ABSOLUTE STEREOSTRUCTURE OF FURANOGERMENONE, A BIOLOGICALLY ACTIVE SESQUITERPENE FROM ZEDOARIAE RHIZOMA

Hirotaka Shibuya,[a] Yoshio Yamamoto,[a] Iwao Miura,[b] and Isao Kitagawa[a]*

a) Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565, Japan
b) Laboratory of Natural Products Chemistry, Otsuka Pharmaceutical Co., Tokushima, 771-01, Japan

Abstract -- The absolute stereostructure of a new bioactive sesquiterpene named furanogermenone (1), which was isolated from Chinese Zedoariae Rhizoma, has been determined on the basis of chemical and physicochemical evidence.

Although many sesquiterpene constituents of Zedoariae Rhizoma from Taiwan were characterized,[1] no work on the same kind of crude drug from China has been reported. Recently, we isolated a new sesquiterpene named furanogermenone, the bioactive principle for the experimental liver-lesion in mice, from Zedoariae Rhizoma from China.[2] This communication is a report on the elucidation of the absolute stereostructure of furanogermenone (1), $C_{15}H_{20}O_2$,[3] mp 46.5-47.5°, $[\alpha]_D^{22}$ +135° ($CHCl_3$), which was obtained as the major component (in 23% yield) by HPLC of the n-hexane extractive of the crude drug.[4]

The ir spectrum (CCl_4) of 1 shows the ketone absorption band at 1710 cm^{-1}, whereas the uv spectrum (EtOH) shows the presence of a furan ring (λ_{max} 217 nm, ε= 6900), which is further supported by a prominent fragment ion (A) observed at m/e 108 in the mass spectrum[1a,c] and by the ^1H nmr signals due to α-H (12-H) and β-CH_3 (11-CH_3) in the furan ring (Table). Further, the ^1H nmr spectrum exhibits signals due to a vinyl methyl group (10-CH_3), an olefinic proton (1-H), and a sec. methyl group (4-CH_3, 4-H). Based on these findings together with the molecular composition, furanogermenone (1) has been presumed to have a furanogermacrene skeleton.

The facts, that two AB quartet signals (due to 6-H_2 and 9-H_2) are observed in the ^1H nmr spectrum of 1 and the irradiation (in $CDCl_3$) at δ1.09 (4-CH_3) changed a multiplet at δ2.54 (4-H) into doublets of doublet (J= 10.4, 3.4 Hz), have defined the plain structure of furanogermenone as 8,12-oxido-germacra-1(10),7,11-trien-

5-one (1, except the C-4 configuration and the definition of geometry of the 1(10) double bond).[5] The NOE experiments (in C_6D_6) have substantiated the geometry of the 1(10) double bond in 1. Thus, the irradiation at δ1.53 (10-CH_3) did not affect the signal intensity at δ5.03 (1-H), which suggested E geometry of the double bond. Further, the irradiation of two AB quartet signals [at δ3.11 and δ3.21 for 6-H_2 and 9-H_2 (cf. Table)] increased the signal intensity at δ5.03 (1-H) with 9% and 26%, respectively.[1b,d,6]

In order to define the absolute configuration at C-4, which is the sole asymmetric carbon of furanogermenone (1), the direct comparison of 10 derived from 1 with 15 synthesized from (+)-citronellol (11) was designed. $LiAlH_4$ reduction of 1 in THF gave in 96% yield an isomeric mixture (2),[7] $C_{15}H_{22}O_2$; ir (CCl_4): 3600, 3440 cm^{-1}, which resumed the parent ketone (1) by PCC oxidation[8] in 76% yield. On oxidation with OsO_4 in pyridine at 0°, the acetate (3), $C_{17}H_{24}O_3$; ir (CCl_4): 1739, 1244 cm^{-1}, yielded a diastereomeric mixture of triol-monoacetate (4), $C_{17}H_{26}O_5$; ir ($CHCl_3$): 3560 cm^{-1}, in 98% yield. $NaIO_4$ oxidation of 4 in EtOH furnished the keto-aldehyde acetate (5), $C_{17}H_{24}O_5$; ir (CCl_4): 2800, 1735, 1242 cm^{-1}; ^1H nmr (CCl_4): δ9.88 (1H, narrow t-like, -CHO), in 96% yield. $LiAlH_4$ reduction of 5 in THF gave, in 95% yield, a triol mixture (6), CI(CH_4)-MS: m/e 271 (M^++1); ir ($CHCl_3$): 3370(br) cm^{-1}, which, on treatment with benzoyl chloride in CH_2Cl_2-pyridine (2:1) at room temperature, was converted to the monobenzoate (7), CI(CH_4)-MS: m/e 375 (M^++1), in 95% yield. Mesylation of 7 furnished the monobenzoyl-dimesylate (8), EI-MS: m/e 530 (M^+), which was then treated with t-BuOK in DMSO followed by quenching with benzyl bromide to afford an unstable benzyl ether (9). Without isolation of the product in the pure form, 9 was subjected to ozone oxidation in n-hexane at -78°. $LiAlH_4$ reduction of the resulting ozonide yielded a diol-monobenzyl ether (10), $C_{13}H_{20}O_2$, $[\alpha]_D^{17}$ -5.5° ($CHCl_3$); ir ($CHCl_3$): 3600-3200 (br), 1601 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 0.90 (3H, d, J= 6 Hz, sec. CH_3), 3.42 (2H, d, J= 6 Hz, >CH-CH_2OH), 3.47 (2H, t, J= 6 Hz, -CH_2-CH_2OBn), 4.44 (2H, s, -CH_2Ph), 7.30 (5H, s, arom. protons), in 75% yield from 8. The diol-monobenzyl ether (10) thus obtained comes from C-1 to C-5 of 1 having the 4-CH_3 function and retaining the C-4 configuration.

