A SYNTHETIC APPROACH TOWARDS THE IDENTIFICATION OF PERIPLANETA SEX PHEROMONES

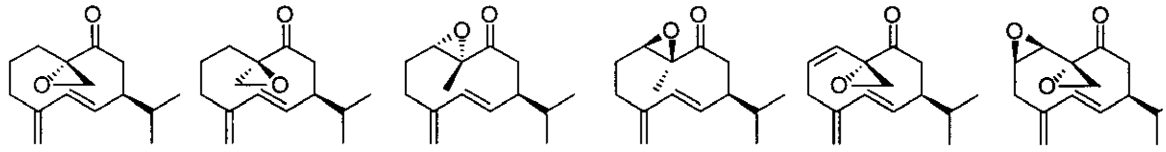
Hajime Iwamoto[a], Takeo Harada[a], Takashi Takahashi,[a]* and Shozo Takahashi[b]

[a]Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152,
Japan
[b]Faculty of Agriculture, Kyoto University, Sakyo-ku, Kyoto 606, Japan

Abstract – Syntheses of the proposed structure of periplanone J (**3**) and its diastereomer (**4**), and the discussion on the true structure of PJ based on spectral analysis of **3**,**4** and the natural PJ are described.

Periplanone A (PA) (**5**) and periplanone B (PB) (**6**) are the very potent sex attractant and excitation pheromones of the American cockroach *Periplaneta americana*, which are also very effective with other species of cockroach, such as *Periplaneta japonica*, *Periplaneta brunnea* and *Periplaneta orientalis*. PA and PB were first isolated by the Persoons group from *Periplaneta americana* in 1974,[1] and tentative structures were proposed.[2] Since then, there have been quite a number of synthetic and biological studies reported, due to the unique biological activities and minute amount of endogenous material.[3] The proposed structure of PB was finally established to be **6** by Still and Nakanishi in 1979.[4] On the other hand, the proposed structure of PA was corrected to be **5** based on its isolation[5] and synthesis.[6]

Periplanone J (PJ) is a newly isolated sex pheromone of the Japanese cockroach *Periplaneta japonica*, isolated by the Kyoto group in 1989.[7] Due to the limited amount of isolated PJ, NMR spectra could not be obtained. The tentative structure shown in **1** was suggested by comparison of the mass spectra, IR spectra, and biological activities with those of PA and PB. As our previous work[8] has shown that both PJ **1** and its epimer (**2**) are not identical to the natural PJ, the new structure (**3**) and (**4**) were proposed as the true PJ structure. Thus, the syntheses of both compound (**3**) and (**4**) are required to confirm the true structure of PJ. In this paper, we describe the syntheses of the proposed periplanone J (**3**) and (**4**).

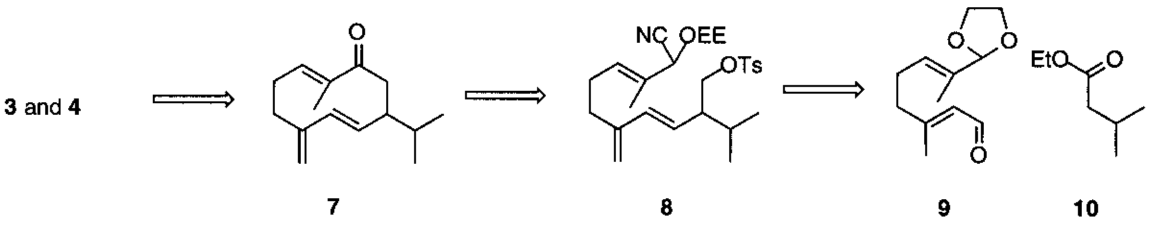


1 **2** **3** **4** PA (**5**) PB (**6**)

