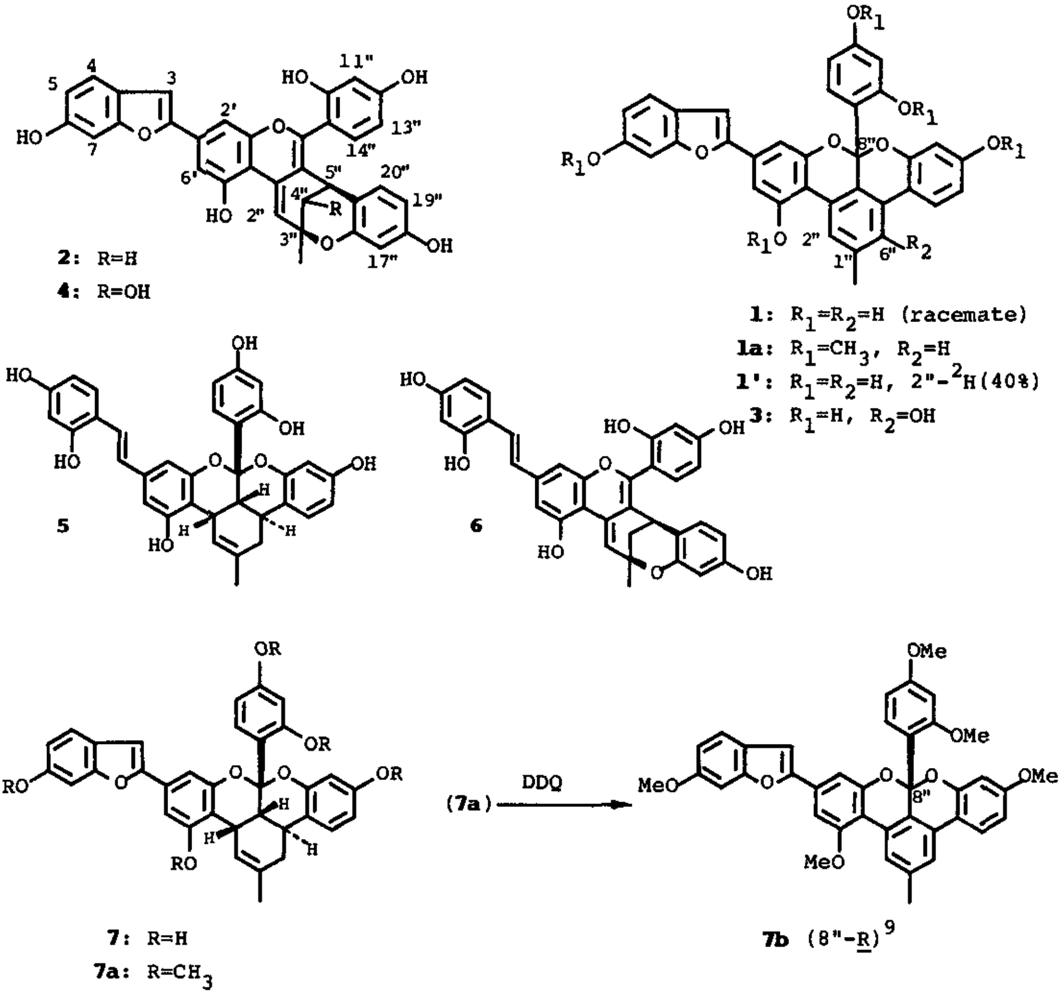
CORRELATION BETWEEN ALBANOL B AND MULBERROFURAN I, AND STRUCTURE OF MULBERROFURAN S, NOVEL 2-ARYLBENZOFURAN DERIVATIVE

Yoshio Hano, Yoko Miyagawa, Mamiko Yano, and Taro Nomura*
Faculty of Pharmaceutical Sciences, Toho University, 2-2-1,
Miyama, Funabashi-shi, Chiba 274, Japan

Abstract —— Albanol B (1), obtained from the Morus root bark, was derived from mulberrofuran I (2) by silica gel column chromatography. The result suggests that 1 is an artifact derived from 2 through the autoxidation. From this point of view, mulberrofuran P (3) is also suggested to be an artifact from mulberrofuran S (4), a new 2-arylbenzofuran derivative, isolated from the reddish violet powder on the surface of the Morus root bark.

