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# Total Synthesis of Fusicogigantones A and B and Fusicogigantepoxide via the Singlet Oxygen-Oxidation of Fusicoccadienes. "Fusicogigantepoxide B", a Missing Congener Metabolite

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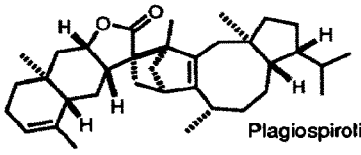
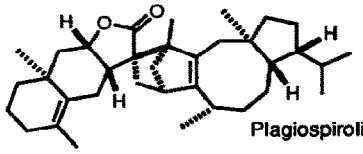
***Abstract:*** Fusicocca-2(6),3-diene and fusicocca-2,5-diene, yet to be identified as natural products, were converted to fusicogigantones A and B and fusicogigantepoxide by oxidation with singlet oxygen. The NMR spectral analysis established their identity with natural products. Also synthesized was 2α,3α:5α,6α-diepoxyfusicoccane, a regioisomer of fusicogigantepoxide.

Recently, we have synthesized fusicocca-2(6),3-diene (**1a**) and fusicocca-2,5-diene (**1b**) and utilized them to convert into plagiospirolides A and B (Chart 1),[1] isolated from a liverwort, *Plagiochila moritziana*[2] *via* a biogenesis-type Diels-Alder reaction with diplophyllolide A and diplophyllin, sesquiterpenic metabolites originally isolated from *Diplophyllum albicans*.[3,4]



Plagiospirolide A

(Chart 1)



Plagiospirolide B

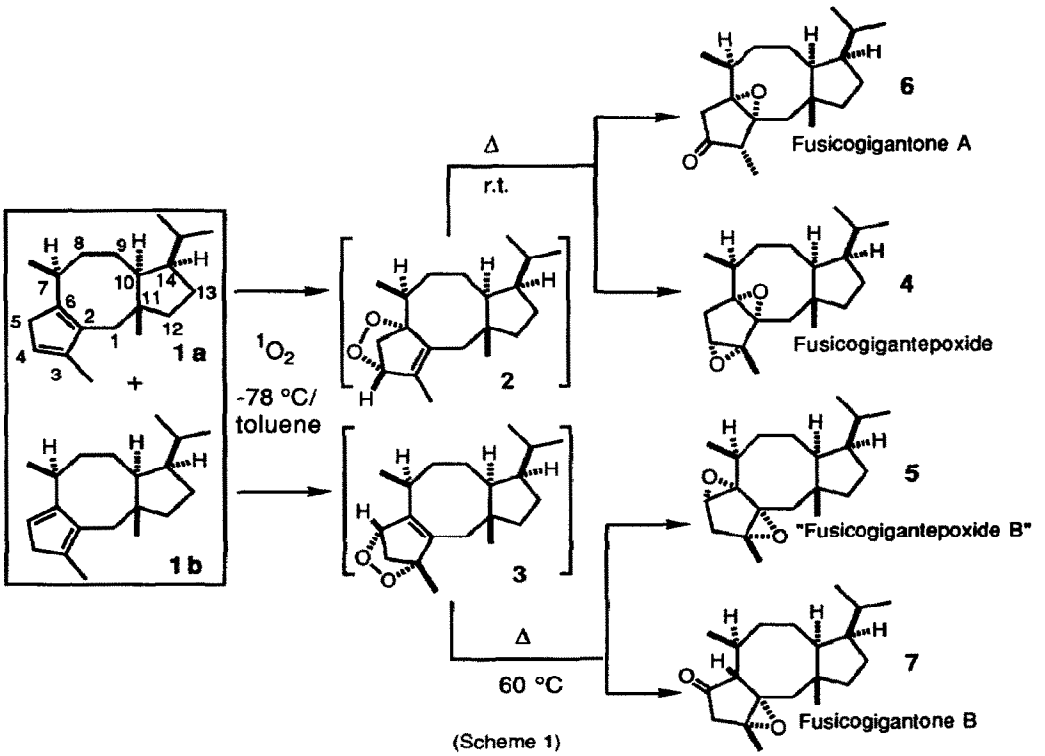
Since there are several other natural products hypothetically biosynthesized from **1**, it will be worthy of synthesizing the derivatives *via* biomimetic pathways. Herein described are synthesis of fusicogigantones A and B,[5] fusicogigantepoxide[5] and its regioisomer, 2α,3α:5α,6α-diepoxyfusicoccane, by singlet oxygen ($^1O_2$) oxidation of **1a** and **1b**. These metabolites are closely related with anadensin, another oxygenated fusicoccane also isolated from a liverwort, *Anastrepta orcadensis*.[6]

