Communications to the Editor

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CHEMICAL CONVERSION OF (4S,5S)-(+)-GERMACRONE 4,5-EPOXIDE, A PLAUSIBLE BIOGENETIC INTERMEDIATE FOUND IN THE ESSENTIAL OIL OF ZEDOARIAE RHIZOMA FROM YAKUSHIMA, JAPAN

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The biogenetic-type chemical conversion of (4S,5S)-(+)-germacrone 4,5-epoxide (2) was examined. It was found that acidic treatment of 2 furnished three guaiane-sesquiterpenoids: GU-1 (3), GU-2 (4), and GU-3 (5), while alkaline treatment of 2 provided an eudesmane-sesquiterpenoid EU-1 (6) as respective major reaction products. The structures of these conversion products were determined on the basis of their spectral data. GU-2 (4) was further analyzed by X-ray crystallography. The GU-1 (3) and GU-2 (4) were found in minor quantities in Zedoariae Rhizoma from Yakushima, Japan. The previously proposed structure of procurcumenol is revised as 3.

KEYWORDS —— Zedoariae Rhizoma; (4S,5S)-(+)-germacrone 4,5-epoxide; biogenetic-type chemical conversion; guaiane-sesquiterpenoid X-ray analysis; procurcumenol absolute configuration

In 1982, we reported the isolation[1] and the absolute stereostructure elucidation[2] of furanogermenone (1), an experimental anti-hepatitis principle in Zedoariae Rhizoma imported from China. Since then, we have undertaken comparative studies of the essential oil constituents of Zedoariae Rhizoma (Gajutsu in Japanese) from China, Taiwan, and Yakushima (Japan),[3] and have isolated from the rhizoma of Yakushima (4S,5S)-(+)-germacrone 4,5-epoxide (2), which appears to be an important biogenetic intermediate for various sesquiterpenoids hitherto isolated from several kinds of Zedoariae Rhizoma, and have elucidated its absolute stereostructure.[4] Very recently, we have found that furanogermenone (1) and (4S,5S)-(+)-germacrone 4,5-epoxide (2) have an experimental anti-ulcer effect.[5]

As a part of our biogenetic-type chemical transformation studies,[6] we have examined the behavior of (4S,5S)-(+)-germacrone 4,5-epoxide (2) under various acidic and alkaline conditions. This paper deals with the structure of those biogenetic-type conversion products.[7]

Treatment of (4S,5S)-(+)-germacrone 4,5-epoxide (2) with *p*-toluenesulfonic

acid in benzene-toluene (1:1) at room temperature under an N_2 atmosphere for 1 h furnished three guaiane-sesquiterpenoids: GU-1 (3), GU-2 (4), and GU-3 (5), in 11.0, 23.3, and 46.5% yields, together with several minor products. Similar products were obtained by treating 2 with aluminum chloride in dry ether under an N_2 atmosphere at -18°C for 30 min.

The major product, GU-3 (5), $C_{15}H_{22}O_2$,[8] mp 79-81°C (colorless needles from n-hexane-ether), $[\alpha]_D^{20}$ +131° ($CHCl_3$), gave spectral data (Table I, II) suggesting the guai-1(10)-ene sesquiterpenoid structure (5) whereas spectral data for GU-1 (3), $C_{15}H_{22}O_2$, colorless oil, $[\alpha]_D^{18}$ +256° ($CHCl_3$) and GU-2 (4), $C_{15}H_{22}O_2$, mp 96-98°C (colorless needles from n-hexane-ether), $[\alpha]_D^{18}$ -44° ($CHCl_3$) led us to assign to them the guai-9-ene and guai-10(15)-ene structures (3, 4), respectively. The detailed ^1H NMR examinations of 3-5 at 500 MHz, including the NOE experiments (d_5-pyridine), suggested the A/B *trans* junctions (1α-H, 5β-H) in 3 and 4. In order to substantiate the proposed structures (3, 4, 5), we have analyzed GU-2 (4) by X-ray crystallography and have found them correct (Fig. 1).[9] Consequently, the absolute configuration of 4 have been established as 1R, 4S, and 5S.

In the formation of *trans*-guaiane-sesquiterpenoids (3, 4) from (4S,5S)-(+)-germacrone 4,5-epoxide (2) under the present reaction conditions, conformer B (ii) appears to be the plausible intermediary although conformer A (i) was proposed as a possible intermediary for the general formation of *cis*-guaiane-sesquiterpenoids (iii) from germacrone 4,5-epoxide.[10]

Treatment of GU-2 (4) with potassium carbonate in methanol at room temperature for 40 min yielded GU-1 (3) (57.1%), a cross-conjugated isomer of 4, and GU-2-OMe (7) (23.8%), $C_{16}H_{26}O_3$, mp 85-87°C (colorless needles from n-hexane-AcOEt), $[\alpha]_D^{23}$ -36° ($CHCl_3$), which was formed presumably by the addition of methanol. Thus, the absolute stereostructure of GU-1 (3) has been further confirmed. The structure of GU-2-OMe (7) has been supported by its spectral properties (Table I, II) and the NOE examinations have substantiated the stereostructure.

On the other hand, treatment of (4S,5S)-(+)-germacrone 4,5-epoxide (2) with potassium carbonate in methanol at room temperature for 24 h provided an eudesmane sesquiterpenoid EU-1 (6), $C_{15}H_{22}O_2$, colorless oil, $[\alpha]_D^{18}$ +11° ($CHCl_3$) in 65% yield together with several minor products. The stereostructure (6) has been assigned on the basis of the spectral data (Table I): δ ($CDCl_3$): 1.00 (s, 10-CH_3), 1.82, 1.89 [both s, 11-$(CH_3)_2$], 2.0-2.2 (m, 3-H_2), 2.06 (d, J=2.0 Hz, 4-CH_3), 2.37 (dd, J=14.0, 12.0 Hz, 8β-H), 2.91 (dd, J=14.0, 6.0 Hz, 8α-H), 3.72 (dd, J=12.0, 6.0 Hz, 9α-H), together with the NOE experiments.

Next, we examined the presence of the conversion products (3-6) in various Zedoariae Rhizoma and it was interestingly found that the n-hexane-soluble portion of the methanol extract of Rhizoma from Yakushima (Japan) contained GU-1 (3) and GU-2 (4) (0.002% and 0.006% in Rhizoma) whereas Rhizoma from Taiwan contained GU-1 (3) (0.005%).

Finally, since the physicochemical data [IR (CCl_4), UV (EtOH), MS, ^1H NMR (CCl_4)] reported for procurcumenol[11] coincide with those for the present GU-1 (3) except in the magnitude of the specific rotation [$[\alpha]_D$ +140.9° ($CHCl_3$)[11]], the previously proposed structure (8)[11] of procurcumenol should be revised to 3.

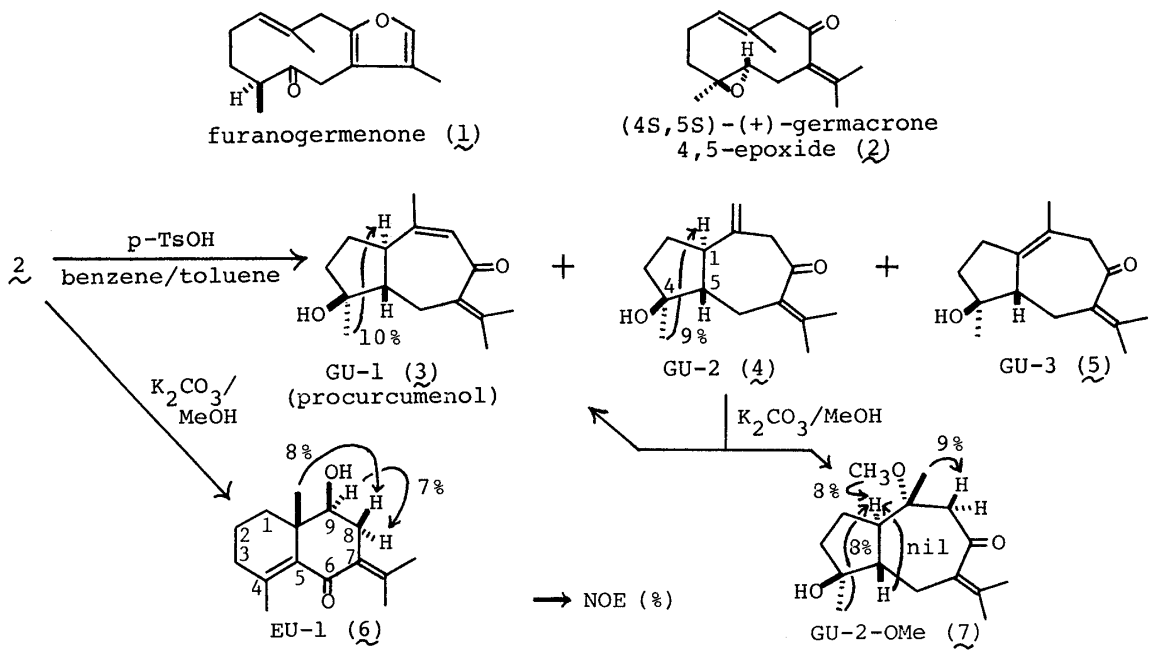

Table I. IR and UV Data for 3~7

		IR cm^{-1}	UV (MeOH): nm (ε)
3	CCl_4	3600, 3440, 1645, 1620 (sh)	248 (7800), 275 (5600)
4	KBr	3260, 1673, 1640, 1603	250 (7100)
5	KBr	3240, 1680, 1620	250 (6600)
6	$CHCl_3$	3600, 3460, 1660, 1620	280 (9500)
7	$CHCl_3$	3600, 3430, 1665, 1600	252 (7400)

Table II. ^{1}H NMR Data for 3~7 (500 MHz, d_6-Benzene, δ, Hz)

	3	4	5	7
1-H	1.4-1.5[a)]	1.79 (m)	———	1.89 (ddd, J= 12.0, 8.5, 8.5)
5-H	1.80 (ddd, J= 13.0, 12.0, 2.5)	1.27 (ddd, J= 12.5, 12.0, 1.0)	2.05-2.2[a)]	1.18 (dd, J= 12.0, 12.0)
6α-H	1.95 (dd, J= 14.0, 13.0)	1.67 (dd, J= 14.0, 12.5)	2.05-2.2[a)]	1.66 (dd, J= 15.5, 12.0)
6β-H	2.59 (br d, J= ca. 14)	2.71 (br d, J= ca. 14)	2.80 (d, J= 13.0)	2.70 (d, J= 15.5)
9-H(1 or 2)	5.96 (q, J= 1.0)	3.07, 3.27 (ABq, J= 14.0)	2.85 (d, J= 15.0) 3.35 (dq, J= 15.0, 1.0)	2.61, 2.73 (ABq, J= 12.0)
4-CH_3	1.01 (s)	0.95 (s)	1.00 (s)	0.91 (s)
10-CH(2 or 3)	1.90 (d, J= 1.0)	4.77, 4.87 (both s)	2.00 (d, J= 1.0)	1.11 (s)
11-$(CH_3)_2$	1.48, 1.50 (both s)	1.62, 2.00 (both s)	1.45, 1.63 (both s)	1.58, 2.03 (both s)
				10-OCH_3: 2.93 (s)

a) These signal patterns were complicated due to their overlapping.

