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Studies on Chemical Conversion of Alpinenone to Furopelargone B

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The process of the chemical conversion of alpinenone into furopelargone B, both of which had been isolated from the rhizomes of *Alpinia japonica* (Zingiberaceae), was studied by means of conformational analysis and consideration of the frontier electron densities of the reaction intermediates obtained by molecular mechanics calculation (MM2) and molecular orbital calculation (modified neglect of differential overlap (MNDO)) methods.

Keywords——*Alpinia japonica*; alpinenone; furopelargone B; sesquiterpene; guaiane; molecular mechanics calculation; MM2; molecular orbital calculation; MNDO; Zingiberaceae

Introduction

The structure of alpinenone (**1**), which is a guaiane-type sesquiterpene isolated from *Alpinia japonica*, has already been reported.[1)] The absolute structure of alpinenone was determined on the basis of the fact that alpinenone is chemically converted into furopelargone B (**3**). The possible reaction mechanism was discussed in our previous paper.[1)] However, the involvement of **1a** in the reaction appeared to be controversial. Therefore, this mechanism was re-examined by the use of molecular mechanics calculations, molecular orbital calculations and also chemical evidence. A modified reaction mechanism is reported in this paper.

Results and Discussion

The reductive cleavage of alpinenone (**1**) with lithium aluminum hydride ($LiAlH_4$) gave

