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Synthetic and stereochemical aspects of pheromone chemistry

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Abstract: Recent synthetic works on pheromones are described, the key steps in which are the enzymatic desymmetrizations of *meso*-diacetates or a *meso*-diol to give optically active monoacetates. The target molecules are the pheromones of the gypsy moth (**3**), the ruby tiger moth (**4**), the African palm weevil (**5**), the Asian palm weevil (**6**), the Israeli pine bast scale (**7**), and the spined citrus bug (**42**). The relationships between absolute configuration and bioactivity of pheromones are also summarized.

INTRODUCTION

The first insect pheromone whose structure was elucidated by Butenandt in 1959 was an achiral alcohol bombykol, the female-produced silkworm moth pheromone (Fig. 1). Subsequently, a number of chiral pheromones such as *exo*-brevicomin, the western pine beetle pheromone, were identified in late 1960's. The stereochemistry of a chiral pheromone must be investigated so as to establish the absolute configuration of the naturally occurring material and also to clarify the relationship between stereochemistry and pheromone activity. In 1973, the dermested beetle pheromone, which was levorotatory, was shown to be the (*R*)-enantiomer, because the synthetic (*S*)-isomer was dextrorotatory (1, 2). The enantiomers of *exo*-brevicomin were synthesized in 1974 from the enantiomers of tartaric acid (3), and only the (+)-isomer was bioactive (4).