When a toluene-$d_8$ solution of a 2:3-mixture of **1a** and **1b** was oxygenated with $^1O_2$ generated by tetraphenylporphin (TPP) at -78 °C under oxygen atmosphere for 50 min, the endoperoxides [**2**: δ(H) 4.47(1H, d, *J*=2 Hz, C-4-H) at -30 °C, and **3**: δ(H) 4.61(1H, d, *J*=1.5 Hz, C-5-H)] were formed according to the $^1H$ NMR spectroscopy. It has been known that, the endoperoxides, *proto*-products, formed by $^1O_2$-oxidation of cyclopentadienes are highly reactive to give various secondary products; unsubstituted cyclopentadiene predominantly gave 4,5-epoxy-2-pentenal (Chart 2-a),[7] and 3,3-dimethyloxepin-2-one was one of the ring-cleavage products from 6,6-dimethylfulvene (Chart 2-b).[8] However, the endoperoxide derived from spiro[2.4]heptadiene gave a diepoxide and epoxy ketones, without ring cleavage (Chart 2-c).[9] Taking this into account, the thermal reaction of the endoperoxides (**2** and **3**) was monitored $^1H$-NMR spectrometrically. Although both **2** and **3** were stable

below 0 °C, **2** gradually changed into **4** and **6** during a period of 10 h at ambient temperature. The more stable endoperoxide **3** also gave two products, **5** and **7**, by heating at 60 °C for 1 h. Silica-gel column chromatography of the mixture furnished **4**, **5**, **6**, and **7** in 12, 8, 23, and 8% yields, respectively. Since all of these products were stable under the reaction conditions, it is clear that they were formed directly from **2** and **3** independently.

Comparisons of the physical properties[10] of these products with reported data[5] identified as **4**=fusicogigantepoxide [colorless prisms, mp 108.5-110 °C. $[\alpha]_D^{19}$ +43° (*c* 0.10, $CHCl_3$) (lit. $[\alpha]_D$ +48°)], **6**=fusicogigantone A [a colorless oil. $[\alpha]_D^{18}$ +29° (*c* 0.50, $CHCl_3$) (lit. $[\alpha]_D$ +28°)], and **7**=fusicogigantone B [a colorless oil. $[\alpha]_D^{18}$ +6° (*c* 0.23, $CHCl_3$) (lit. $[\alpha]_D$ +5.9°)]. The optical rotation of each compound is identical within an experimental error with the same sign, and, therefore, this constitutes not only the first total synthesis of **4**, **6** and **7**, but also determination of their absolute stereostructures.

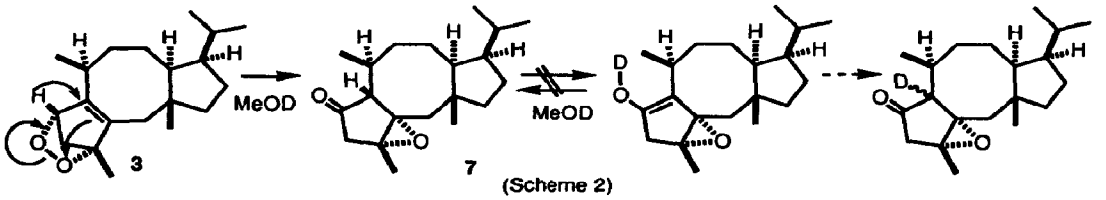
The $^1H$ and $^{13}C$ NMR spectra of the remaining product, **5** [a colorless oil; *m/z*=304 ($M^+$)], were heavily broadened because of its conformational mobilities. It was, however, clear that **5** is another diepoxide, regioisomer of **4**, from the mechanistic considerations and the $^1H$ NMR spectrum obtained at 50 °C; δ(H)=0.85(3H, d, *J*=7 Hz), 0.90(3H, d, *J*=6.5 Hz), 0.94(3H, s), 1.07(3H, br), 1.29(3H, s), 1.58(1H, dd, *J*=15.5, 3.5 Hz), 1.96(1H, br d, *J*=15.5 Hz), 2.05(1H, d, *J*=16 Hz), 2.19(1H, m), 2.44(1H, br s), and 3.32(1H, d, *J*=3.5 Hz). The most broadened methyl group (C7-Me) appeared at δ 1.07 was confirmed to be a secondary one, since this signal splits into two of doublets at 0 °C, δ 0.77(d, *J*=6.5 Hz), and 1.15(d, *J*=6.5 Hz) in a ratio of 1:4.




(Scheme 1)

Recently, the stereochemistry of the 3,4-epoxy group of **4** was revised from β- to α-configuration by X-ray crystallographic study as depicted,[11] and the structure of **6** had been confirmed by its conversion to anadensin.[5, 12] Therefore, the endoperoxide **2**, a precursor of **4** and **6**, was deduced to be a product *via* an α-attack of $^1O_2$ to **1a**. The exclusive α-side attack of $^1O_2$ was consistent with the MO-MM calculations,[13] in which α-attack of $^1O_2$ to **1a** is more favorable than β-attack by $\Delta E$ = 5.4 kcal/mol.

