

ABSOLUTE CONFIGURATION OF NATURAL DIELS-ALDER TYPE ADDUCTS FROM
THE MORUS ROOT BARK

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Abstract — Absolute configuration of optically active Diels-Alder type adducts from the Morus root bark, which are regarded as adducts of chalcones and dehydroprenylphenols, were determined on the basis of X-ray crystallographic analysis and the cd spectra. Absolute configuration of the chiral centers on the methylcyclohexene ring in the cis-trans adducts was established to be 3"S, 4"R, 5"S, while in the all-trans adducts to be 3"R, 4"R, 5"S.

Optically active Diels-Alder type adducts of chalcones with dehydroprenylphenols have been isolated from the root bark of mulberry tree.² Generally these adducts have three chiral centers on the methylcyclohexene ring in some structures, such as of kuwanon G (1),³ mulberrofuran C (2)⁴ and so on. In the previous paper, we reported the determination of the absolute configuration of the chiral centers in

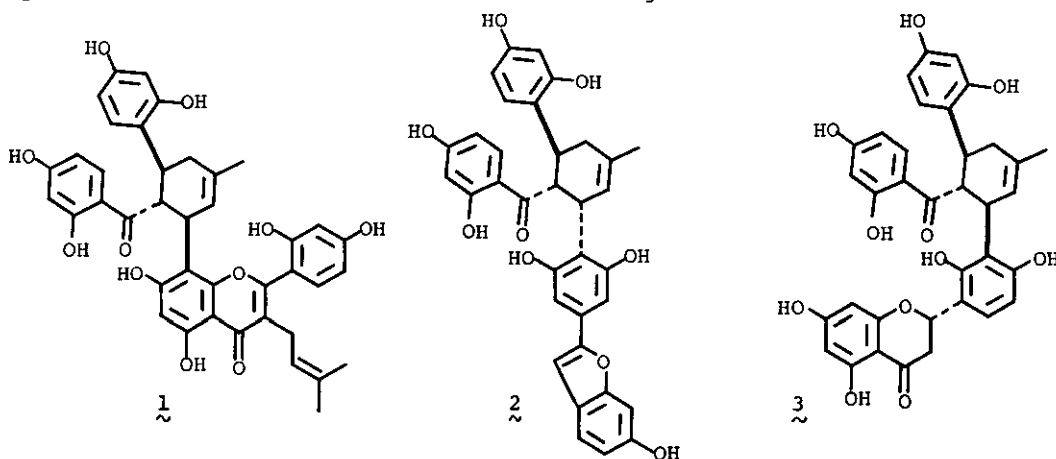


Fig. 1

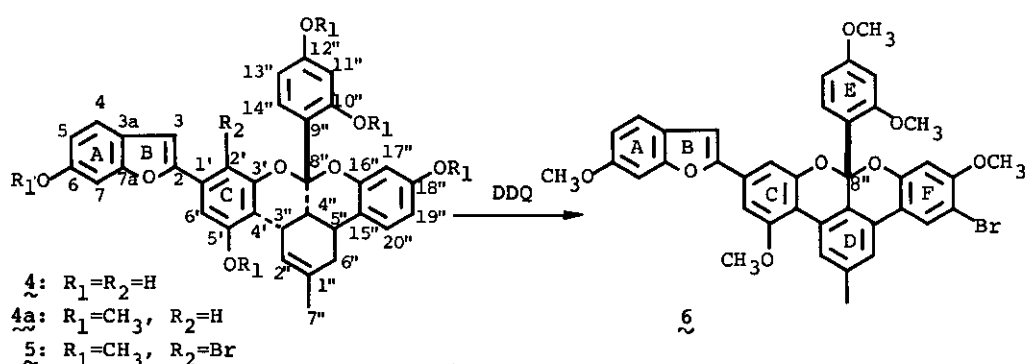


Chart 1

Table 1 ^{13}C nmr chemical shifts (ppm) in $CDCl_3$

$\sim$ 5		$\sim$ 6		$\sim$ 5		$\sim$ 6		$\sim$ 5		$\sim$ 6	
C-2	158.0	158.4	C-1"	129.7	139.6	C-15"	118.3	122.3			
C-3	104.0	101.7	C-2"	121.0	126.1	C-16"	151.8*	151.2*			
C-3a	121.8	122.5	C-3"	36.4	130.3	C-17"	99.8	104.5			
C-4	121.0	122.1	C-4"	27.4	111.8	C-18"	154.5*	152.7*			
C-5	111.6	112.2	C-5"	34.3	127.5	C-19"	107.9	102.7			
C-6	157.8*	156.0*	C-6"	35.3	120.7	C-20"	126.2	127.1			
C-7	95.3	95.9	C-7"	23.8	22.2						
C-7a	156.9*	154.5	C-8"	102.5	104.4		55.0	55.1			
C-1'	133.2	131.5	C-9"	117.4	118.3		55.1	55.8x2			
C-2'	101.2	102.1	C-10"	158.5*	159.8*		55.3	56.1			
C-3'	149.1*	156.7*	C-11"	101.4	100.1		55.5	56.3			
C-4'	114.7	116.3	C-12"	160.7*	161.7*		55.7				
C-5'	152.0*	158.0	C-13"	106.8	107.3						
C-6'	104.1	102.3	C-14"	129.2	131.3						

*; Assignments may be interchanged.

the cyclohexene ring of kuwanon L ($\sim$ 3) which is regarded as a Diels-Alder type adduct of chalcone with 3'-dehydroprenylflavanone, to be 3" $\underline{R}$, 4" $\underline{R}$, 5" $\underline{S}$ by using dibenzoate rule in the circular dichroism (cd) spectroscopy.⁵ In this paper, we report the determination of the absolute configuration of Diels-Alder type adducts from the Morus root bark by using X-ray crystallographic analysis and the cd spectroscopy.

Previously we reported that mulberrofuran G (=albanol A, $\sim$ 4) was derived from mulberrofuran C (2) through the ketalization reaction under acidic condition.⁶ while Rama Rao reported the structure of $\sim$ 4 by the X-ray crystallographic analysis of albanol A pentamethyl ether ($\sim$ 4a) by direct method,⁷ these results suggest that the absolute configuration of $\sim$ 2 should be confirmed by determining that of $\sim$ 4. For the purpose of this determination by the X-ray analysis, we attempted

