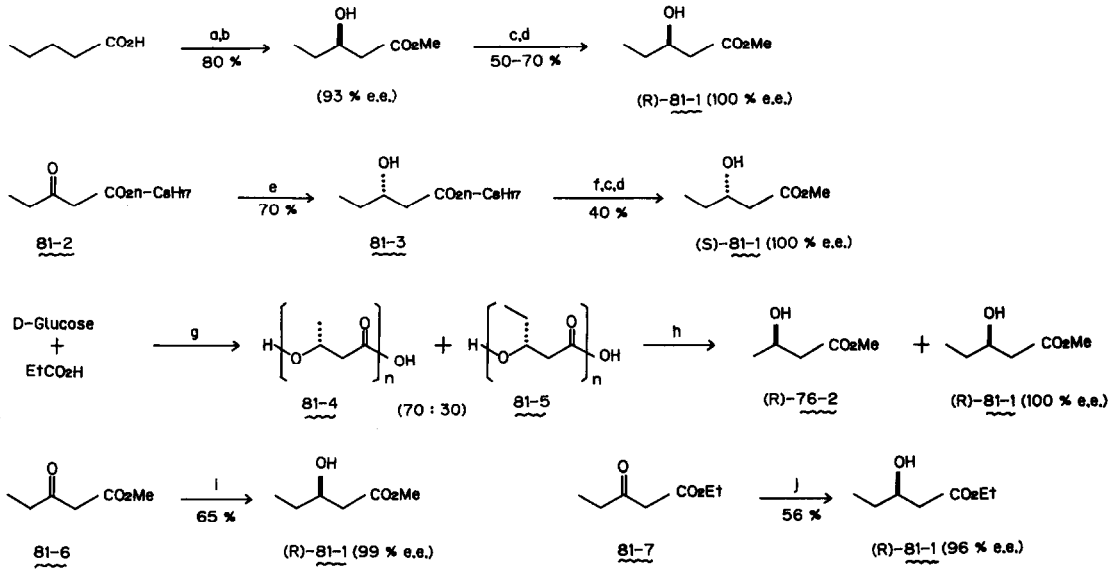
6.6. *Optically active methyl 3-hydroxypentanoate as a building block*

6.6.1. *Preparation of the enantiomers of methyl 3-hydroxypentanoate.* β-Oxidation of pentanoic acid with a mutant of *Candida rugosa* is known to give (*R*)-3-hydroxypentanoic acid (93% e.e.).[344] The corresponding methyl ester (*R*)-**81-1** can be purified via its crystalline 3,5-dinitrobenzoate giving (*R*)-**81-1** (100% e.e.) (Fig. 81).[345]

Reduction of octyl 3-oxopentanoate **81-2** with baker's yeast yielded octyl (*S*)-3-hydroxypentanoate **81-3** (97% e.e.). Conversion of this ester to the methyl ester (*S*)-**81-1** was followed by its purification as the corresponding 3,5-dinitrobenzoate giving (*S*)-**81-1** (100% e.e.).[346] Seebach and Züger used a mixed biopolymer PHB/PHV(Poly-β-hydroxyvalerate) **81-4/81-5** produced by *Alcaligenes eutrophus* NC1B for the preparation of (*R*)-**81-1**.[347]

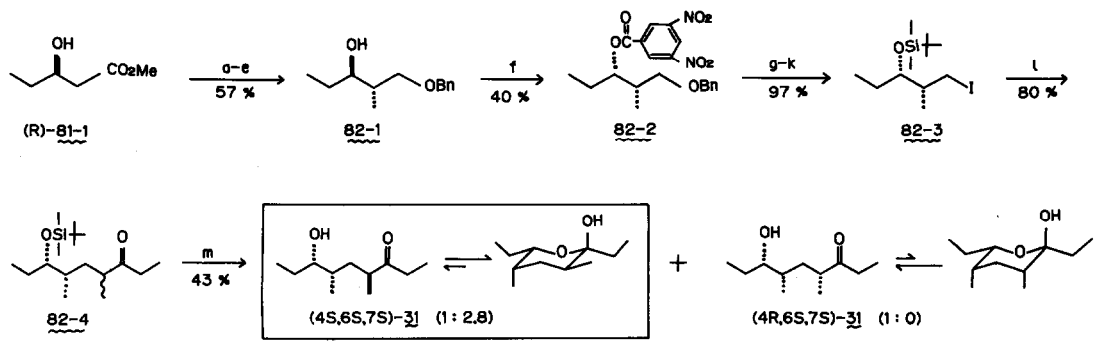
Ohno and his coworkers employed *Hansenula polymorpha* DL-1 grown in a medium containing methanol for the reduction of **81-6** to (*R*)-**81-1**.[348] Baker's yeast reduced **81-7** to (*R*)-**81-1**, if a small amount of allyl alcohol was added to the culture medium.[349]