On the other hand, stereochemistry of natural **7** seems to be not yet determined, and its probable biogenetic precursor **5** has not yet been characterized as the natural product. Consequently, the deduction of the stereochemistry of our synthetic **5** or **7** constitutes the structure verification of the natural product. In order to solve the problem,[14] we have carried out the reaction in a deuterio medium; when irradiating a mixture of **1a** and **1b** (1:4.7)[1] in benzene-$d_6$ and methanol-$d_4$ (1:1) with added Rose Bengal at 0 °C under oxygen atmosphere for 12 min, a much enhanced oxygenation took place.[15] After heating at 60 °C for 1 h, the product mixture was chromatographed on a silica-gel column to afford **4** (2%), **5** (17%), **6** (9%), and **7** (9% yields). All the products, however, revealed no incorporation of the deuterium, indicating no enolization step involved in the isomerization to **6** and **7**.




(Scheme 2)

Thus, it can be concluded that **7** has formed *via* a 1,2-hydride migration under kinetically controlled conditions. As shown in Scheme 2, **7** should possess the trans relationship for the methine hydrogen at C-6 and the 2,3-epoxy oxygen.

In the $^1$H NMR spectrum of **7**, clear NOE's were observed between C3-Me and C-1α-H (6.0%), C-1β-H and C-6-H (6.3%), and C11β-Me and C-1β-H groups (5.0%). These observations are explainable only for **7** (Fig. 1) derived from α-attacked endoperoxide **3**.

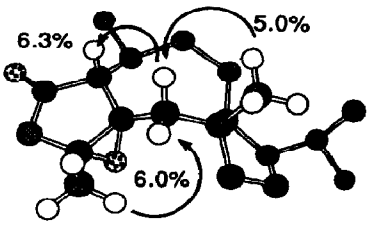



Fig. 1. Optimized structure of **7** and observed NOE's.

Observed NOE between C-1β-H and C-6-H clearly excludes the other candidate, since a possible isomer of **7** derived from β-attacked endoperoxide must have α-oriented hydrogen at C-6.

Therefore, 2α,3α-epoxy structure of **7** is evident. Accordingly, since **5** and **7** were derived from a same precursor, **5** is 2α,3α:5α,6α-diepoxyfusicoccane and **7**, 2α,3α-epoxyfusicoccan-5-one.

Biogenetic pathway from **1b** to **5** and **7** *via* **3** has now been verified, and since an occurrence of **5** in the liverwort is probable, it can be designated as "fusicogigantepoxide B".

It is interesting that both dienes **1a** and **1b** reacted with $^1O_2$; only **1b** reacted with α-methylene-γ-lactones.[1] Yet, the attack of $^1O_2$ had occurred exclusively from the α-side of dienes, **1a** and **1b**, as same to the case of methylene γ-lactones. Detailed discussion on this point should be a subject of a full paper.

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(a) (b) (c)

(Chart 2).

10. The $^1$H NMR spectra were identical with the reported data, and the $^{13}$C NMR (in $CDCl_3$ at 125 MHz) of synthesized samples revealed the following chemical shifts, and the chemical shift differences with those natural compounds,[5] $\Delta\delta$ values (= $\delta_{synthetic} - \delta_{natural}$), are cited in parentheses:
**4**: δ(C)=16.9(±0), 18.1(±0), 19.6(+0.1), 21.0(+0.2), 23.0(±0), 23.8(+0.1), 25.3(+0.1), 25.4(+0.1), 28.8(+0.1), 32.9(±0), 34.8(+0.1), 42.2(+0.2), 42.4(+0.1), 45.0(+0.1), 46.9(+0.1), 47.4(+0.2), 62.4 (±0), 66.3(±0), 66.5(+0.1), and 79.2(+0.1). **6**: δ(C)=9.1(±0), 17.4(±0), 18.7(+0.1), 20.5(±0), 21.0 (+0.1), 23.3(+0.1), 23.6(+0.2), 28.2(+0.1), 31.5(±0), 33.7(+0.1), 38.4(±0), 41.7(+0.1), 42.4(+0.1), 44.4(+0.1), 46.2(+0.2), 48.2(+0.1), 49.6 (+0.5), 70.0(±0), 70.4(±0), and 213.3(-0.2). **7**: δ(C)=15.1 (±0), 20.2(+0.1), 23.1(±0), 23.7(±0), 24.1(+0.1), 24.5(±0), 26.5(+0.1), 28.3(±0), 30.6 (+0.1), 34.6 (+0.2), 38.2(+0.1), 41.2(+0.1), 41.3(+0.1), 43.5(+0.1), 45.9(±0), 47.3(+0.2), 61.0(±0), 62.5(+0.1), 68.6(±0), and 210.2(-0.1).
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12. Related metabolite, anadensin[6] has been derived from **6** in ref. 5. Thus, this study also constitutes a formal synthesis of anadensin.
13. The transition structure of the reaction site was obtained by semi-empirical molecular orbital calculations (MNDO/PM3) for Diels-Alder type reaction between 1,2,3-trimethylcyclopentadiene and $^1O_2$. Then, the rest of the molecules of **2** and **3** was optimized by molecular mechanistic calculations (CAChe MM; licensed from CAChe Scientific Inc., Beaverton, Oregon, U. S. A.). Detailed discussion on the calculative studies will be a subject of a full paper.
14. The MO-MM calculation for **1b** to **3** indicated no significant difference between two transition states; α-attack is slightly favored toward β-attack by $\Delta E$ = 0.6 kcal/mol.
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