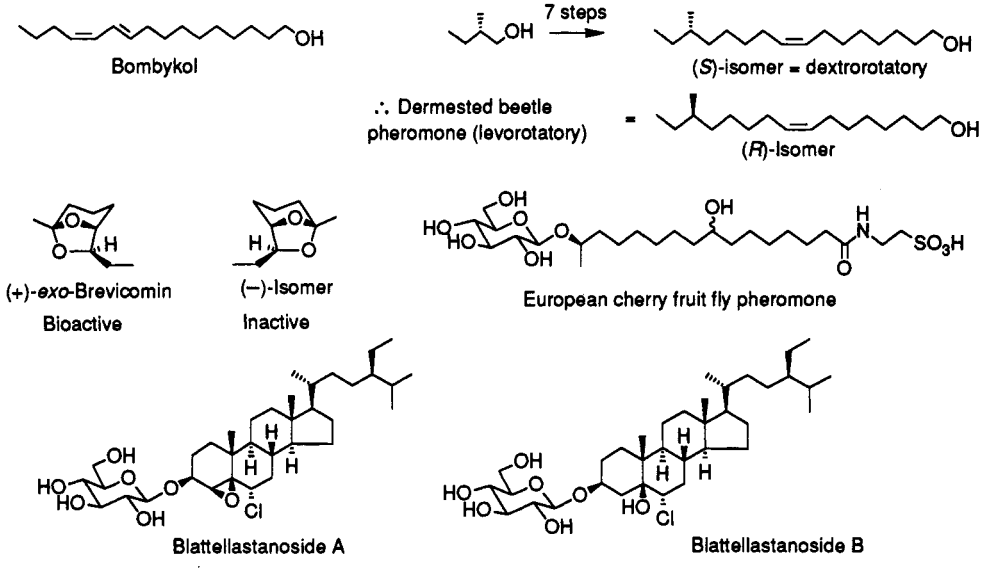

Fig. 1. Structures of some insect pheromones

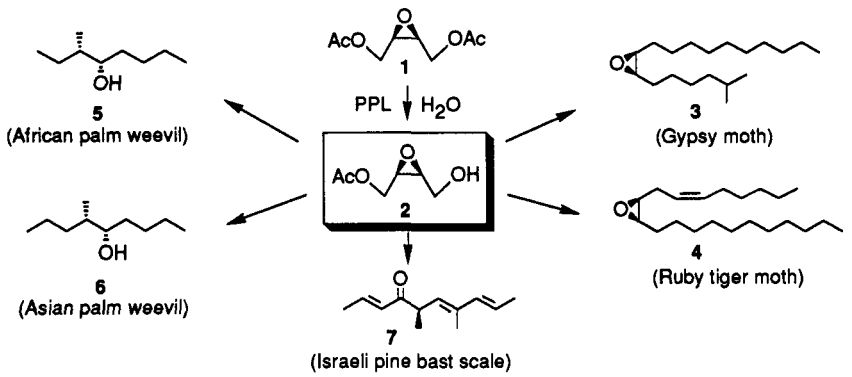

Fig. 2. Pheromones synthesized from epoxide **2**

Many pheromones are volatile, and *exo*-brevicomin is an extremely volatile compound. There are, however, some pheromones which are non-volatile glucosides. The oviposition-deterring pheromone of the European cherry fruit fly is one of them (5). This taurine-containing glucoside was synthesized by three groups (6–8). Other glucoside pheromones are blattellastanosides A and B, which are the aggregation pheromone of the German cockroach (9). These steroid glucosides were synthesized by us (10). In this lecture I will talk on the new syntheses of volatile pheromones by employing enzymes as tools to desymmetrize *meso*-compounds. The relationship between absolute configuration and pheromone activity will also be discussed.

PHEROMONE SYNTHESES *VIA* AN EPOXY BUILDING BLOCK

Desymmetrization of **1** (Fig. 2) with pig pancreatic lipase (PPL) gives **2** (11, 12), which serves as a useful building block for the syntheses of not only pheromone epoxides (**3** and **4**) but also pheromone alcohols (**5** and **6**) and a ketone (**7**).

Syntheses of Pheromone Epoxides

Our syntheses of pheromone epoxides **3** and **4** are straightforward as shown in Fig. 3 (12). Because the enzymatic desymmetrization of **1** gave **2** of imperfect enantiomeric purity (90.8% e.e.), **2** was converted to crystalline **10**, which was purified by recrystallization. Chain-elongation of **9** (~100% e.e.) *via*

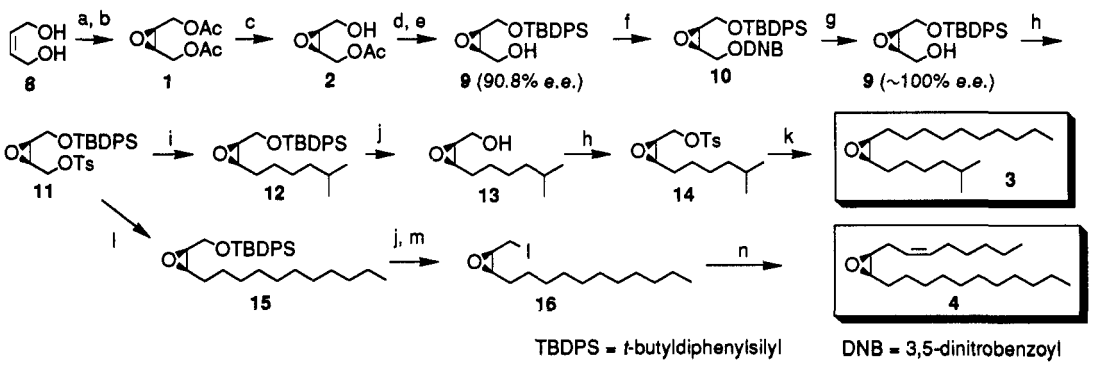

Fig. 3. Synthesis of pheromone epoxides **3** and **4**

Reagents: (a) Ac_2O, C_5H_5N (quant).—(b) MCPBA, CH_2Cl_2 (98%).—(c) PPL, $(i\text{-Pr})_2O$, phosphate buffer (pH 7) (71%).—(d) TBDPSCl, DMAP, Et_3N, CH_2Cl_2 (quant).—(e) K_2CO_3, MeOH (98%).—(f) DNBCl, C_5H_5N/Et_2O;recryst'n (53%).—(g) K_2CO_3, THF/MeOH (99%).—(h) TsCl, DMAP, Et_3N, CH_2Cl_2 (quant).—(i) $[Me_2CH(CH_2)_3]_2CuLi$, Et_2O (74%).—(j) $(n\text{-Bu})_4NF$, THF (92% for **13**).—(k) $(n\text{-}C_9H_{19})_2CuLi$, Et_2O (65%).—(l) $(n\text{-}C_{10}H_{21})_2CuLi$, Et_2O (75%).—(m) I_2, Ph_3P, imidazole, Et_2O/MeCN (83% for 2 steps).—(n) (Z)-$Me(CH_2)_4CH$=$CHMgBr$, CuI, HMPA/THF (86%).