6.6.2. *Synthesis of serricornin from methyl 3-hydroxypentanoate.* Serricornin (4*S*, 6*S*, 7*S*)-**31** is the sex pheromone produced by the female cigarette beetle, *Lasioderma serricorne*, which is a serious pest of cured tobacco leaves.[350] Starting from (*R*)-**81-1**, serricornin **31** and its 4*R*-isomer were synthesized by us (Fig. 82).[345] Dianion alkylation of (*R*)-**81-1** with methyl iodide was followed by several steps to give **82-1**. This was submitted to the Mitsunobu inversion using 3,5-dinitrobenzoic acid to give **82-2** (100% e.e.) (42% yield) after repeated recrystallization. The iodide **82-3** was



Reagents: (a) *Candida rugosa*; (b) H_2SO_4/MeOH; (c) 3,5-$(O_2N)_2C_6H_3CO_2H$, DMAP, DCC/CH_2Cl_2; recrystallization; (d) KOH/THF—MeOH aq; (e) *Saccharomyces cerevisiae*; (f) K_2CO_3/MeOH; (g) *Alcaligenes eutrophus* NCIB; (h) MeOH/H_2SO_4, $ClCH_2CH_2Cl$; fractional distillation; (i) methanol grown *Hansenula polymorpha* DL-1; (j) *Saccharomyces cerevisiae* in the presence of CH_2=$CHCH_2OH$ (2.0 g/l).

Fig. 81. Preparation of the enantiomers of methyl 3-hydroxypentanoate.



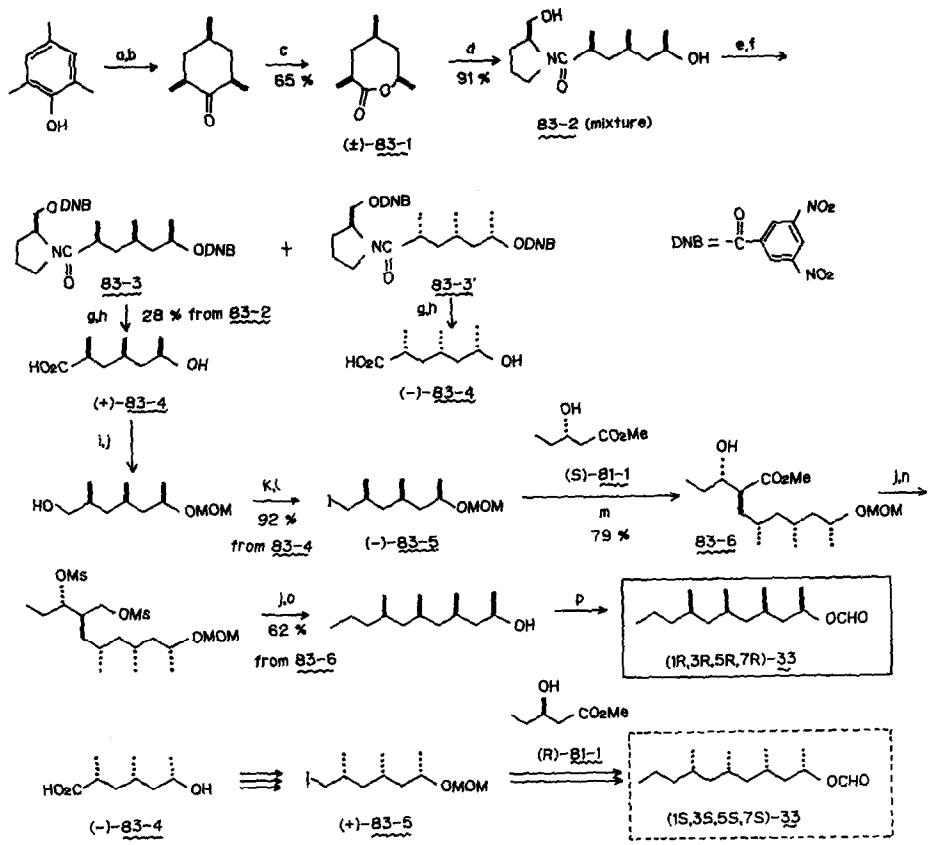
Reagents: (a) LDA, MeI; (b) DHP, PPTS; (c) LAH; (d) NaH, BnCl; (e) TsOH/MeOH; (f) 3,5-$(O_2N)_2C_6H_3CO_2H$, Ph_3P, EtO_2CN=NCO_2Et; recrystallization; (g) KOH; (h) *t*-$BuSiMe_2Cl$, imidazole; (i) H_2/Pd—C; (j) $TsCl/C_5H_5N$; (k) NaI; (l) Et_2CO, LDA; (m) AcOH—THF aq.

