STRUCTURE OF MULBERROFURAN J, A 2-ARYLBENZOFURAN DERIVATIVE FROM THE CULTIVATED MULBERRY TREE (*MORUS LHOU*(*SER.*) KOIDZ.

Toshio Fukai,[a] Yoshio Hano,[a] Kazuhiro Hirakura,[a] Taro Nomura,*,[a]
Jun Uzawa,[b] and Kazutaka Fukushima[c]

a) Faculty of Pharmaceutical Sciences, Toho University,
2-2-1, Miyama, Funabashi-shi, Chiba 274, Japan
b) The Institute of Physical and Chemical Research,
Wako-shi, Saitama 351, Japan
c) Research Institute of Chemobiodynamics, Chiba University,
1-8-1, Inohana-chō, Chiba-shi, Chiba 280, Japan

Abstract —— A 2-arylbenzofuran derivative, named mulberrofuran J, was isolated from ethyl acetate extracts of the root bark of cultivated mulberry tree (*Morus Lhou*(*ser.*) Koidz.), and its structure was determined to be **1** on the basis of the spectral evidence. Mulberrofuran J is a 3"-stereoisomer on the cyclohexene ring of mulberrofuran C (**2**) obtained from the root bark of cultivated mulberry tree (*Morus alba* L. and *M. bombysis* Koidz.).

In the previous paper, we reported the structure of two natural hypotensive Diels-Alder type adducts, mulberrofuran F and G, isolated from the root bark of *Morus Lhou*(*ser.*) Koidz. (Japanese name "Rosō").[1] Further extensive fractionation of ethyl acetate extracts of the root bark led to isolation of a new 2-arylbenzofuran derivative, named mulberrofuran J (**1**), in $2.1\times10^{-3}\%$ yield. We report herein the structure elucidation of the compound.

Mulberrofuran J (**1**), amorphous powder, $[\alpha]_D^{18}$ -341° ($c = 0.079$, MeOH), $FeCl_3$ test (dark brown), gave its heptamethyl ether (**1a**), amorphous powder, $FeCl_3$ test (negative), as the exhaustive methylation product [$(CH_3)_2SO_4$ and K_2CO_3 in acetone, reflux, 5 h]. While the FD-MS spectrum of **1** showed the molecular ion peak at *m/z* 580, the molecular formula of **1** was determined to be $C_{34}H_{28}O_9$ by the high-resolution mass spectrum [m/z 678.2831, M^+ ($C_{41}H_{42}O_9$), 100 %] of **1a**. In accordance with this formula, the ^{13}C nmr spectrum (Table 1) indicated the presence of thirty four carbon atoms [nine aliphatic carbons (1xCH_3-, 1x-CH_2-, 3x>CH-, 1x>C=CH-, and 1x-CH=$\underset{|}{C}$-O-), twenty four aromatic carbons (11xCH, 5xC, 8xC-O) and one carbonyl carbon]. The compound showed the following spectra: ir ν_{max}^{KBr} cm^{-1}: 3350 (br), 1640 (sh), 1620, and 1600; uv λ_{max}^{EtOH} nm (log ε): 209 (4.97), 283 (4.51), 293 (sh 4.46), 310 (infl. 4.57), 321 (4.67), and 337 (4.56); $\lambda_{max}^{EtOH+AlCl_3}$: 210 (4.78), 222 (sh 4.68), 288 (sh 4.39), 310 (sh 4.63), 320 (4.65), 335 (sh 4.52), and 370 (sh 3.52). The uv spectra were similar to those of mulberrofuran C (**2**)[2] and albafuran C (**3**)[3]. These results, coupled with comparison of the ^{13}C nmr spectrum of **1** with that of **2** (Table 1, cf. C-4'), indicate that **1** would be a 4'-substituted 3',5',6-trihydroxy-2-arylbenzofuran derivative.

The EI-mass spectra of **1** and **1a** showed almost the same fragments as the corresponding of **2**[2] and its heptamethyl ether[2] (**2a**), indicating that **1** must be a Diels-Alder type adduct such as **2** and **3**: **1a**, m/z 540.2141 ($C_{33}H_{32}O_7$), 350.1535 (**4**), 328.1285 (**5**), 297.1131 ($C_{18}H_{17}O_4$), 284.1059 (**6a**), 165.0556 (**7**), and 151.0732 ($C_9H_{11}O_2$); **1**, m/z 294, 293, 242 (**6**), and 110 (**8**).