the introduction of bromine into 4a. After N-bromosuccinimide (NBS, 30 mg) was added to a solution of 4a (100 mg) in carbon tetrachloride (5 ml), the solution was allowed to stand for 17 h at room temperature. From the reaction mixture, the compound A (5, 30 mg) was obtained as a main product (Chart 1), which forms colorless crystalline powder, mp 162-164 °C, $[\alpha]_D^{20} +581^\circ$ ($c=0.085$, CHCl_3), and showed the molecular ion peak in the mass spectrum at m/z 710 accompanied by the isotope peak of ^{81}Br at m/z 712 demonstrating a mono-bromo derivative. The location of Br was confirmed from the facts that the ^1H nuclear magnetic resonance (nmr) spectrum of 5⁸ showed only one-proton singlet signal at δ 7.05 ppm in the C-ring as compared with the spectrum of 4a⁶, and that the ^{13}C nmr spectrum of 5 showed five methoxyl carbon signals at δ 55.0, 55.1, 55.3, 55.5 and 55.7 ppm (Table 1). On the other hand, Dhimi reported that the aromatic methoxyl carbon atom signal(s) appear(s) at $\delta \sim 55$ ppm in the case of mono-ortho substitution of the methoxyl group and at $\delta \sim 60$ ppm in the case of di-ortho substitution.⁹ From the above results, compound A was represented by formula 5. For the purpose of obtaining the crystalline form for X-ray analysis, the following reaction was carried out. The mixture of 5 (32 mg) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 21 mg) in dry benzene (30 ml) was refluxed for 8 h, and the product was purified by preparative TLC to afford compound B (6, 15 mg) (Chart 1) as yellow needles, mp 268-272 °C, $[\alpha]_D^{26} +73^\circ$ ($c=0.18$, CHCl_3). The mass spectrum of 6 showed the molecular ion peak at m/z 706 accompanied by isotope peak at m/z 708. In the ^1H nmr spectrum of 6 (CDCl_3), all the cyclohexene ring proton signals of 5 disappeared and, in place of these signals, the two aromatic proton signals assignable to C-2"-H and C-6"-H appeared at δ 8.27 and 7.45 ppm, respectively. Other signals were analysed by comparing with the ^1H nmr spectrum of 6 as follows; 2-arylbenzofuran moiety [δ 6.87 (1H, dd, $J=2$ and 8 Hz, C-5-H), 6.94 (1H, d, $J=1$ Hz, C-3-H), 7.04 (1H, d, $J=2$ Hz, C-6'-H), 7.07 (1H, br d, $J=2$ Hz, C-7-H), 7.15 (1H, d, $J=2$ Hz, C-2'-H), 7.43 (1H, d, $J=8$ Hz, C-4-H)], E-ring [δ 6.02 (1H, dd, $J=2$ and 8Hz, C-13"-H), 6.41 (1H, d, $J=2$ Hz, C-11"-H), 6.44 (1H, d, $J=8$ Hz, C-14"-H)], F-ring [δ 6.61 and 7.85 (each 1H, s, C-17"-H and C-20"-H)], aromatic methyl group [δ 2.54 (3H, s, C-1"-CH₃)], and five methoxyl groups [δ 3.62, 3.84, 3.88, 4.00, and 4.04 (each 3H, s)]. These findings suggest the migration of Br caused by the treatment of 5 with DDQ, and the formula 6 was proposed for the compound B.²³

