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Recent results in pheromone synthesis

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Abstract: New and enantioselective syntheses of three known insect pheromones - faranal **1**, matsuone **2** and olean **3** - were achieved. Lurlene **4**, the sex pheromone of the green flagellate *Chlamydomonas allensworthii*, was synthesized by employing a palladium-catalyzed carbon-carbon bond formation reaction as the key step. Several analogs of blattellastanoside A **5**, the aggregation pheromone of the German cockroach, were synthesized, and the fluorinated analog **74** was found to be biologically more potent than the natural pheromone **5**.

INTRODUCTION

Although the first insect pheromone bombykol which was discovered by Butenandt in 1959 was an achiral alcohol, many chiral pheromones have been identified since the late 1960's. The importance of the absolute configuration of a chiral pheromone in its expression of bioactivity is now well recognized due to the combined efforts of biologists and chemists (1, 2). Owing to the very limited amount (a few pg or μg to mg) of the natural pheromones available, their enantioselective syntheses are required for the purpose of both the elucidation of their absolute configuration and the clarification of the stereochemistry-bioactivity relationships (3). Asymmetric synthesis of pheromones is also of industrial importance, because in some cases only one enantiomer of the pheromone is bioactive and its antipode inhibits the pheromone action. Rapid progress in the methodology for asymmetric synthesis now enables us to develop new and more efficient enantioselective syntheses of pheromones. In this paper, new syntheses of three insect pheromones - faranal **1**, matsuone **2** and olean **3** - will be described. The first synthesis of lurlene **4**, the sex pheromone of the green flagellate *Chlamydomonas allensworthii*, will also be reported.

Is there any pheromone analog which shows bioactivity stronger than the original natural product ? An answer to this question will be reported by referring to our recent synthesis of the analogs of blattellastanoside A **5**, the aggregation pheromone of the German cockroach.

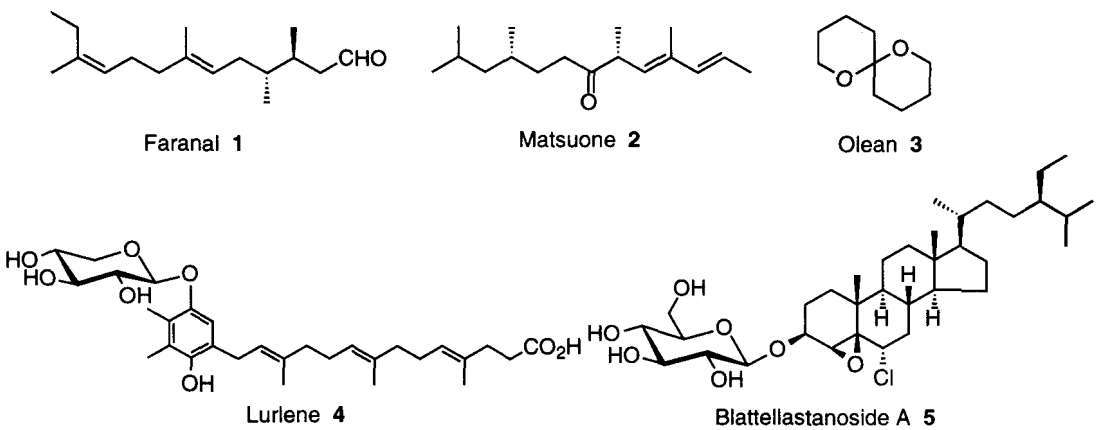

Fig. 1. Structures of the target pheromones.

NEW SYNTHESES OF INSECT PHEROMONES

Faranal, the Trail Pheromone of the Pharaoh's Ant

In 1977, Ritter and his co-workers isolated and identified faranal **1**, the trail-following pheromone of the worker Pharaoh's ant (*Monomorium pharaonis*) (4). The first synthesis of (+)- and (-)-**1** was achieved in 1980 by Ogura and his co-workers (5) by employing farnesyl pyrophosphate synthase for the construction of the chiral center at C-4 of **A** (Fig. 2) and its antipode. Our synthesis of the enantiomers of **1** in 1981 utilized the lactone **B** and its antipode obtained by the optical resolution of (±)-**B** (6). Subsequently in 1986, Szántay and his co-workers (7) synthesized (+)-**1** by employing the lactone **C** as their intermediate, which was obtained by enzymatic resolution. The bioassay of the synthetic enantiomers of **1** revealed that only (+)-**1** is bioactive (5,6).

