Synthetic Photochemistry. LXVIII. Singlet-Oxyggen Oxidation of Fusicoccadienes. In-vitro-Conversion to Mould Metabolites

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Synthetic Photochemistry. LXVIII.[1] Singlet-Oxygen Oxidation of Fusicoccadienes. In-vitro-Conversion to Mould Metabolites[2]

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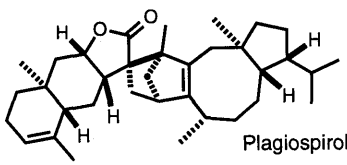
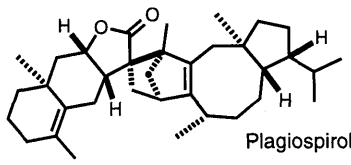
With an oxidation with singlet oxygen, both fusicocca-2(6),3-diene and fusicocca-2,5-diene, biogenetic precursors of some oxygenated 5-8-5-membered tricyclic diterpenoids, respectively afforded the sole endoperoxides, stereospecifically. These endoperoxides were isomerized thermally under very mild conditions to bisepoxides and keto epoxides. These transformations constitute biogenetic type synthesis of fusicogigantepoxides and fusicogigantones.

Introduction

Recently, in connection to our series of synthetic studies on the 5-8-5-membered tricyclic terpenoids,[3] 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),[4] isolated from a liverwort, *Plagiochila moritziana*[5] *via* a biogenesis-type Diels-Alder reaction with diplophyllolide A and diplophyllin, sesquiterpenic metabolites originally isolated from *Diplophyllum albicans*.[6,7]



Plagiospirolide A



Plagiospirolide B

(Chart 1)

Since these hydrocarbons, **1**, are common biogenetic precursors of oxygenated fusicoccanes, it will be worthy of utilizing **1** for further biogenetic conversion into other natural products. Herein described are synthesis of fusicogigantones A and B,[8] fusicogigantepoxide[8] and its regioisomer, $2\alpha,3\alpha:5\alpha,6\alpha$-diepoxyfusicoccane, by singlet oxygen ($^1O_2$) oxidation of **1a** and **1b**.

Results and Discussion

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℃ under oxygen atmosphere, the endoperoxides [**2**: δ (H) 4.47 (1H, d, J=2 Hz, C-4-H) at −30℃, and **3**: δ (H) 4.61 (1H, d, J=1.5 Hz, C-

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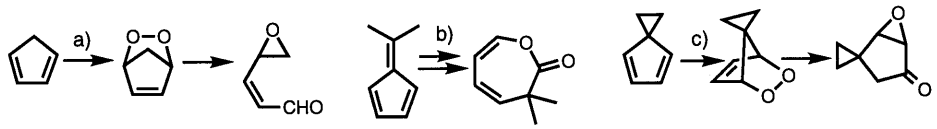
5-H)] were formed according to the ^{1}H NMR spectroscopy. It has been known that, the $^1O_2$-oxidation of cyclopentadienes gives endoperoxides, *proto*-products, which, due to the high reactivity, transformed to various secondary products; unsubstituted cyclopentadiene predominantly gave 4,5-epoxy-2-pentenal (Chart 2; a),[9] and 3,3-dimethyloxepin-2-one was one of the ring-cleavage products from 6,6-dimethyl-fulvene (Chart 2; b).[10] However, the endoperoxide derived from spiro[2.4]heptadiene gave a diepoxide and epoxy ketones, without ring cleavage (Chart 2; c).[11]