In order to determine the absolute configuration of sole chiral center at C-8" of 6, the X-ray crystallographic analysis of 6 was carried out and the following

crystallographic data were obtained; $C_{39}H_{31}O_8Br$, molecular weight=707.6, rhombic, space group $P2_12_12_1$, lattice constants, $a=19.5549 \text{ \AA}$, $b=21.9659 \text{ \AA}$, $c=7.5550 \text{ \AA}$, $\alpha=\beta=\gamma=90^\circ$, $Z=4$, the final R value 0.056. The crystal structure of **6** was determined as shown in Fig. 2 and the absolute configuration at C-8" was shown to be R. On the other hand the relationship between C-4"-H and the phenyl group at C-8" in mulberrofuran **G** (**4**) has been found to be cis.^{6,7} Accordingly the absolute configurations of four chiral centers of **4** were 3"S, 4"R, 5"S, 8"R. As stated above, mulberrofuran **G** (**4**) was derived from mulberrofuran **C** (**2**). Consequently the absolute configurations of three chiral centers on the methylcyclohexene ring of **2** were determined to be 3"S, 4"R, 5"S. The cd spectra of eight Diels-Alder type adducts from the Morus root bark were shown in Fig. 3. These adducts can be divided into following two types, the all-trans type adducts (in relative configuration of the three substituents on the methylcyclohexene ring) and cis-trans type adducts (Fig. 5). Comparison of the cd curves of the all-trans type adducts with those of the cis-trans type adducts shows that the former tend to be negative, while the latter tend to be positive. Particularly this tendency is remarkable in a pair of stereoisomers, e.g. kuwanons **X** (**7**)^{2d} and **Y** (**8**)^{2f}, sanggenons **C** (**9**)¹⁰ and **D** (**10**)¹¹, mulberrofurans **C** (**2**) and **J** (**11**)^{2d}. In the cd spectra, magnitude of $\Delta\epsilon$ values of **2** and **11** are larger than in any others, and both spectra exhibit split Cotton curves suggesting an exciton coupling.¹² In order to clarify this suggestion, lithium aluminum hydride ($LiAlH_4$) reduction of **2** and **11** was carried out. A solution of **2** (15 mg) and $LiAlH_4$ (20 mg) in ether (20 ml) was refluxed for 2 h,