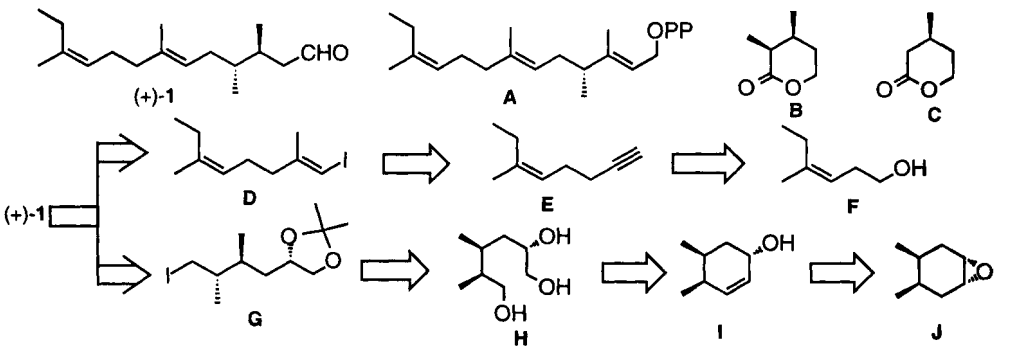

Fig. 2. Retrosynthetic analysis of faranal (+)-**1**.

The drawbacks of these previous syntheses were (i) inapplicability to a large-scale synthesis in the case of Ogura's enzymatic synthesis (5) and (ii) difficulty in securing the resolved intermediates with high enantiomeric purity in the cases of optical resolutions (6,7). Our new retrosynthetic analysis of (+)-**1** is shown in Fig. 2. The coupling of **D** with **G** yields eventually (+)-**1**. The olefin **D** is a known compound (8), which can be prepared from **F** via **E**. The iodide **G** is to be prepared from a known compound **H** (9), which originates from the *meso*-epoxide **J**. The intermediate **I** can be prepared in enantiomerically pure form (9).

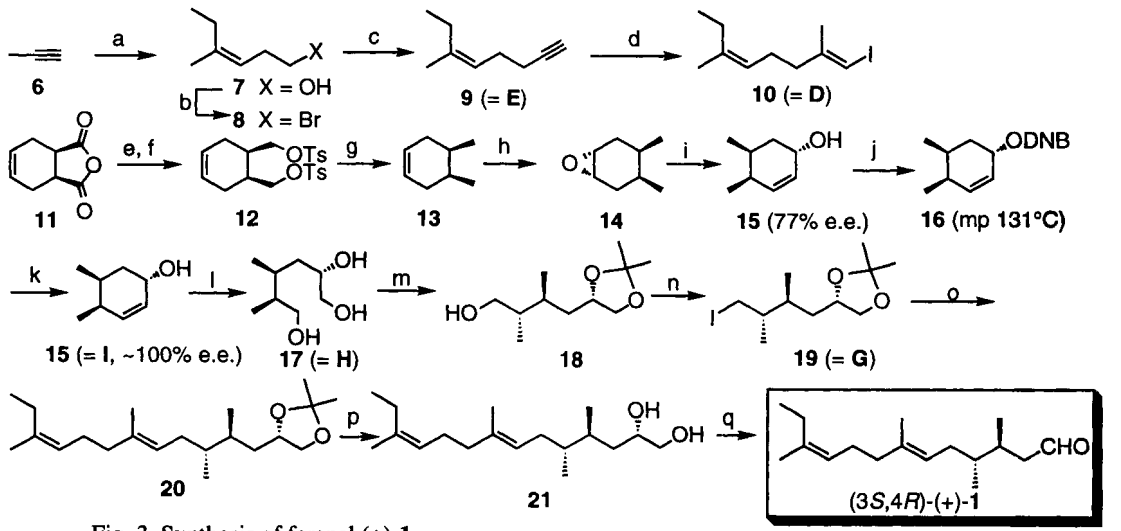

Fig. 3. Synthesis of faranal (+)-**1**.

Reagents : (a) 1) EtMgBr, CuBr • Me_2S, Me_2S/Et_2O; 2) *n*-PrC≡CH, *n*-BuLi, Et_2O/HMPA; 3) ethylene oxide (59%). - (b) 1) TsCl, C_5H_5N; 2) LiBr, Me_2CO (83%). - (c) LiC≡CH • $H_2N(CH_2)_2NH_2$, DMSO (76%). - (d) Me_3Al (3 eq), Cp_2ZrCl_2 (0.2 eq), H_2O (1.5 eq), CH_2Cl_2; then I_2 (83%). - (e) $LiAlH_4$, THF. - (f) TsCl, DMAP, C_5H_5N (84% based on **11**). - (g) $LiAlH_4$, *N*-methylmorpholine. - (h) MCPBA, $NaHCO_3$, CH_2Cl_2 (68% based on **12**). - (i) (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine, *n*-BuLi, THF (97%). - (j) DNBCl, DMAP, C_5H_5N; recryst'n (45%). - (k) KOH, THF/aq. MeOH (97%). - (l) 1) O_3, CH_2Cl_2; 2) $NaBH_4$. - (m) Me_2CO, TsOH (85% based on **16**). - (n) I_2, Ph_3P, imidazole, C_6H_6 (quant.). - (o) **10**, *t*-BuLi, Et_2O (49%). - (p) PPTS, MeOH (90%). - (q) $NaIO_4$, Et_2O, H_2O (92%).