The ^1H nmr spectrum (24 °C, 400 MHz, acetone-d_6) of **1** showed a complex pattern with broad signals. This implies that **1** would exist as an equilibrium mixture of conformational isomers in the solution.[4] Supporting this, at higher temperature (65 °C), all the signals, except the four proton signals [δ 6.60-6.85 (2H, br, 2'- and 6'-H), ~3.65 (1H, br, 5"-H), and one of the protons at C-6" (not observed)], appeared more clearly. Careful analysis of the spectrum (65 °C) by sequential decoupling and a comparison of the spectra of **2**,[2] **3**,[3] and kuwanon I[5] (**9**) revealed

Table 1 ^{13}C nmr chemical shifts in acetone-d_6

No of C	**1**	**2**	No of C	**1**	**2**	**10**	No of C	**1**	**2**
2	156.5*	156.5*	5'	157.0*	156.5*		11"	101.7	102.0
3	102.8	103.6	6'	103.9	104.8		12"	164.8	167.0
3a	122.0	121.9	1"	134.3	134.1	133.2	13"	107.7	108.8
4	121.8	121.9	2"	125.1	124.2	126.2	14"	130.3	128.8
5	113.1	113.1	3"	38.8	33.2	38.9	15"	122.5	122.5
6	155.3*	155.4*	4"	46.8	47.9	46.6	16"	157.1*	157.8*
7	98.4	98.4	5"	38.8	33.2	38.9	17"	104.6	103.6
7a	158.2*	157.8*	6"	37.7	32.4	38.9	18"	156.5*	157.8*
1'	130.5	130.9	7"	23.4	23.8	23.5	19"	107.5	107.5
2'	103.9	104.8	8"	209.8	209.5		20"	133.9	135.0
3'	157.0*	156.5*	9"	117.2	116.4				
4'	115.9	113.6	10"	166.0	166.0				

* : Assignments may be interchanged.