On the other hand, after protection of the primary carbinol with an ethoxyethyl group, (+)-citronellol (11) was subjected to ozone oxidation in n-pentane at -78° then $LiAlH_4$ reduction to furnish the alcohol (12), $C_{11}H_{24}O_3$, $[\alpha]_D^{17}$ +0.8° (MeOH); ir (film): 3400 (br) cm^{-1}; ^1H nmr ($CDCl_3$, δ): 0.90 (3H, d, J= 6 Hz, sec.

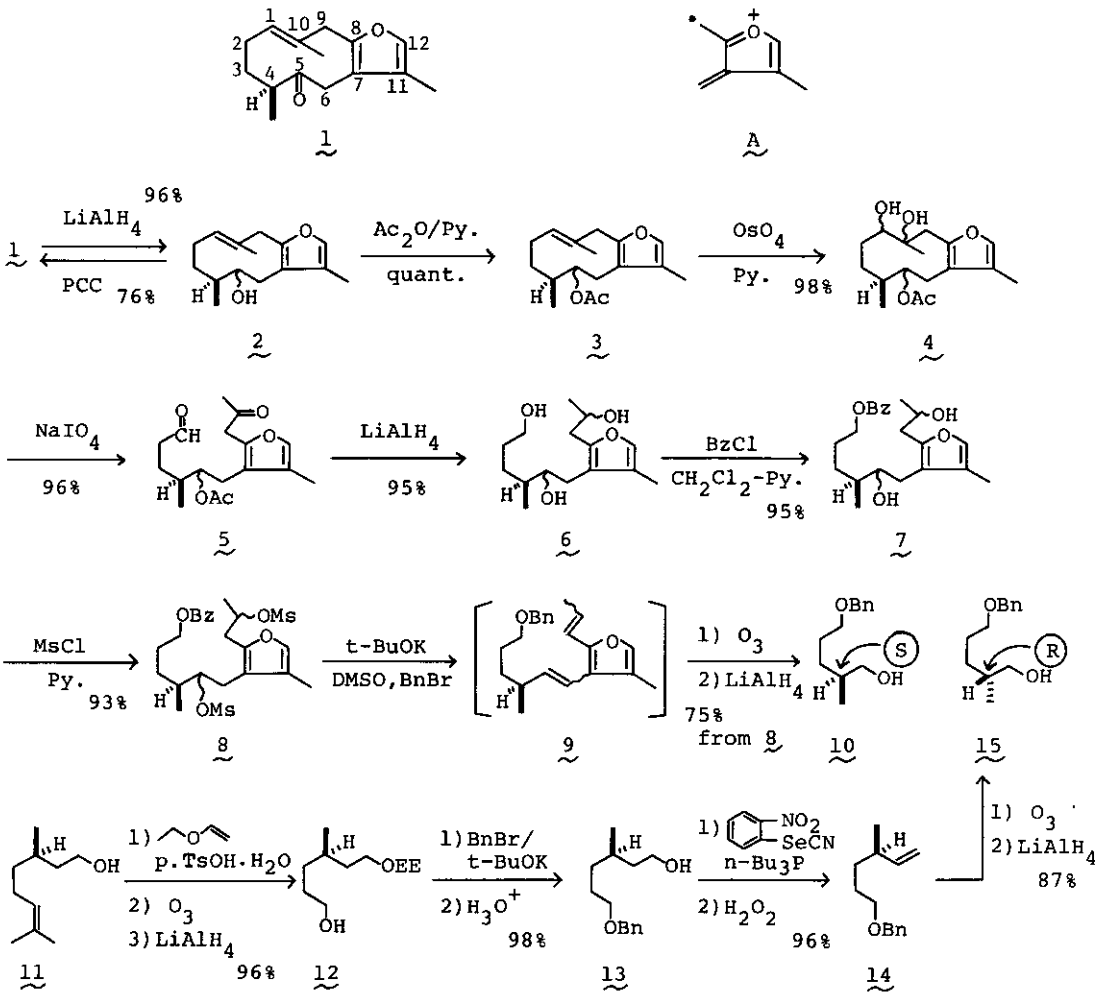

Table ^{1}H nmr Data (δ, Hz) for Furanogermenone (1)