The synthesis of **10** (= **D**) started from **6** as shown in Fig. 3 (10). We modified Baker's procedure at the step to convert **9** to **10**. By employing Negishi's zirconocene-mediated carboalumination reaction as modified by Wipf (11), **10** was obtained from **9** in 83% yield. For the preparation of **19** (= **G**) , the *meso*-epoxide **14** was submitted to the asymmetric cleavage of the epoxy ring with a chiral lithium amide as reported by Asami (12) to give **15** (9). This was purified as its crystalline 3,5-dinitrobenzoate **16** to yield enantiomerically pure **15**, which was converted to the iodide **19** (= **G**) by the standard method as shown in Fig. 3. The lithiate derived from **10** was alkylated with **19** to give geometrically and enantiomerically pure **20**, which afforded (3*S*,4*R*)-(+)-faranal **1** via **21**. The overall yield of (+)-**1** was 12.5% based on **6** (8 steps) or 8.3% based on **11** (13 steps). The present work (10) constitutes the first chemical asymmetric synthesis of (+)-**1**, while the previous syntheses depended on biochemical methods (5,7) or chemical optical resolution (6).

Matsuone, the Sex Pheromone of *Matsucoccus* Pine Bast Scales

In 1989 the late Lanier et al. identified the primary component of the female-produced sex pheromone of the red pine scale (*Matsucoccus resinosae*) as matsuone **2** (13). The ketone **2** is also the pheromone of the Japanese pine scale (*M. matsumurae*) and *M. thumbergianae* (13). The absolute configuration of matsuone as depicted in **2** was determined by our unambiguous synthesis of **2** and its antipode (14), followed by their bioassay to prove only **2** is bioactive (15). Our 1993 synthesis (14), however, was lengthy and inefficient to give **2** and its antipode in 2.2~2.6% overall yield (22 steps) by starting from the enantiomers of citronellol.

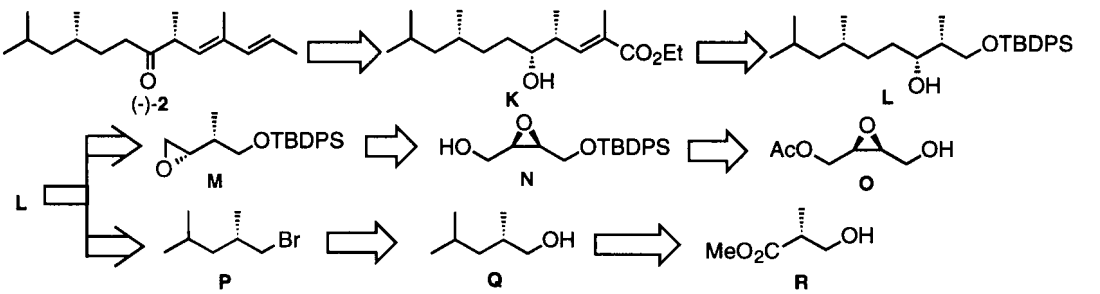

Fig. 4. Retrosynthetic analysis of matsuone (-)-**2**.