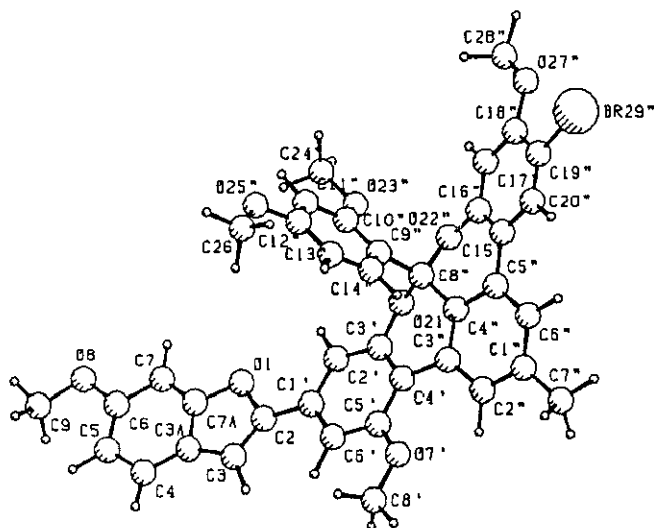


Fig. 2 The crystal structure of **6**

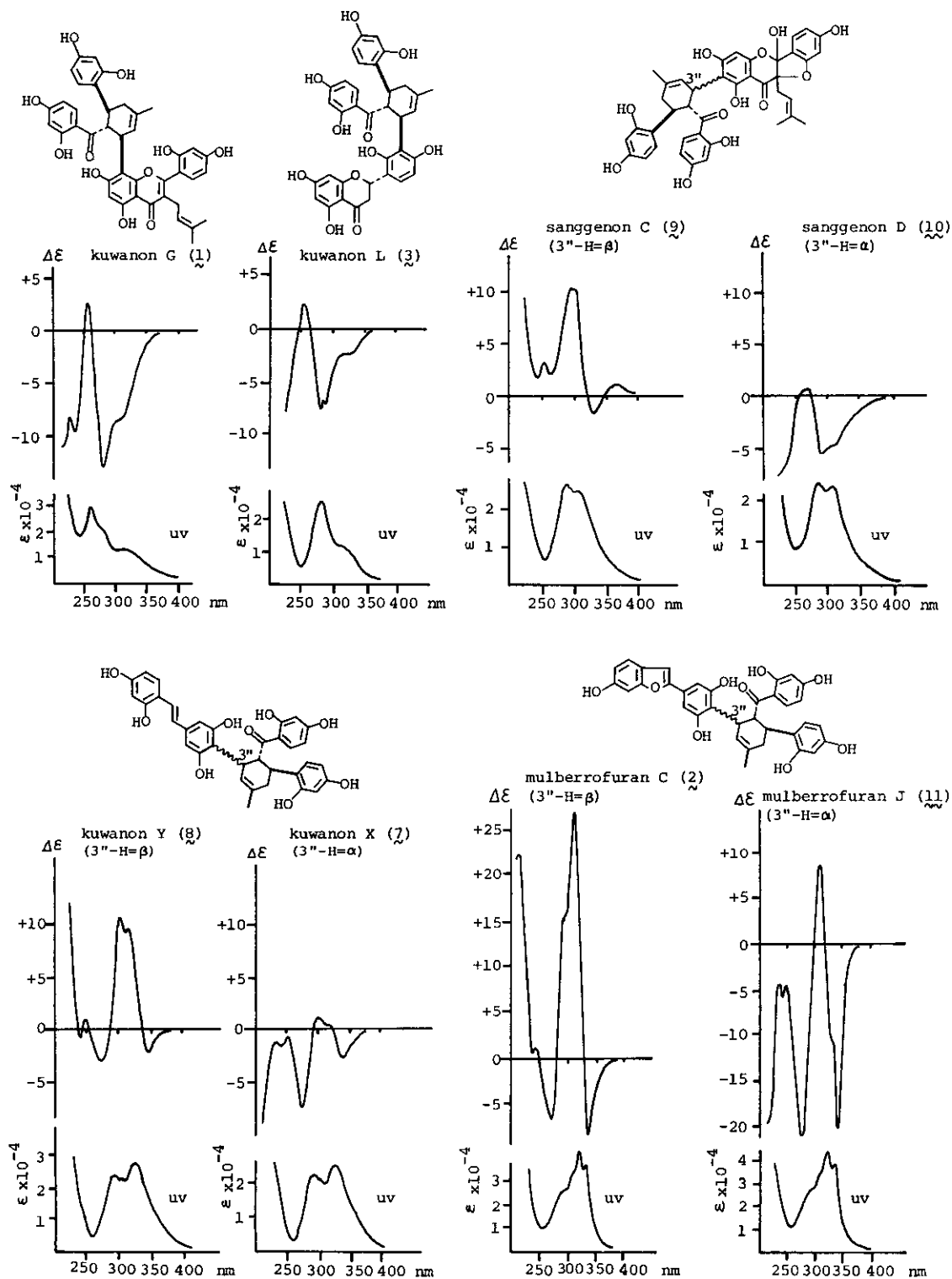


Fig. 3

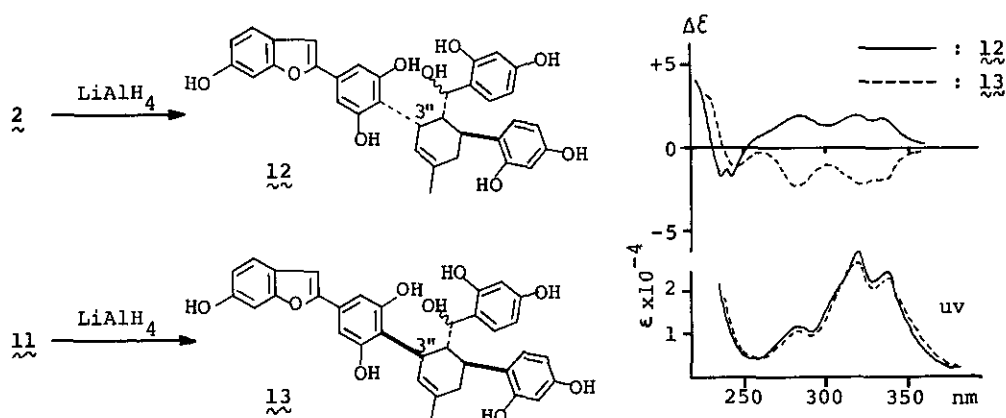


Fig. 4

and the products were purified by preparative thin layer chromatography to afford compound **12** (5 mg).¹³ LiAlH_4 reduction of **11** was also carried out in the same way to afford compound **13**.¹⁴ No split Cotton curve was observed in the cd spectra of **12** and **13** (Fig. 4), and $\Delta\epsilon$ values decreased remarkably as compared with those of **2** and **11**. These results clearly indicate that the exciton coupling takes place between 2,4-dihydroxybenzoyl and 2-arylbenzofuran chromophores in **2** and **11**.¹² In addition, the cd spectra of **12** and **13** showed the curves opposite to each other in the absorption range of 2-arylbenzofuran chromophore. These findings indicate that the absolute configurations at the C-3'' positions bearing the 2-arylbenzofuran moiety in **12** and **13** are opposite to each other. Namely, the absolute configurations at C-3'' positions in **2** and **11** are also opposite to each other. Therefore, the absolute configurations of mulberrofuran J (**11**) were determined to be 3''R, 4''R, 5''S.

As stated above, the cd curves of the cis-trans adducts, which are of the same relative configuration as that of mulberrofuran C (**2**), tend to be positive as **12**, while the all-trans adducts such as mulberrofuran J (**11**) tend to be negative as **13** (Fig. 3 and 4). Furthermore, comparison of the optical rotations were carried out in the Diels-Alder type adducts from the Morus root bark, and the results were summarized in Table 2. The cis-trans adducts exhibit positive optical rotations, while the all-trans adducts exhibit negative values. In the absolute configurations of **2** and **11**, the difference is found only at C-3''. Consequently, one may conclude that the configuration at the C-3'' chiral center influences the sign of the cd curves and that of the optical rotation. Hence, the absolute configurations of the cis-trans adducts would be the same as that of mulberrofuran C (**2**), while those of the

all-trans adducts would be the same as that of mulberrofuran J (11).