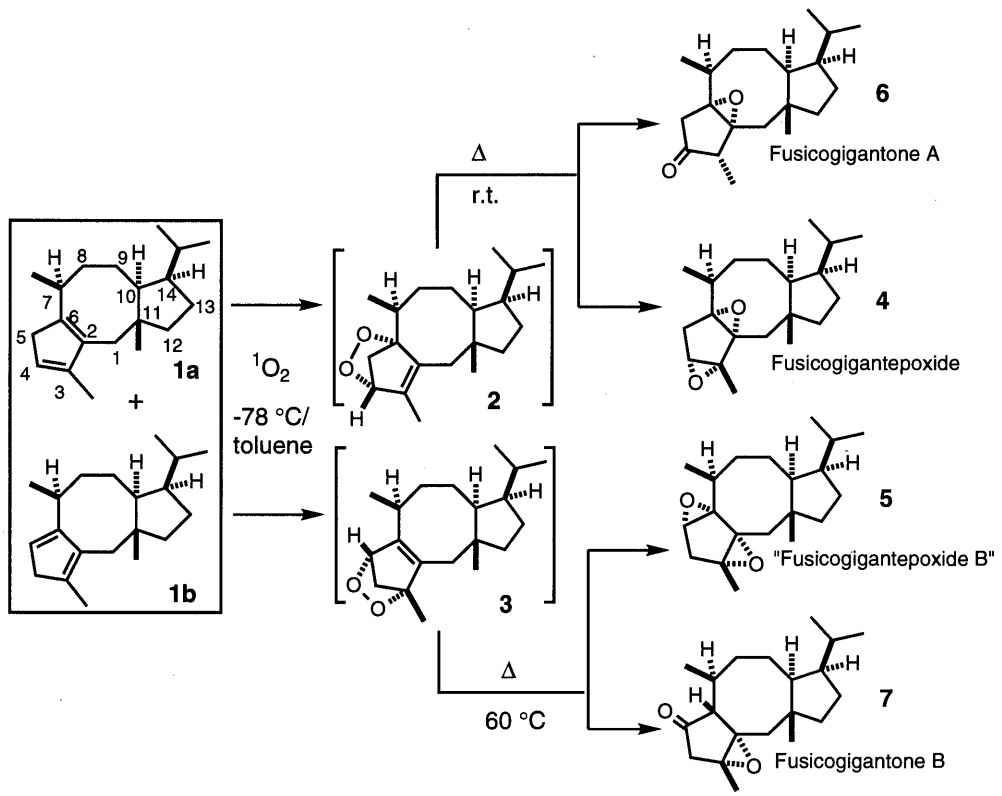
(Chart 2)

Taking this into account, the thermal reaction of the endoperoxides (**2** and **3**) was monitored ^{1}H-NMR spectrometrically. Although both **2** and **3** were stable below 0℃, **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℃ for 1 h. Silica-gel column chromatography of the mixture furnished **4**, **5**, **6**, and **7** in 30, 13, 58, and 13% yields, respectively. Since all of these products were stable under the reaction conditions and did not cause interconversions, it is clear that they were formed directly from **2** and **3** independently.

Comparisons of the physical properties of these products with reported data[8] identified as **4**=fusicogigantepoxide [colorless prisms, mp 108.5-110℃. $[\alpha]_D^{19}+43°$ (*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* 0.25, $CHCl_3$) (lit. $[\alpha]_D+5.9°$)]. The optical rotation of each compound is identical within 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 most of the ^{1}H and ^{13}C NMR spectral signals of the remaining product, **5** [a colorless oil; m/z=304 (M^+)], were broadened because of conformational mobilities of compound **5**. It is, however, clear that **5** is another diepoxide, *regio*-isomer of **4**, from the mechanistic considerations and the IR spectrum, showing neither ν_{OH} nor $\nu_{C=O}$ bands, in addition to the ^{1}H NMR spectrum obtained at 50℃; particularly, there was a still broadened signal ascribable to the secondary C-7-methyl group at δ =1.07, which, according to measurement at 0℃, was consisted of a pair of doublets at 0℃, δ 0.77 (d, J=6.5 Hz), and 1.15 (d, J=6.5 Hz) in a ratio of 1:4. Thus, an existence of conformers is evident.

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,[12] and the structure of **6** had been confirmed by its conversion to anadensin.[8,13] 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,[14] in which α-attack of $^1O_2$ to **1a** is more favorable than β-attack by ΔE=5.4 kcal/mol.

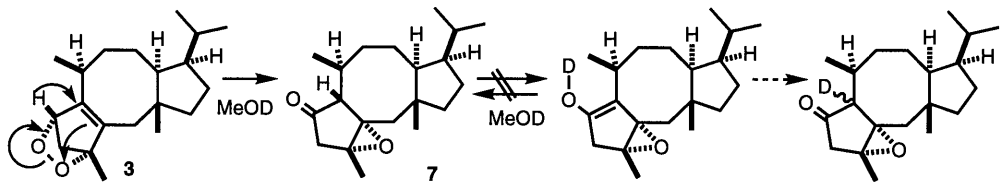


(Scheme 1)

However, the stereochemisty of natural **7** seems to have not yet been determined, and its possible biogenetic congener **5** has not yet been characterized as the natural product, and the stereochemistry of these products derived from **1b** needed a careful investigation; as the compound **5** exists as a mixture of conformers, while the compound **7** possesses the epimerizable methine hydrogen at the A/B-ring juncture, the deduction of the stereochemistry from the nuclear Overhauser effect (NOE) experiment should be ambiguous.