candidates of PJ

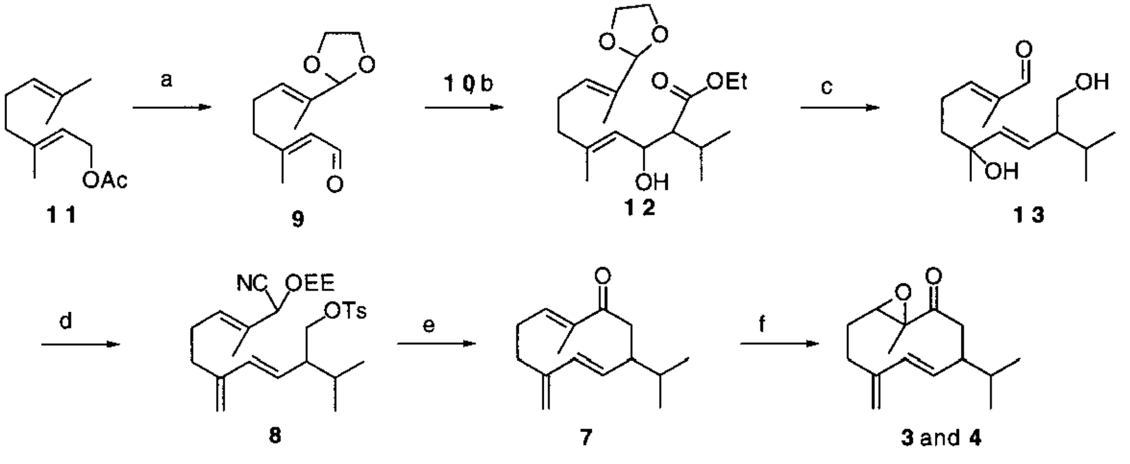
Figure 1

Three problems were recognized in synthesizing the proposed structure (**3**) and its diastereomer (**4**). 1) the rapid introduction of the carbon chain, 2) the efficient formation of the ten-membered ring skeleton, 3) and the introduction of the α-epoxy ketone. Our synthetic plan (Scheme 1) involves three key steps corresponding to the above problems. 1) Aldol reaction between **10** and the aldehyde (**9**), 2) intramolecular alkylation of the cyanohydrin ether (**8**),[9] 3) conjugated epoxidation of the enone (**7**).



Scheme 1

The actual synthesis was performed as shown in Scheme 2. The citral derivative (**9**) was obtained from geranyl acetate; allylic oxidation (SeO_2; MnO_2; 42%), acetalization (ethylene glycol; H^+), hydrolysis of the acetate (K_2CO_3, MeOH) and oxidation (MnO_2, 57% yield in 3 steps). The aldol reaction between **9** and **10** was carried out in THF at -78 °C using lithium diisopropyl amide. Reduction of ester (**12**) ($LiAlH_4$) was followed by deprotection of the acetal (1 M HCl, 60% yield in 3 steps) to give the diol aldehyde (**13**), which was formed by allylic rearrangement under acidic conditions. Selective tosylation of the homoallylic alcohol in **13** (TsCl, pyridine, 0 °C, 77%) and subsequent transformation of the aldehyde into the cyanohydrin ether in 3 steps,[9] (TMS-CN, 18 crown 6·KCN, $ZnCl_2$, 1 M HCl/THF=1:9, ethyl vinyl ether/benzene/CH_2Cl_2/*p*-TsOH at 0 °C) provided the protected cyanohydrin (**8**). During the protection of the alcohol, dehydroxylation of the tertiary alcohol afforded the three olefin isomers. The desired exo olefin was obtained 17% overall yield, and two diastereomixtures of the endo olefin was obtained in 26% overall yield. Cyclization[9] of **8** was carried out using 10 equiv. of $LiN(TMS)_2$ in dioxane at 70 °C, followed by acid and base treatment afforded the key intermediate enone (**7**) in 54% overall yield. The epoxidation of **7** with an excess of *t*-BuOOK in THF at 0 °C provided two stereoisomers of PJ in a ratio of