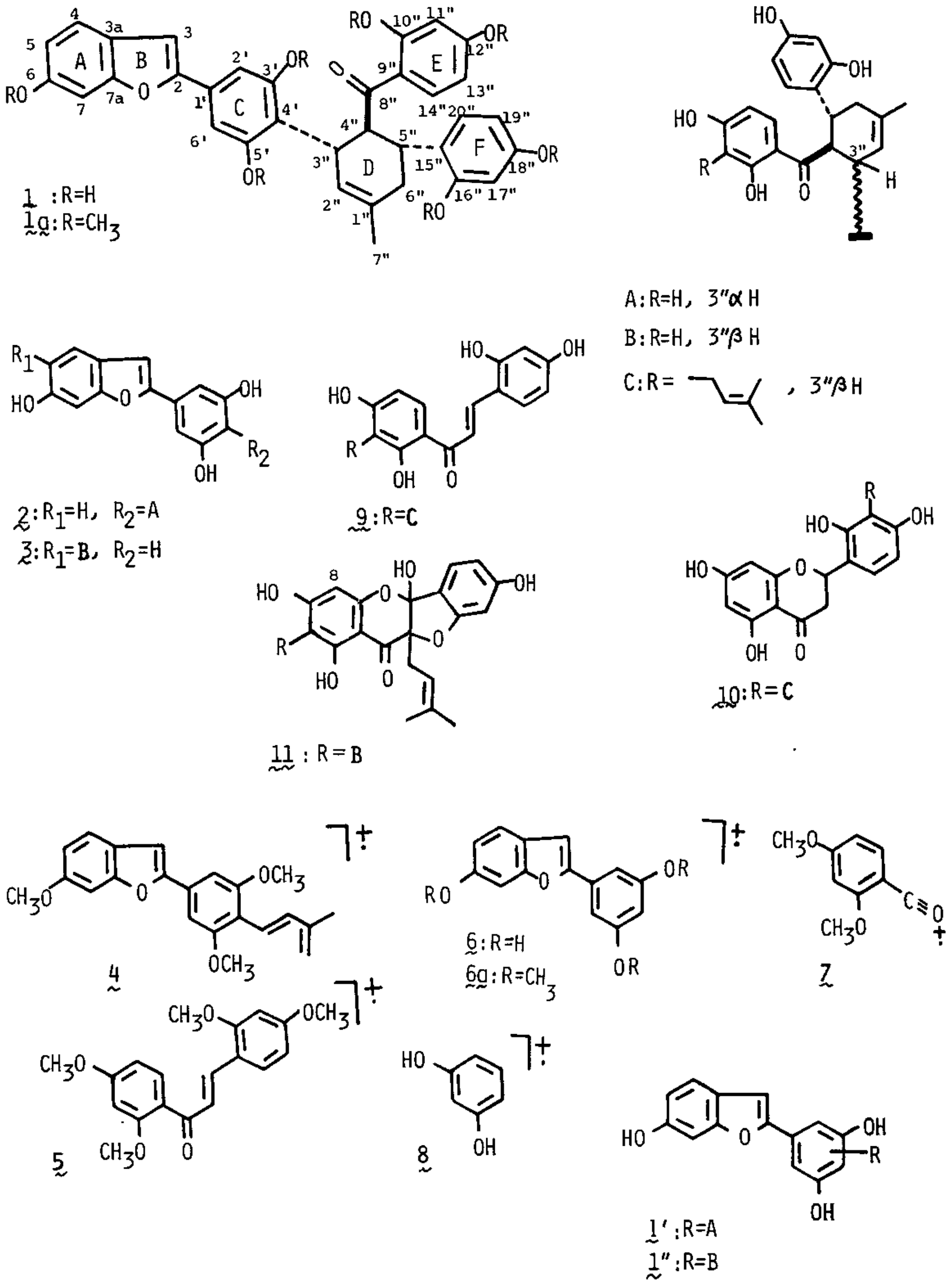
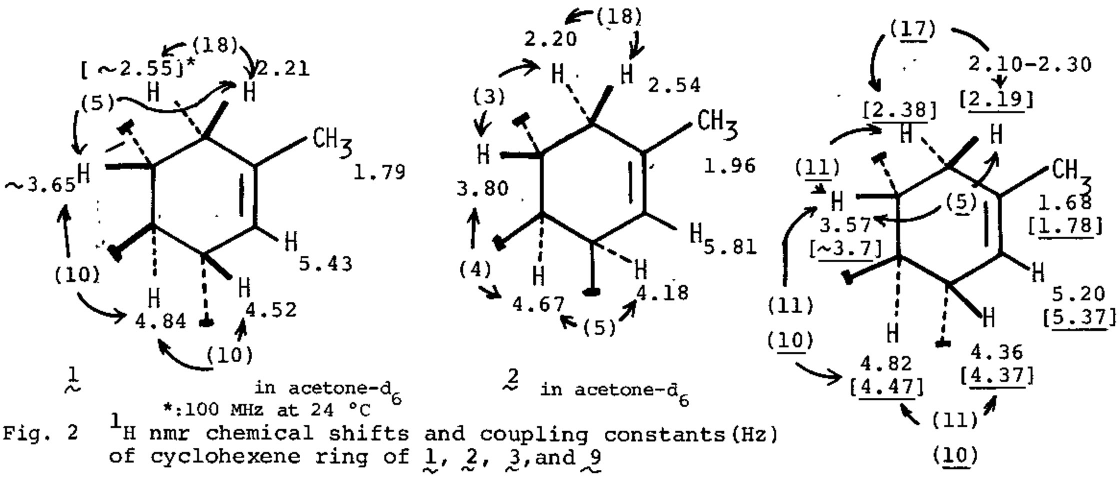

1 : R=H
1a: R=CH3
A: R=H, 3"α H
B: R=H, 3"β H
C: R= , 3"β H
2: R1=H, R2=A
3: R1=B, R2=H
9: R=C
10: R=C
11 : R = B
4
5
6: R=H
6a: R=CH3
7
8
1': R=A
1": R=B

Fig. 1



1 in acetone-d_6
*:100 MHz at 24 °C

2 in acetone-d_6

Fig. 2 ^1H nmr chemical shifts and coupling constants (Hz) of cyclohexene ring of 1, 2, 3, and 9