Taking the above results into consideration along with the magnitude of the coupling constants between the proton signals on the methylcyclohexene ring of the all-trans adducts ($J_{3''H-4''H} \neq J_{4''H-5''H} \neq 10 \text{ Hz}$)^{2,3} and the cis-trans adducts ($J_{3''H-4''H} \div 5 \text{ Hz}$, $J_{4''H-5''H} \neq 4 \text{ Hz}$)^{2,4}, the absolute configurations of the methylcyclohexene ring, including the conformation of the cyclohexene ring (Fig. 5), in the cis-trans adducts was determined to be 3"S, 4"R, 5"S and those of the all-trans adducts to be 3"R, 4"R, 5"S.¹⁵ The absolute configuration of kuwanon L (3) resolved in the previous paper was in fair agreement with this conclusion.⁵

On the other hand, the ketalized compounds, mulberrofurans F (14)⁶ K (15)¹⁶ and kuwanol A (16)^{2b} also isolated from the Morus root bark, have been derived from chalcomoracin (17)¹⁷ and kuwanon Y (8) under acidic condition, respectively.

Considering the absolute configuration of mulberrofuran G (4) stated above and $[\alpha]_D$ values of these compounds (Table 3), the absolute configurations of 14, 15 and 16 was also determined to be 3"S, 4"R, 5"S, 8"R as in 4. However, the conformation of the cyclohexene ring of these ketal compounds seems to be different from that of mulberrofuran C (2), chalcomoracin (17) and kuwanon Y (8). For example, the the coupling constant ($J=4\text{Hz}$) between C-4"-H and C-5"-H changed into 11 Hz in 4 indicating that the conformation of the cyclohexene ring in 2 has been reversed through the ketalization reaction to 4. Therefore, the conformation of the cyclohexene ring of ketalized compounds, mulberrofurans G (4), F (14), K (15) and kuwanol A (16) can be shown as illustrated in Fig. 6.

Table 2 Optical rotations ($[\alpha]_D$) of Diels-Alder type adducts

<u>all-trans</u>		<u>cis-trans</u>	
mulberrofuran J (<u>11</u>)	-341°	mulberrofuran C (<u>2</u>)	+153°
kuwanon G (<u>1</u>)	-534°	kuwanon J ¹⁸	+85°
kuwanon H ¹⁹	-536°	kuwanon Q ¹⁸	+160°
kuwanon I ²⁰	-454°	kuwanon R ¹⁸	+56°
kuwanon K ²¹	-218°	kuwanon V ¹⁸	+145°
kuwanon L (<u>3</u>)	-227°	kuwanon Y (<u>8</u>)	+172°
kuwanon N ²²	-188°	chalcomoracin (<u>17</u>)	+193°
kuwanon O ²²	-243°	sanggenon C (<u>9</u>)	+304°
kuwanon P ^{2d}	-509°	sanggenon P ^{2e}	+215°
kuwanon W ^{2c}	-440°		
kuwanon X (<u>7</u>)	-322°		
sanggenon D (<u>10</u>)	-145°		
sanggenon E ^{2e}	-86°		