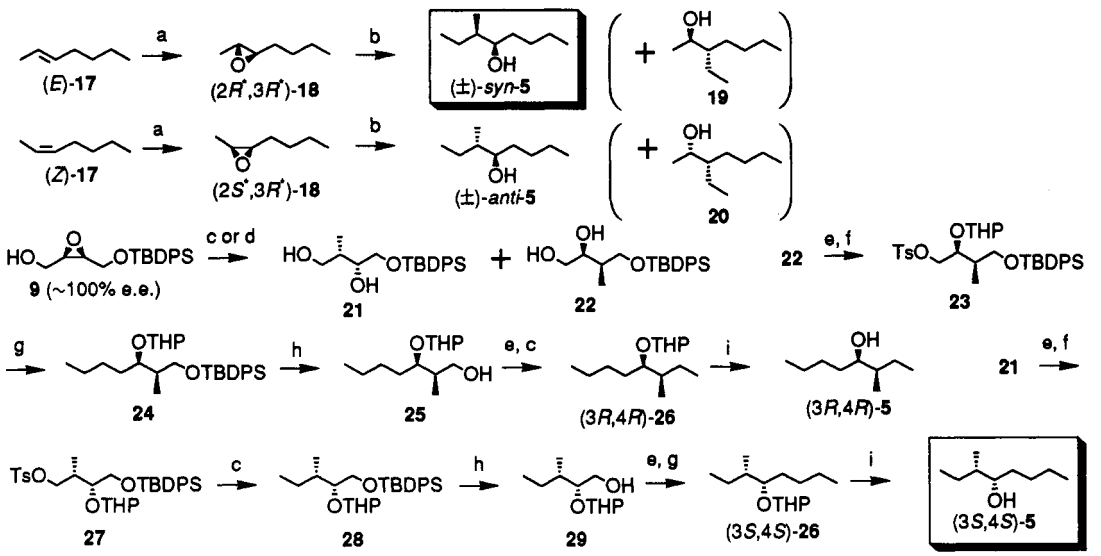

Fig. 4. Synthesis of pheromone alcohol **5**

Reagents: (a) MCPBA, CH_2Cl_2 [71% for (2*R**,3*R**)-**18**, 72% for (2*S**,3*R**)-**18**].—(b) EtMgBr, CuBr, Et_2O [25% for (±)-*syn*-**5** with 22% of **19**; 12% for (±)-*anti*-**5** with 17% of **20**].—(c) Me_2CuLi, Et_2O [68% of **21** and 23% of **22**; 68% for (3*R*,4*R*)-**26**; 85% for **28**].—(d) Me_3Al, pentane/CH_2Cl_2 (24% of **21** and 62% of **22**).—(e) TsCl, C_5H_5N.—(f) DHP, TsOH, CH_2Cl_2.—(g) $(n\text{-Pr})_2CuLi$, Et_2O [40% for **24**; 40% for (3*S*,4*S*)-**26**].—(h) $(n\text{-Bu})_4NF$(94% for **25**; 96% for **29**).—(i) TsOH, MeOH [97% for (3*R*,4*R*)-**5**; 85% for (3*S*,4*S*)-**5**].

tosylate **11** by means of organocopper chemistry yielded (+)-disparlure (**3**, the pheromone of the gypsy moth, *Lymantria dispar*) and the pheromone **4** of the ruby tiger moth, *Phragmatobia fuliginosa*. The present synthesis (15.8% overall yield) of **3** is more efficient than our previous ones by either starting from (+)-tartaric acid (1.1% overall yield) (13, 14) or by employing the Sharpless asymmetric epoxidation (12.2% overall yield) (15, 16). The epoxy building block **9** can also be employed in the synthesis of other pheromone epoxides.