Previously, we reported the structure determination of 2-arylbenzofuran derivatives named mulberrofurans I (2)[1] and P (3)[2], and of two stilbene derivatives, kuwanols A (5) and B (6)[3], from the reddish violet powder obtained from the surface of the Morus root bark. We also isolated albanol B (1)[4,5a] from the same sourse.[5b] In this communication, we report the correlation between 1 and 2 revealed by silica gel column chromatography using methanol, and described the structure of a new 2-arylbenzofuran derivative, mulberrofuran S (4).

To confirm the structure of albanol B (1), we attempted to correlate 1 with mulberrofuran G (=albanol A, 7)[4,5] as follows: A solution of mulberrofuran G pentamethyl ether (7a, 49 mg) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 50 mg) in dry benzene (17 ml) was refluxed for 3.5 h. The reaction product was purified by preparative tlc (silica gel, n-hexane:AcOEt=2:1) to give the dehydro-product (7b, 26 mg). The compound (7b) was obtained as colorless prisms, mp 250-254 °C, $[\alpha]_D^{22}$ +118° (c=0.038, $CHCl_3$) and showed the following spectra: EI-ms m/z 628 (M^+); ir ν_{max}^{KBr} cm^{-1}: 1605, 1595(sh), 1580(sh), 1500, 1490, 1155, 1040, 820; uv λ_{max}^{EtOH} nm (log ε): 220 (4.79), 272 (422), 282 (4.24), 314 (4.41), 333 (4.60), 348 (4.75), 367 (4.69); ^1H nmr (400 MHz, $CDCl_3$): δ 2.50 (3H, s, C-1"-CH_3), 3.58, 3.74, 3.85, 3.99, 4.00 (each 3H, s, OCH_3), 5.98 (1H, dd, J=2 and 8, C-13"-H), 6.40 (1H, d, J=2,



2: R=H

4: R=OH

1: $R_1=R_2=H$ (racemate)

1a: $R_1=CH_3$, $R_2=H$

1': $R_1=R_2=H$, 2"-^{2}H(40%)

3: $R_1=H$, $R_2=OH$

5

6

7: R=H

7a: $R=CH_3$

7b (8"-R)[9]

Fig. 1

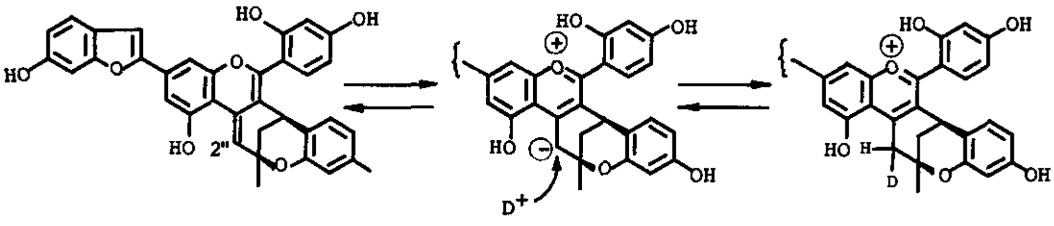


Fig. 2 Mechanism of coloration of 2 in acidic condition and that of the exchange for deuterium at C-2" in acidic solution (acetone-d_6 + trifluoroacetic acid-d_1).[7]

