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Recent results in the synthesis of ecologically important bioregulators*

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Abstract: Absolute configuration was established for the following semiochemicals: (*S*)-polyzonimine (**1**), (*S*)-9-methylgermacrene-B (**2**) and (1*S*,3*S*,7*R*)-3-methyl-α-himachalene (**3**). The stereoisomers of 2,6-dimethylheptane-1,7-diol monotetrahydropyranyl ether served as useful building blocks for the synthesis of *syn*- or *anti*-1,5-dimethylated aliphatic pheromones such as **4** and **5**. Synthesis of analogs of the Israeli pine bast scale pheromone **6**, which exhibits both pheromonal and kairomonal activities, enabled us to find a strong pheromone mimic **7** without any kairomonal activity.

INTRODUCTION

Chemical communications among individual organisms in the same species are mediated by pheromones, which have been studied in depth recently [1]. Chemical defense by defense substances or repellents is also a well-known phenomenon to protect an organism from attacks by enemies. These bioactive substances are produced by an individual in a trace amount, and, therefore, a sufficient amount of them must be prepared by synthesis to make their further studies possible. This paper describes our recent results on the synthesis of a defense substance **1** (Fig. 1), pheromones **2**–**6** and pheromone mimics such as **7** to clarify their absolute configuration and bioactivities.

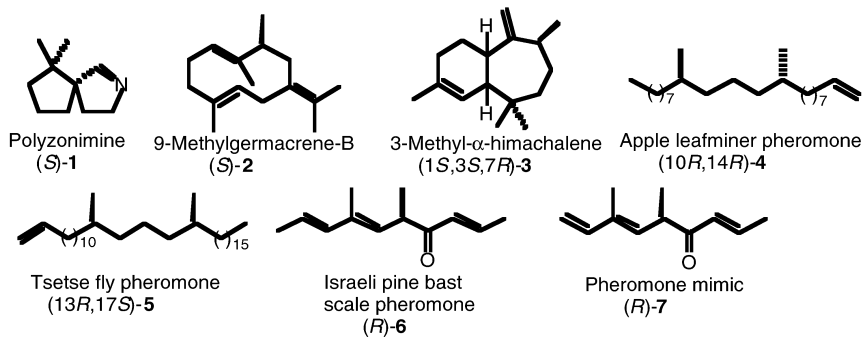

Fig. 1. Structures of the target semiochemicals.

SYNTHESIS AND ABSOLUTE CONFIGURATION OF POLYZONIMINE

Chemical defense against predation by other organisms is an important research subject in chemical ecology as pioneered by Eisner [2]. In 1975, in the course of their studies on compounds from the defen-

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sive glands of a milliped *Polyzonium rosalbum*, Meinwald, Eisner, and their coworkers isolated and identified the following two nitrogen-containing spirocyclic compounds [3,4]. (+)-Polyzonimine (**1**) was isolated as a volatile insect repellent, which acts as a topical irritant to predating insects such as ants and cockroaches [3]. Its structure as monoterpene alkaloid **1** (without assigning absolute configuration) was suggested by the X-ray analysis of a closely related minor component of the secretion, (+)-nitropolyzonamine (**8**) [4,5]. The absolute configuration of **8** was derived from the X-ray analysis of the perchlorate salt of **8**, and shown to be 4*S*,5*R*,6*S* [5]. Because (+)-polyzonimine (**1**) co-occurs with (+)-nitropolyzonamine (**8**), it is highly probable that the former shares the same *S* configuration at the spiro center as that of the latter. However, this must be proved. The structures **1** and **8** proposed for these milliped alkaloids were confirmed by the synthesis of their racemates [3,4,6]. A previous asymmetric synthesis of (+)-**1** with 68% ee could not tell us anything about its absolute configuration [7].

Figure 2 shows our synthesis of the enantiomers of polyzonimine (**1**), and conversion of (+)-**1** to the naturally occurring (+)-nitropolyzonamine [(4*S*,5*R*,6*S*)-**8**] [8]. This synthesis unambiguously determined the absolute configuration of the naturally occurring (+)-**1** as *S*. The key step was the Michael addition of enamine **10** prepared from the known aldehyde **9** to nitroethylene to give **11**, which afforded (+)-**1** of 76% ee via **12** and **13**. The enantiomeric purity of the above (+)-**1** could be enriched by recrystallizing its D-tartrate salt **14** to secure enantiomerically pure (+)-**1**, $[\alpha]_D^{22}$ = +3.3 ($CHCl_3$). Treatment of (+)-**1** with 3-iodo-1-nitropropane in pyridine afforded (4*S*,5*R*,6*S*)-(+)-**8**, mp 69.5–70.5, $[\alpha]_D^{24}$ = +6.1 ($CHCl_3$). Our synthetic enantiomers of polyzonimine (**1**) showed no significant repellent activity against the German cockroach (*Blattella germanica*), but showed oviposition deterrant activity against the webbing clothes moth (*Tineola bisselliella*).