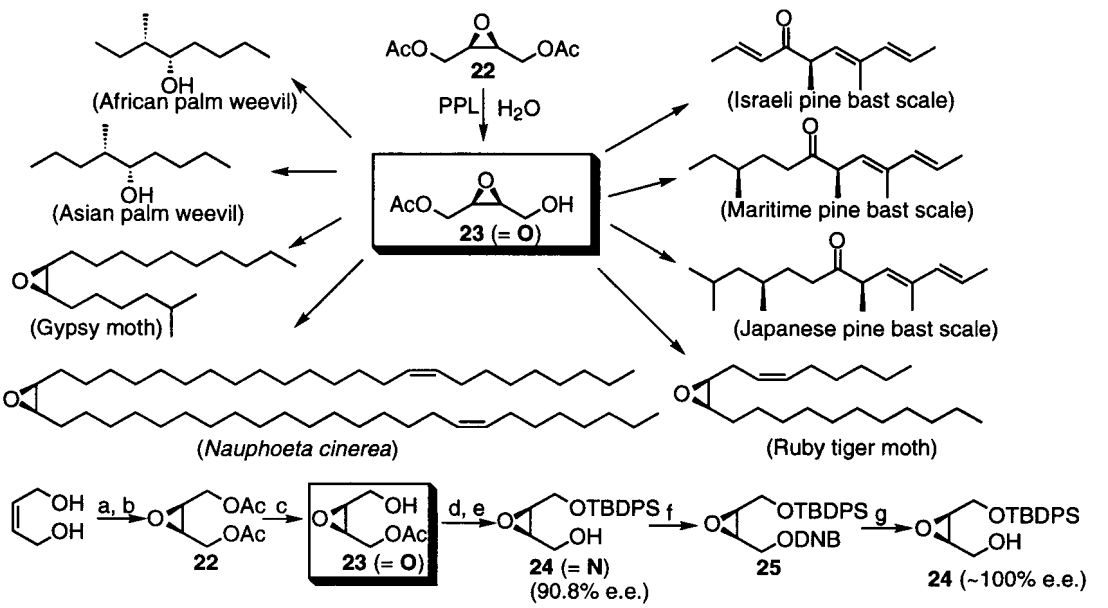

Fig. 5. Preparation and use of the optically active epoxide **23**.

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%).

We therefore planned a more efficient synthesis of **2**. Fig. 4 shows our new retrosynthetic analysis of **2**. The diene moiety of **2** is to be constructed via **K** by stepwise olefination by starting from **L**, which can be prepared by the coupling of **M** with **P**. The former (**M**) is a known compound (16) and obtainable from **O** via enantiomerically pure **N** (vide infra). The bromide **P**, whose precursor is **Q**, can be prepared from the commercially available (*R*)-hydroxy ester **R**.

Preparation and use of the optically active half acetate **O** is shown in Fig. 5. Asymmetric hydrolysis of the *meso*-diacetate **22** with pig pancreatic lipase (PPL) yields optically active **23** (= **O**), which can be purified by recrystallization of **25** (17). Removal of the acyl group of **25** gives enantiomerically pure **24** (= **N**). The epoxide **23** is a versatile starting material in pheromone synthesis as shown in Fig. 5 (cf. 2). Preparation of the coupling partners **M** and **P** in matsuone synthesis is illustrated in Fig. 6. The epoxide **24** was treated with trimethylaluminum to give **26** as the major product with two by-products, one of which

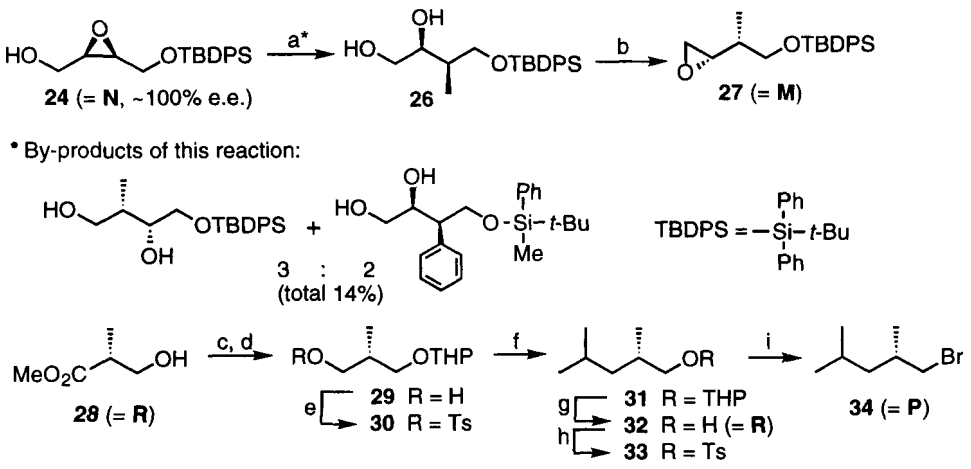

Fig. 6. Synthesis of the building blocks **M** and **P**.

Reagents : (a) Me_3Al, CH_2Cl_2/pentane (56%). - (b) 1) TsCl, C_5H_5N; 2) K_2CO_3, MeOH (80%). - (c) DHP, TsOH, Et_2O. - (d) $LiAlH_4$, Et_2O (88% based on **28**). - (e) TsCl, C_5H_5N (97%). - (f) *i*-PrMgBr, Li_2CuCl_4, THF. - (g) TsOH, MeOH. - (h) TsCl, C_5H_5N (60% based on **30**). - (i) LiBr, Me_2CO (90%).

