

## A SYNTHETIC APPROACH TOWARDS THE IDENTIFICATION OF PERIPLANETA SEX PHEROMONES

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**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,<sup>1</sup> and tentative structures were proposed.<sup>2</sup> 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.<sup>3</sup> The proposed structure of PB was finally established to be **6** by Still and Nakanishi in 1979.<sup>4</sup> On the other hand, the proposed structure of PA was corrected to be **5** based on its isolation<sup>5</sup> and synthesis.<sup>6</sup>

Periplanone J (PJ) is a newly isolated sex pheromone of the Japanese cockroach *Periplaneta japonica*, isolated by the Kyoto group in 1989.<sup>7</sup> 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<sup>8</sup> 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**).

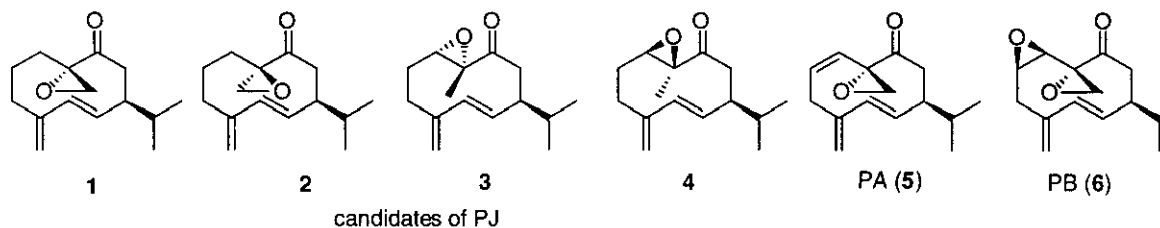
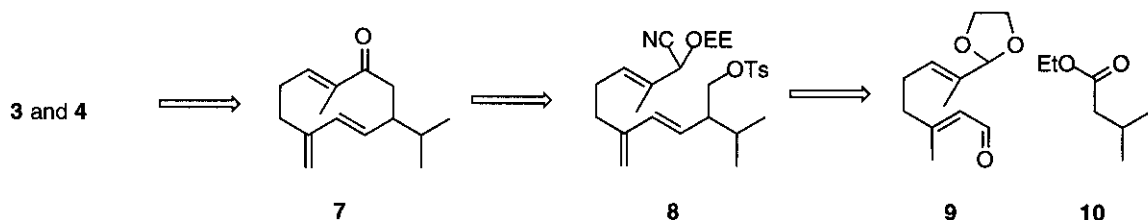


Figure 1

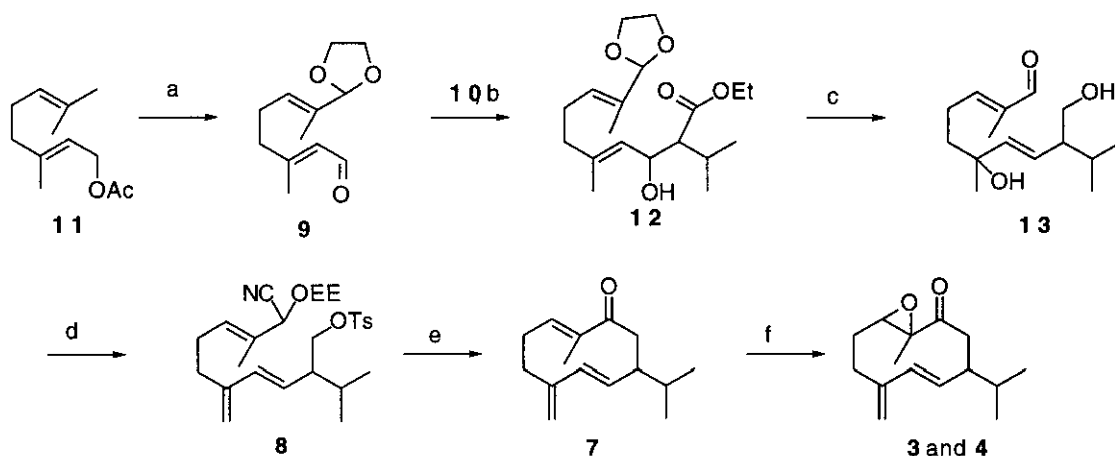
Three problems were recognized in synthesizing the proposed structure (**3**) and its diastereomer (**4**). 1) the rapid introduction of the carbon chain, 2) the efficient formation of the ten-membered ring skeleton, 3) and