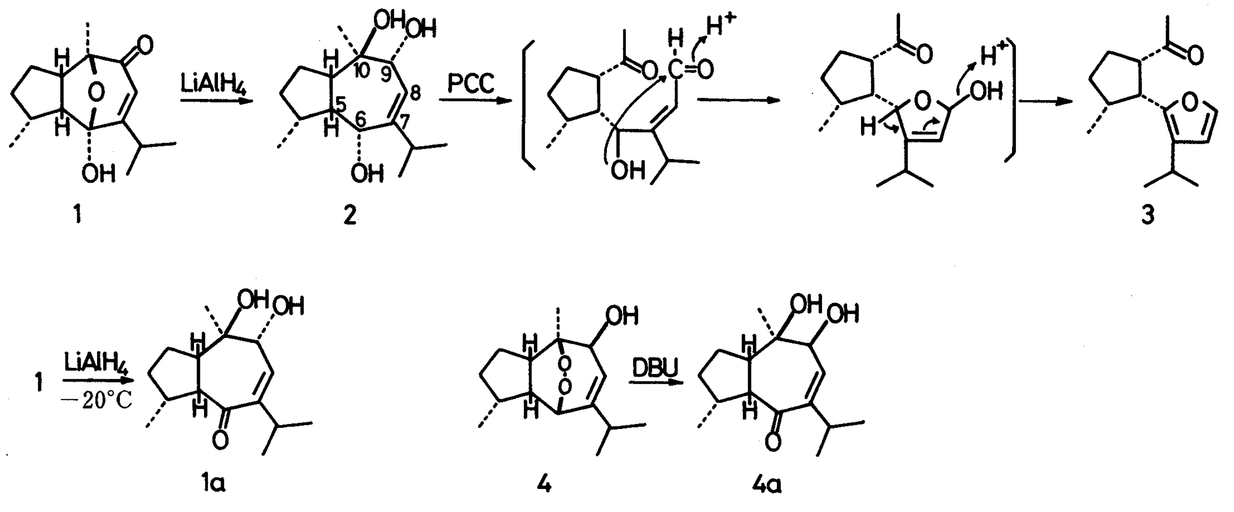

Chart 1

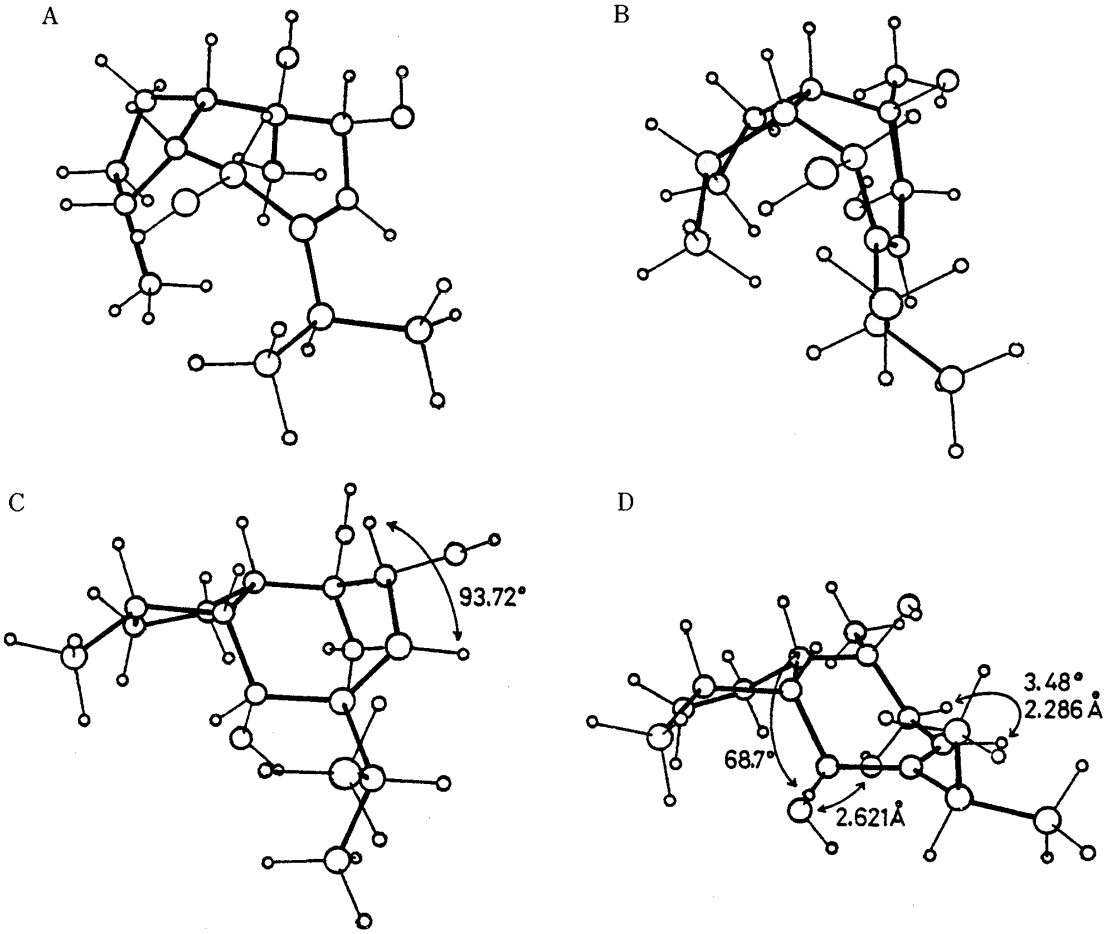

Fig. 1. Four Possible Conformers of **2**

A, S.E. 44.6033 kcal/mol; B, S.E. 41.0628 kcal/mol; C, (5.1%) S.E. 34.0922 kcal/mol [−122.3806 kcal/mol]; D, (94.9%) S.E. 32.3336 kcal/mol [−125.8519 kcal/mol].
S.E., steric energy; ( ), population estimated from S.E. of MM2; [ ], heat of formation calculated by the MNDO method.

the 6,9,10-triol compound (**2**), and the oxidative ring cleavage of the seven-membered carbocycle of **2** with pyridinium chlorochromate (PCC) gave furopelargone B (**3**), as shown in Chart 1.

When the same reduction was carried out with the calculated amount of $LiAlH_4$ at low temperature, **1a** was obtained by the cleavage of the hemiketal followed by reduction only at C-9 (Chart 1). On the other hand, the cleavage with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) of the peroxide linkage in hanalpinol (**4**), which was also isolated from *A. japonica*,2) gave **4a** (Chart 1). Because the spectral data of **1a** were not identical with those of **4a**, the configuration of the hydroxyl group substituted at C-9 of **2** was determined to be α. As the reduction of **1** to **2** proceeded *via* **1a**, and as **1a** was considered to take a basket-like conformation, the configuration of the hydroxyl group at C-6 of **2** was also considered to be α.

The molecular mechanics calculations with MM2 3) were carried out for four possible conformers A—D at the seven-membered ring of **2**. The calculated steric energies and the molecular structures with the minimum energy are shown in Fig. 1. According to the calculation, the most stable conformer was conformer D (25 °C in the gas phase) and the same conclusion was reached from the spectral data in the liquid phase as described below. The infrared (IR) spectrum in highly diluted CCl_4 solution shows the absorption caused by intramolecular hydrogen bonding at 3480 cm^{-1} (the distance between the C-6 oxygen atom and C-9 oxygen atom in D is 2.621 Å from the above calculation). In the proton nuclear

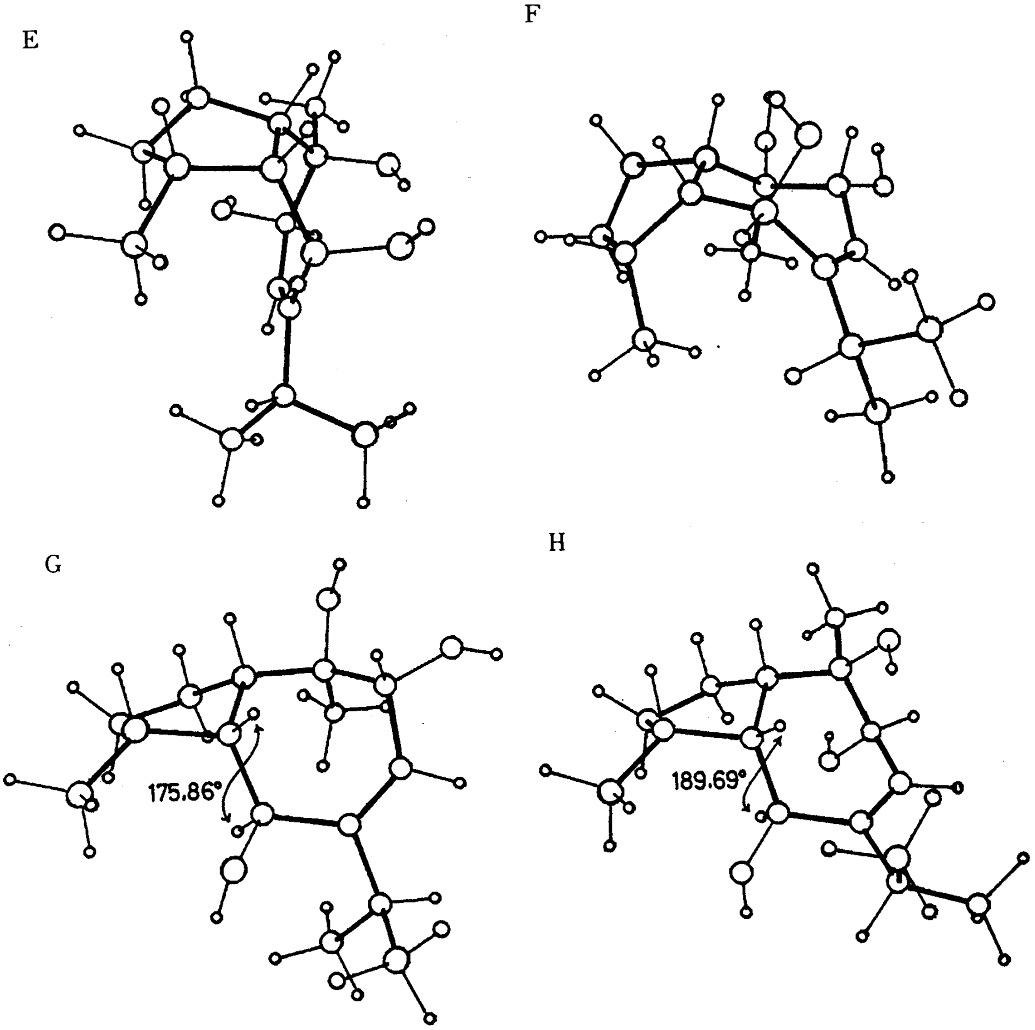

Fig. 2. Four Possible Conformers of the Compound When the C-6 Hydroxyl of **2** is *β*

E, S.E. 41.4321 kcal/mol; F, S.E. 36.6303 kcal/mol; G, S.E. 35.4346 kcal/mol; H, S.E. 33.6272 kcal/mol.

magnetic resonance (^{1}H-NMR) spectrum ($CDCl_3$), the coupling constant between H-8 and H-9 was 5.1 Hz (the dihedral angle is 3.48 ° in D from the above calculation) and the nuclear Overhauser effect (NOE) between them was 5.5% (the distance between them is 2.286 Å in D from the above calculation). The ^{1}H-NMR signal of H-6 appeared as a broad singlet (the dihedral angle between H-5 and H-6 is 68.7 ° in D from the above calculation). These spectral data are consistent with conformer D.

If the hydroxyl group at C-6 takes *β*-orientation, there are four possible conformers E—H, corresponding to the above conformers A—D (Fig. 2). According to the molecular mechanics calculation (MM2), the dihedral angles between H-5 and H-6 of the most stable and the second most stable conformers (H and G) are 189.69 ° and 175.86 °, respectively: they do not agree with the experimental data presented above.

The conformer C is considered to be the conformer of the intermediate involved in the PCC oxidation reaction conducted in methylene chloride. In the ^{1}H-NMR spectrum (0.04 mmol each), the H-8 and H-9 signals appear as a doublet having the coupling constant between H-8 and H-9 of $J=7.0$ Hz in CCl_4, as a broad doublet with $J=5.1$ Hz in $CDCl_3$, and as a broad singlet in CD_2Cl_2. The predominance of conformer C in CD_2Cl_2 is confirmed by the NMR signal and the above calculation which showed that the dihedral angle between H-8

TABLE I. Frontier Electron Densities of Oxygen Atoms of Conformers C and D

Oxygen atom	Frontier electron density [$f_r^{(E)}$] Conformer C	 Conformer D
Oxygen atom at C-6	0.02723	0.04683
Oxygen atom at C-9	0.01164	0.05515
Oxygen atom at C-10	0.05778	0.06683

and H-9 is 93.72°.

The oxidative cleavage of the 9, 10-diol in **2** with periodic acid also gave **3**. This reaction may be explained as follows. First, the cleavage of 1,2-diol occurs to form an aldehyde group and then the hydroxyl group at C-6 attacks the aldehyde group to form a furan ring. A reaction similar to that described above is considered to be involved in the reaction of **2** to **3** with PCC. However, **1a**, which had been considered to be an intermediate in the reaction of **2** to **3** was not converted into **3** with an acid catalyst. Therefore, the reaction mechanism proposed in the previous paper[1)] was proved to be incorrect.

Furthermore, the frontier electron densities ($2 \times \mathrm{HOMO}^2$) of conformers D and C in the ground state (available for electrophilic reactions) were calculated by the modified neglect of differential overlap (MNDO) method (Table I).[4)] The frontier electron density of the hydroxyl oxygen at C-10 is higher than that of the other hydroxyl oxygens. The initial stage of PCC oxidation is said to be the esterification of hydroxyl groups, as in the case of periodic acid oxidation. Therefore, the calculation showed that the hydroxyl group at C-10 of **2** is in a state of high reactivity. However, whether the C-10 and C-9 hydroxyl groups are both esterified to form a five-membered ring or not is obscure.

Experimental

The spectral data were obtained on the following instruments; optical rotations on a JASCO DIP-4, IR on a JASCO A-302, ultraviolet (UV) on a Hitachi 557, NMR on a Brucker AM 400, and mass (MS) on a Hitachi M-80. High-performance liquid chromatography (HPLC) was carried out on a CIG column system (Kusano Scientific Co., Tokyo) with Iatrobeads (60 μ silica gel, IATRON Co., Tokyo) as the stationary phase. Molecular mechanics calculations were carried out with the MM2 program made by N.L.Allinger and modified for a microcomputer by E. Osawa. Molecular orbital calculations were carried out with the NMDO program in MOPAC distributed by Quantum Chemical Program Exchange (QCPE) using a HITAC M-280H computer at the Computer Centre, the University of Tokyo.

Reduction of 1 with $LiAlH_4$——An ether solution of **1** (100 mg) was treated with $LiAlH_4$ (500 mg) in dry ether under a nitrogen atmosphere for 3 h at room temperature. After being treated in the usual way, the product was subjected to HPLC (*n*-hexane : ethyl acetate = 1 : 1) to give **2** as a colorless oil (80 mg). MS *m/z* (%): 236 (M^+—18, 10), 218 (10), 193 (52), 175 (80), 123 (100), 95 (86), 81 (66). IR ($CDCl_3$) cm^{-1}: 3610, 3400, 2960, 2880, 1600, 1465, 1380, 1050, 1020, 900; 3480 cm^{-1} (0.002 mol/l of CCl_4, cell length 2 mm) ^1H-NMR ($CDCl_3$) δ ppm: 1.03 (3H, d, J=6.9 Hz), 1.04 (3H, d, J=6.7 Hz), 1.12 (3H, d, J=6.9 Hz), 1.38 (3H, s), 4.03 (1H, br d, J=5.1 Hz), 4.24 (1H, br s), 5.73 (1H, br d, J=5.1 Hz); (CCl_4) δ ppm: 1.04 (6H, d, J=7.0 Hz), 1.12 (3H, d, J=7.0 Hz), 1.31 (3H, s), 3.89 (1H, d, J=7.0 Hz), 4.14 (1H, br s), 5.65 (1H, d, J=7.0 Hz); (CD_2Cl_2) δ ppm: 1.04 (3H, d, J=6.8 Hz), 1.05 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=6.9 Hz), 1.34 (3H, s), 4.01 (1H, br s), 4.25 (1H, s), 5.71 (1H, br s).

Reduction of 1 with $LiAlH_4$ Equivalent to 1 at Low Temperature——An ether solution of **1** (50 mg) was treated with $LiAlH_4$ (2 mg) in dry ether under a nitrogen atmosphere for 30 min at −20 °C. After being treated in the usual way, the product was subjected to HPLC (*n*-hexane : ethyl acetate = 7 : 3) to give **1a** as a colorless oil (30 mg). **1a**: $[\alpha]_D + 40.0°$ (c=0.23, $CHCl_3$). MS *m/z* (%): 252 (M^+, 4), 234 (66), 191 (100), 163 (99), 109 (73), 58 (86). IR (CCl_4) cm^{-1}: 3620, 3440, 2970, 2880, 1685, 1465, 1385, 1375, 1090, 1055, 985, 930. ^1H-NMR ($CDCl_3$) δ ppm: 0.90 (3H, s), 0.96 (3H, d, J=6.9 Hz), 1.06 (3H, d, J=6.9 Hz), 1.13 (3H, d, J=6.9 Hz), 2.83 (1H, d, J=6.9 Hz), 2.98 (1H, dd, J=5.4, 8.1 Hz), 4.48 (1H, s), 5.99 (1H, s). ^{13}C-NMR ($CDCl_3$) δ ppm: 14.9 (q), 18.2 (q), 21.1 (q), 22.5(q), 23.5 (t), 29.8 (t), 30.8 (d), 38.2 (d), 52.8 (d), 57.5 (d), 76.2 (d), 76.7 (s), 134.7 (d), 149.7 (s), 204.4 (s). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 240 (4222).

Conversion of 4 to 4a——**4** (70 mg) was stirred with DBU (43 mg) in methylene chloride (4 ml) for 1 d at room temperature. After concentration, the product was subjected to HPLC (*n*-hexane : ethyl acetate = 3 : 2) to give **4a** as a colorless oil (48.2 mg). **4a**: $[\alpha]_D + 37.5°$ ($c = 0.48$, $CHCl_3$). MS *m/z* (%): 234 ($M^+ - 18$, 53), 191 (100), 149 (96), 125 (74), 83 (80). IR ($CHCl_3$) cm^{-1}: 3610, 3560, 2960, 2880, 1670, 1460, 1380, 1090, 1050. ^1H-NMR ($CDCl_3$) δ ppm: 1.00 (3H, d, $J = 6.8$ Hz), 1.06 (3H, d, $J = 6.8$ Hz), 1.12 (3H, d, $J = 6.7$ Hz), 1.31 (3H, s), 4.19 (1H, d, $J = 4.5$ Hz), 6.08 (1H, dd, $J = 1.1$, 4.5 Hz). ^{13}C-NMR ($CDCl_3$) δ ppm: 19.9 (q), 20.9 (q), 21.7 (q), 22.1 (q), 25.2 (t), 29.2 (d), 33.9 (t), 36.1 (d), 50.2 (d), 61.1 (d), 75.2 (s), 75.2 (d), 137.7 (d), 147.9 (s), 205.8 (s). UV λ_{max}^{EtOH} nm (ε): 424 (5840).

Oxidative Conversion of 2 with PCC to 3——**2** (20 mg) was treated with PCC (50 mg) in methylene chloride (2 ml) for 15 min at room temperature. Then, dry ether (20 ml) was added. The reaction mixture was filtered, and the filtrate was evaporated. Purification by HPLC (*n*-hexane : benzene : ethyl acetate = 10 : 10 : 1) gave **3** as a colorless oil (5 mg).

Oxidative Conversion of 2 with Periodic Acid to 3——**2** (30 mg) was treated with periodic acid (30 mg) in dioxane–H_2O (9 : 1) for 10 min at room temperature. Then, dry ether was added. The reaction mixture was washed with water and concentrated. The product was subjected to HPLC (*n*-hexane : ethyl acetate = 15 : 1) to give **3** as a colorless oil (15 mg).

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