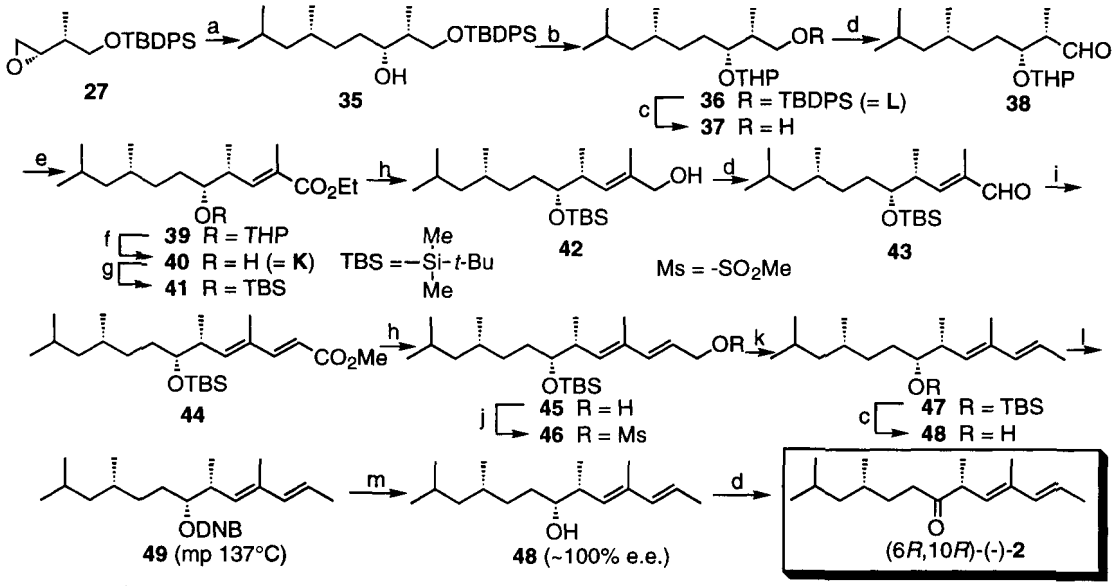

Fig. 7. Synthesis of matsuone (-)-**2**.

Reagents : (a) **34**, Mg, THF; CuBr (96%). - (b) DHP, PPTS, CH_2Cl_2 (93%). - (c) $(n\text{-Bu})_4NF$, THF (90~94%). - (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (95% for **2**). - (e) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6. - (f) TsOH, EtOH (83% based on **37**). - (g) TBSCl, imidazole, DMF (quant.). - (h) $(i\text{-Bu})_2AlH$, Et_2O (95~98%). - (i) $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, THF (90% based on **42**). - (j) *n*-BuLi, Ms_2O, THF. - (k) $LiBEt_3H$, THF (73% based on **45**). - (l) 1) DNBCl, C_5H_5N, Et_2O; 2) recryst'n (72%). - (m) NaOH aq., THF/MeOH (quant.).

was generated by the migration of a phenyl group on the silicon to C-2. The diol **26** was converted to the desired epoxide **27** (= **M**). The bromide **34** (= **P**) was synthesized from **28** by extending the carbon-chain of **30** by means of Schlosser's copper-catalyzed Grignard coupling (18) to give **31**, which finally afforded **34** via **32** and **33**.

Conversion of **27** to (-)-matsuone **2** is summarized in Fig. 7. Treatment of **27** with the Grignard reagent prepared from **34** in the presence of copper(I) bromide gave **35**, which was converted to **38** via **36** and **37**. Wittig olefination of **38** to give **39** was followed by further functional group transformation to afford **43**. Horner olefination of **43** gave **44**, which was reduced to furnish **45**. The corresponding mesylate **46** was reduced with lithium triethylborohydride to give **47**. Removal of the silyl protective group of **47** afforded the alcohol **48**, which was purified by recrystallization of the corresponding 3,5-dinitrobenzoate **49**. Pure **48**, liberated by the removal of the 3,5-dinitrobenzoyl group of **49**, was oxidized to give (-)-matsuone **2** (19). The overall yield of **2** was 12% based on **24** (19 steps).

Olean, the Sex Pheromone of the Olive Fruit Fly

In 1980, Baker, Francke and their co-workers isolated and identified olean **3** (1,7-dioxaspiro[5.5]undecane) as the major component of the female-produced sex pheromone of the olive fruit fly, *Bactrocea oleae* (formerly *Dacus oleae*) (20). (4*R**,6*R**)-4-Hydroxyolean **50** (Fig. 8) and (3*R**,6*R**)-3-hydroxyolean **51** were also isolated as the minor components (21). Bioassay of the synthetic enantiomers of **3** revealed that (*R*)-**3** is active on male insects, while (*S*)-**3** is active on females, and the female insects produce (±)-**3** as proved by GC analysis (22). Our 1985 synthesis of the enantiomers of **3**, **50** and **51** employed (*S*)-malic acid as the starting material and was lengthy (23, 24). It occurred to me that the enzymatic resolution of (±)-**50** might simplify the synthesis of the enantiomers of **3**, because **50** was known to give **3** by two-step deoxygenation (24). Fig. 8 summarizes our synthesis of the enantiomers of **50** (25). For the preparation of (±)-**50**, we adopted the method of Kocienski and Yeates to add **52** to **53** (26). Acetylation of (±)-**50** afforded (±)-**54** in 38% yield based on **52** (3 steps). After screening a number of hydrolytic enzymes, pig liver esterase (PLE) was found to be the appropriate one when employed at a low temperature at pH 7.5 with methanol as the co-solvent (cf. 27). Thus asymmetric hydrolysis of (±)-**54** with PLE gave (4*S*,6*S*)-**50** and (4*R*, 6*R*)-**54**. The acetate (4*R*, 6*R*)-**54** gave (4*R*, 6*R*)-**50** by deacetylation. The present synthesis of **50** is simple and efficient enough to allow the preparation of gram quantities of both the enantiomers of **50**.