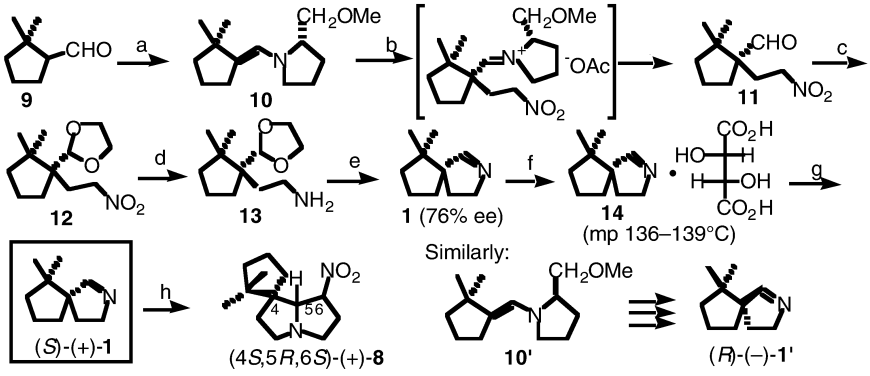

Fig. 2. Synthesis of polyzonimine (**1**) and nitropolyzonamine (**8**).
Reagents: (a) (*S*)-prolinol methyl ether, MS 4A, C_6H_6; (b) i) $AcOCH_2CH_2NO_2$, *N*-ethylmorpholine, MeCN; ii) SiO_2 chromatog.; (c) $HO(CH_2)_2OH$, TsOH, $HC(OEt)_3$ (78% based on **9** via **10**); (d) $LiAlH_4$, THF; (e) 2 M HCl, THF (54% based on **12**); (f) D-tartaric acid (1 eq.), recrystallization from EtOH (23%); (g) K_2CO_3, H_2O; extraction; distillation (44%); (h) $I(CH_2)_3NO_2$, C_5H_5N (34%).

SYNTHESIS AND ABSOLUTE CONFIGURATION OF 9-METHYLGERMACRENE-B AND 3-METHYL-α-HIMACHALENE, THE SANDFLY PHEROMONE

The sandfly *Lutzomyia longipalpis* is the vector of the protozoan parasite *Leishmania chagasi*, the causative agent of leishmaniasis in South and Central America. In 1996, Hamilton *et al*. proposed 9-methylgermacrene-B (**2**, unknown absolute configuration) as the structure of the male sex pheromone of *L. longipalpis* from Lapinha, Brazil [9]. In order to verify the proposed structure, we first synthesized (±)-**2** [10], and then both (*R*)- and (*S*)-**2** were synthesized [11]. The absolute configuration of the natural pheromone was *S* on the basis of gas chromatographic comparison and bioassay [12].

Our synthesis of (*S*)-9-methylgermacrene-B (**2**) is summarized in Fig. 3. The synthesis started from a popular and nonracemic building block, methyl (*R*)-3-hydroxy-2-methylpropanoate (**15**), and the key-step was the intramolecular cyclization of (*S*)-**23** according to the protocol of Takahashi *et al*. [13]. Another critical step was the attachment of the isopropylidene group to (*S*)-**25**, which was achieved by employing samarium and chromium according to Utimoto *et al*. [14]. Although the present 28-step synthesis of (*S*)-**2** from (*R*)-**15** was inefficient (1.3% overall yield), the target pheromone could be obtained with the enantiomeric purity of about 95% ee. Similarly, the unnatural isomer (*R*)-**2′** was synthesized from (*S*)-**15'**. The bioactivity of (*S*)-**2** was demonstrated to be far stronger than that of (*R*)-**2′** [12].