Fig. 82. Synthesis of serricornin.

derived from **82-2**. Alkylation of diethyl ketone with **82-3** yielded **82-4**, deprotection of which gave a mixture of serricornin (4*S*, 6*S*, 7*S*)-**31** and its 4*R*-isomer. Separation of these two isomers was readily achieved owing to the large difference in their ease of hemiacetal formation (Fig. 82).

6.6.3. *Synthesis of lardolure from methyl 3-hydroxypentanoate.* In 1982, lardolure **33** was isolated by Kuwahara *et al.* as the aggregation pheromone of the acarid mite, *Lardoglyphus konoi*, which is the primary pest for stored products such as dried meat and fish meal.[351]

After determination of its stereochemistry as (1*R*, 3*R*, 5*R*, 7*R*)-**33**,[352] we carried out the synthesis of lardolure and its antipode employing both enantiomers of methyl 3-hydroxypentanoate (Fig. 83).[198] Three out of the four chiral centers of **33** were derived from the lactone (±)-**83-1** after



Reagents: (a) H_2, Raney Ni/EtOH; (b) Jones CrO_3; (c) MCPBA/CH_2Cl_2; (d) (*S*)-prolinol/toluene, heat; (e) 3,5-$(O_2N)_2C_6H_3COCl/C_5H_5N$; (*f*) chromatographic separation (SiO_2); (g) K_2CO_3/MeOH; (h) dil HCl; (i) MOMCl, $(i\text{-}Pr)_2NEt/CH_2Cl_2$; (j) LAH; (k) TsCl/$C_5H_5N$; (l) NaI/$Me_2CO$—DMF; (m) LDA/THF—HMPA; (n) MsCl, Et_3N; (o) HCl/MeOH; (p) HCO_2H.

Fig. 83. Synthesis of lardolure.

resolving it by separation of a diastereomeric mixture of **83-3** and **83-3'**. The mixture of prolinol amide **83-2** could not be fractionated. Hydrolysis of **83-3** and **83-3'** gave the crystalline acids (+)-**83-4** and (−)-**83-4**, respectively. The acid (+)-**83-4** was converted to (−)-**83-5**, which was used for the alkylation of the dianion derived from (*S*)-**81-1** giving **83-6** stereoselectively. The remaining steps to (1*R*, 3*R*, 5*R*, 7*R*)-(−)-lardolure **33** were straightforward. The overall yield of (−)-lardolure **33** from 2,4,6-trimethylphenol was 6.7% in 18 steps. Similarly, (−)-**83-4** afforded (1*S*, 3*S*, 5*S*, 7*S*)-(+)-**33**. Only the naturally occurring (−)-lardolure was bioactive.

The enantiomers of methyl 3-hydroxypentanoate were proved to be quite useful in pheromone synthesis (Fig. 84).

