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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

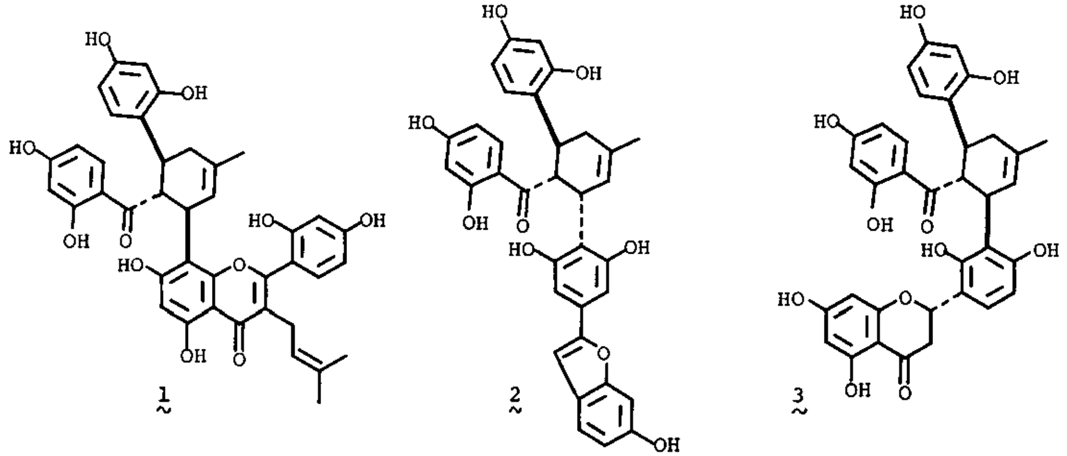
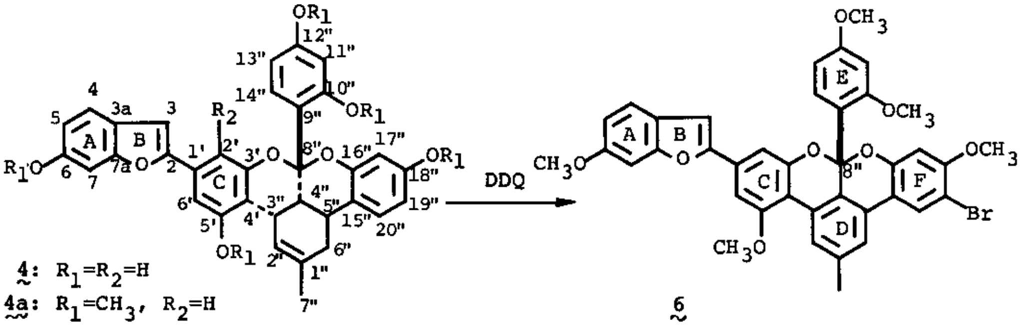


Fig. 1



4: $R_1=R_2=H$
4a: $R_1=CH_3$, $R_2=H$
5: $R_1=CH_3$, $R_2=Br$

6

Chart 1

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

	5	6		5	6		5	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	OCH_3	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 (3) which is regarded as a Diels-Alder type adduct of chalcone with 3'-dehydroprenylflavanone, to be 3"*R*, 4"*R*, 5"*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, 4) was derived from mulberrofuran C (2) through the ketalization reaction under acidic condition.[6] while Rama Rao reported the structure of 4 by the X-ray crystallographic analysis of albanol A pentamethyl ether (4a) by direct method,[7] these results suggest that the absolute configuration of 2 should be confirmed by determining that of 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° (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 ^{1}H nuclear magnetic resonance (nmr) spectrum of 5[8] showed only one-proton singlet signal at δ 7.05 ppm in the C-ring as compared with the spectrum of 4a[6], 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, Dhami reported that the aromatic methoxyl carbon atom signal(s) appear(s) at δ ~ 55 ppm in the case of mono-ortho substitution of the methoxyl group and at δ ~ 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° (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 ^{1}H 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 ^{1}H 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"-CH_3)], 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 Å, b=21.9659 Å, c=7.5550 Å, $\alpha=\beta=\gamma=90°$, 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 $\Delta\varepsilon$ 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,