Thus, the deduction of the stereochemistry of our synthetic **5** or **7** constitutes the proof of structures of the natural products. In order to solve the problem,[15] we have carried out the reaction in a deuterated medium; when irradiating a mixture of **1a** and **1b** (1: 4.7)[4] in benzene-d_6 and methanol-d_4 (1: 1) with added Rose Bengal at 0℃ under oxygen atmosphere for 12 min, a much enhanced oxygenation took place.[16] After heating at 60℃ for 1 h, the product mixture was chromatographed on a silica-gel column to afford **4** (13%), **5** (21%), **6** (50%), and **7** (11% yields). All the products, however, revealed no incorporation of the deuterium, indicating no enolization step involved in the isomerization to **6** and **7**.

Thus, it can be concluded that **7** has been 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. This indicates the NOE experiments applicable for elucidation of the stereochemistry of **7**; the NOE in the



(Scheme 2)

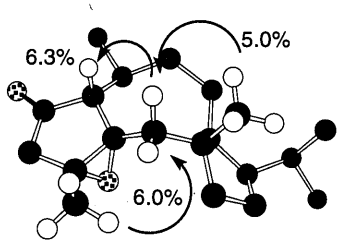


Fig. 1 Optimized structure of **7** and observed NOB's

^{1}H NMR spectrum of **7**, there were clear NOE's between C-3-Me and C-1 α-H (6.0%), C-1 β-H and C-6-H (6.3%), and C-11 β-Me and C-1 β-H groups (5.0%). These led to conclude that **7** (Fig. 1) and **5** are derived from α-attacked endoperoxide **3**, *i.e.*, **7** is 2α, 3α-epoxyfusicoccan-5-one and **5** is 2α, 3α: 5α, 6α-diepoxyfusicoccane.

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".[17]

The present result consitutes the total synthesis of anadensin, another oxygenated fusicoccane also isolated from a liverwort, *Anastrepta orcadensis*,[9] since it has been transformed from **6**, fusicogigantone A.[8]

It is interesting that both dienes **1a** and **1b** reacted with $^1O_2$; only **1b** reacted with sesquiterpenoid α-methylene-γ-lactones.[4] Moreover, the reactivity towards $^1O_2$ was larger in **1a** than **1b**. 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.

Experimental

Singlet Oxygen Oxidation of Fusicoccadienes Fusicocca-2(6),3-diene and Fusicocca-2,5-diene). A toluene-d_8 solution (0.5 cm^3) of a 2:3-mixture of **1a** and **1b** (23 mg) in an NMR tube was irradiated in the presence of added tetraphenylporphin (TPP) with a 400-W tungsten lamp at −78℃ under O_2 atmosphere for 50 min. The reaction was monitored by the NMR spectrometrically, and at the final stage, the mixture was essentially constituted with endoperoxides **2** [^{1}H NMR δ =4.47 (1H, d, J=2 Hz, C-4-H)] and **3** [^{1}H NMR δ =4.61 (1H, d, J=1.5 Hz, C-5-H)], according to the ^{1}H NMR spectroscopy at −30℃.

The mixture was then heated to 60℃ for 1h, heated in vacuo to remove the solvent, and chromatographed on a silica-gel column to give **4** [colorless prisms, mp 108.5−109℃, 3 mg, 12% (30% based on **1a**). $[\alpha]_D^{19}$+43° (c 0.10, $CHCl_3$) (lit. $[\alpha]_D$+48°); ^{1}H NMR δ =0.82 (3H, d, J=6.7 Hz), 0.89 (3H, d, J=6.7 Hz), 0.98 (3H, s), 1.03 (3H, d, J=6.6 Hz), 1.53 (1H, d, J=13.6 Hz), 1.63 (3H, s), 1.93 (1H, d, J=15.9 Hz), 2.05 (1H, m), and 3.54 (1H, d, J=14.7 Hz); ^{13}C NMR δ =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), 46.9 (+0.1), 47.4 (+0.2), 62.4 (±0), 66.3 (±0), 66.5 (+0.1),