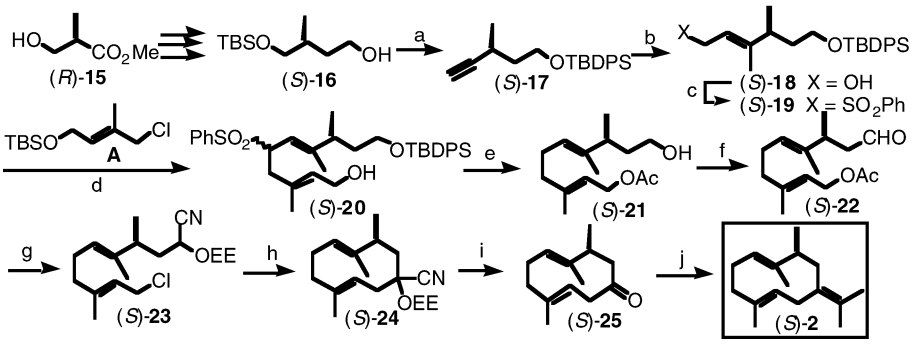

Fig. 3. Synthesis of (*S*)-9-methylgermacrene-B (**2**).
Reagents: (a) i) TBDPSCl, imidazole, DMF; ii) AcOH, THF, H_2O (84%); iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; iv) Ph_3P, CBr_4, CH_2Cl_2; v) *n*-BuLi, Et_2O (78%); (b) i) Me_3Al, Cp_2ZrCl_2, CH_2Cl_2, H_2O; ii) *n*-BuLi, hexane, $(CH_2O)_n$, THF (80%); (c) i) Ph_3P, CCl_4; ii) $PhSO_2Na$, DMF (84%); (d) i) *n*-BuLi, THF, HMPA, **A**; ii) AcOH, THF, H_2O (70%); (e) i) $LiBHEt_3$, $PdCl_2(dppp)$, THF; ii) Ac_2O, C_5H_5N; iii) TBAF, THF (64%); (f) Dess-Martin periodinane, CH_2Cl_2 (85%); (g) i) TMSCN, KCN-18-crown-6; ii) $BnNMe_3F$, THF, H_2O; iii) $EtOCH{=}CH_2$, TsOH; iv) K_2CO_3, MeOH; v) MsCl, LiCl, DMF, *s*-collidine (76%); (h) NaHMDS, THF (53%); (i) PPTS, MeOH, then NaOH aq., Et_2O (50%); (g) CBr_2Me_2, Sm, SmI_2, $CrCl_3$, THF (64%).

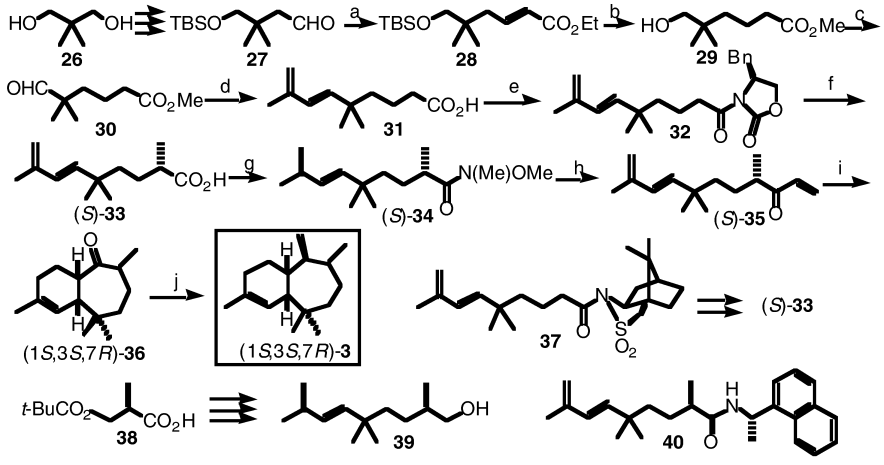

Fig. 4. Synthesis of (1*S*,3*S*,7*R*)-3-methyl-α-himachalene (**3**).
Reagents: (a) $Ph_3P{=}CHCO_2Et$, C_6H_6 (89%); (b) i) Mg, MeOH; ii) HF aq., MeCN (72%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (83%); (d) i) $CH_2{=}C(Me)CH_2PPh_3Cl$, *t*-BuOK, THF; ii) KOH, MeOH (83%); (e) i) PivCl, Et_3N, CH_2Cl_2; ii) (*S*)-4-benzyl-2-oxazolidinone, *n*-BuLi, THF (78%); (f) i) NaHMDS, MeI, THF; ii) LiOH, H_2O_2, aq. THF (64%); (g) MeO(Me)NH•HCl, EDC, *i*-Pr_2NEt, DMAP, CH_2Cl_2 (80%); (h) $CH_2{=}CHMgBr$, THF; (i) i) Et_2AlCl, CH_2Cl_2; ii) MPLC (41%, 2 steps); (j) $Cp_2Ti(Cl)CH_2AlMe_2$ (Tebbe reagent), THF, toluene (70%).