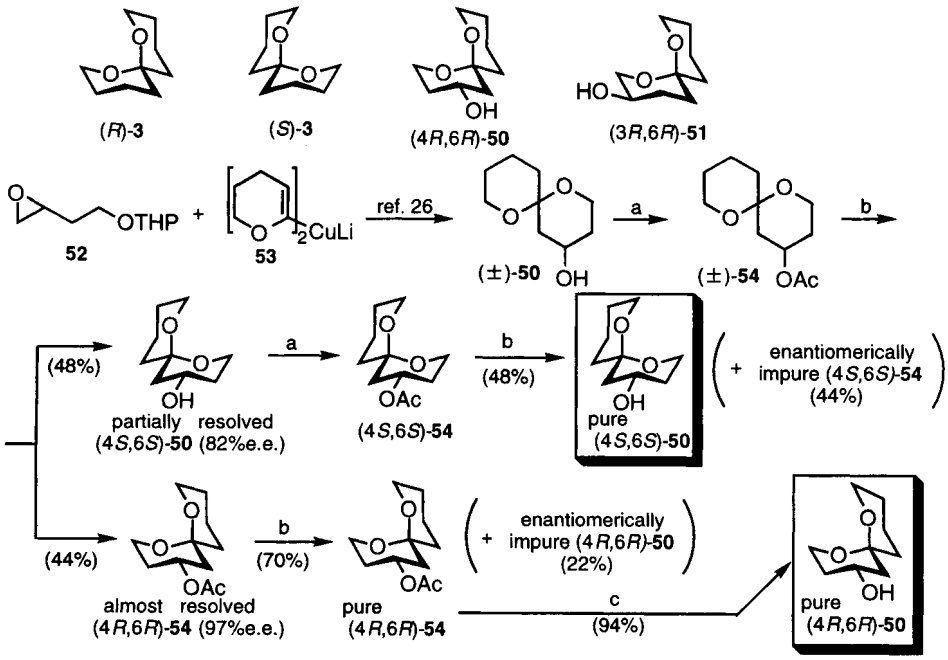

Fig. 8. Synthesis of the enantiomers of 4-hydroxyolean **50**.

Reagents : (a) Ac_2O, C_5H_5N. - (b) PLE, 20% MeOH in phosphate buffer (pH = 7.5), -12~-13°C, 30 h. - (c) K_2CO_3, MeOH.

SYNTHESIS OF LURLENE, THE SEX PHEROMONE OF THE GREEN FLAGELLATE *Chlamydomonas allensworthii*

The green flagellate *Chlamydomonas eugametos* and its sexuality were extensively studied by Moewus in 1930's to 1950's (28), whose work later turned out to be a scientific fraud (29-31). I have been interested in the *Chlamydomonas* story since my high school days when I read Kubota's review article on this subject (32). In 1995, the sex pheromone produced by female gametes of *Chlamydomonas allensworthii* was isolated, named as lurlene, and identified by Starr, Jaenicke and Marner (33,34). Lurlene [**4**, (4*E*,8*E*,12*E*)-14-[2'-hydroxy-3',4'-dimethyl-5'-(1"-β-D-xylopyranosyloxy)phenyl]-4,8,12-trimethyltetradeca-4,8,12-trienoic acid] attracts male gametes at a concentration as low as 1 pM (33).

Fig. 9 summarizes our synthesis of lurlene **4** (35). Commercially available geranylgeraniol **55**, 2,3-dimethyl-*p*-hydroquinone **60** and D-xylose were the starting materials. Standard methods were employed for the conversion of **55** to **59** via **56**, **57** and **58**. Then the organotin compound **64** was derived from **60** so as to apply the Hegedus-Stille palladium-catalyzed coupling reaction (36) to the connection of **64** with **59**. The coupling proceeded smoothly to give **65** in 98% yield. Deprotection of the THP protective group of **65** yielded **66**, which was treated with acetobromo-D-xylose in the presence of silver triflate to furnish **67**. Deprotection of the protective groups of **67** afforded lurlene **4**. The *Chlamydomonas* biology now stands on a sound chemical basis at least in the case of *C. allensworthii*.