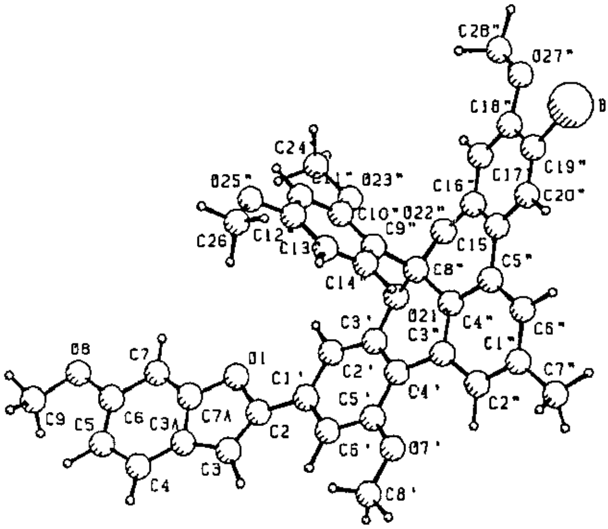


Fig. 2 The crystal structure of 6

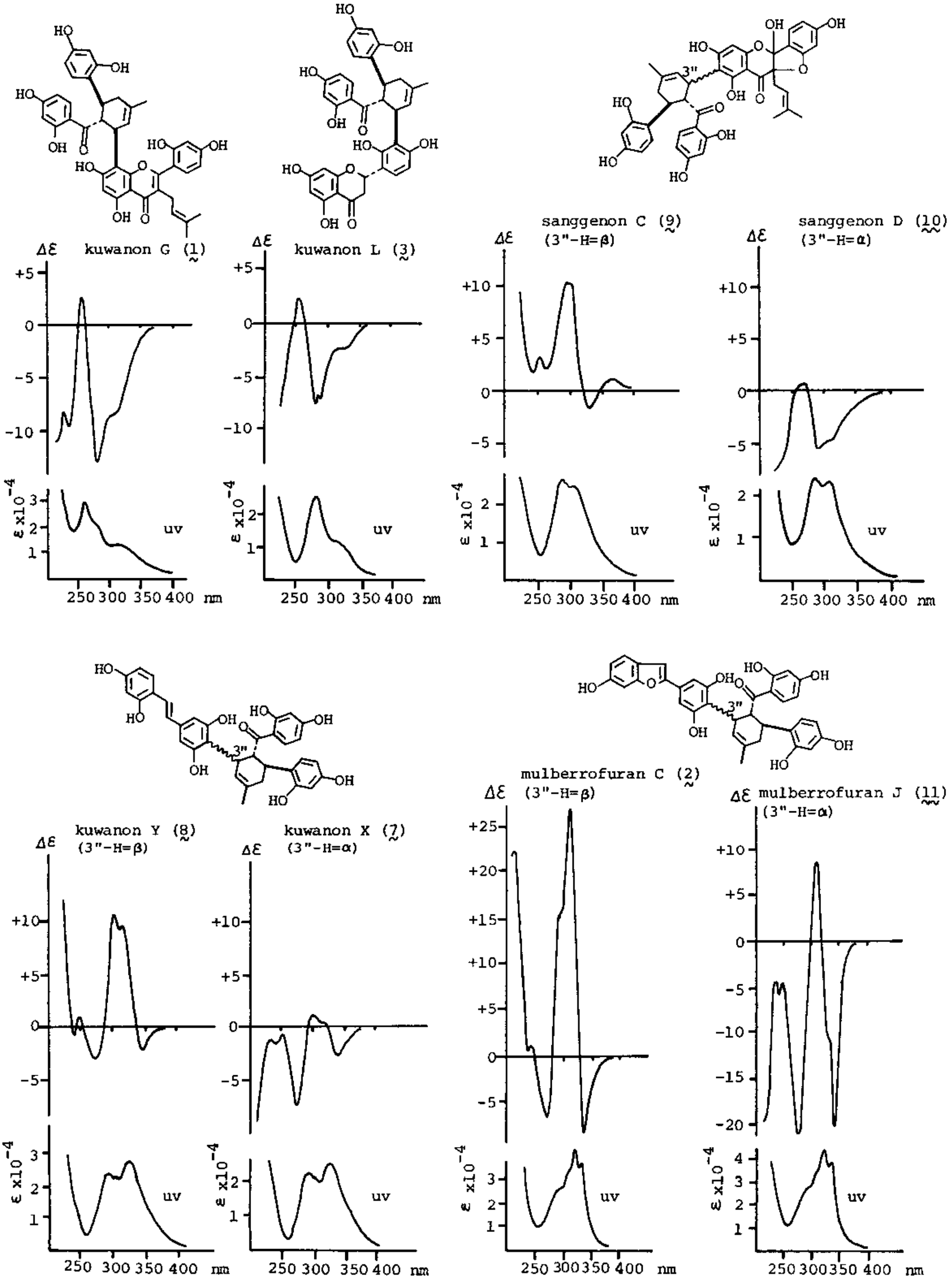

kuwanon G (1)
kuwanon L (3)
sanggenon C (9)
(3"-H=β)
sanggenon D (10)
(3"-H=α)
kuwanon Y (8)
(3"-H=β)
kuwanon X (7)
(3"-H=α)
mulberrofuran C (2)
(3"-H=β)
mulberrofuran J (11)
(3"-H=α)
Δε
ε x10⁻⁴
uv
250 300 350 400 nm
3"
HO
OH
O

Fig. 3

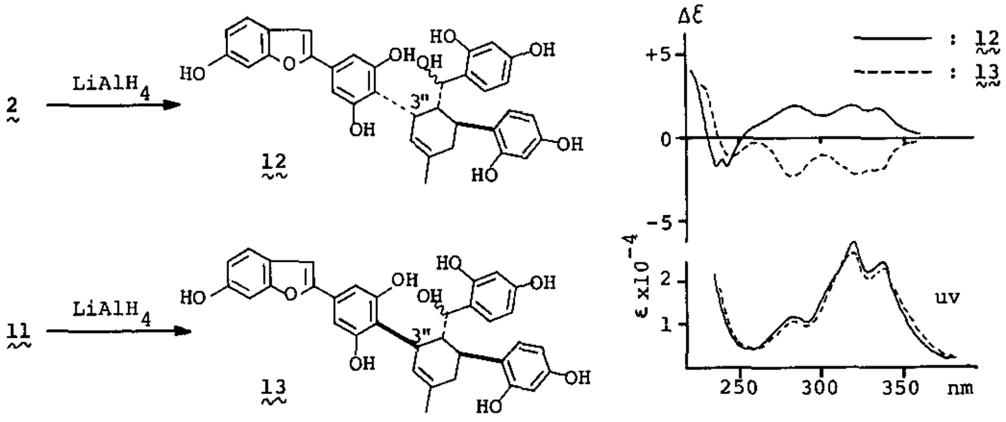


Fig. 4

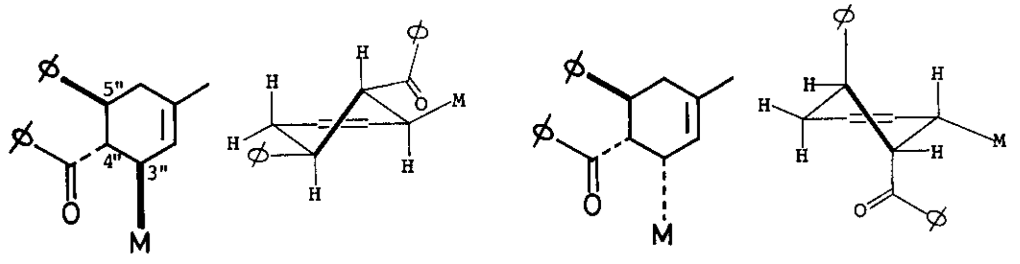
and the products were purified by preparative thin layer chromatography to afford compound 12 (5 mg).[13] LiAlH$_4$ reduction of 11 was also carried out in the same way to afford compound 13.[14] No split Cotton curve was observed in the cd spectra of 12 and 13 (Fig. 4), and Δε values decreased remarkably 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 ($J_{3''H-4''H} \fallingdotseq J_{4''H-5''H} \fallingdotseq 10$ Hz)[2,3] and the *cis*-*trans* adducts ($J_{3''H-4''H} \fallingdotseq 5$ Hz, $J_{4''H-5''H} \fallingdotseq 4$ 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≈4Hz) 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

all-*trans*		*cis*-*trans*	
mulberrofuran J (**11**)	-341°	mulberrofuran C (**2**)	+153°
kuwanon G (**1**)	-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 (**3**)	-227°	kuwanon Y (**8**)	+172°
kuwanon N[22]	-188°	chalcomoracin (**17**)	+193°
kuwanon O[22]	-243°	sanggenon C (**9**)	+304°
kuwanon P[2d]	-509°	sanggenon P[2e]	+215°
kuwanon W[2c]	-440°		
kuwanon X (**7**)	-322°		
sanggenon D (**10**)	-145°		
sanggenon E[2e]	-86°		



