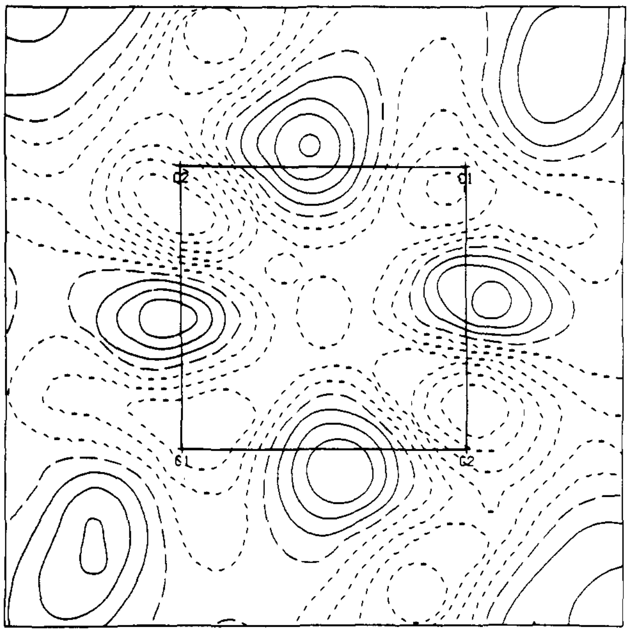

Figure 3. Difference map derived from difference Fourier synthesis. The maximum of the electron density is observed outside the direct C–C bond vectors.

Due to the better agreement of model II to the experimental data and to the results of all the previous investigations on this molecule as well (electron diffraction, spectroscopy, theoretical calculations, as discussed above), we believe model II to be the more reliable one and model I to be a less likely alternative.

Model II was also tested in the other two possible space groups, *I*2 and *Im*. The refinement converged if hydrogen atoms were kept at those positions obtained in *I*2/*m*, but became unstable when hydrogen atoms were allowed to refine.

The time- and space-averaged crystal packing is given in Figure 2. The general arrangement is the same in both models and in all tested space groups. The molecules form stacks parallel to the monoclinic *b* axis. In the *a,c* plane the molecules are slightly rotated around the *b* axis. The angle between the *a* axis and C(1)–C(1)′ is 13°. No particular close H–H contacts are observed.

The residual electron density (Figure 3) shows significant maxima in positions between the carbon atoms. These maxima are displaced tangentially by 0.10 (3) Å to the outside of the C–C bond vectors of the time- and space-averaged molecule, indicating a "banana bond" type electronic arrangement which is frequently found in highly strained small ring systems. In cyclopropane the covalent bonding maxima are displaced by 0.2 Å from the C–C vectors of the carbon triangle. Since in cyclobutane there is reduced ring strain our observation is in good agreement with the cyclopropane findings.

Acknowledgment. We thank the Graduiertenkolleg "Struktur und Synthese niedermolekularer Verbindungen" (A.S.) and the Fonds der Chemie for the granted studentships (C.W.L.) and for further financial support. We thank one of the referees for suggesting some improvements in the handling of refinement for model II.

Supplementary Material Available: List of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

Atropisomerism in Natural Products. Absolute Stereochemistry of Biflavone, (−)-4′,4‴,7,7″-Tetra-*O*-methylcupressuflavone, As Determined by the Theoretical Calculation of CD Spectra

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Contribution from the Institute for Chemical Reaction Science, Tohoku University, 2-1-1 Katahira, Aoba, Sendai 980, Japan, Department of Chemistry, Aligarh Muslim University, Aligarh 202002, India, and Department of Medicinal Chemistry, Indian Institute of Chemical Biology, Calcutta 700032, India. *Received October 3, 1991*

Abstract: The molecular asymmetry due to the atropisomerism of biflavone, (−)-4′,4‴,7,7″-tetra-*O*-methylcupressuflavone (**1**), has been studied by CD spectroscopy, and its absolute stereochemistry has been theoretically determined by the π-electron SCF-CI-DV MO calculation of CD spectra. The molecular geometry of compound (*aR*)-**1** was calculated by molecular mechanics to give a stable conformation with a counterclockwise screw sense, in which the dihedral angle of the biphenyl part was 91°. The calculated CD and UV curves of (*aR*)-**1** were in very good agreement, including sign, position, and amplitude, with those of observed spectra of the natural product: calcd UV, λ_{max} 322.6 nm (ϵ 66 200), and 226.8 (78 300); calcd CD, λ_{ext} 359.7 nm ($\Delta\epsilon$ +28.6), 317.5 (−45.0), and 263.2 (+21.7); obsd UV, λ_{max} 324.2 nm (ϵ 40 900), 273.0 (41 400), and 225.8 (51 800); obsd CD, λ_{ext} 362.0 nm ($\Delta\epsilon$ +25.6), 326.2 (−54.4), and 267.5 (+21.3). The absolute stereochemistry of biflavone (−)-**1** has thus been theoretically determined to be *aR* (or *M* helicity).

Introduction

Optically active biflavones are unique natural products in the sense that they are chiral molecules with molecular dissymmetry. Although monomeric flavones have no chiral center and hence are optically inactive, some biflavones can exist as chiral molecules due to the atropisomerism of the biflavone moiety.[2,3] Such optically active biflavones have been isolated as natural products from various plants and their plane structures have been reported.[2-6] However, the absolute stereochemistry of these natural

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[1] (a) Tohoku University. (b) Aligarh Muslim University. (c) Indian Institute of Chemical Biology.

[2] Ilyas, M.; Usmani, J. N.; Bhatnagar, S. P.; Ilyas, M.; Rahman, W.; Pelter, A. *Tetrahedron Lett.* **1968**, 5515.

[3] Rahman, W.; Ilyas, M.; Okigawa, M.; Kawano, N. *Chem. Pharm. Bull.* **1982**, *30*, 1491.

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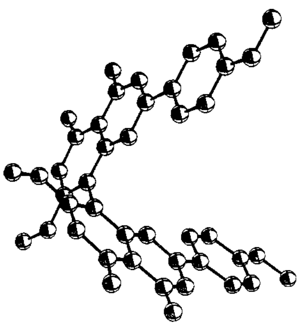

(aR)-1

Figure 1. Stereoscopic view of the stable conformation of biflavone, (*aR*)-4',4''',7,7''-tetra-*O*-methylcupressuflavone (**1**), calculated by the molecular mechanics.

atropisomers has remained undetermined for over 20 years.[7] In this paper, we report the first determination of the absolute stereochemistry of an optically active biflavone, (−)-4',4''',7,7''-tetra-*O*-methylcupressuflavone (**1**), by theoretical calculation of CD spectra.

The CD spectrum of biflavone (−)-**1** exhibits intense bisignate Cotton effects of positive first and negative second signs around 400–300 nm. Therefore, application of the exciton chirality method could be considered. However, we emphasize that the exciton method could not be applied in a straightforward way in the case of biflavone **1** with a complex π-electron system; instead, theoretical calculation of CD and UV spectra by the π-electron SCF-CI-DV MO method provided a powerful tool for the determination of the absolute stereochemistry of atropisomer **1**.

Since the previous determination of the dimeric structure of biflavone **1** was mainly based on empirical studies of ^{1}H NMR chemical shifts,[2-5] we first confirmed the 8–8'' linkage structure in an unambiguous manner by application of more modern ^{1}H and ^{13}C NMR techniques. The stable conformation of the dimer was calculated by the method of molecular mechanics (MMP2).[8] By use of the atomic coordinates obtained, the CD and UV spectra were calculated by application of the π-electron SCF-CI-DV MO method.[9-11] The calculated CD and UV spectral curves were in good agreement with the observed spectra, leading to nonempirical determination of the absolute stereochemistry of biflavone **1**.

Methods of Calculation

Molecular Geometry and Stable Conformation. The molecular framework and conformation of atropisomerism of biflavone (*aR*)-**1** were calculated by molecular mechanics (MMP2)[8] to give the stable conformation depicted in Figure 1. The calculated dihedral angle between the two flat flavone moieties was 91°.

Calculation of CD and UV Spectra. The CD and UV spectral curves of (*aR*)-**1** were calculated by the π-electron SCF-CI-DV MO method.[9-11] In the dipole velocity method, the rotational strength R_{ba} and dipole strength D_{ba} are expressed as follows:

$$R_{ba} = 2(\varphi_a|\nabla|\varphi_b)(\varphi_a|\mathbf{r} \times \nabla|\varphi_b)\beta_M{}^2/(\pi\sigma_{ba}) \qquad (1)$$

$$D_{ba} = 2(\varphi_a|\nabla|\varphi_b)^2\beta_M{}^2/(\pi\sigma_{ba})^2 \qquad (2)$$

where ∇ is the del operator, $\mathbf{r}$ is a distance vector, β_M is the Bohr magneton, and σ_{ba} is the excitation wavenumber of the transition a → b. The z-axis component of the electric and magnetic transition moments are expressed, respectively, as[10,11]

$$(\varphi_a|\nabla|\varphi_b)_z = \Sigma_{\text{bonds}}(C_{ra}C_{sb} - C_{sa}C_{rb})\langle\nabla_{rs}\rangle \cos Z_{rs} \qquad (3)$$

$$(\varphi_a|\mathbf{r} \times \nabla|\varphi_b)_z = \Sigma_{\text{bonds}}(C_{ra}C_{sb} - C_{sa}C_{rb})\langle\nabla_{rs}\rangle(X_{rs} \cos Y_{rs} - Y_{rs} \cos X_{rs}) \qquad (4)$$

$$\cos Z_{rs} = (Z_r - Z_s)/R_{rs} \qquad (5)$$

$$X_{rs} = (X_r + X_s)/2 \qquad (6)$$

where C_{ra} is the coefficient of atomic orbital r in the wave function φ_a, $\langle\nabla_{rs}\rangle$ is the expectation value of a dipole velocity vector ∇_{rs} which is directed along the bond rs in the direction r → s, X_r, Y_r, and Z_r are the x, y, and z coordinates of an atom r, respectively, and R_{rs} is the interatomic distance between atoms r and s. In a similar way, the x and y components of the electric and magnetic transition moments were calculated.

In the π-electron SCF-CI-DV MO calculation, the following values of atomic orbital parameters were employed: for sp^2 carbon, $Z(\text{C}) = 1.0$, $W(\text{C}) = -11.16$ eV, $(\text{rr}|\text{rr})(\text{C}) = 11.13$ eV, $\beta(\text{C–C}, 1.388 \text{ Å}) = -2.18$ eV, $\langle\nabla\rangle(\text{C–C}, 1.388 \text{ Å}) = 4.70 \times 10^7$ cm^{-1}; for carbonyl oxygens, $Z(\text{O}) = 1.0$, $W(\text{O}) = -17.28$ eV, $(\text{rr}|\text{rr})(\text{O}) = 14.58$ eV, $\beta(\text{C–O}) = -2.39$ eV, $\langle\nabla\rangle(\text{C–O}) = 5.00 \times 10^7$ cm^{-1}; for ether oxygen, $Z(\text{O}) = 2.0$, $W(\text{O}) = -33.00$ eV, $(\text{rr}|\text{rr})(\text{O}) = 21.53$ eV, $\beta(\text{C–O}) = -1.98$ eV, $\langle\nabla\rangle(\text{C–O}) = 6.00 \times 10^7$ cm^{-1}. The electric repulsion integral (rr|ss) was estimated by the Nishimoto–Mataga equation. The resonance integral and del value were calculated by employing the following equations, respectively:

$$\beta = [S/S(1.388 \text{ Å})]\beta(1.388 \text{ Å}) \cos \theta \qquad (7)$$

$$\langle\nabla\rangle = [\langle\nabla\rangle(\text{empir}, 1.388 \text{ Å})/\langle\nabla\rangle(\text{theor}, 1.388 \text{ Å})] \times \langle\nabla\rangle(\text{theor}) \cos \theta \qquad (8)$$

where θ is a dihedral angle. The overlap integral S and $\langle\nabla\rangle$(theor) were calculated on the basis of the Slater orbitals. The configuration interaction between 200 singly excited states of lower energy were included.

The curves of the component CD and UV bands were approximated by the Gaussian distribution:

$$\Delta\epsilon(\sigma) = \Sigma\Delta\epsilon_k \exp[-((\sigma - \sigma_k)/\Delta\sigma)^2] \qquad (9)$$

$$\epsilon(\sigma) = \Sigma\epsilon_k \exp[-((\sigma - \sigma_k)/\Delta\sigma)^2] \qquad (10)$$

where $2\Delta\sigma$ is the $1/e$ bandwidth. The $\Delta\sigma$ value of 2500 cm^{-1} was adopted as a standard value.

Numerical calculations were carried out on the NEC ACOS 2000 computer at the Computer Center of Tohoku University.

Results and Discussion

Confirmation of the Dimeric Structure of 4',4''',7,7''-Tetra-*O*-methylcupressuflavone. The title compound was isolated from *Garcinia mangostana* L. and was identified as optically active cupressuflavone tetramethyl ether (−)-**1** by a direct comparison of spectral data with those of the authentic sample isolated earlier from *Araucaria cunninghamii* and *A. cookii*.[2] Compound **1** is a dimeric flavone as indicated by the MS spectral data of molecular ion peak at m/z 594 and has a chiral C_2-symmetrical structure because it exhibits an optical rotation of $[\alpha]^{27}{}_{\text{D}}$ −25.3° and signals corresponding to a monomer unit in ^{1}H and ^{13}C NMR spectra. The dimeric structure and 8–8''-linkage of **1** were originally determined by synthesis of (±)-**1** via Ullmann coupling of 8-iodo-5,7,4'-trimethylapigenin[4] and by ^{1}H NMR.[2-5] However, since the previous ^{1}H NMR signal assignment was based on comparison of chemical shift data with those of monomeric flavone **2**[12] and related compounds, the structure determination of **1** has

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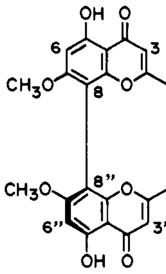
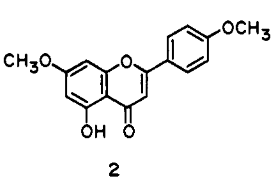


(aR)-(−)-1



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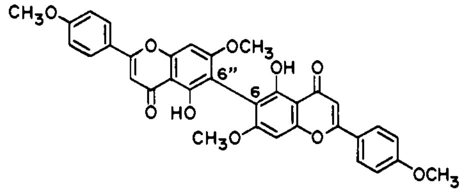

1a

remained empirical. To establish the dimeric structure and 8–8″ linkage, we performed ^{1}H and ^{13}C NMR studies in detail by use of ^{1}H NOESY, heteronuclear gated decoupling ^{13}C NMR, ^{1}H–^{13}C COSY, and long range ^{1}H–^{13}C COSY (COLOC) methods and achieved full assignment of all proton and carbon signals leading to an unambiguous structure determination, as discussed below.

The ring B protons of dimer **1** showed upfield chemical shifts in comparison with those of the monomer:[12] δ 7.428 ppm (2′- and 6′-H) of **1** vs 7.82 ppm of **2**: 6.665 (3′- and 5′-H) vs 7.00, whereas the ring A protons showed slight downfield shifts and 3-H remained almost unaffected. These data imply the 8–8″ linked structure **1** because in the stereostructure the B-ring lies on the top of the other flavone moiety, and therefore upfield shifts due to the ring current effect are expected.[13] In the case of the alternative 6–6″ linked structure **1a**, such upfield shifts are not expected.[14]

The ^{1}H NOESY measurement revealed that 2′-H at δ 7.428 ppm exhibited a NOE with one of the two overlapping signals at δ 6.595 and 6.587 ppm (3- and 6-protons) in addition to the NOE with 3′-H at δ 6.665 ppm. The data indicate that compound **1** has a proton at C-3, and therefore the possibility of 3–3″ linkage was excluded. The 3′-proton showed a NOE with the 4′-methoxyl group at δ 3.823 ppm, and therefore the remaining methoxyl signal at δ 3.799 ppm was assigned to the 7-methoxyl group which exhibited a NOE with a neighboring proton. However, since the two signals due to 3- and 6- or 8-protons were very close to each other (δ 6.595 and 6.587 ppm), it was difficult to assign these two resonances. The ^{1}H–^{13}C COSY spectrum clarified the relation of δ 6.587 ^{1}H/95.33 ^{13}C and 6.595 ^{1}H/103.57 ^{13}C (see Experimental Section).