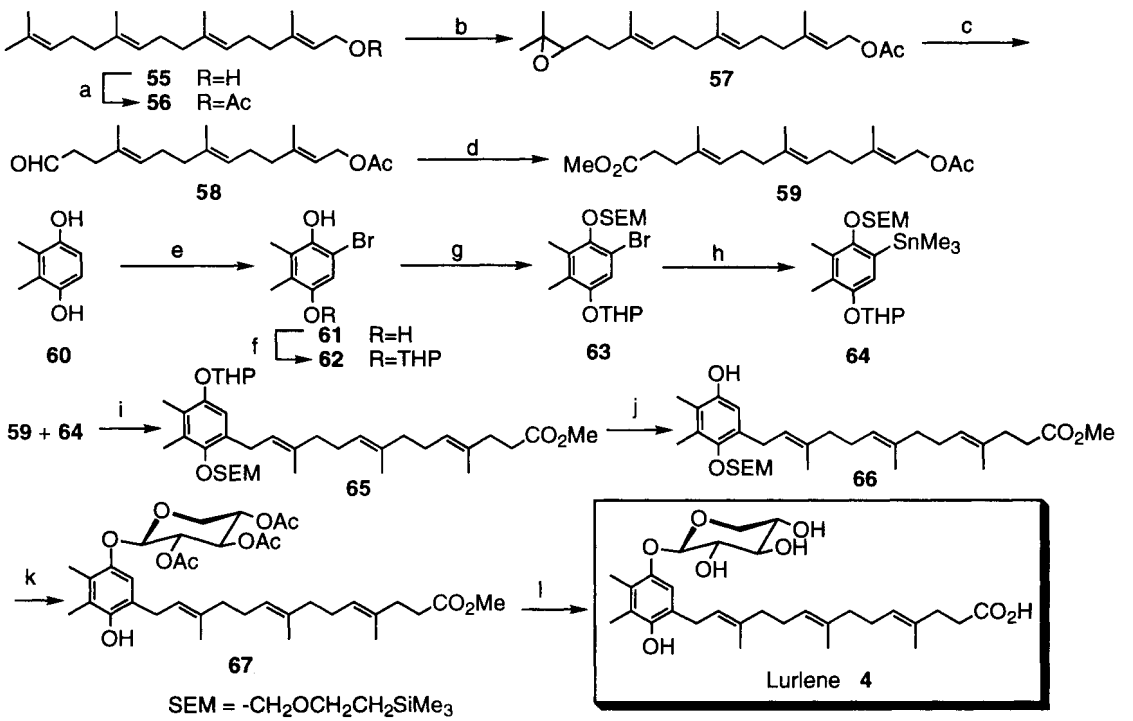

Fig. 9. Synthesis of lurlene **4**.

Reagent : (a) Ac_2O, C_5H_5N (96%). - (b) 1) NBS, aq. DME; 2) K_2CO_3, MeOH; 3) Ac_2O, C_5H_5N (52%). - (c) $HIO_4 \cdot 2H_2O$, Et_2O (78%). - (d) 1) Jones CrO_3, Me_2CO; 2) CH_2N_2, Et_2O (86%). - (e) Br_2, THF (76%). - (f) DHP, TsOH, THF (72%). - (g) SEMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 (92%). - (h) *n*-BuLi, Me_3SnCl, THF (73%). - (i) $Pd(dba)_2$, LiCl , DME (98%). - (j) AcOH/aq. THF (86%). - (k) acetobromo-D-xylose, AgOTf, *N*,*N*,*N'*,*N'*-tetramethylurea, CH_2Cl_2 (The SEM group was removed in the course of this reaction.).- (l) 1) NaOH, aq. MeOH; 2) dil. AcOH (ca. 10% based on **66**).

SYNTHESIS OF THE ANALOGS OF BLATTELLASTANOSIDE A

In 1993, Sakuma and Fukami isolated and identified the arrestant components of the aggregation pheromone of the German cockroach (*Blattella germanica*) as blattellastanosides A **5** and B **76** (37). The correctness of the proposed structures **5** and **76** was confirmed by our synthesis (38). The structures **5** and **76** are quite unique as chlorinated steroidal glucosides with no volatility at all, which means that they are

contact pheromones. Blattellastanoside A **5** is reported to be 70 times more bioactive than B **76** as the arrestant (37).

We synthesized some analogs of blattellastanoside A, and found the fluorinated analog **74** to be more active than the natural **5** (39). Our synthesis of the fluorinated analog **74** is summarized in Fig. 10. The synthesis started from β-sitosterol **68**, and essentially followed the route employed for the synthesis of blattellastanoside A **5**, except that **69** was fluorinated to give **70**. The desired and crystalline analog **74** was obtained via **71**, **72** and **73**. The result of preliminary bioassay is also shown in Fig. 10. The fluorinated analog **74** was more active than the natural pheromone **5**, while the analog **75** with cholestane skeleton was only slightly less active than **5** and more active than blattellastanoside B **76**. The analog **77** without the steroidal side-chain was inactive. The D-galactoside analog **78** as well as the aglycones **79** and **80** were also inactive. We conclude that (i) the steroidal side-chain is required for the bioactivity, and (ii) the D-glucose moiety of the pheromone is necessary and cannot be replaced by D-galactose. It is noteworthy that **74** is more potent than the natural pheromone **5**, since it is generally believed that the natural pheromone is the most suitable one to be perceived by its receptor.