and 79.2 (+0.1); IR ν: 2954, 1732, 1463, 1387, 1274, 1147, 872, and 849 cm^{-1}], **5** [a colorless oil, 2 mg, 8% (13% based on **1b**). ^1H NMR δ =0.85 (3H, d, J=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) (at 50℃); ^{13}C NMR δ =20.0, 24.2, 24.7, 28.5, 32.7, 44.6, 47.0, 67.1, and 74.2; MS *m/z*, 304 (M^+) and 95 (100); IR ν: 2954, 2872, 1464, 1390, 1310, 928, and 871 cm^{-1}], **6** [a colorless oil, 6 mg, 23% (58% based on **1a**). $[\alpha]_D^{18}$ +29° (*c* 0.50, $CHCl_3$) (lit. $[\alpha]_D$ +28°); ^1H NMR δ =0.75 (3H, d, J=7.0 Hz), 0.89 (3H, d, J=6.6 Hz), 0.89 (3H, s), 1.08 (3H, d, J=6.7 Hz), 1.16 (3H, d, J=7.1 Hz), 1.23-1.32 (2H, m), 1.39 (1H, d, J=14.5 Hz), 1.69-1.8 (3H, m), 2.01 (1H, m), 2.19 (1H, m), 2.32 (1H, d, J=14.7 Hz), 2.36 (1H, d, J=18.7 Hz), 2.43 (1H, d, J=18.7 Hz), and 2.72 (1H, q, J=7.1 Hz); ^{13}C NMR δ =9.1 (±0), 17.4 (±0), 18.7 (+0.1), 20.5 (±0), 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); IR ν: 2954, 1753, 1462, 1389, 1260, 1210, 1151, 1067, 925, and 864 cm^{-1}], and **7** [a colorless oil, 2 mg, 8% (13% based on **1b**). $[\alpha]_D^{18}$+6° (*c*0.23, $CHCl_3$) (lit. $[\alpha]_D$+5.9°); ^1H NMR δ =0.85 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.8 Hz), 0.90 (3H, s), 1.16 (1H, dd, J=11.5, 6.7 Hz), 1.23 (3H, d, J=6.5 Hz), 1.42 (3H, s), 1.90 (1H, d, J=15.1 Hz), 2.03 (1H, d, J=15.3 Hz), 2.10 (1H, m), 2.20 (1H, d, J=10.1 Hz), 2.45 (1H, d, J=18.1 Hz), 2.48 (1H, d, J=17.9 Hz), and 2.51 (1H, m); ^{13}C NMR δ =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); IR ν: 2952, 1749, 1454, 1382, 1305, 1256, 1218, 1183, 1077, and 862 cm^{-1}].

Enrichment of 1b via BuLi Treatment of a Mixture of a and 1b. A mixture of **1a** and **1b** (2:3, 39 mg) was dissolved in anhydrous THF (2.5 cm^3) and BuLi (hexane solution, 15%, 0.45 cm^3) was added at −78℃ under Ar atmosphere. The mixture was kept stirring and allow to raise temperature to −20℃. The mixture was cooled again to −78℃ and *tert*-BuOH was added. Mixture was reacted with $NaHCO_3$ and extracted with hexane and water. The organic layet was washed with aq NaCl, and dried over $MgSO_4$. Preparative thin-layer chromatography afforded a sample consisted of **1a: 1b** (1: 4.7, 26 mg, 67%).

Singlet Oxygen Oxidation of Fusicoccadienes in MeOD. A mixed solution of C_6D_6 and CD_3OD (1: 1, 0.8 cm^3) of **1a** and **1b** (1: 4.7, 41 mg) in an NMR tube was externally irradiated with added Rose Bengal (1 mg) under O_2 stream by means of a 400-W tungsten lamp for 12 min at 0℃. The mixture was then warmed to 60℃ for 1h, and analyzed by ^1H NMR spectrometrically. Silica-gel columm chromatography afforded **4**, 1 mg, 2% (13% based on **1a**), **5**, 8 mg, 17% (21% based on **1b**), **6**, 4 mg, 9% (11% based **1a**), and **7**, 4 mg, 9% (11% based on **1b**). No uptake of deuterium into **6** was confirmed by direct ^1H NMR spectroscopic analysis of reaction mixture and the sample obtained after isolation.

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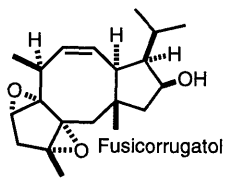

(Chart 3)