SYNTHETIC APPROACH TO IDENTIFICATION OF PERIPLANETA SEX PHEROMONES

Takeo Harada and Takashi Takahashi * Tokyo Institute of Technology, Meguro, Tokyo 152, JAPAN

Shozo Takahashi Faculty of Agriculture, Kyoto University, Sakyo-ku, Kyoto 606, JAPAN

SUMMARY: Syntheses of the proposed structure of periplanone J (1) and its epimer 2, and the discussion on the true structure of PJ based on the spectral study of 1,2 and the natural PJ are described.

Periplanone A (PA) (3) and periplanone B (PB) (4) are the very potent sex attractant and excitation pheromone of American cockroach *Periplaneta americana*, and are also very effective to the other species of cockroach, such as *Periplaneta japonica*, *Periplaneta brunnea* and *Periplaneta orientalis*. PA and PB were first isolated by Persoons group in 1974^{1}). And the structures of PA and PB were proposed by the same group in 1982^{2a} and 1976^{2b} respectively. Since then, there have been quite a number of synthetic and biological studies reported due to its unique biological activities and minute amount of storage.³⁾ The proposed structure of PB was finally established to be 4 by Still's synthesis in $1979.^{4)}$ On the other hand, the proposed structure of PA was recently corrected to be 3 based on its isolation⁵⁾ and the synthesis.⁶⁾

Periplanone J (1) is a newly isolated sex pheromone of the Japanese cockroach *Periplaneta japonica*, by Kyoto group in 1989.⁷) But the isolated amount of PJ was not enough for obtaining the NMR spectra. The tentative structure shown in 1 was suggested from the comparison of the mass spectra, IR spectra, and its biological activities with those of PA and PB. Thus, the syntheses of both PJ 1 and its epimer 2 are essential for elucidating the true structure of PJ. In this paper we describe non-stereoselective syntheses of the proposed periplanone J 1 and its isomer 2.



We have recognized three problems toward the convenient synthesis of the proposed structure 1 and its epimer 2 which are 1) the selective construction of diene system, 2) the efficient formation of ten-membered skeleton, 3) the introduction of epoxy ketone. Our synthetic plan (scheme 1) involves three key steps corresponding to those problems, 1) Wittig reaction of 7 with the aldehyde 8, 2) intramolecular alkylation of the cyanohydrin ether $6,^{8)}$ 3) non-stereoselective epoxidation of the enone 5.



The actual synthesis was performed as shown in scheme 2. Alkyaltion of 1,3-dibromopropane with dimethyl malonate using K₂CO₃ in acetone reflux gave the tetraester **9** in 80% yield. Reduction of the sodium dienolate of **9**, generated with NaH in THF, with LiAlH4 provided the diol **10** in 70% yield. Monoprotection of **10** (0.3 equiv. DHP/CH₂Cl₂/PPTS; 70% yield in 3 times of recycle), followed by bromination of the resulting alcohol in two steps (MsCl, NEt3, excess LiBr/THF at r.t.) afforded the allyl bromide **11** in 85% yield. Reaction of **11** with triphenylphosphine in acetonitrile reflux gave the Wittig salt **7** in 50% yield after reprecipitation from Et₂O. The aldehyde **8** was prepared in the following way. Alkylation of 2iodopropane with dimethyl malonate using NaH in THF provided the diester **12** in 91 % yield. Complete reduction of **12** with LiAlH4 (58% yield), and partial protection of the resulting diol **13** using 0.3 equiv. of dihydropyrane gave the monoalcohol **14** in 60% yield after 3 times of recycle. Swern oxidation of **14** afforded the aldehyde **8** in 66% yield. No formation of Z olefin was observed. Deprotection of the THP groups in **15** (p-TsOH in MeOH), selective oxidation of the allylic alcohol in **16** with MnO₂, and tosylation of the homo allylic alcohol in **16** (TsCl, Py, O °C)



afforded the aldehyde 17 in 67% overall yield. Transformation of the aldehyde into the cyanohydrin ether in 3 steps,⁸⁾ (TMS-CN, 18 crown 6.KCN, 1N-HCl/THF=1:9, ethyl vinyl ether/benzene/PPTS at r.t.) gave the protected cyanohydrin 6 in 68% overall yield. Cyclization⁸⁾ of 6 was carried out under 10 equiv. of LiN(TMS)2 in dioxane at 80-100 °C, followed by acid treatment and base treatment afforded the key intermediate enone 5 in 50% overall yield; NMR(200MHz) 5.83(d, 15.8Hz), 5.61(d, 1.8Hz), 5.519(s), 5.45(dd, 10.6Hz, 15.8Hz), 4.86(s), 4.85(s). The epoxidation of 5 with the excess amount of 'BuOOK in THF at 0°C provided the both stereo isomers of PJ 1 and 2 in the ratio of 1:1(50% combined yield). Stereochemistries of the epoxide in 1 and 2 have not been determined; NMR(500 MHz) one isomer (PJa), 6.08(d, 15.87Hz), 5.63(dd, 9.28, 15.87Hz), 4.81(s), 4.77(s), 2.87(d, 4.88Hz), 2.23(d, 4.88Hz), the other isomer (PJb), 5.91(d, 16.1Hz), 5.83(dd, 10.1, 16.1Hz), 4.78(s), 2.67(d, 4.88Hz), 2.64(d, 4.88Hz).

Although the correspondence between synthetic PJ 1, 2 and proposed structure 1, 2 has not yet been determined, the careful comparison of mass spectra of synthesized products shows one major difference in which the existence of $m/z = 219(M^+-15)$ of the natural PJ was not observed in the synthetic PJs, and m/z=203 of the synthetic PJs was not observed in the natural PJ. It should be concluded that neither of synthetic PJs are structurally identical to the natural PJ.9)

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 10³ and the other synthetic PJ (PJb) is approximately 10⁸ less effective to the Periplaneta japonica when compared to the natural PJ. But concerning the dose, the synthetic PJs still possess quite strong pheromone activity. It is worth remarking that all periplanones (PA, PB and the proposed PJ) show pheromone activity toward the same species of cockroach such as Periplaneta americana and Periplaneta japonica. Concerning the similarity of their global minima (fig.2), the existence of the close relationships between conformation and the biological activity is suggested.







PA population 93%

PB population 99%

PJ population 53%

fig. 2

	10 waru 1		.umericu	intu and	I .juponi			
		DOSE(g)						
		10 ¹³	1012	1011	1010	109	108	107
РА	P.japonica			-	~	-	+	+
	P.americana			+ +	++	+++	+++	+++
РВ	P.japonica	+	++	+++	+++			
	P.americana	+++	+++	+++	+++			
isolated PJ	P.japonica	+++	+++	+++	+++			
	P.americana	+	+++	+++	+++			
PJ(a)	P.japonica	-	-	-	-	+	++	+++
	P.americana	-	-	-	+	+ +	++	+++
PJ(b)	P.japonica							+
	P.americana						++	++

Comparison of pheromone activity . PA, PB, PJs toward males of *P.americana* and *P.japonica*.

Colonies of *Periiplaneta americana* and *Periplaneta japonica* were fed on a mouse food and water, and maintained in a light cycle of 12L-12D at 25 ± 2 °C. 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

Reference and Notes

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- 9) Assuming from the fragmentation pattern of mass spectra, the true structure corresponds to one of the geometrical isomers of olefin.

(Received in Japan 18 October 1991)

Table 1