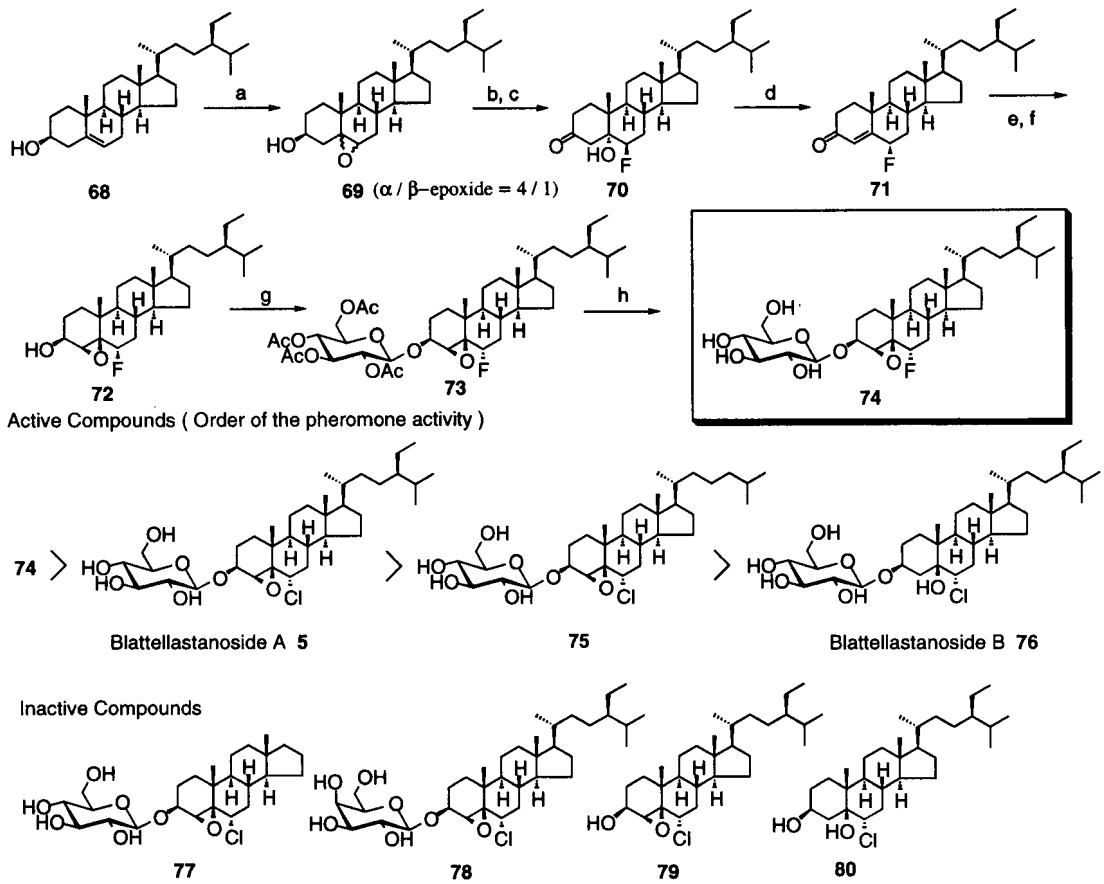

Fig.10. Synthesis and bioactivity of analogs and relatives of blattellastanoside A
Reagents : (a) MCPBA, CH_2Cl_2 (98%). - (b) $BF_3 \cdot OEt_2$, $MgSO_4$, 46% HF, C_6H_6 / Et_2O. - (c) Jones CrO_3, Me_2CO (62% based on **69**). - (d) 37% HCl, $MgSO_4$, $CHCl_3$ (89%). - (e) $LiAl(O\text{-}t\text{-}Bu)_3H$, THF.- (f) MCPBA, CH_2Cl_2 (80%). - (g) acetobromo-D-glucose, $Hg(CN)_2$, C_6H_6 / $MeNO_2$ (68%). - (h) NaOMe, MeOH / THF (67%).

CONCLUSION

Bioorganic chemistry of pheromones has now matured since its birth in 1959 (40). There are, however, many things to be clarified and understood. Organic synthesis will continue to be a useful tool to study chemical communications.

It is my privilege to acknowledge the contribution of my co-workers whose names appear in the references. I thank Dr. H. Takikawa for his help in preparing the camera-ready manuscript.

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