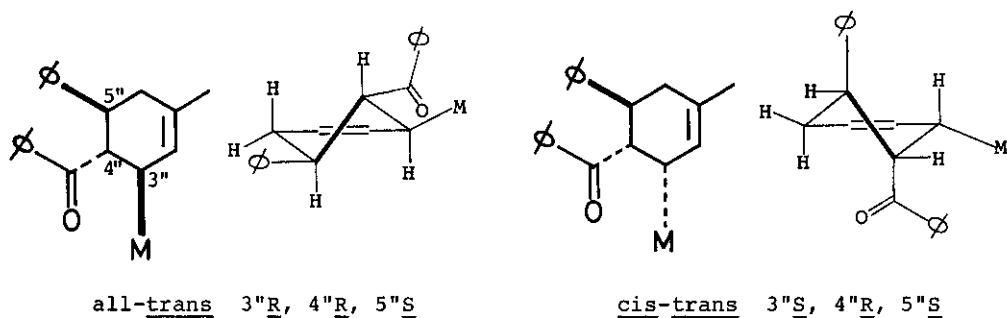


Fig. 5

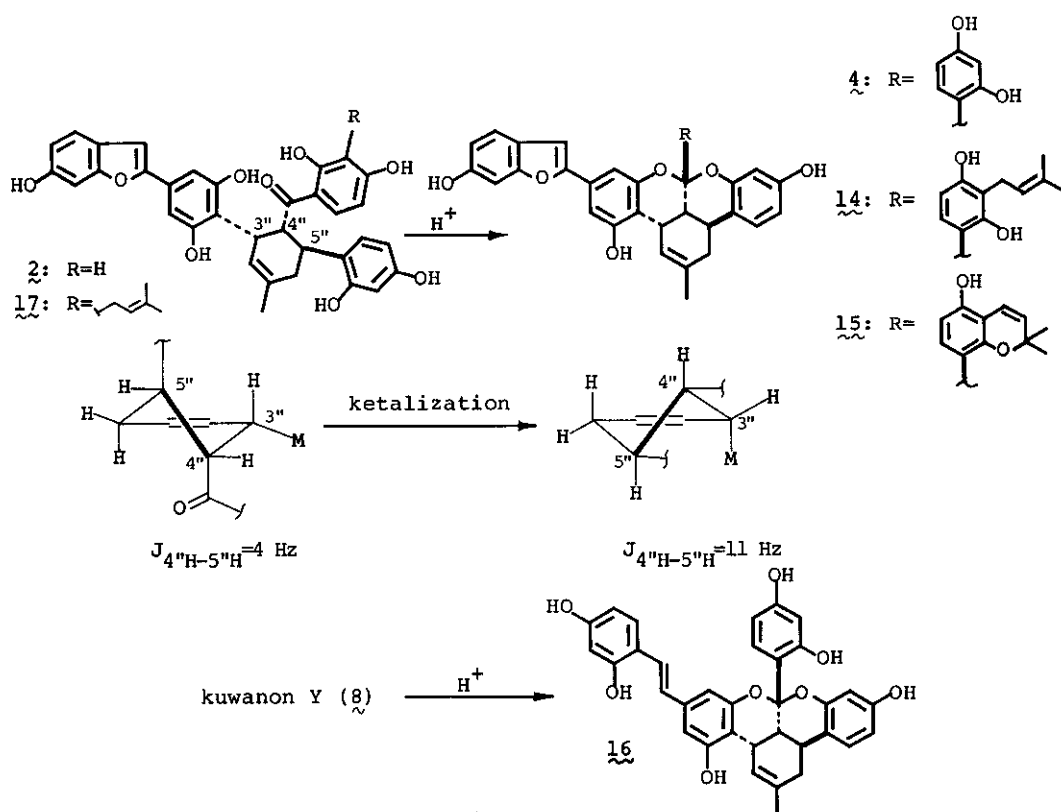


Fig. 6

Table 3 Optical rotations ($[\alpha]_D$) of ketalized compounds

mulberrofuran G (4)	+546°
mulberrofuran F (14)	+513°
mulberrofuran K (15)	+455°
kuwanol A (16)	+577°

ACKNOWLEDGEMENT

We are grateful to Prof. H. Ishii, Faculty of Pharmaceutical Sciences, Chiba University, for the cd spectral measurements.