C-11"-H), 6.45 (1H, d, J=8, C-14"-H), 6.55 (1H, dd, J=2 and 8, C-19"-H), 6.60 (1H, d, J=2, C-17"-H), 6.85 (1H, dd, J=2 and 8, C-5-H), 6.90 (1H, d, J=1, C-3-H), 7.00 (1H, d, J=2, C-6'-H), 7.04 (1H, br d, J=2, C-7-H), 7.16 (1H, d, J=2, C-2'-H), 7.40 (1H, d, J=8, C-4-H), 7.45 (1H, br s, C-6"-H), 7.59 (1H, d, J=8, C-20"-H), 8.21 (1H, br s, C-2"-H). Albanol B pentamethyl ether (1a) was obtained from 1 by treating the latter with dimethyl sulfate and anhydrous potassium carbonate in acetone. The compound (1a), mp 246-248 °C, $[\alpha]_D^{22}$ 0° (c=0.040, $CHCl_3$), was shown to be identical with 7b by ir and ^1H nmr spectral comparison, and by mixed melting point determination. The remarkable difference between the specific optical rotation values of 1a and 7b positively indicated albanol B pentamethyl ether (1a) to be racemic compound.

To confirm whether albanol B (1) is an artifact or not, the following experiments were carried out.[6] Mulberrofuran I (2, 112 mg) was chromatographed on silica gel (Wakogel C-200, 50 g) with methanol as an eluent. The eluates were evaporated, and the residue was fractionated by preparative tlc (Wakogel B-5F, $CHCl_3$:MeOH=8:1) to give 2 (77 mg) and albanol B (1, 7 mg). Albanol B thus obtained was identified with authentic sample (spectral data and optical rotation value[6]).

On the other hand, mulberrofuran I (2) in acidic solution showed a red color which faded when neutralized.[1] The ^1H nmr spectrum of 2 in acetone-d_6 + trifluoroacetic acid-d_1 solution showed that the olefinic proton at C-2" can be replaced by deuterium (Fig. 2).[7] To confirm the correlation between 1 and 2, the similar experiment was carried out. A solution of 2 (75 mg) and trifluoroacetic acid-d_1 (0.03 ml) in acetone-d_6 (1 ml) was kept at room temperature for 36 h. The reaction mixture was purified by preparative tlc ($CHCl_3$:MeOH=6:1) to give albanol B (1', 20 mg) and 2 (20 mg). The ^1H nmr spectrum of 1' thus obtained and that of authentic sample are shown in Fig. 3. In the spectrum of 1', the proton signal at C-2" decreased in area (ca. 40%) due to replacement by deuterium.

Further evidence for the correlation between 1 and 2 was obtained from the following experiment. The methanol solution of mulberrofuran I (2) was kept at room temperature for 15 days, and then the uv spectra were measured (Fig. 4). The differrentiated and difference uv spectra of the above methanol solution showed that albanol B (1) can be derived from mulberrofuran I (2) in the solution.

From the above results, albanol B (1) was confirmed to be an artifact derived from mulberrofuran I (2), and the possible mechanism can be described as shown in Fig. 5.[8] From this point of view, mulberrofuran P (3) seems to be an artifact derived from

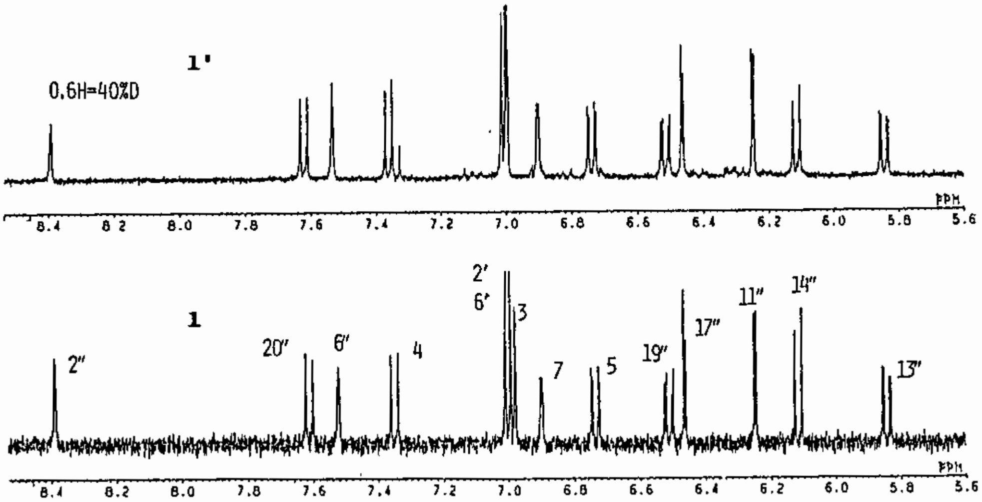


Fig. 3 ^{1}H Nmr spectra (CD_3OD) of albanol B (1) and 1' in aromatic region.

