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SYNTHESIS OF A SIMPLE ANALOG OF PERIPLANONE-B

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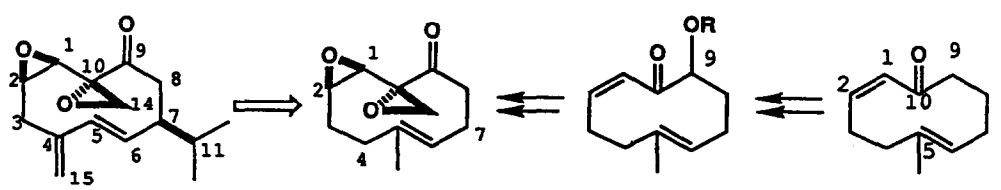
Summary: The synthesis of a simple analog (1) of periplanone-B with high biological activity is described mainly on the examination of the conformational property of the key intermediate 3 by molecular mechanics calculation and dynamic NMR spectroscopy.

Periplanone-B (P-B) is the major sex pheromone component of the American cockroach, *Periplaneta americana*[1]. The potent attractant activity (threshold: $10^{-7}\mu g$)[2] was expected to serve as an efficient controlling agent of this tenacious pest. However, the synthetic methods[3] reported for P-B usually required multistep and sophisticated procedures, because of the difficulty of constructing the 10-membered ring skeleton and stereocontrollings of the four chiral centers. Thus, we have investigated the possibility to generate structurally simplified P-B analogs which are suitable to the practical use.

Recently, we pointed out that the oxygen-containing functionalities on the molecules and their unique 3-dimentional placements appeared to be important to the pheromonal activity[4], on the basis of the structure-activity study on periplanones and some germacranoid analogs. Considering these points, we attempted to synthesize a simplified analog 1, which lacks isopropyl group at C-7 and exo-methylene group at C-4 of P-B, from easily obtainable 10-membered ring compound 2. Since these groups were postulated to play an important role to the conformational property of the flexible 10-membered ring system[5], the examinations of stereoselectivity on the synthetic intermediates and the conformational analogy of the final product are critical for the success of this synthesis.



Periplanone-B (P-B) 1 3 2

The starting material 2 could be obtained in large scale by a modified method of Wharton *et al.*[6], in which the (E)-cyclodecene skeleton was constructed via facile Grob fragmentation. The compound 2 was converted into the corresponding silylenol ether (LDA/TMSCl,-15°), which was treated with mCPBA (hexane, <0°) and following protection (Et_3SiCl/Py) of hydroxyl group gave **3a**, the key intermediate of this synthesis, in 65% overall yield.

For the prediction of the stereoselectivity of the epoxidation at C-1 and 2, molecular mechanics (MM) calculation was applied on **3b** (R=t-Bu). The initial geometries were exhaustively generated by high-speed computer program CONFLEX2[7], and their energy minimizations on MM2-85 identified eight energy minima within 4 kcal/mol. The most stable conformers and the Boltzmann distribution at 300K were illustrated in Fig. 1. The mechanistic consideration of the peripheral attack epoxidation[5] at C-1 and 2 suggested that the lower energy conformers (A-D) and higher ones (E-H) should lead to α- and β-epoxides related to C-10, respectively. As the combined ratio of the former conformers was calculated to be 97% at 258K and 99% at 195K, this reaction would proceed with high α-selectivity.

To verify the result of MM-calculation, we examined the compound **3a** by ^1H-NMR spectroscopy (500 MHz, in $CDCl_3$) in various temperature. The lower field signals (Fig.2), which could be assigned to be three olefinic protons at C-1, 2 and 6, and one C-9 siloxy methine proton, is severely broadened at 300K, of which the feature was rather improved at 323K. In contrast, as the sample is cooling, each of the four signals begins to separate into three signals, which is essentially complete by 223K. Assuming that these signals (a-c) are arisen from the lower energy conformers A-C[8], this result was essentially in consistent with the MM prediction, although the conformer distribution (68:17:16) observed at 223K was not accurately agreed with the calculated ratio (88:6:6).

In practice, the epoxidation (tBuOOH-KH/THF, -15°) of **3a** gave **4** as the only detectable stereoisomer in 56% yield. When the conformational property of **4** was assumed to be similar to that of **3a**, the introduction of spiro epoxy group by employing chloromethyllithium reagent[9] (/THF, -78°) should give **5** in high stereoselectivity. This reaction proceeded smoothly to afford single bisepoxide in 85% yield. Then, conventional deprotection (Bu_4NF) and oxidation (PCC-MS3A) of the C-9 hydroxyl group gave crystalline compound **1**[10] (m.p. 66.5-68°) in 73% yield. The X-ray crystallographic analysis[11] established the correct relative stereochemistry at C-1, 2 and C-10. As can be seen in Fig. 3, the outline along the three oxygen-containing functionalities of the crystal structure of **1** overlaps well with that of P-B[12]. Bioassay[2] of the compound **1** showed high activity (threshold 10^{-3}μg), which is 10^4 times more active than germacrene-D[13], one of the potent periplanone-mimics.