Syntheses of Pheromone Alcohols

Palm weevils are the major pests of coconut and oil palm crops. In 1993 Rochat *et al.* identified 3-methyl-4-octanol (**5**) as the male-produced aggregation pheromone of the African palm weevil (*Rynchophorus phoenicis*) in Ivory Coast (17). Fig. 4 demonstrates the way how we clarified the relative and absolute configuration of the natural **5** by stereoselective syntheses coupled with GC analysis (18). In order to determine the relative configuration of the pheromone, the racemates of both *syn*- and *anti*-**5** were synthesized from (*E*)- and (*Z*)-**17**. Their GC comparison with the natural pheromone revealed it to be *syn*-**5**. Both the enantiomers of *syn*-**5** were then synthesized from the chiral building block **9**. Cleavage of **9** was executed under two different conditions. When **9** was treated with lithium dimethylcuprate (19), the major product isolated in 68% yield was **21**, and the regioisomer **22** was the minor product (23%). On the other hand, treatment of **9** with trimethylaluminum (20) yielded **22** (62% yield) as the major product with 24% of **21**. After chromatographic separation, these two regioisomers **21** and **22** were converted into (3*R*,4*R*)-**5** and (3*S*,4*S*)-**5**, respectively, by employing organocopper chemistry as shown in Fig. 4. GC analysis of the enantiomers of *syn*-**5** was carried out on a Cyclodex-B column. Coinjection of the synthetic products with the natural pheromone proved it to be (3*S*,4*S*)-**5** (18). In the same manner, the enantiomers of *syn*-4-methyl-5-nonanol (**6**), the major component of the male-produced aggregation pheromone of the Asian palm weevil (*Rhynchophorus vulneratus*) (17), were synthesized, and the natural pheromone was shown to be (4*S*,5*S*)-**6** (21).