6.7. *Other chiral building blocks obtainable by the reduction of carbonyl compounds with baker's yeast*

In Fig. 85 are listed other chiral building blocks obtainable by reduction of carbonyl compounds with baker's yeast. The hydroxy ketone **85-2** is a versatile building block for the synthesis of cyclic terpenes. It was prepared by reducing the prochiral diketone **85-1** with baker's yeast.[361] Reduction of cyclic β-keto esters such as **85-3** to β-hydroxy esters like **85-4** was studied by Deol *et al.*[324] and also by Seebach *et al.*[362] Yeast reduction of methyl tetrahydro-4-oxo-2H-thiopyran-3-carboxylate **85-5** gave **85-6** (83% e.e.), which was purified via **85-7** giving **85-6** (100% e.e.).[363]

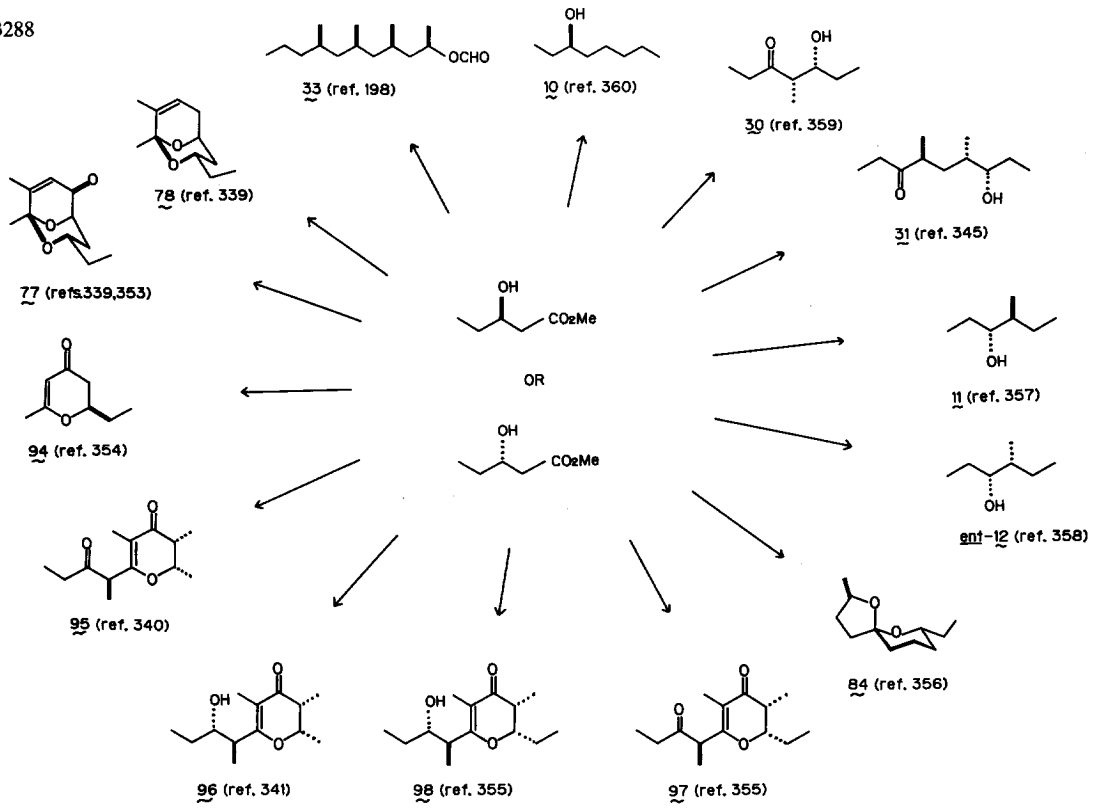


Fig. 84. Pheromones synthesized from methyl 3-hydroxypentanoate.