In conclusion, the successful synthesis of the bioactive analog **1** indicated the possibility to create more simplified and practically useful analogs[14], and confirmed the importance of the

Fig. 1 Energy minima of 3b (R=t-Bu)

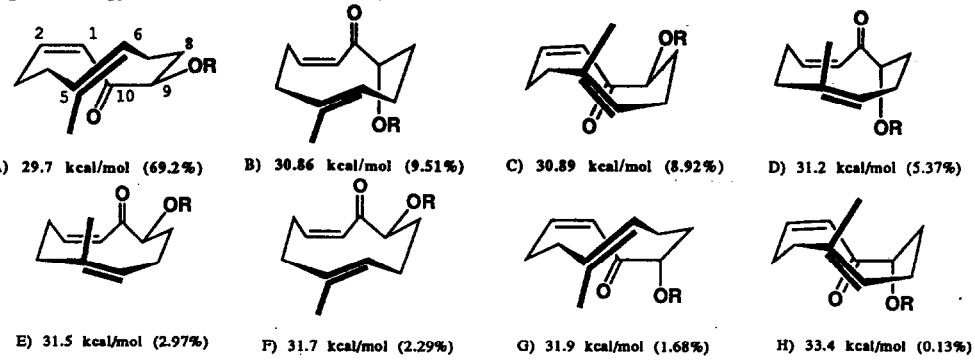
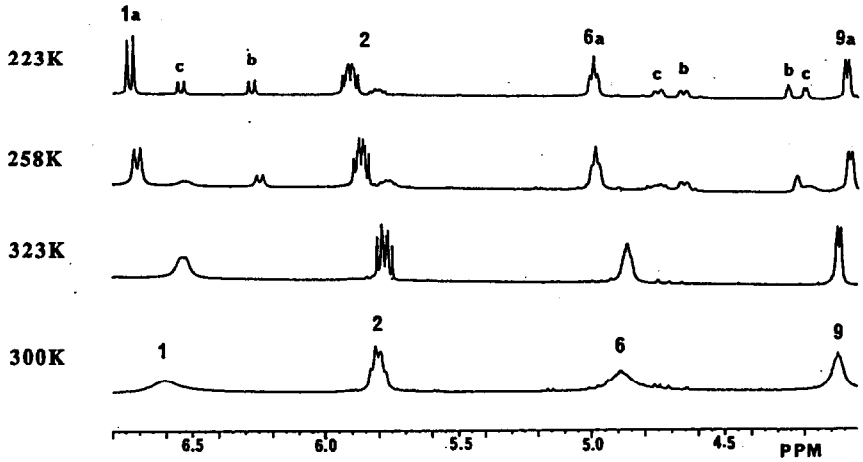


Fig. 2



Scheme

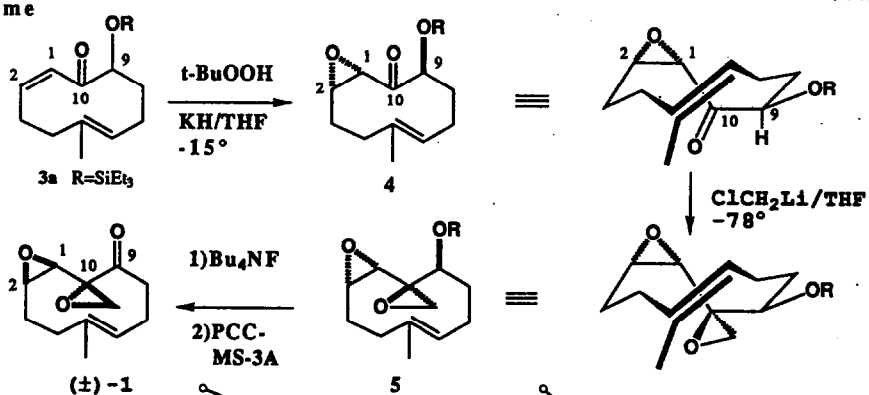
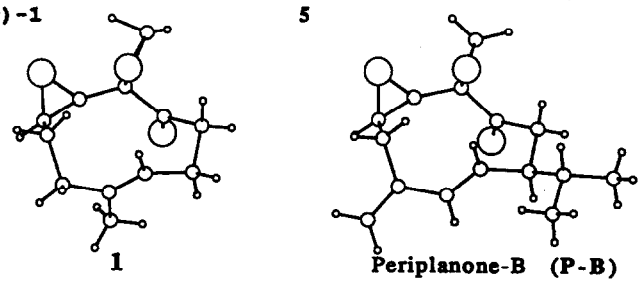


Fig. 3



oxygen-containing functionalities and their 3-dimensional placements, which are depend on the ring conformation, to the pheromonal activity. It is also noteworthy that MM-calculation is a useful tool for the conformational analysis of medium-sized ring system, such as the compound **3**, of which the NMR spectrum is not interpretable by standard methods.