Interestingly, the sandfly *L. longipalpis* from Jacobina, Brazil, employs a different homosesquiterpene, 3-methyl-α-himachalene (**3**, unknown stereochemistry), as the male sex pheromone [15]. Clarification of the relative stereochemistry of the naturally occurring **3** was executed by synthesizing the four stereoisomers of (±)-**3** [16]. One of them, (1*R**,3*R**,7*S**)-**3**, showed MS, ^{1}H NMR and GC retention time identical to those of the natural pheromone [16]. Enantiomer separation of (1*R**,3*R**,7*S**)-**36** was achieved by preparative HPLC on Chiralcel® OD, and the absolute configuration of the resolved enantiomers was assigned on the basis of CD measurements and MM3 calculation [17]. Identity of (1*S*,3*S*,7*R*)-(+)-**3** with the natural pheromone was proved by GC comparison and bioassay [18].

To further confirm the assignment of (1*S*,3*S*,7*R*)-stereochemistry to the naturally occurring pheromone, we synthesized (1*S*,3*S*,7*R*)-**3** as shown in Fig. 4 [17,19]. The key step was the intramolecular Diels-Alder reaction of (*S*)-**35** as catalyzed by diethylaluminum chloride to give (1*S*,3*S*,7*R*)-**36**. The precursor of (*S*)-**35** was the acid (*S*)-**33**, which could be prepared by employing either Evans' asymmetric alkylation reaction [**32** → (*S*)-**33**] or Oppolzer's asymmetric alkylation employing **37**. The *S* configuration of the synthesized (+)-acid **33** was proved unambiguously by converting the (*R*)-acid **38** to (*R*)-alcohol **39** and also by X-ray analysis of **40** [19]. The Diels–Alder adduct (1*S*,3*S*,7*R*)-**36** was converted to (1*S*,3*S*,7*R*)-(+)-3-methyl-α-himachalene (**3**) by treatment with Tebbe reagent. The sandfly pheromone (1*S*,3*S*,7*R*)-**3** (99% ee as determined by GC analysis on Chirasil-DEX®-CB) was obtained in 5.0% overall yield based on **27** (13 steps). These pheromones **2** and **3** may be useful in population control of the sandfly *Lutzomyia longipalpis*.

SYNTHESIS OF PHEROMONES BY EMPLOYING THE BUILDING BLOCKS DERIVED FROM STEREOISOMERS OF 2,6-DIMETHYLHEPTANE-1,7-DIOL

Many insect pheromones are known which possess *syn*- or *anti*- oriented methyl groups at the 1,5-positions of their carbon chains.

As shown in Fig. 5, we developed a route to synthesize (2*R*,6*S*)-*syn*-2,6-dimethylheptane-1,7-diol monotetrahydropyranyl ether (**44**) starting from the commercially available enantiomers of **15** and

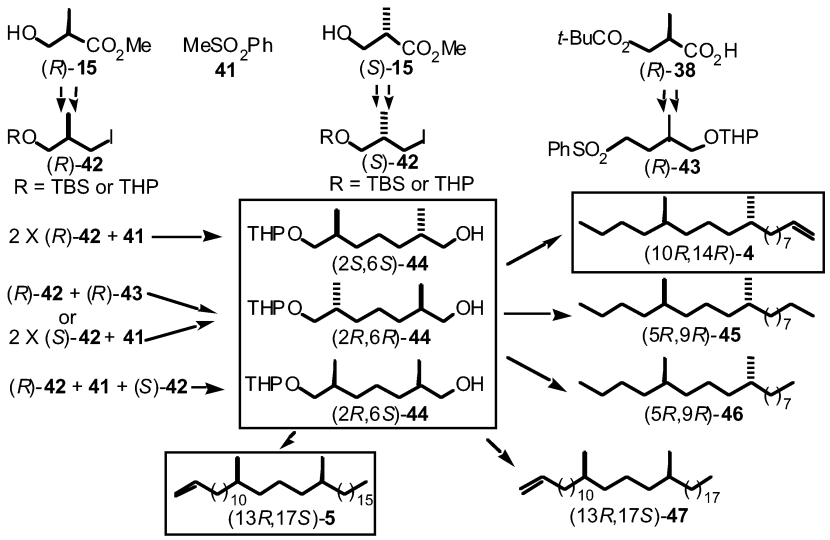

Fig. 5 Synthesis of stereoisomers of the building block **44** and their conversion to the female sex pheromone components **4**, **45**, and **46** of the apple leafminer (*Lyonetia prunifoliella*) and the female contact sex pheromone **5** and **47** of the tsetse fly (*Glossina austeni*).