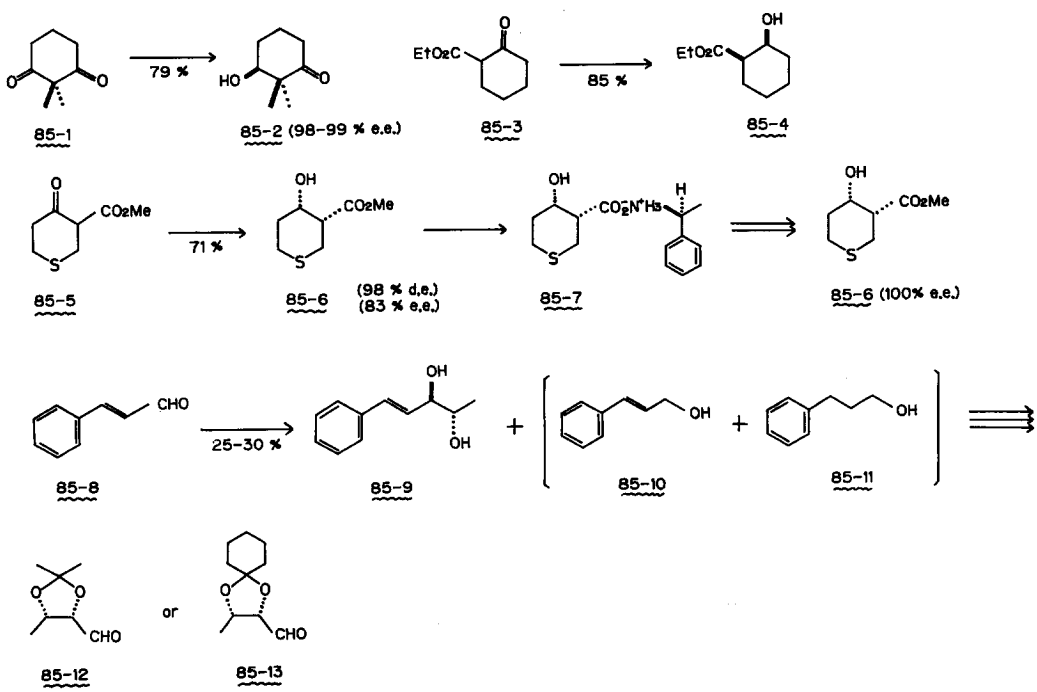


Fig. 85. Chiral building blocks obtainable by reduction of carbonyl compounds with baker's yeast.

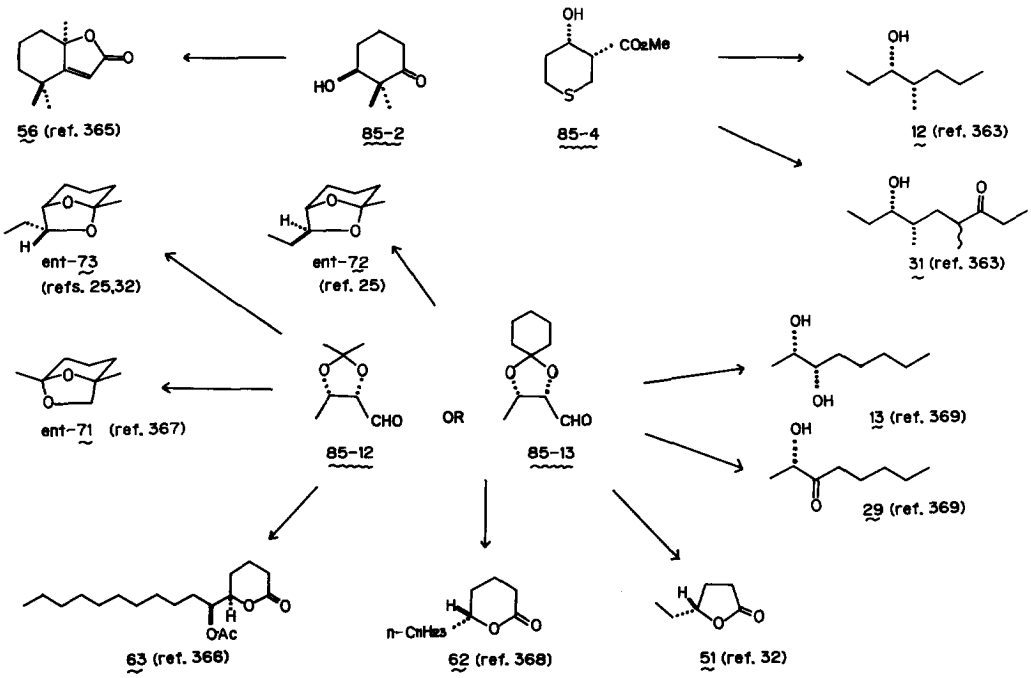


Fig. 86. Pheromones synthesized from the chiral building blocks listed in Fig. 85.

