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SHORT STEP-SYNTHESIS AND BIOLOGICAL ACTIVITY OF HAUPTMANN'S PERIPLANONE A AND ITS STEREOISOMER

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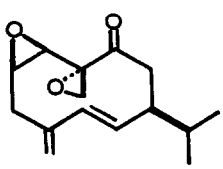
Summary: Hauptmann's periplanone A and its stereoisomer as a racemic form have been synthesized from germacrene-D in 8 steps. On the basis of male electroantennogram (EAG) responses, the former has been proved to enter into the periplanone A receptor, but not into the periplanone B receptor. The stereoisomer, which has been synthesized by Macdonald et al., shows no EAG response. Finally, acid-catalyzed cyclization of Hauptmann's periplanone A has not afforded Persoons' periplanone A, but the known hydroazulenone.

Two sex pheromones of the American cockroach Periplaneta americana, periplanone A and periplanone B, which enter into the corresponding different receptors,[1,2] have been isolated by Persoons et al.[3] Of these two pheromones, the stereostructure of periplanone B has been unambiguously determined as 1.[4] Furthermore, a tentative structure (2) of periplanone A has been also proposed by the same authors.[5] On the basis of molecular mechanics calculations together with ^{1}H NMR spectral data, however, the stereostructure of Persoons' periplanone A has been revised to be 3.[6] On the other hand, Hauptmann et al. have isolated a new germacratrienone oxide (4) and named it as periplanone A,[7] which is regarded as an important precursor of periplanone B (1). In addition, intramolecular double cyclization of 4 including transannular reaction may lead to the direct formation of Persoons' periplanone A (3). Quite recently, Macdonald et al. also proposed that germacratrienone oxide (5), a stereoisomer of 4, is periplanone A.[8] We describe herein short step-synthesis of two germacratrienone oxides (4 and 5) from germacrene-D, which has been obtained from the plant Solidago altissima L. as almost racemic form.[9] Furthermore, biological activity of these two synthetic compounds is also presented.

The known germacrone (6),[10] derived from germacrene-D in 3 steps, was acetylated with Ac_2O - pyridine (room temp., 4.8 h) to afford an acetate (7),[11] in 87% yield, which was further treated with p-TsNHNH$_2$ (0.85 equiv.) - $MgSO_4$ - HCl in THF (refluxing temp., 3.5 h) to give the corresponding hydrazone (8),[11] in 73% yield. This compound so far obtained was treated with Bu^{n}Li (1.5 equiv.) - N,N,N',N'-tetramethyl ethylene diamine (5.1 equiv.) in THF under argon (0 °C, 7.2 h) to give rise to the desired olefin (9)[11] and a hydrazone (10),[11] in 5 and 21% yields, respectively.[12] Furthermore, the former (9) was oxidized with freshly prepared MnO_2 in benzene (refluxing temp., 2.2 h) to give an α,β-unsaturated ketone (11)[11] as a sole product. According to essentially the same procedure as reported by Hauptmann et al.,[7] epoxidation of 11 was carried out using TBHP (9.1 equiv.) - KH in THF (-23 °C, 40 min) to afford two germacratrienone oxides (4 and 5)[13] in 53 and 31% yields, respectively.[14] As judged from the ^{1}H NMR spectral data, the oxide (4) are identical with Hauptmann's peri-



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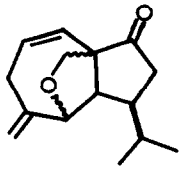

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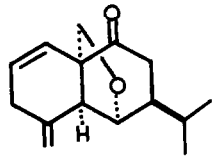

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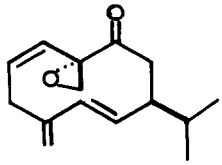

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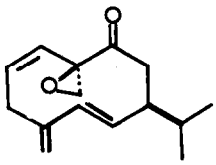