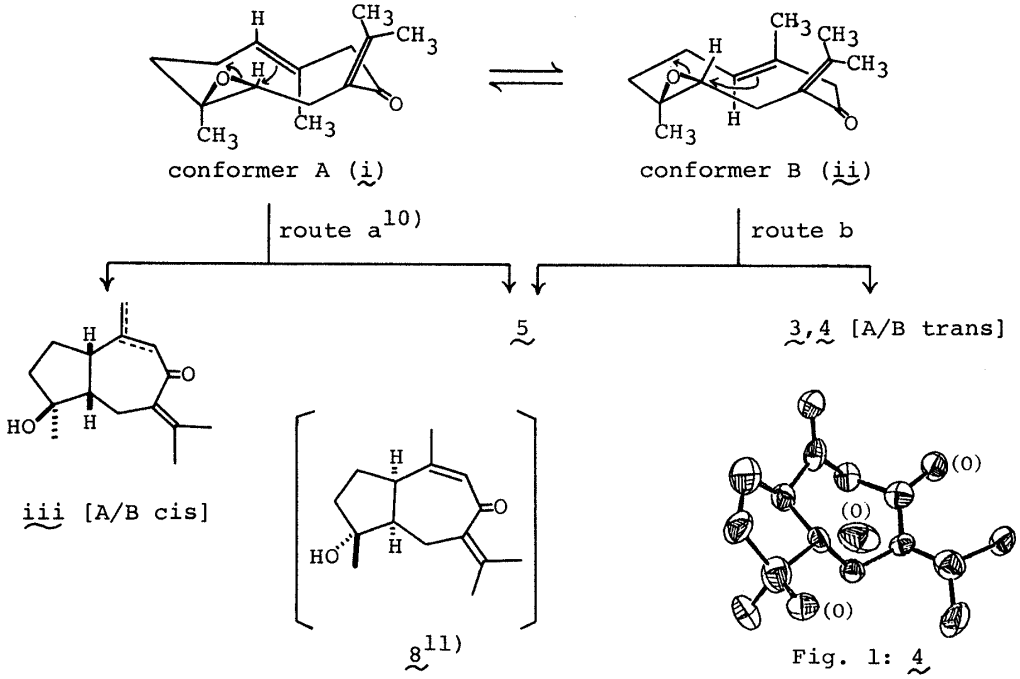

Fig. 1: 4

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6) Previous works: I. Kitagawa, S. Tsujii, F. Nishikawa, and H. Shibuya, Chem. Pharm. Bull., 31, 2639 (1983), and the preceding papers of the series.
7) M. Yoshihara, H. Shibuya, Y. Cai, Z. Cui, and I. Kitagawa, presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, held in Kanazawa, Apr. 3-5, 1985. Abstract Papers, p. 491.
8) The elemental composition of 3~7 was determined by high resolution mass spectrometry.
9) The X-ray diffraction intensities from a colorless crystal (0.4x0.3x0.3 mm) of GU-2 (4) were measured on a Rigaku Afc diffractometer equipped with a rotating anode X-ray generator (40Kv-200mA), using Ni-filtered Cu-Kα radiation. A total of 1168 independent reflections with $2\theta \leqq 120°$ were collected by $\omega/2\theta$ scanning mode, no absorption effects being corrected. Crystal data were: $C_{15}H_{22}O_2 \cdot H_2O$, monoclinic, space group $P2_1$, a=9.803(1), b=8.385(1), c=9.750(1)Å, β=114.096(7)°, z=2, D_c=1.145 g/cm^3. The crystal structure was solved by the automatic structure analysis package for a microcomputer developed by Prof. Y. Katsube (to be published). This package is composed of the programs of MULTAN, peak search, block-diagonal least-squares, etc. Hydrogen atoms were located from the difference Fourier synthesis after several cycles of refinement of non-hydrogen atoms with anisotropic temperature factors. The R factor was reduced to 0.04 with extra cycles of refinement including hydrogen atoms.
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