methyl phenyl sulfone (**41**) [20]. This route enabled us to prepare highly pure (2*R*,6*S*)-**44** (about 100% ee) due to the availability of the highly pure enantiomers of **15**. Similarly, both (2*R*,6*R*)-*anti*- and (2*S*,6*S*)-*anti*-**44** were also prepared starting from (*R*)- or (*S*)-**42** and **41** or (*R*)-**43**. In preparing **44**, two building blocks **42** were connected by employing **41** as the linchpin [21]. For the preparation of (2*R*,6*R*)-**44**, (*R*)-**43** and (*R*)-**42** were connected to give the same product as that resulting from 2 eq. of (*S*)-**42** and 1 eq. of **41** [21]. These stereoisomers of **44** were converted to the female sex pheromone components **4**, **45,** and **46** of the apple leafminer (*Lyonetia prunifoliella*) [21], and also to the female contact sex pheromone **5** and **47** of the tsetse fly, *Glossina austeni* [20]. Three stereoisomers of **44** were thus shown to be very useful building blocks for the synthesis of 1,5-dimethylated aliphatic pheromones.

PHEROMONAL AND KAIROMONAL ACTIVITIES CAN BE SEPARATED: SYNTHESIS AND BIOACTIVITY STUDIES OF PINE BAST SCALE SEX PHEROMONES AND THEIR ANALOGS

Pine bast scales of the genus *Matsucoccus* are troublesome pests in pine forests [22]. As shown in Fig. 6, three of their pheromones were recently identified. An interesting aspect of their bioactivity is the fact that the pheromone **6** of the Israeli pine bast scale, *M. josephi*, is also the kairomone employed by their predator, *Elatophilus hebraicus*. Although two other pheromones (that of *M. feytaudi* in Western Europe and that of *M. matsumurae* in the Far East) are totally inactive against *M. josephi*, they are active as the kairomone against *E. hebraicus* which is absent in both Western Europe and the Far East. It therefore seems that the kairomone receptor of *E. hebraicus* is much less specific than the pheromone receptors of the pine bast scales.

We became interested to know whether there can be a pheromone mimic which is devoid of the kairomonal activity in the presence of the pheromonal activity. If we can make it, it will not attract the beneficial predator (*E. hebraicus*) and only attract the harmful pine bast scale (*M. josephi*). This may be possible, considering the recent success in developing various pheromone mimics [23]. Synthesis and biological evaluation of seven pheromones and pheromone mimics (**6**, **48**, **49**, **50**, **51**, **52**, and **7**) revealed the fact that compound **7** shows strong pheromonal activity against *M. josephi* with no

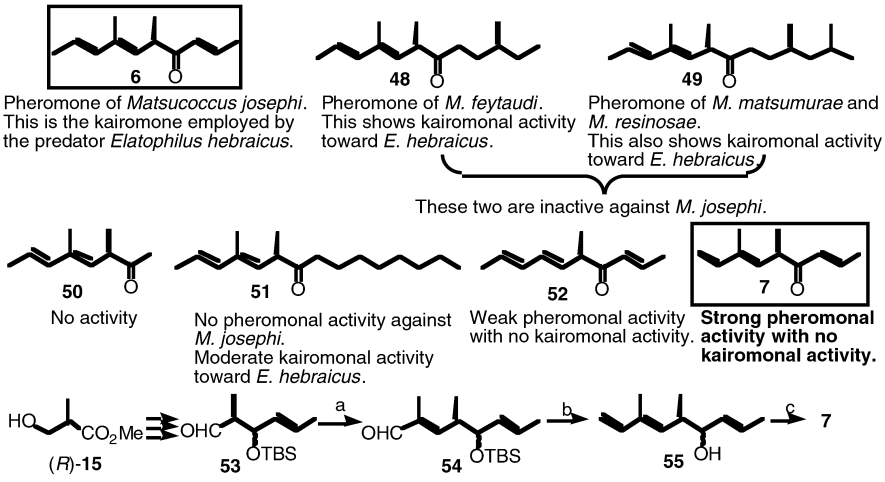

Fig. 6. Bioactivities of the pine bast scale pheromones and their analogues. The synthetic route to analogue **7** is also shown.