Acknowledgement

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References and Notes

1. C.J.Persoons, F.J.Ritter and W.J.Lichtendonk, *Proc. Kon. Ned. Akad. Wetensch. Amsterdam*, 1974, C77, 201.
2. K.Okada, M.Mori, S.Kuwahara, T.Kitahara, K.Mori, K.Shimazaki and T.Chuman, *Agric. Biol. Chem.*, **54**, 575 (1990); K.Okada, M.Mori, K.Shimazaki and T.Chuman, *J. Chem. Ecol.*, (1990) in press.
3. T.Kitahara, M.Mori, and K.Mori, *Tetrahedron*, **43**, 2689 (1987), and references cited therein. For recent progress on the synthesis of **P-B**, see: S.Kuwahara and K.Mori, *Heterocycles*, **28**, 167 (1989).
4. M.Mori, K.Okada, K.Shimazaki, T.Chuman, S.Kuwahara, T.Kitahara and K.Mori, *J. Chem. Soc., Perkin 1*, (1990) in press.
5. W.C.Still, *J. Am. Chem. Soc.*, **101**, 2493 (1979); T.Takahashi, Y.Kanda, H.Nemoto, K.Kitamura, J.Tsuji and Y.Fukazawa, *J. Org. Chem.*, **51**, 3394 (1986); T.Takahashi, T.Doi and H.Nemoto, *J. Synth. Org. Chem., Japan*, **47**, 135 (1989).
6. P.S.Wharton and M.D.Baird, *J. Org. Chem.*, **36**, 2932 (1971).
7. H.Gotō and E.Ōsawa, *J. Am. Chem. Soc.*, **111**, 8950 (1989); QCPE No. 592.
8. The coupling patterns of the three C-9 methine protons (9a-c in Fig. 2) well reflect the dihedral angles between H-9 and C-8 methylene protons of the conformers **A-C**.
9. K.M.Sadhu and D.S.Matteson, *Tetrahedron Lett.*, 27, 795 (1985).
10. Spectroscopic data for **1**; MS: $C_{12}H_{16}O_3$ (m/z 208.1102 (M^+)); IR (KBr film): 2992(m), 2932(m), 2868(m), 1709(s), 1450(m), 1332(m), 1267(m), 1046(m), 1017(m), 922(s), 835(s) cm^{-1}; ^{1}H-NMR (500MHz, in $CDCl_3$) δ_{TMS} 1.62(3H,d,J=1.4Hz,-Me), 1.78(1H,m,H-6), 1.87(1H,m, H-7), 2.01(1H,ddd,J=12.8,5.4,2.7 Hz, H-2), 2.17(1H,m,H-7'), 2.23(1H,br.,H-3), 2.43(1H,br.,H-6'), 2.63(1H,m,H-3'), 2.72(1H,d,J=5.7Hz,spiroepoxy), 2.91(1H,ddd,J=12.5, 10.0,3.0Hz,H-2'), 2.97(1H, d, J=5.7Hz,spiroepoxy), 2.98(1H,dt, J=10.7,3.8Hz,H-8), 3.82(1H, dd,J=3.8,0.4Hz,H-9), 5.49(1H,m,H-4).
11. crystal data for **1**: $C_{12}H_{16}O_3$, formula weight 208.26; monoclinic, $P2_1/c$ (#14); a=12.014 (2), b=7.086(2), c=13.586(2)Å, β=112.151(9)°; V=1071.3(4)Å^3; Z=4; D_{calc}=1.291 gcm^{-3}; F_{000}=448; λ(CuKα)=0.71069Å; μ(CuKα)=0.86 cm^{-1}; The data were collected at a temperature of -120° so as to avoid sublimation of the sample; No. of reflections measured, total: 2156, unique: 2054; R, R_w=0.034, 0.043. Details will be reported in our full paper.
12. H.Hauptmann, G.Mühlbauer and N.P.C.Walker, *Tetrahedron Lett.*, 27, 1315 (1986). We thank Prof. Hauptmann of the University of Regensburg for sending X-ray crystallographic data of **P-B**.
13. S.Tahara, M.Yoshida, J.Mizutani, C.Kitamura and S.Takahashi, *Agric. Biol. Chem.*, **39**, 1517 (1975).
14. Syntheses of the other periplanone-analogs from **3** are now under way.

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