Reduction of cinnamaldehyde **85-8** with baker's yeast gave **85-9** in 25–30% yield in addition to the direct reduction products **85-10** and **85-11**.[364] Conventional conversion of **85-9** to **85-12** or **85-13** generated useful chiral building blocks for pheromone synthesis.

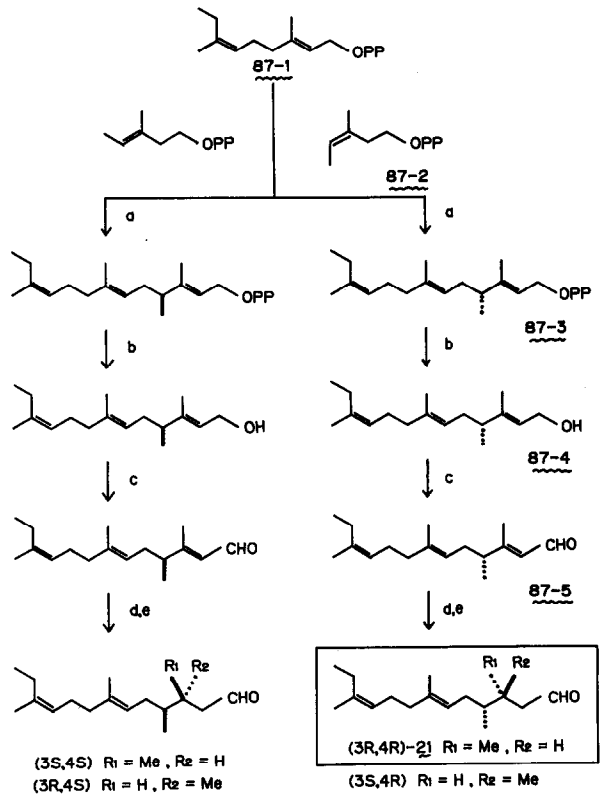
Figure 86 shows the pheromones synthesized from the chiral building blocks listed in Fig. 85. (−)-Dihydroactinidiolide **56**, the pheromone component of the red imported fire ant, was synthesized from the ketol **85-2**.[365] Hoffmann's sulfur-containing hydroxy ester **85-4** yielded (3*S*, 4*S*)-4-methyl-3-heptanol **12** and (4*RS*, 6*S*, 7*S*)-serricornin **31**.[363] Fuganti's protected dihydroxy aldehydes **85-12** and **85-13** were converted into various pheromones (Fig. 86).[25,32,366–369]

6.8. *Synthesis of faranal by asymmetric carbon–carbon bond formation catalyzed by an enzyme*

Ogura *et al.* achieved a unique synthesis of faranal **21**, the trail pheromone of the Pharaoh's ant, and its stereoisomers by employing farnesyl pyrophosphate synthetase as the catalyst to execute the key asymmetric step. Enzymatic condensation of homogeranyl pyrophosphate **87-1** with (*Z*)-3-methyl-3-pentenyl pyrophosphate **87-2** furnished **87-3** (Fig. 87). Removal of the pyrophosphate group of **87-3** with alkaline phosphatase gave **87-4**, which was oxidized with manganese dioxide giving **87-5**. Reduction of **87-5** was followed by chromatographic fractionation of the mixture giving faranal (3*R*, 4*R*)-**21**.[370] As shown in Fig. 87, all of the possible stereoisomers of **21** were prepared by this bio-organic synthesis. Only the (3*R*, 4*R*)-isomer was shown to be bioactive as the trail pheromone.

7. CONCLUSION—THE SIGNIFICANCE OF CHIRALITY IN PHEROMONE PERCEPTION

How about stereochemistry–pheromone activity relationships? The results so far obtained are summarized in Fig. 88. The relationships are far more complicated than I assumed them to be in 1973.



Reagents: (a) farnesyl pyrophosphate synthetase; (b) alkaline phosphatase; (c) MnO_2; (d) $(Ph_3P)_3RhCl$, Et_3SiH/C_6H_6; (e) K_2CO_3/EtOH aq.

Fig. 87. Bioorganic synthesis of (3*R*, 4*R*)-(+)-faranal and its stereoisomers.

Like other bioactive natural products, many of the chiral pheromones belong to category **A** of Fig. 88. In the case of those pheromones in group **A**, only one enantiomer is biologically active, and no inhibitory action can be observed with the inactive antipode. However, there are other unusual cases as shown in categories **B–H**.