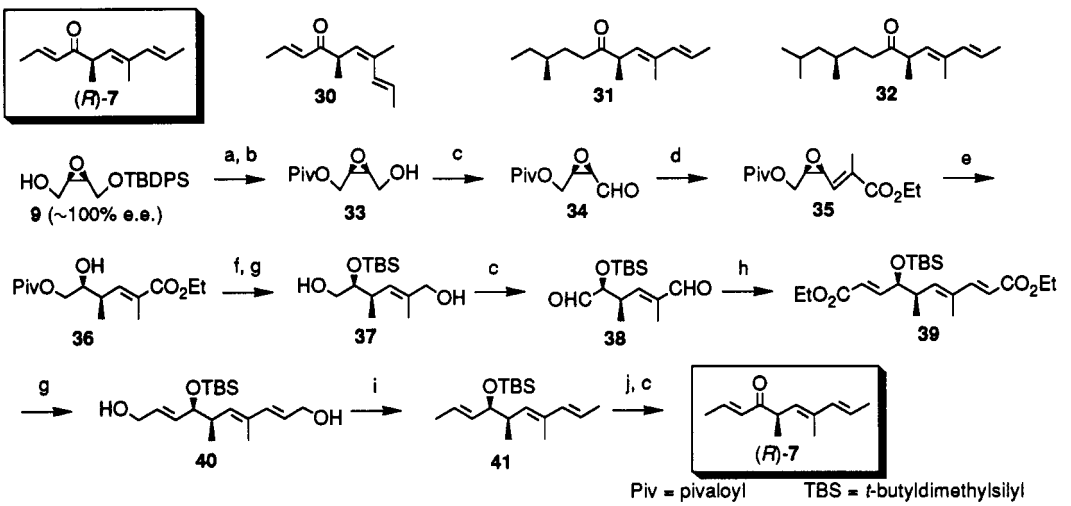

Fig. 5. Synthesis of pheromone ketone **7**

Reagents: (a) PivCl, C_5H_5N/CH_2Cl_2 (93%).—(b) HF, $(n\text{-}Bu)_4NF$, THF (91%).—(c) $(COCl)_2$,DMSO, Et_3N, CH_2Cl_2 [69% for **34**; 96% for **38**; 845 for (*R*)-**7** (2 steps)].—(d) $Ph_3P{=}C(Me)CO_2Et$, THF (91%).—(e) Me_3Al (10 eq), H_2O (6 eq), CH_2Cl_2 (92%).—(f) TBSCl, imidazole, DMF (92%).—(g) $(i\text{-}Bu)_2AlH$, hexane/Et_2O (89% for **37**; 93% for **40**).—(h) $(EtO)_2P(O)CH_2CO_2Et$, *n*-BuLi, THF (72%).—(i) 1) $SO_3{\cdot}C_5H_5N$, THF. 2) $LiAlH_4$ (39%).—(j) $(n\text{-}Bu)_4NF$, THF.

Syntheses of a Pheromone Ketone

(2*E*,4*E*,8*E*)-4,6-Dimethyl-2,4,8-decatrien-7-one (**7**, Fig. 5) is the major and highly active component of the female-produced sex pheromone of the Israeli pine bast scale (*Matsucoccus josephi*), which is the pest of pine forests in Israel (22). The minor component **30** is much less active than **7**. Although a synthesis of (±)-**7** was reported recently (23), the absolute configuration of the natural **7** has remained unknown. Our experience in the syntheses of related pheromones such as the pheromone of *Matsucoccus feytaudi* **31** (24) and the pheromone of *Matsucoccus matsumurae* (matsuone) **32** (25) suggested that the pheromone of *Matsucoccus josephi* might be (*R*)-**7**. The chiral building block **9** was therefore converted to (*R*)-**7**. The enantiomerically pure **9** furnished epoxy ester **35**, which was treated with trimethylaluminum in the presence of a small amount of water (26) to give **36**. Dialdehyde **38** derived