Scheme 2: a) SeO_2, salicylic acid, TBHP, CH_2Cl_2; MnO_2, PhH, CH_2Cl_2, 42% in 2 steps; cat. *p*-TsOH, ethyleneglycol; K_2CO_3, MeOH; MnO_2, PhH, CH_2Cl_2, 57% in 3 steps; b) LDA, -78 °C, THF; c) $LiAlH_4$, THF; 1 M HCl, THF, 60% in 3 steps; d) TsCl, pyridine, $CHCl_3$, 77%; TMS(CN), cat. 18-crown-6, KCN, $ZnCl_2$; 1 M HCl, THF; cat. *p*-TsOH, ethyl vinyl ether, 17% overall yield; e) $LiN(TMS)_2$, dioxane, 70 °C; cat. *p*-TsOH, MeOH; 2% aq. NaOH, ether, 54% from **8**; f) *t*-BuOOK, THF, 0°C, 58%.

72:28 (58% combined yield). The stereochemistries of the epoxides have not been determined; NMR(270 MHz) major isomer (PJa), 6.31 (d, 16.5 Hz, 1 H), 5.47 (dd, 9.9, 16.5 Hz, 1 H), 5.04 (s, 1 H), 4.99 (s, 1 H), 3.01 (dd, 8.1, 12.4 Hz, 1 H), 2.89 (dd, 1.5, 10.0 Hz, 1 H), 2.57 (dd, 1.0 10.0 Hz, 1 H), 2.5 - 2.3 (m, 4 H), 1.7 - 1.5 (m, 2 H), 1.39 (s, 3 H), 0.98 (d, 6.6 Hz, 3 H), 0.87 (d, 6.6 Hz, 3 H), the minor isomer (PJb), 5.87(d, 15.5 Hz, 1 H), 5.68(dd, 10.2, 15.5 Hz, 1 H), 4.99(s, 1 H), 4.93(s, 1 H), 2.93 (dd, 11.2, 11.2 Hz, 1 H), 2.68 (dd, 2.6, 10.6 Hz), 2.6 - 2.5 (m, 2 H), 2.4 - 2.2 (m, 1 H), 2.2 - 2.0 (m, 2 H), 1.7 - 1.2 (m, 2 H), 1.60 (s, 3 H), 0.94 (d, 6.6 Hz, 3 H), 0.92 (d, 6.6 Hz, 3 H). Conformational analyses[10] of **7** and its *E*, *Z* - enolate derivative showed that the epoxides (**3**) and (**4**) were formed in the ratio of 84:16.

Although the correspondence between the synthetic PJ (**3**, **4**) and the proposed structures (**3**, **4**) has not yet been determined, careful comparison of the mass spectra of synthesized products shows one major difference. The m/z=219(M^+-15) peak observed from the natural PJ was not observed in the synthetic PJs, and m/z=216(M^+-18) of the synthetic PJs was not observed in the natural PJ. Based on this information, it is concluded that neither of the synthetic PJs are structurally identical to the natural PJ.[11]

Moreover, we examined the biological activities toward the various species of cockroach to verify the difference between natural PJ and synthetic PJs (Table 1). One of the synthetic PJs (PJa) is approximately 10^7 and the other synthetic PJ (PJb) is approximately 10^9 less effective against *Periplaneta japonica* when compared to the natural PJ.

Table 1 Comparison of pheromone activity PJs toward males of *P. americana* and *P. japonica*.

		DOSE (g)					
		10^{-11}	10^{-10}	10^{-9}	10^{-8}	10^{-7}	10^{-6}
isolated PJ	*P. japonica*	+++	+++				
	P. americana	+++	+++				
PJ(a)	*P. japonica*					–	++
	P. americana					–	++
PJ(b)	*P. japonica*					–	–
	P. americana					–	–

Colonies of *Periiplaneta americana* and *Periplaneta japonica* were fed with mouse chow and water, and maintained in a light cycle of 12L-12D at 25 + 2 ℃. After imaginal ecdysis, about 100 males were isolated in a sheltered container (34x79x27 cm). Two weeks later, samples to be tested were put on a glass plate (2x2 cm) and placed 10 cm away from the shelter.