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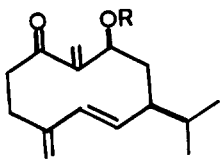
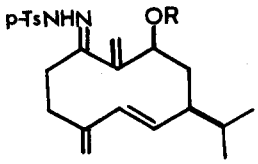


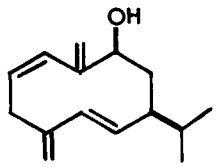
6 R = H

7 R = Ac



8 R = Ac

10 R = H



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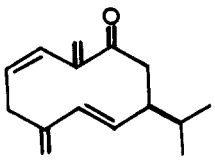

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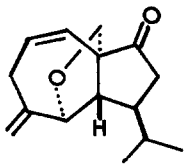

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planone A as well as with Nishino's periplanone A,[15] whereas the latter (5) is identical with Macdonald's germacratrienone oxide.

According to Nishino's method, thus, the electroantennogram (EAG)[1] and behavioral responses[16] to these epoxides (4 and 5) were examined in the American cockroch. As shown in Table 1, the EAG responses from male antennae of the American cockroch were observed in both natural periplanone A[15] and synthetic epoxide (4), whereas there was no response in 5. In the case of behavioral responses, the same results were also obtained: both natural

Table 1. EAG responses from male antennae of the American cockroach*

compound** trial	I	II	III	IV	V	VI	VII	VIII (mV)	average (mV)
Nishino's PA	1.39	1.03	1.21	0.83	1.26	1.05	1.12	0.93	1.11 ± 0.17
(±)-4***	0.47	0.53	0.68	0.48	0.38	0.29	0.65	0.55	0.50 ± 0.12
(±)-5	0.00	0.00	0.02	0.00	0.00	0.00	0.00	0.00	0.00 ± 0.01

* Bioassay of these compounds was carried out according to Nishino's method.[1]

** 3×10^{-3} μg of each sample was used.

*** Only one of the enantiomers can enter into the periplanone A receptor.

periplanone A and (±)-4 exhibited the lowest threshold of activity at 2×10^{-4} μg and 5×10^{-4} μg, respectively. However, any behavioral response was not recorded in 5 even at 1.0 μg. Therefore, the sample of the germacratrienone oxide, synthesized by Macdonald et al., probably contains a small amount of 4.[8]

From a biogenetic point of view, Persoons' periplanone A (3) is expected to be derived from 4. Thus, acid-catalyzed double cyclization of Hauptmann's periplanone A was carried out using a catalytic amount of TFA in CH_2Cl_2 (0 °C, 30 min) to afford the known hydroazulenone (12),[17] the stereostructure of which had been already determined unambiguously, in 72% yield.[18] At present, we can not necessarily ruled out a possibility that Persoons' periplanone A (3) with biological activity (10^{-4} μg) is enzymatically formed from Hauptomann's one (4), although the former is considered to be produced artificially in the course of isolation. Further synthetic study on Persoon's periplanone A (3) is in progress.

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11. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: 7 as a colorless oil: $C_{17}H_{24}O_3$ (m/z 276.1737 (M^+)); IR (film) 1735, 1670, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99(3H, s) and 5.60(1H, dd, J= 3, 10 Hz). 8 as colorless needles: mp 117 - 118 °C; $C_{24}H_{33}O_4N_2S$ (m/z 445.2167 ($M^+ + 1$)); IR (film) 3240, 1730, 1625, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67(3H, d, J = 6 Hz), 0.73 (3H, d, J = 6 Hz), 2.02(3H, s), 2.45(3H, s), 4.48(1H, d, J = 16 Hz), 4.61(1H, d, J = 2 Hz), 5.00(1H, d, J = 2 Hz), 5.03(1H, dd, J = 9, 16 Hz), 5.57(1H, s), 5.60(1H, s), 5.63 (1H, complex), 7.43(2H, d, J = 8 Hz), and 7.94(2H, d, J = 8 Hz); 9 as a colorless oil: