

CONFORMATIONAL ANALYSES OF STEGOBINONE AND 1'-EPI-STEGOBINONE¹⁾

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Abstract — Conformational analyses of stegobinone **1**, the sex pheromone of the drugstore beetle, and 1'-*epi*-stegobinone **2** were performed by the combination of detail NOE measurements and molecular mechanics calculations.

Stegobinone ((2*S*,3*R*,1'*R*)-2,3-dihydro-2,3,5-trimethyl-6-(1'-methyl-2-oxobutyl)-4*H*-pyran-4-one) **1** is the sex pheromone produced by the female drugstore beetle, *Stegobium paniceum* L.²⁾ As can be seen in Figure 1, it has a very unique structure with a tetrasubstituted dihydro- γ -pyron ring. We have previously reported the synthesis of stegobinone **1**³⁾ and 1'-*epi*-stegobinone **2**.⁴⁾ Very recently, Kodama et al. reported that 1'-*epi*-stegobinone **2** strongly inhibited the pheromone activity of stegobinone **1** in the male drugstore beetle.⁵⁾ In order to investigate this

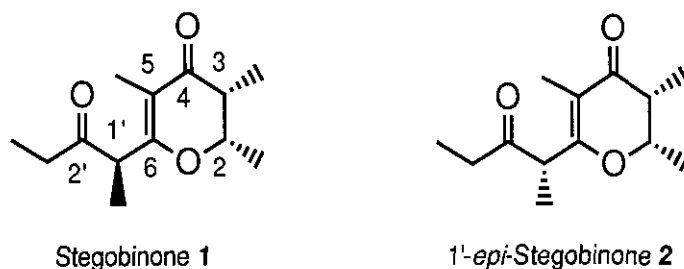


Figure 1. Structure of stegobinone **1** and 1'-*epi*-stegobinone **2**

inhibitional activity in detail, it is essential that both the three dimensional structures of stegobinone **1** and 1'-epi-stegobinone **2** are clarified. In this paper, we report the conformational analyses of these two compounds.

Conformation for the dihydro- γ -pyron ring As can be seen from the Figure 2, there are two possible conformers, (A) and (B), for the dihydro- γ -pyron ring of **1**

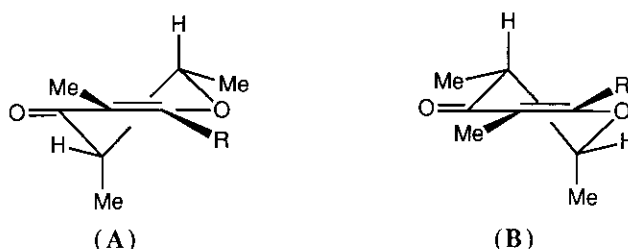
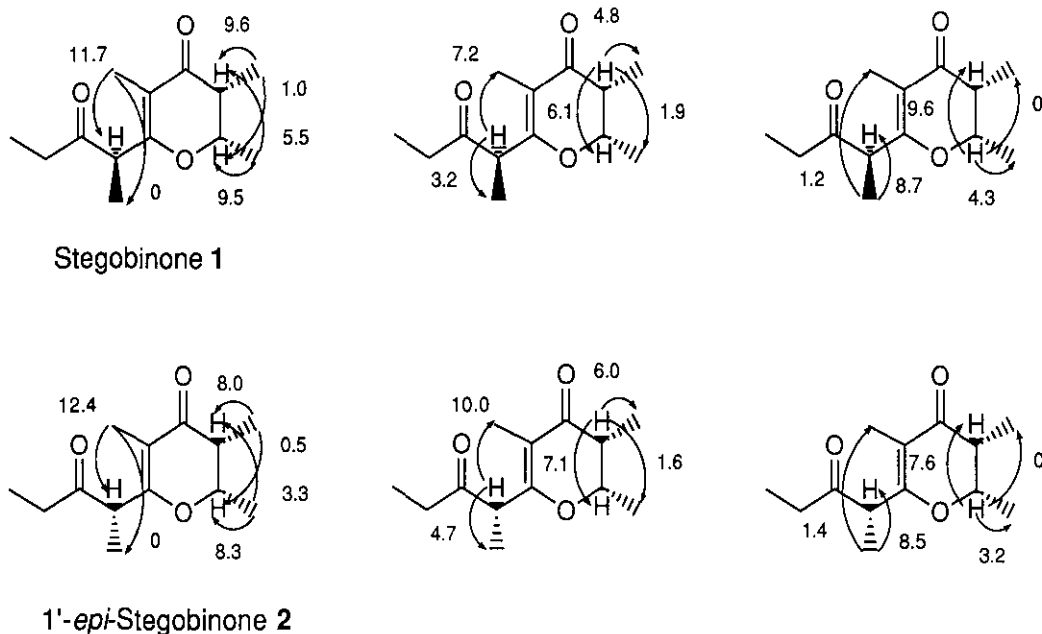


Figure 2. The possible conformers for the dihydro- γ -pyron ring

and **2**. Up to the present, two groups have published papers on their work on the deduction of the conformation of the dihydro- γ -pyron ring of stegobinone **1**. In the earlier paper, Sakakibara et al. reported⁶⁾ the comparison of ^{13}C -nmr data of racemic cis isomeric mixture and racemic trans isomeric mixture. They deduced that (B) was the more probable conformer based on the remarkable difference between both chemical shifts of C-2 methyl group. On the other hand, Hoffmann et al. reported⁷⁾ another deduction based on the cd spectral analysis. In short, both of stegobinone **1** and 1'-epi-stegobinone **2** showed negative extrema due to the enone $n\text{-}\pi^*$ chromophore in the 350 nm region. They applied the Snatzke rule⁸⁾ to this region and deduced that (A) was the more probable. However, neither of these deductions were based on decisive proof. In order to resolve this conformational ambiguity, we performed NOE experiments on **1** and **2** in detail. The results are shown in Figure 3. Remarkable enhancement of both the C-3 methine hydrogen signal and the C-2 methyl hydrogen signal of **1** and **2** was observed upon reciprocal irradiation experiments, while those of the C-2 methine hydrogen and C-3 methyl hydrogen were not observed. To explain these results without any inconsistency, both the C-2 methyl group and the C-3 methine hydrogen of **1** and **2** must occupy pseudoequatorial positions. That is to say, as a result of our studies, we concluded that conformer (A) is the correct one for the dihydro- γ -pyron ring.

Figure 3. NOE value (%) of **1** and **2****Direction of the C-6 side chain**

As can be seen from the Table I, there are significant differences in the cd spectral data of **1** and **2** in 250 to 300 nm region.

Table I. Cd spectral data of **1** and **2**

1		2	
λ (nm)	$\Delta\epsilon$	λ (nm)	$\Delta\epsilon$
360	-0.46	360	-0.88
345	-0.86	345	-2.18
332	-0.69	331	-2.34
290	-12.9	285	+13.4
262	+8.8	261	-10.9

If both the dihydro- γ -pyron rings of **1** and **2** have the conformation as described above, the cd value of this region would be greatly influenced by the C-1' chiral

center. This suggests that significant conformational differences on C-6 side chain exist between **1** and **2**. Indeed, molecular mechanics calculations on **1** and **2** revealed that the C-6 side chains of the major conformers of **1** and **2** are on directly opposite sides to each other, as shown in Figure 4. These results were also confirmed by NOE experiments. A remarkable NOE enhancement of both the C-1' methine hydrogen signal and the C-5 methyl hydrogen signal of **1** and **2** was observed upon reciprocal irradiation experiments, while no NOE was observed between C-1' and C-5 methyl groups. (Figure 3) Consequently, we conclude that the perturbation of C-2' carbonyl group from opposite side raised these differences in the cd spectral data of **1** and **2**.

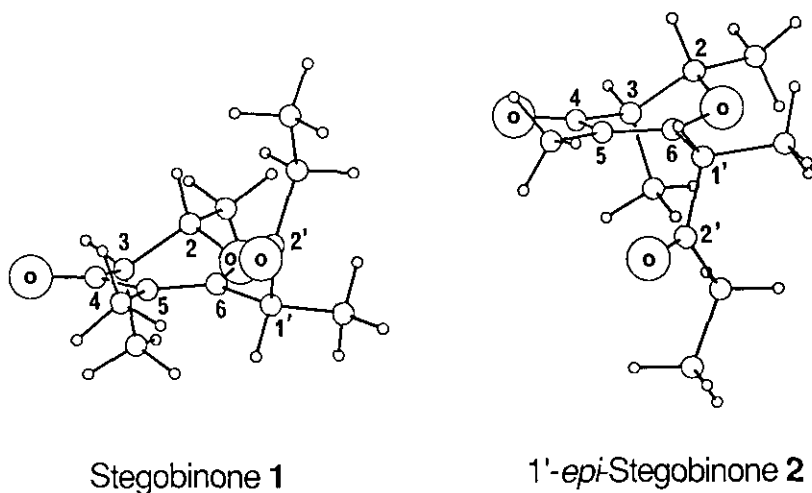


Figure 4. Major conformer of **1** and **2** obtained from MM calculations

In conclusion, the three dimensional structures of stegobinone **1** and 1'-*epi*-stegobinone **2** have been clarified by detail NOE measurements and molecular mechanics calculations.

General Methods

NOE measurements NOE experiments were performed on a Bruker AM-500 instrument equipped with an Aspect 3000 computer. The Bruker program (NOE differences modified by us) was used with relaxation of 4s, NOE generation for 8s (ca. 3-5 x T₁), repetitive cycling with accumulation of eight scans on and off resonance and four

dummy scans to assure saturation. The differences were accumulated by 16-20 times. Enhancements are reported in percent relative to the irradiation signal.

MM calculations The molecular mechanics calculations were performed by CHARMM program (Polygen Corporation, Waltham, MA, USA) on IRIS 4D/80GT work station. Stable conformations of stegobinone **1** and 1'-epi-stegobinone **2** were selected from all energy minima obtained by MM minimizations of each 72 initial conformations.

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Received, 8th January, 1990