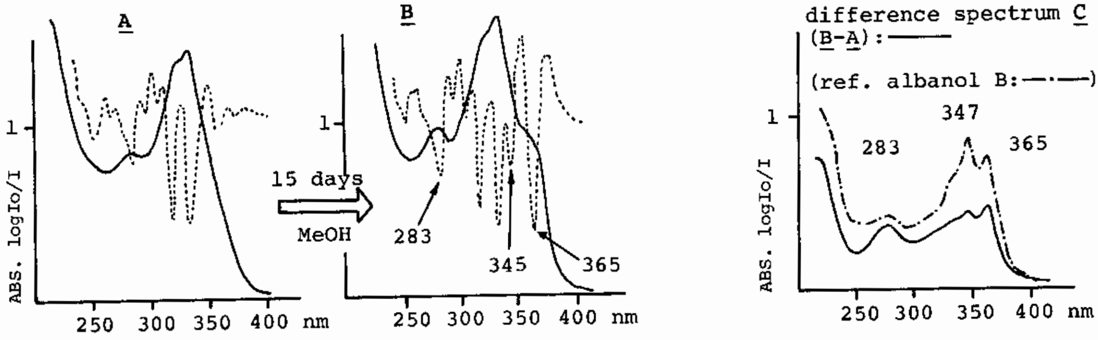


Fig. 4 Uv spectra of mulberrofuran I (2) in MeOH (A and B : ——), its difrentiated spectra (----), and difference spectrum C (B-A).

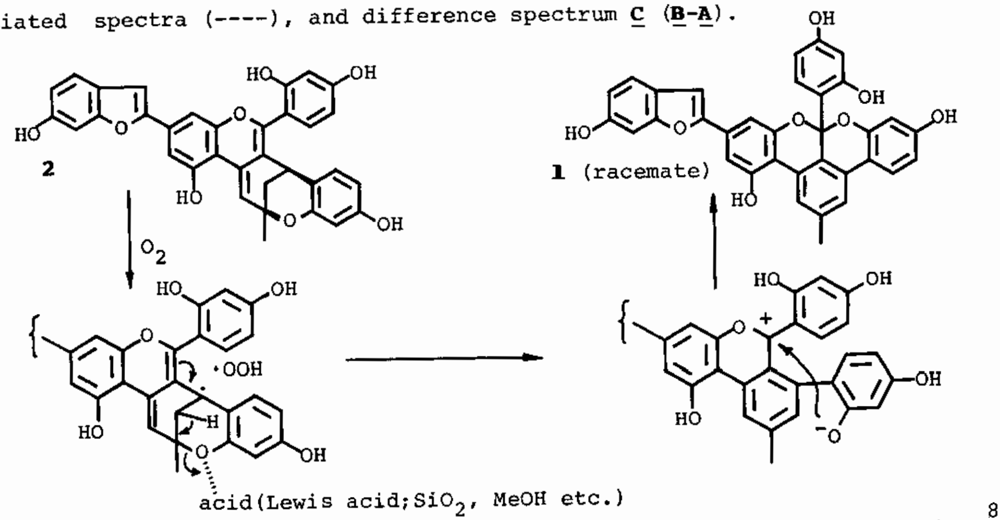


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Fig.5 Possible mechanism of the formation from 2 to 1 by autoxidation.