3 and 9 [_] (_): 3 in acetone-d_6
9: dmso-d_6 at 120 °C

the presence of the following moieties; a cyclohexene ring (Fig. 2), a 2-aryl-benzofuran moiety [δ 6.77 (1H, dd, J = 8.3 and 2.2, 5-H), 6.60-6.85 (2H, br), 6.82 (1H, d, J = 1, 3-H), 6.92 (1H, d, 7-H),[6] and 7.33 (1H, d, J = 8.3, 4-H)], a 2,4-dihydroxyphenyl moiety [δ 6.13 (1H, dd, J = 8.3 and 2.4, 19"-H), 6.23 (1H, d, J = 2.4, 17"-H), and 6.91 (1H, d, J = 8.3, 20"-H)], a 2,4-dihydroxybenzoyl moiety [δ 5.97 (1H, d, J = 2.4, 11"-H), 6.02 (1H, dd, J = 8.7 and 2.4, 13"-H), and 7.64 (1H, d, J = 8.7, 14"-H)]. The existence of the 2,4-dihydroxyphenyl and 2,4-dihydroxybenzoyl moieties was also supported by comparison of the ^{13}C nmr spectrum of 1 with those of 2[2] and other Diels-Alder type adducts[7] (Table 1). These results, combined with analogy of the biogenetic pathway of the Diels-Alder type adducts obtained from Morus species[7] indicate formulas 1' and 1" for mulberrofuran J. The remaining problems are the relative configuration of the substituents on the cyclohexene ring and the location of the cyclohexene ring. The presumption that 1 would possess the same relative configuration as 3 and 9 concerning the cyclohexene ring was deduced from comparison of the ^1H nmr spectrum of 1 with those of 2,[2] 3,[3] and 9[5] (Fig. 2) and the ^{13}C nmr spectra of 1, 2,[2] and kuwanon O (10)[8] (Table 1). Furthermore, comparative examination of the ^{13}C nmr spectra of 1 and 2 (Table 1) and the following ^1H nmr spectrum of 1 indicated that the relevant cyclohexene ring would be located on the C-ring of 1: at low temperature (24 °C, 400 MHz, acetone-d_6) the C-ring protons appeared as separate signals at δ 6.67 (1H, br s) and δ 6.83 (1H, br s), while at higher temperature (65 °C), these two protons were observed as a broad signal at δ 6.60–6.85, indicative of equivalence of these two protons. Irradiation of the signal at δ 6.67 resulted in disappearance of the signal at δ 6.85, and that of the signal at δ 6.85 that of the signal at δ 6.67. The similar phenomena had been observed for the double irradiation experiments of the proton at C-8 of sanggenon D (**11**)[4,9]: The ^{1}H nmr spectrum of **11** (24 °C, 400 MHz, CD_3CN) showed the signals at δ 5.60 (0.4H, br s, 8-H), and δ 5.78 (0.6H, br s, 8-H), and when the signal at δ 5.60 was irradiated, the signal at δ 5.78 disappeared. It follows that the protons at C-2' and -6' are equivalent, and hence the cyclohexene ring in question must be located at the C-4' position. All these results, mulberrofuran J is a 3"-stereoisomer on the cyclohexene ring of **2**, and the structure of mulberrofuran J is therefore represented by formula **1**.

ACKNOWLEDGEMENT We are grateful to Prof. S. Sakai, Faculty of Pharmaceutical Sciences, Chiba University, for mass spectrum measurement.

REFERENCES AND FOOTNOTES

1. T. Fukai, Y. Hano, K. Hirakura, T. Nomura, J. Uzawa, and K. Fukushima, Heterocycles, 1984, **22**, 473.

2. T. Nomura, T. Fukai, J. Matsumoto, and T. Ohmori, Planta Med., 1982, **46**, 28.

3. M. Takasugi, S. Ishikawa, S. Nagao, and T. Masamune, Chem. Lett., 1982, 1223.

4. T. Nomura, T. Fukai, Y. Hano, and J. Uzawa, Heterocycles, 1982, **17**, 381.

5. T. Nomura, T. Fukai, J. Matsumoto, A. Imashimizu, S. Terada, and M. Hama, Planta Med., 1982, **46**, 167.

6. The signal overlapped with the signal at δ 6.91.

7.a T. Nomura and T. Fukai, Heterocycles, 1981, **15**, 1531 and references cited therein; b T. Nomura, Kagaku no Ryoiki, 1982, **36**, 596 and references cited therein; c Y. Hano, S. Takizawa, E. Mizuno, and T. Nomura, Chem. Pharm. Bull., 1983, **31**, 2936 and references cited therein.

8. Y. Hano, K. Hirakura, T. Nomura, S. Terada, and K. Fukushima, Planta Med., in press.

9. Unpublished data.

Received, 24th December, 1983