	in CCl_4 a)	in C_6D_6 a)	in $CDCl_3$ b)
1-H	5.31(br.t)	5.03(br.t)	5.17(br.t)
4-H	2.50(m)	2.29(m)	2.54(m) irr. at 1.09 → d.d(J=10.4, 3.4)
6-H_2 c)	3.10,3.37(ABq,J=17)	2.86,3.36(ABq,J=17)	3.21,3.35(ABq,J=17.4)
9-H_2	3.11,3.39(ABq,J=17)	3.05,3.37(ABq,J=16)	3.32(m)
12-H	6.98(br.s)	6.94(br.s)	7.08(br.s)
4-CH_3	1.06(d,J=7)	0.95(d,J=7)	1.09(d,J=7.0)
10-CH_3	1.66(br.s)	1.53(br.s)	1.69(br.s)
11-CH_3	1.91(d,J=1)	1.79(d,J=1)	1.88(d,J=1.2)

a) at 90 MHz. b) at 400 MHz. c) The respective assignments for 6-H_2 and 9-H_2 have not yet been made definitely.

CH_3), 2.01 (1H, br.s, OH, disappeared on D_2O addition), 3.2-3.9 (6H, m), 4.69 (1H, q, J= 5 Hz, -OCH(CH_3)-OEt), in 96% yield from 11. Treatment of 12 with BnBr-t-BuOK in DMSO followed by acidic hydrolysis yielded the diol-monobenzyl ether (13), $C_{14}H_{22}O_2$, $[\alpha]_D^{17}$ +2.3° ($CHCl_3$); ir (film): 3360 (br), 3035, 3020, 1601 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 0.88 (3H, d, J= 6 Hz, sec. CH_3), 3.42, 3.58 (2H each, both t, J= 6 Hz), 4.50 (2H, s), 7.24 (5H, s), in 98% yield. Dehydration of 13 by treatment with tri-n-butylphosphine and o-nitrophenyl selenocyanate in THF then with H_2O_2[9] furnished the vinyl derivative (14), $C_{14}H_{20}O$, $[\alpha]_D^{17}$ -4.8° ($CHCl_3$); ir (film): 3028, 3020, 1635 cm^{-1}; ^1H nmr (CCl_4, δ): 0.99 (3H, d, J= 6 Hz, sec. CH_3), 3.34 (2H, t, J= 6 Hz), 4.38 (2H, s), 4.7-5.9 (3H, ABC, vinyl protons), 7.16 (5H, s), in 96% yield. Finally, ozone oxidation followed by $LiAlH_4$ reduction of 14 gave the diol-monobenzyl ether (15), $C_{13}H_{20}O_2$, $[\alpha]_D^{17}$ +5.6° ($CHCl_3$).

Two diol-monobenzyl ethers (10 and 15), obtained above respectively from furanogermenone (1) and (+)-citronellol (11), were found to be identical each other by their physicochemical properties except the sign of their specific rotations. Thus, the absolute configuration at C-4 of furanogermenone (1) has been defined as S.

References and Notes

1) e.g. a) H. Hikino, K. Agatsuma, and T. Takemoto, Tetrahedron Lett., 1968, 2855; b) H. Hikino, C. Konno, T. Takemoto, K. Tori, M. Ohtsuru, and I. Horibe, Chem. Commun., 1969, 662; c) S. Fukushima, M. Kuroyanagi, A. Ueno, Y. Akahori, and Y. Saiki, Yakugaku Zasshi, 90, 863 (1970); d) H. Hikino, C. Konno, K. Agatsuma, T. Takemoto, I. Horibe, K. Tori, M. Ueyama, and K. Takeda, J. Chem. Soc. Perkin I, 1975, 478.

2) J. Yamahara, H. Matsuda, T. Sawada, H. Kushida, H. Shibuya, and I. Kitagawa, Yakugaku Zasshi, to be published.

3) The molecular compositions of the compounds given with the chemical formulae were determined by high resolution mass spectrometry.

4) The crude drug was extracted with hot MeOH and the extractive was partitioned into an n-hexane-MeOH mixture. Evaporation of the n-hexane phase under reduced pressure gave the n-hexane extractive.

5) J. Yamahara, H. Matsuda, T. Sawada, H. Shibuya, I. Kitagawa, and I. Miura, presented at the 101st Annual Meeting of the Pharmaceutical Society of Japan, held at Kumamoto, April 2-4, 1981. Abstract paper p. 469. The detail will be reported in our full paper.

6) K. Takeda, K. Tori, I. Horibe, H. Minato, N. Hayashi, S. Hayashi, and T. Matsuura, J. Chem. Soc. (C), 1970, 985.

7) All compounds except 1 were obtained as colorless oils.

8) E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2647.

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