+++	30 males responded immediately
++	more than 10 males responded in less than 30 seconds.
+	less than 10 males responded in 1 minutes

Thus, proposed PJ structure (**3**) and (**4**) were synthesized, and both structures were determined the different structure of PJ. Further study on the elucidation of true structure of PJ is correctly under investigation in our laboratory.

REFERENCE AND NOTES

1 C. J. Persoons, F. J. Ritter, and W. J. Lichtendonk, *Proc. Kon. Akad. Wetensch.*, 1974, **C77**, 201.

2 C. J. Persoons, P. E. J. Verwiel, F. J. Ritter, and W. J. Nooijen, *J. Chem. Ecol.*, 1982, **8**, 439; C. J. Persoons, P. E. J. Verwiel, F. J. Ritter, E. Talman, P. J. F. Nooijen, and W. J. Nooijen, *Tetrahedron Lett.*, 1976, 2055.

3 S. Takahashi, and C. Kitamura, *Proc. Symp. Insect Pheromones Their Appl.*, 1976, **77** ,1976; E. Talman, P. E. J. Verwiel, F. J. Ritter, and C. J. Persoons, *Isr. J. Chem.*, 1978, **17**, 227; S. L. Schreiber, and C. Santini, *J. Am. Chem. Soc.*, 1984, **106**, 4038; H. Hauptmann, G. Muhlbauer, and N. P. C. Walker, *Tetrahedron Lett.*, 1986, **27**, 1315; T. Takahashi, Y. Kanda, H. Nemoto, K. Kitamura, J. Tsuji, and Y. Fukazawa, *J. Org. Chem.*, 1986, **51**, 3394; T. Kitahara, M Mori, K. Koseki, and K. Mori, *Tetrahedron Lett.*, 1986, **27**, 1343; Y. Shizuri, K. Matsunaga, and S. Yamamura, *Tetrahedron Lett.*, 1989, **30**, 3693.

4 W. C. Still, *J. Am. Chem. Soc.*, 1979, **101**, 2493; M. A. Adams, K. Nakanishi, W. C. Still, E. V. Arnold, J. Clary, and C. J. Persoons, *J. Am. Chem. Soc.*, 1979, **101**, 2495.

5 H. Hauptmann, G. Mühlbauer, and H. Sass, *Tetrahedron Lett.*, 1986, **27**, 6189; C. Nishino, S. Manabe, K. Kuwabara, R. Kimura, and H. Takayanagi, *Insect Biochem.*, 1983, **13**, 65; C. Nishino, K. Kobayashi, M. Fukushima, M. Imanari, K. Nojima, and S. Kohno, *Chem. Lett.*, 1988, 517.

6 H. Hauptmann, G. Mühlbauer, and H. Sass, *Tetrahedron Lett.*, 1986, **27**, 6189; T. L. Macdonald, V. M. Delahunty, and J. S. Sawer, *Heterocycles*, 1987, **25**, 305; T. Takahashi, Y. Yamashita, T, Doi, and J. Tsuji, 30th Symposium on The Chemistry of Natural Products Symposium Papers, 1988, 410; S. Takahashi, H. Takegawa, T. Takahashi, and T. Doi, *J. Pesticide Sci.* 1988, **13**, 501; Y. Shizuri, K. Matsunaga, and S. Yamamura, *Tetrahedron Lett.*, 1989, **30**, 3693; K. Mori, S, Kuwahara, *Tetrahedron,* 1990, **46**, 8083.

7 H. Takegawa and S. Takahashi, *Appl. Ent. Zool*, 1989, **24**, 435.

8 T. Harada and T. Takahashi, *Tetrahedron Lett.*, 1992, **33**, 369.

9 T. Takahashi, T. Nagashima, and J. Tsuji, *Tetrahedron Lett.*, 1981, **22**, 1359.

10 Stereoselectivity of epoxdation can be predicted using confomational analysis of 10-membered enone: T. Takahashi, Y. Yamashita, T. Doi, and J. Tsuji, *J. Org. Chem.*, 1989, 54, 4274.

11 Assuming from the fragmentation pattern of MS spectra, the true structure corresponds to one of the geometrical isomers of epoxide.

Received, 1st May, 1997