all-trans 3"R, 4"R, 5"S   cis-trans 3"S, 4"R, 5"S

Fig. 5

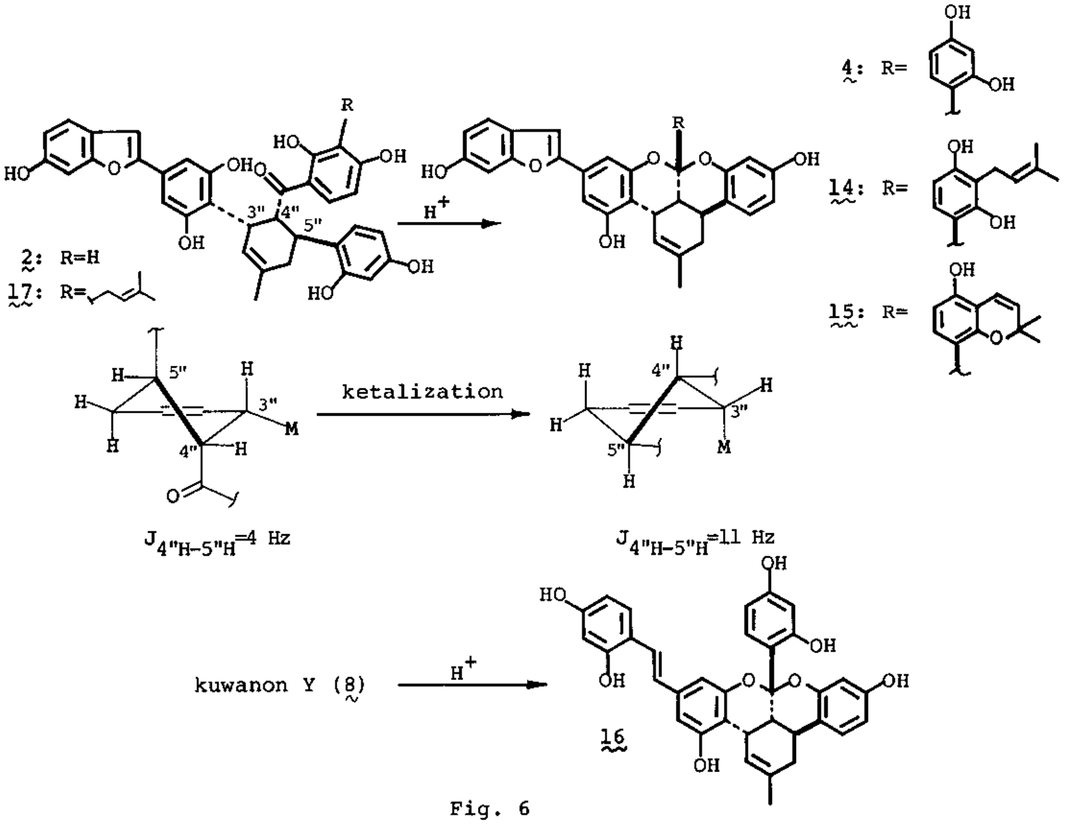


Fig. 6

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°

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8. In the ^{1}H nmr spectrum of **5** (CDCl$_3$), the proton signals were observed as follows: δ 1.79 (3H, s, C-1"-CH$_3$), 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, OCH$_3$), 3.77 (6H, s, OCH$_3$ x2), 3.85, 3.87 (each 3H, s, OCH$_3$), 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 λ_{max}^{EtOH}nm (log ε): 220(4.40), 284(4.22), 306(infl. 4.35), 318(4.52), 332(4.45). ^{1}H 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 x10^{-5}): $\Delta\varepsilon_{max}$; $\Delta\varepsilon_{322}$ +3.2, $\Delta\varepsilon_{318}$ +3.7, $\Delta\varepsilon_{283}$ +3.7, $\Delta\varepsilon_{246}$ -3.6.

14. The spectral data of **13** were as follows: FD-Ms m/z: 582 (M^+). uv λ_{max}^{EtOH} nm (log ε): 224(sh 4.30), 285(4.14), 310(infl. 4.27), 321(4.43), 337(4.35). ^{1}H nmr (acetone-d_6); δ 1.76(3H, s), ∼ 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 x10^{-5}): $\Delta\varepsilon_{max}$; $\Delta\varepsilon_{337}$ -4.6, $\Delta\varepsilon_{322}$ -4.6, $\Delta\varepsilon_{285}$ -5.4, $\Delta\varepsilon_{248}$ -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.

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