the posturated compound (4). We re-examined the extract of the reddish violet powder of the Morus root bark to find the compound (4). From the acetone extract (8.5 g), the compound (4, 5 mg), named mulberrofuran S, was isolated sequentially by silica gel column chromatography ($CHCl_3$-acetone as an eluent, eluates with 10% acetone), and by preparative tlc (benzene:AcOEt=2:1, $CHCl_3$:MeOH=6:1, Et_2O only). Mulberrofuran S (4) was obtained as reddish amorphous powder, $[\alpha]_D^{23}$ +166° (c=0.13, EtOH), and showed the following spectra: FAB-ms m/z: 577 $(M+H)^+$, 576 (M^+); ir ν_{max}^{KBr} cm^{-1}: 3400, 1660, 1620, 1600(sh), 1500, 1490, 1460. The uv spectrum of 4 showed the following maxima: uv λ_{max}^{EtOH} nm (log ε): 284 (3.87), 324 (4.13), 335 (4.12), and was similar to that of mulberrofuran I (2). Acidic solution of 4 showed a red color, which faded when neutralized, and the uv spectrum of the acidic solution showed a bathochromic shift as follows: $\lambda_{max}^{EtOH+HCl}$ nm (log ε): 285 (3.87), 324 (4.08), 335 (4.10), 460 (3.39), 545 (3.76). The ^1H nmr spectrum (acetone-d_6) was analysed by comparison with the spectrum of 2 as follows: δ 1.60 (3H, s, C-3"-CH_3), 3.75 (1H, d, J=4, C-5"-H), 3.92 (1H, dd, J=1.8 and 4, C-4"-H), 6.21 (1H, dd, J=2 and 8, C-19"-H), 6.22 (1H, br, C-17"-H), 6.55 (1H, d, J=8, C-20"-H), 6.59 (1H, d, J=2, C-11"-H), 6.60 (1H, d, J=1.8, C-2"-H), 6.62 (1H, dd, J=2 and 8, C-13"-H), 6.82 (1H, dd, J=2 and 8, C-5-H), 6.97 (1H, br d, J=2, C-7-H), 7.00 (1H, d, J=2, C-6'-H), 7.12 (1H, d, J=2, C-2'-H), 7.13 (1H, d, J=1, C-3-H), 7.39 (1H, d, J=8, C-14"-H), 7.41 (1H, d, J=8, C-4-H). These spectral data suggest that mulberrofuran S is 4"-hydroxymulberrofuran I (4). Being observed the long-range coupling (J=1.8 Hz) between the C-2"-H and C-4"-H, the relationship between C-5"-H and C-4"-H is trans configuration in relative. From the above results, the structure (4) was proposed for mulberrofuran S. Considering the correlation of albanol B (1) to mulberrofuran I (2), mulberrofuran P (3) may be also an artifact from mulberrofuran S (4).[10]

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6. The optical rotation value of albanol B (**1**) was not given in reference 4, while our group reported the optical rotation value in reference 5 as follows: $[\alpha]_D^{20}$ -15° (c=0.02, MeOH). We re-examined the optical rotation value of **1** and obtained the following result: $[\alpha]_D^{20}$ 0° (c=0.12, MeOH).

7. Y. Hano, T. Fukai, H. Tsubura, and T. Nomura, Abstract Papers of 27th Symposium on the Chemistry of Natural Products, p. 710, Oct. 1985, Hiroshima, Japan.

8. Since albanol B (**1**) could be derived from **2** as a racemic form, the hydrogen at C-5" position should be eliminated in the reaction process before the attack of the phenoxy ion to the carbonium cation. While we have not obtained the experimental proof, it seems that oxygen molecule takes part in the reaction.

9. Since the absolute configuration of mulberrofuran G (**7**) has been confirmed, the absolute configuration at C-8" position of **7b** is *R*. : Y. Hano, S. Suzuki, T. Nomura, and Y. Iitaka, *Heterocycles*, 1988, **27**, 2315.

10. On the course of separation of **1** and **3**, we used silica gel column chromatography and thin layer chromatography (tlc) with solvent mixture containing methanol.[2,5a]

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