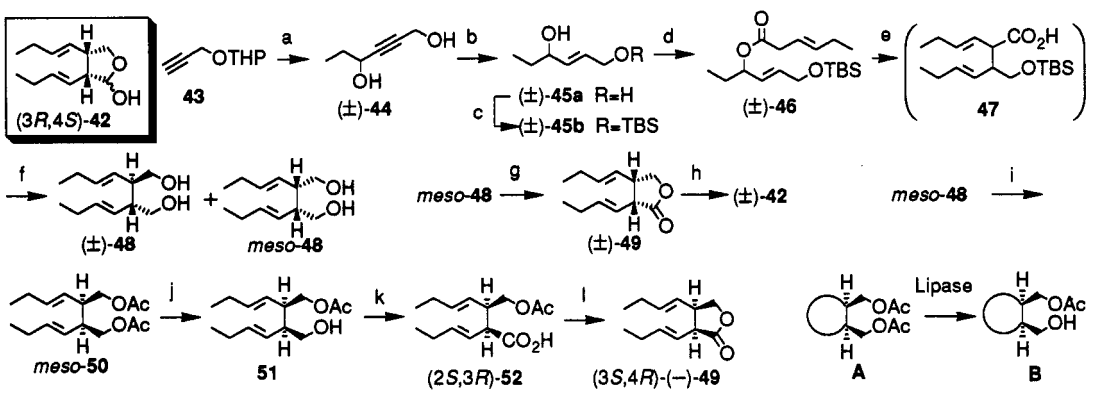

Fig. 6. Synthesis of pheromone hemiacetal **42** —1

Reagents : (a) 1) EtMgBr, THF; EtCHO; 2) *p*-TsOH, MeOH (74%).—(b) $LiAlH_4$, NaOMe, THF (89%).—(c) TBSCl, DMAP, Et_3N, CH_2Cl_2 (99%).—(d) (*E*)-$EtCH{=}CHCH_2CO_2H$, DCC, DMAP, CH_2Cl_2 (87%).—(e) 1) $LiN(SiMe_3)_2$, HMPA/THF; 2) TMSCl; 3) dil.HCl.—(f) $LiAlH_4$, THF [89%; (±)-**48**:*meso*-**48**=11:89].—(g) Ag_2CO_3/Celite, C_6H_6 (85%).—(h) $(i\text{-}Bu)_2AlH$, toluene (88%).—(i) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2 (quant).—(j) lipase AK, phosphate buffer (pH 7) (89%).—(k) Jones CrO_3, Me_2CO (70%).—(l) 1) K_2CO_3, MeOH; 2) dil.HCl; 3) $EtO_2CN{=}NCO_2Et$, Ph_3P, THF (81%).

from **36** was submitted to chain-elongation reaction at the both ends of the molecule to give diester **39**. The corresponding diol **40** was deoxygenated (27) at the both ends to give **41**, whose deprotection and oxidation afforded (*R*)-**7**. Synthesis of (*S*)-**7** is in progress. The bioassay of (*R*)-**7** is now under way by Dr. E. Dunkelbaum in Israel.

SYNTHESIS OF THE PHEROMONE OF THE SPINED CITRUS BUG

The spined citrus bug (*Biprorulus bibax*) is an important pest of citrus in southern Australia (28). Oliver *et al.* (29) isolated and identified a new hemiacetal **42** (Fig. 6) as the major component of the male-produced pheromone of *B. bibax*. The absolute configuration of the natural **42** was shown to be 3*R*,4*S* (30, 31). We became interested in developing an efficient synthesis of (±)-**42** so as to use it practically. Ireland's ester-enolate Claisen rearrangement (**46**→**47**) (32) was successfully employed for that purpose as shown in Fig. 6, and (±)-**42** was bioactive when combined with other pheromone components like linalool, nerolidol and farnesol (33). The overall yield of (±)-**42** on the basis of **43** was 39% (10 steps) (31).

We then executed desymmetrization of *meso*-**50** by using lipase AK (31). Desymmetrization of a *meso*-diacetate like **A** with lipases is known to give a monoacetate like **B** (34–36). Accordingly, *meso*-**50** was converted to (3*S*,4*R*)-(–)-**49** *via* **51**. The absolute configuration of (–)-**49** was supported by another synthesis of itself by employing Corey's CBS reagent [(*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (**54**)] for the reduction of **53** to give (*S*)-**45b** [79% e.e. as estimated by the HPLC analysis on Chiralcel OJ of (*S*)-**45c**] as shown in Fig. 7 (31). The stereochemistry of (*S*)-**45b** was proved by its conversion to the known lactone (*S*)-**57** (38). Esterification of (*S*)-**45b** with (*E*)-3-hexenoic acid