Reagents: (a) i) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6 (32%); ii) *i*-Bu_2AlH, hexane, CH_2Cl_2; iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) $Ph_3P(Me)Br$, *n*-BuLi, THF (71% based on **54**); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (55%).

kairomonal activity against *E. hebraicus* [24]. Thus, pheromonal and kairomonal activities could be separated. The mimic **7** may therefore be useful as a population monitoring agent against *M. josephi* without causing catches of its predator, *E. hebraicus*. The synthesis of **7** from **15** is summarized in the bottom part of Fig. 6.

CONCLUSION

Recent remarkable progress in chemical ecology, especially in pheromone science [25], has made it possible to employ some pheromones in practical pest control. Synthesis of semiochemicals or ecologically important bioregulators will continue to firmly establish their structures and stereochemistry.

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REFERENCES

1. W. Francke and S. Schulz. In *Comprehensive Natural Products Chemistry*, K. Mori (Ed.), Vol. 8, pp. 197–261, Elsevier, Amsterdam (1999).
2. T. Eisner. In *Chemical Ecology*, E. Sondheimer and J. B. Simeone (Eds.), pp. 157–217, Academic, New York (1970).
3. J. Smolanoff, A. F. Kluge, J. Meinwald, A. T. McPhail, R. W. Miller, K. Hicks, T. Eisner. *Science* **188**, 734 (1975).
4. J. Meinwald, J. Smolanoff, A. T. McPhail, R. W. Miller, T. Eisner, K. Hicks. *Tetrahedron Lett.* 2367 (1975).
5. R. W. Miller and A. T. McPhail. *J. Chem. Res. (S)* 76 (1978).
6. K. D. Hutchinson, J. V. Silverton, J. W. Daly. *Tetrahedron* **50**, 6129 (1994).
7. T. Sugahara, Y. Komatsu, S. Takano. *J. Chem. Soc., Chem. Commun.* 214 (1984).
8. K. Mori and Y. Takagi. *Tetrahedron Lett.* **41**, 6623 (2000).
9. J. G. C. Hamilton, G. W. Dawson, J. A. Pickett, *J. Chem. Ecol.* **22**, 1477 (1996).
10. S. Muto, Y. Nishimura, K. Mori. *Eur. J. Org. Chem.* 2159 (1999).
11. S. Kurosawa and K. Mori. *Eur. J. Org. Chem.* 955 (2000).
12. J. G. C. Hamilton, A. M. Hooper, H. C. Ibbotson, S. Kurosawa, K. Mori, S. Muto, J. A. Pickett. *Chem. Commun.* 2335 (1999).
13. T. Takahashi, H. Nemoto, J. Tsuji. *Tetrahedron Lett.* **24**, 2005 (1983).
14. S. Matsubara, K. Horiuchi, T. Takai, K. Utimoto. *Chem. Lett.* 259 (1995).
15. J. G. C. Hamilton, G. W. Dawson, J. A. Pickett. *J. Chem. Ecol.* **22**, 2331 (1996).
16. S. Sano and K. Mori. *Eur. J. Org. Chem.* 1679 (1999).
17. K. Mori, T. Tashiro, S. Sano. *Tetrahedron Lett.* **41**, 5243 (2000).
18. J. A. Pickett, J. G. C. Hamilton, A. M. Hooper, T. Tashiro, K. Mori. *Chem. Commun.* To be submitted.
19. T. Tashiro, M. Bando, K. Mori. *Synthesis.* 1852 (2000).
20. T. Kimura, D. A. Carlson, K. Mori. *Eur. J. Org. Chem.* In press.
21. Y. Nakamura and K. Mori. *Eur. J. Org. Chem.* 2745 (2000).
22. E. Dunkelblum. In *Pheromones of Non-Lepidopteran Insects Associated with Agricultural Plants*, J. Hardie and A. K. Minks (Eds.), pp. 251–276, CABI Publishing, Wallingford (1999).
23. M. Renou and A. Guerrero. *Annu. Rev. Entomol.* **48**, 605 (2000).
24. S. Kurosawa, M. Takenaka, E. Dunkelblum, Z. Mendel, K. Mori. *ChemBioChem* **1**, 56 (2000).
25. K. Mori. *Acc. Chem. Res.* **33**, 102 (2000).