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 δ 1.79 (3H, s, C-1"-CH₃), 2.10 (1H, dd, J=12 and 17, C-6"-H), 2.65 (1H, dd, J=6 and 17, C-6"-H), 3.04 (1H, dt, J=6 and 12, C-5"-H), 3.31 (1H, dd, J=6 and 12, C-4"-H), 3.37 (1H, brt, J=6, C-3"-H), 3.75 (3H, s, OCH₃), 3.77 (6H, s, OCH₃ x2), 3.85, 3.87 (each 3H, s, OCH₃), 6.24 (1H, brd, J=6, C-2"-H), 6.34 (1H, dd, J=2 and 8, C-13"-H), 6.48 (1H, d, J=2, C-11"-H), 6.57 (1H, d, J=2, C-17"-H), 6.58 (1H, dd, J=2 and 8, C-19"-H), 6.89 (1H, dd, J=2 and 8, C-5-H), 7.05 (1H, s, C-6'-H), 7.06 (1H, brd, J=2, C-7-H), 7.14 (1H, d, J=8, C-20"-H), 7.19 (1H, d, J=8, C-14"-H), 7.48 (1H, d, J=8, C-4-H), 7.54 (1H, d, J=1, C-3-H),
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13. The spectral data of 12 were as follows: FD-MS m/z : 582 (M^+). $uv \lambda_{max}^{EtOH}$ nm ($\log \epsilon$): 220(4.40), 284(4.22), 306(infl. 4.35), 318(4.52), 332(4.45). 1H nmr (acetone- d_6); δ 1.80(3H, s), 1.88(1H, d, $J=16$), 2.53(1H, brd, $J=16$), 2.75(1H, brdd, $J=6$ and 11), 3.26(1H, dd, $J=3$ and 6), 3.39(1H, brs), 5.51(1H, d, $J=11$), 5.66(1H, brs), 6.29(1H, dd, $J=2$ and 8), 6.40(1H, d, $J=2$), 6.45(1H, dd, $J=2$ and 8), 6.50(1H, d, $J=2$), 6.75(1H, d, $J=2$), 6.78(1H, dd, $J=2$ and 8), 6.91(1H, d, $J=2$), 6.92(1H, d, $J=8$), 6.94(1H, brd, $J=2$), 6.96(1H, d, $J=1$), 7.37(1H, d, $J=8$), 7.49(1H, d, $J=8$). cd ($c=3.26 \times 10^{-5}$): $\Delta\epsilon_{max}$; $\Delta\epsilon_{322} +3.2$, $\Delta\epsilon_{318} +3.7$, $\Delta\epsilon_{283} +3.7$, $\Delta\epsilon_{246} -3.6$.
14. The spectral data of 13 were as follows: FD-MS m/z : 582 (M^+). $uv \lambda_{max}^{EtOH}$ nm ($\log \epsilon$): 224(sh 4.30), 285(4.14), 310(infl. 4.27), 321(4.43), 337(4.35). 1H nmr (acetone- d_6); δ 1.76(3H, s), $\sim$ 2.05(1H, overlapping with solvent), 2.14(1H, br), 3.02(1H, br), 3.31(1H, td, $J=11$ and 5), 3.91(1H, d, $J=11$), 5.10(1H, brs), 5.26(1H, br), 5.82(1H, dd, $J=2$ and 8), 6.06(1H, d, $J=2$), 6.50(1H, d, $J=2$), 6.63(1H, d, $J=2$), 6.77(1H, d, $J=1$), 6.79(1H, dd, $J=2$ and 8), 6.79(1H, d, $J=8$), 6.94(1H, brd, $J=2$), 7.17(1H, d, $J=8$), 7.36(1H, d, $J=8$). cd ($c=2.92 \times 10^{-5}$): $\Delta\epsilon_{max}$; $\Delta\epsilon_{337} -4.6$, $\Delta\epsilon_{322} -4.6$, $\Delta\epsilon_{285} -5.4$, $\Delta\epsilon_{248} -2.5$.
15. Previously, in the Symposium Papers, The 28th Symposium on the Chemistry of Natural Products (1986, p 1, Sendai), the absolute configurations for the methylcyclohexene rings of Diels-Alder type adducts have been described as 3"S, 4"R, 5"S for the all-trans adducts, while 3"R, 4"R, 5"S for the cis-trans adducts. We made a careless mistake concerning the symbol for C-3" position of cyclohexene ring. We revised the description to be 3"R, 4"R, 5"S for the all-trans adducts and 3"S, 4"R, 5"S for the cis-trans adducts.
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23. The compound 5 was confirmed to be pure on the basis of nmr (^1H and ^{13}C) spectral evidence. Treatment of 5 with DDQ gave a starting material 5 and a sole product 6. The mechanism of this specific Br migration is now in progress.

Received, 28th May, 1988