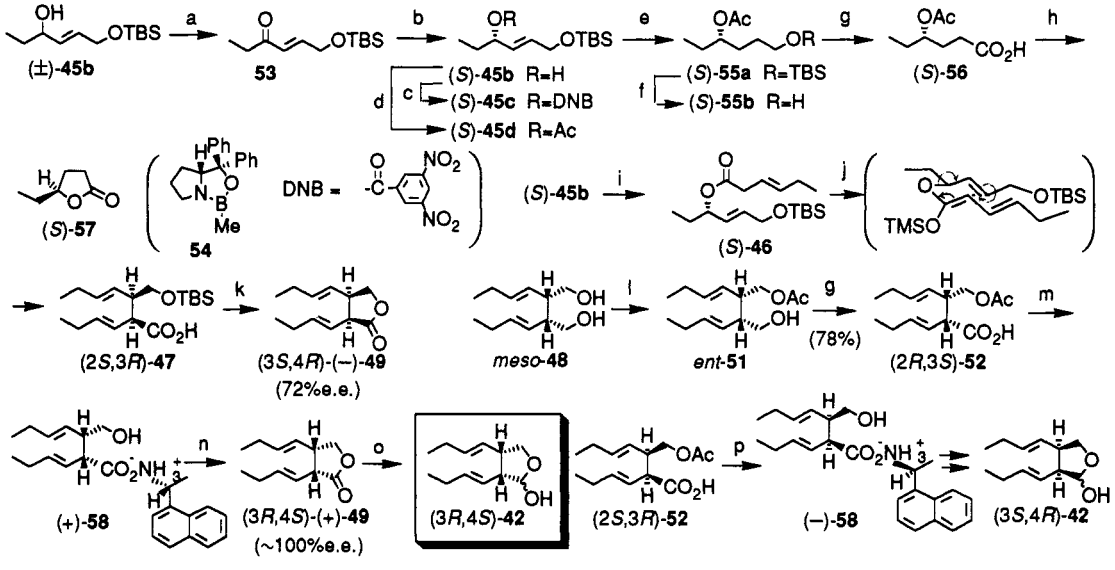

Fig. 7. Synthesis of pheromone hemiacetal **42** —2

Reagents : (a) PDC, MS 3A, CH_2Cl_2 (83%).–(b) **54**, BH_3·THF, THF (65%).–(c) DNBCl, C_5H_5N.–(d) AcO_2, C_5H_5N (92%).–(e) H_2, Pd-C, *n*-hexane.–(f) aq.HF, MeCN (90%, 2steps).–(g) Jones CrO_3, Me_2CO.–(h) 1) K_2CO_3, MeOH; 2) *p*-TsOH, C_6H_6 (51%, 3 steps).–(i) (*E*)-EtCH=CHCH$_2$CO$_2$H, DCC, DMAP, CH_2Cl_2 (91%).–(j) 1) $LiN(SiMe_3)_2$, HMPA/THF; 2) TMSCl; 3) dil.HCl.–(k) 1) aq.HF, MeCN; 2) $EtO_2CN{=}NCO_2Et$, Ph_3P, C_6H_6 [32% based on (*S*)-**46**].–(l) lipase AK, CH_2=CHOAc (63%).–(m) 1) K_2CO_3, MeOH, then dil.HCl; 2) (*R*)-1-naphthylethylamine, recryst'n (51%). - (n) $EtO_2CN{=}NCO_2Et$, Ph_3P, THF (92%).–(o) (*i*-Bu)$_2$AlH, toluene (99%).–(p) 1) K_2CO_3, MeOH, then dil.HCl; 2) (*S*)-1-naphthylethylamine, recryst'n (57%).

gave (*S*)-**46**, which yielded (2*S*,3*R*)-**47** through the Claisen rearrangement. Deprotection-lactonization of (2*S*,3*R*)-**47** furnished (3*S*,4*R*)-**49**. This lactone was levorotatory, supporting the previous assignment of (3*S*,4*R*)-configuration to (–)-**49** on the basis of the enantioselectivity of lipase action.

Finally, we prepared enantiomerically pure (3*R*,4*S*)-**42**, the natural pheromone, and its antipode. Acetylation of *meso*-**48** with vinyl acetate in the presence of lipase AK gave *ent*-**51** of 89% e.e., which was purified by recrystallizing (+)-**58**. Reduction of (+)-**49** with diisobutylaluminum hydride gave the natural pheromone (3*R*,4*S*)-**42**. Similarly, (2*S*,3*R*)-**52** was purified by recrystallization of (–)-**58**, which furnished the unnatural enantiomer (3*S*,4*R*)-**42** of the pheromone. These enantiomers were bioassayed by Dr. D. G. James in Australia. The natural enantiomer (3*R*,4*S*)-**42** was highly attractive against *B. bibax*, but curiously the unnatural enantiomer was also a half as active as the natural one.