In the case of those in group **B**, only one enantiomer is biologically active, but the inactive antipode inhibits the action of the correct enantiomer. Especially in the case of Japanese beetle pheromone **64** as studied by Tumlinson,[91] its racemate lacks biological activity due to the strong inhibition caused by the wrong enantiomer.

In the case of pheromones in group **C**, insects do not discriminate stereoisomers. Thus every stereoisomer of the German cockroach pheromone **27** evoked the response of the male insects.[94]

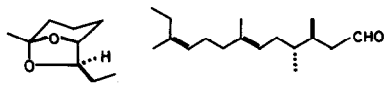
Ipsdienol **16** is the only pheromone which belongs to group **D**. Different species of *Ips* bark beetles use different enantiomers of **16**, and the chirality of the pheromone is quite important in establishing and maintaining a particular *Ips* species.[371]

Sulcatol **14** is the only pheromone both of whose enantiomers are required for pheromone activity in the case of an ambrosia beetle, *Gnathotrichus sulcatus* (group **E**).[372]

Groups **F**, **G** and **H** are also interesting cases. Especially in the case of the olive fruit fly pheromone **80**, its (*R*)-isomer is active on males, while the other is active on females.[373] Only the meso-isomer of the tsetse fly pheromone **1** was bioactive.[374]

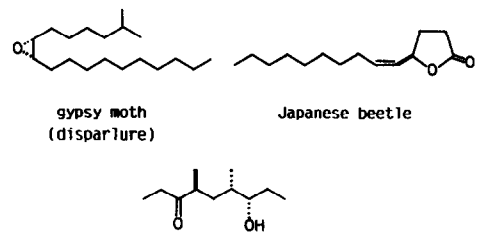
As summarized above, the relationships between stereochemistry and pheromone activity are

A. Only one enantiomer is bioactive, and the antipode does not inhibit the action of the pheromone.



western pine beetle (exo-brevicomin) — pharaoh's ant (faranal) — etc.

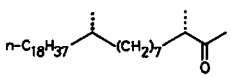
B. Only one enantiomer is bioactive, but the antipode or diastereomer inhibits the action of the pheromone.



gypsy moth (disparlure) — Japanese beetle

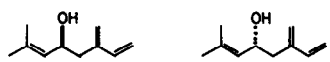
cigarette beetle (serricornin) — etc.

C. All the stereoisomers are bioactive.



German cockroach — etc.

D. Even in the same genus different species use different enantiomers.



Ips paraconfusus [(+)-ipsdienol] — Ips calligraphus [(-)-ipsdienol]

E. Both the enantiomers are required for bioactivity.

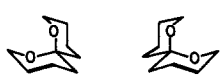
Gnathotrichus sulcatus

[(+)-sulcatol] — [(-)-sulcatol]

F. Only one enantiomer is as active as the natural pheromone, but its activity can be enhanced by the addition of a less active stereoisomer.

(natural pheromone) red flour beetle — (unnatural and less active)

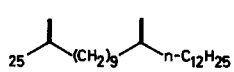
G. One enantiomer is active on male insects, while the other is active on females.



(R) ♂ — (S) ♀

olive fruit fly

H. Only the meso-isomer is active.



tsetse fly (Glossina pallidipes) — etc.

Fig. 88. Relationships between stereochemistry and pheromone activity.

complicated. The precise meaning of this diversity may be clarified only after deeper investigation on the nature of pheromone perception by insects.

In the legends of Figs 2–8, the relationship between stereochemistry and bioactivity of each pheromone is also indicated. The capital letter (**A, B, C, D,..., H**) in parenthesis after the name and origin of the pheromone indicates the category to which that individual pheromone belongs. The capital letter **U** indicates that the stereochemistry–bioactivity relationship of that pheromone still remains unknown.

In conclusion, the endeavours of synthetic chemists to prepare enantiomerically pure pheromones in amounts sufficient for accurate bioassay enabled entomologists to analyze the stereochemical problem in pheromone perception. Development in the synthesis of chiral pheromones is not only of academic interest. It is also of practical value as is exemplified in the commercialization of

pheromone traps for the Japanese beetle, which can be attracted only by the correct enantiomer of the pheromone.

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