the introduction of the  $\alpha$ -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**),<sup>9</sup> 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 ( $\text{SeO}_2$ ;  $\text{MnO}_2$ ; 42%), acetalization (ethylene glycol;  $\text{H}^+$ ), hydrolysis of the acetate ( $\text{K}_2\text{CO}_3$ , MeOH) and oxidation ( $\text{MnO}_2$ , 57% yield in 3 steps). The aldol reaction between **9** and **10** was carried out in THF at  $-78^\circ\text{C}$  using lithium diisopropyl amide. Reduction of ester (**12**) ( $\text{LiAlH}_4$ ) 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** ( $\text{TsCl}$ , pyridine,  $0^\circ\text{C}$ , 77%) and subsequent transformation of the aldehyde into the cyanohydrin ether in 3 steps,<sup>9</sup> ( $\text{TMS-CN}$ , 18 crown 6·KCN,  $\text{ZnCl}_2$ , 1 M HCl/THF=1:9, ethyl vinyl ether/benzene/ $\text{CH}_2\text{Cl}_2$ / $p$ -TsOH at  $0^\circ\text{C}$ ) 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<sup>9</sup> of **8** was carried out using 10 equiv. of  $\text{LiN}(\text{TMS})_2$  in dioxane at  $70^\circ\text{C}$ , 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  $0^\circ\text{C}$  provided two stereoisomers of PJ in a ratio of



Scheme 2: a)  $\text{SeO}_2$ , salicylic acid, TBHP,  $\text{CH}_2\text{Cl}_2$ ;  $\text{MnO}_2$ , PhH,  $\text{CH}_2\text{Cl}_2$ , 42% in 2 steps; cat.  $p$ -TsOH, ethyleneglycol;  $\text{K}_2\text{CO}_3$ , MeOH;  $\text{MnO}_2$ , PhH,  $\text{CH}_2\text{Cl}_2$ , 57% in 3 steps; b) LDA,  $-78^\circ\text{C}$ , THF; c)  $\text{LiAlH}_4$ , THF; 1 M HCl, THF, 60% in 3 steps; d)  $\text{TsCl}$ , pyridine,  $\text{CHCl}_3$ , 77%;  $\text{TMS}(\text{CN})$ , cat. 18-crown-6, KCN,  $\text{ZnCl}_2$ ; 1 M HCl, THF; cat.  $p$ -TsOH, ethyl vinyl ether, 17% overall yield; e)  $\text{LiN}(\text{TMS})_2$ , dioxane,  $70^\circ\text{C}$ ; cat.  $p$ -TsOH, MeOH; 2% aq. NaOH, ether, 54% from **8**; f)  $t$ -BuOOK, THF,  $0^\circ\text{C}$ , 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<sup>10</sup> 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.<sup>11</sup>

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*.

		D O S E (g)					
		$10^{-11}$	$10^{-10}$	$10^{-9}$	$10^{-8}$	$10^{-7}$	$10^{-6}$
isolated PJ	<i>P. japonica</i>	+++	+++				
	<i>P. americana</i>	+++	+++				
PJ(a)	<i>P. japonica</i>					-	++
	<i>P. americana</i>					-	++
PJ(b)	<i>P. japonica</i>					-	-
	<i>P. americana</i>					-	-

Colonies of *Periplaneta americana* and *Periplaneta japonica* were fed with mouse chow and water, and maintained in a light cycle of 12L-12D at  $25 \pm 2$  °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

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.

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Received, 1st May, 1997