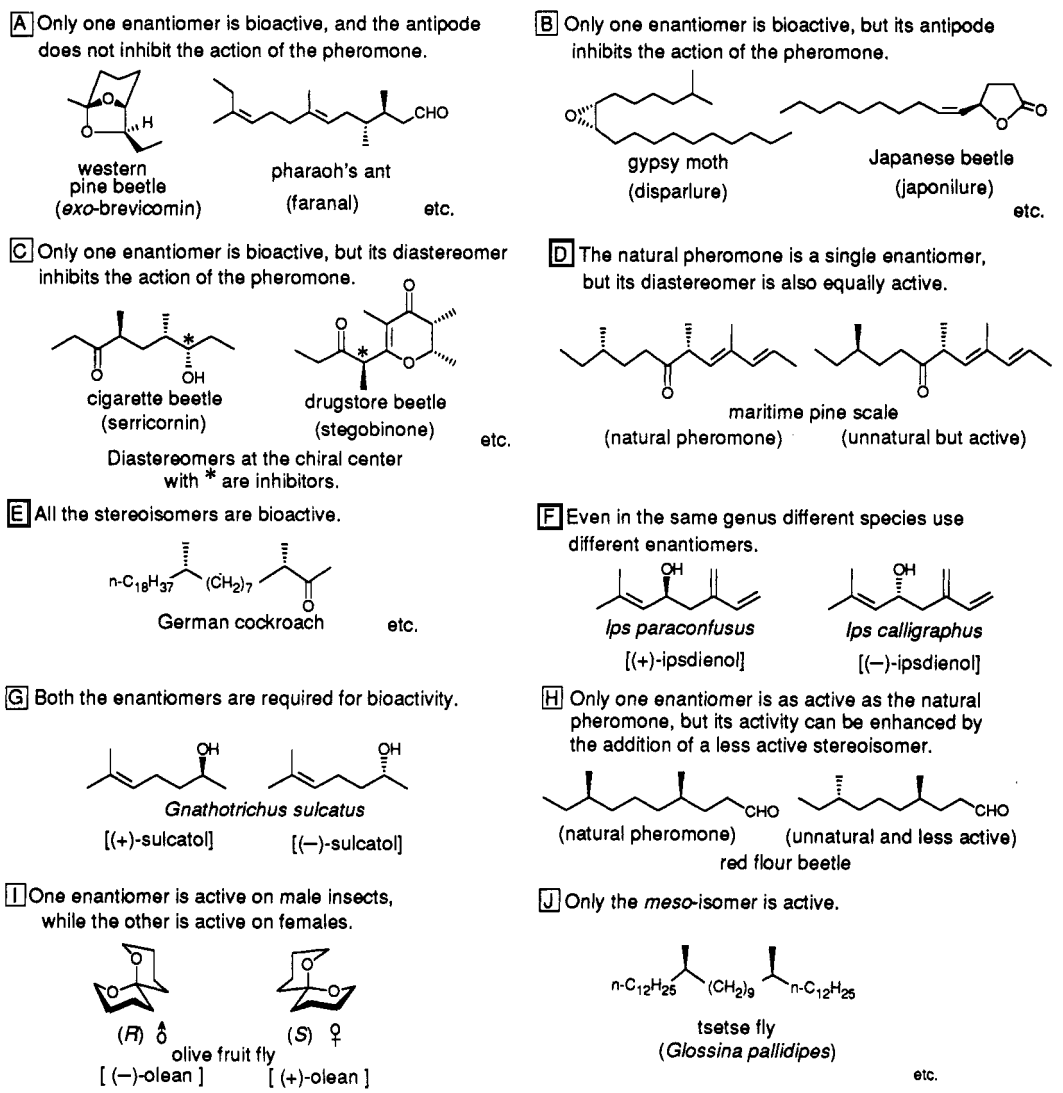

Fig. 8. Relationships between absolute configuration and bioactivity of pheromones

RELATIONSHIPS BETWEEN ABSOLUTE CONFIGURATION AND BIOACTIVITY OF PHEROMONES

As shown in Fig. 8, the relationships between stereochemistry and pheromone activity are not simple but complicated. The precise meaning of this diversity may be clarified only after more extensive investigation of the nature of pheromone perception by insects.

CONCLUSION

Because the available amount of an insect pheromone is limited, synthesis is the indispensable tool for the determination of the absolute configuration of a chiral pheromone and also for the supply of a sufficient amount of a pheromone.

It is my privilege to acknowledge the contribution of my coworkers whose names appear in the references.

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