Heteronuclear gated decoupling ^{13}C NMR showed that the δ 95.33 ppm peak was split into a doublet of doublets, J = 161 and 7 Hz, while the δ 103.57 ppm peak appeared as a doublet, J = 167 Hz. These coupling constant data led to the unambiguous assignment of the δ 95.33 and 103.57 ppm signals to C-6 and C-3, respectively. Thus, C-6 is coupled with 6-H and also, via three bonds, to the proton of 5-OH at δ 13.219 ppm. The hydroxyl proton is fixed by hydrogen bonding with the 4-carbonyl. This assignment was confirmed by long range ^{1}H–^{13}C COSY (COLOC) data; a clear cross peak was observed between the proton signal at δ 13.219 ppm and the carbon signal at δ 95.33 ppm. The long range coupling thus observed can be explained only by the 8–8″ linked structure **1** and not by the alternative 6–6″ linked structure **1a**. The remaining carbon signals could be fully assigned, leading to the dimeric structure **1** (see Experimental Section). The 8–8″ linked structure of **1** was thus unambiguously determined.

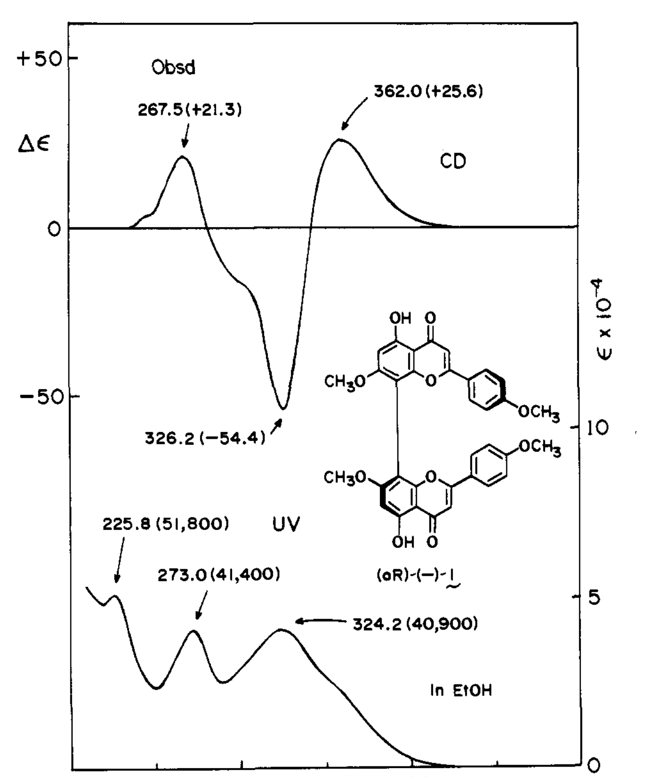

Figure 2. Observed CD and UV spectra of biflavone, 4′,4‴,7,7″-tetra-*O*-methylcupressuflavone ((*aR*)-(−)-**1**), in ethanol.

CD and UV Spectra of Biflavone ((*aR*)-(−)-1). The UV spectrum of (−)-**1** exhibits two intense $\pi \rightarrow \pi^*$ bands at 324.2 and 273.0 nm, both UV bands being accompanied by bisignate CD Cotton effects (Figure 2). The first UV band at 324.2 nm exhibits positive and negative CD Cotton effects at 362.0 and 326.2 nm, respectively, while the second UV band at 273.0 nm is associated with a negative CD shoulder around 300 nm and a positive Cotton effect at 267.5 nm. Therefore, the bands appear to originate from the exciton coupling between the two flavone chromophores.

To determine absolute stereochemistry by the CD exciton chirality method,[11] we need to know the direction and position of the transition moments in the molecule. Qualitatively, the UV bands at 324.2 and 273.0 nm may be assigned to intrachromophoric charge transfer and long axis polarized transitions of *p*-methoxycinnamoyl and *p*-methoxybenzoyl chromophores, respectively. On the basis of such qualitative assignment of transition moments, an *aS* configuration was previously assigned to biflavone (−)-**1**.[15] However, the actual flavone chromophore is a composite of these two moieties. Furthermore, it is difficult to predict the exciton chirality between the long axes of the two *p*-methoxycinnamoyl moieties, even if the transition at 324.2 nm is ascribed to the *p*-methoxycinnamoyl moiety, because the two transition moments incline toward the inside of the molecule. It is thus not easy to deduce the absolute stereochemistry of such a complex system by application of the CD exciton chirality method.[11] In such cases, the numerical calculation of CD and UV spectra by means of the π-electron SCF-CI-DV MO method[9–11] is useful for determination of absolute stereochemistry. In fact, the theoretical

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(13) See upfield shifts in the system of 9,9′-spirobifluorene derivatives: Harada, N.; Ono, H.; Nishiwaki, T.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1991**, 1753.

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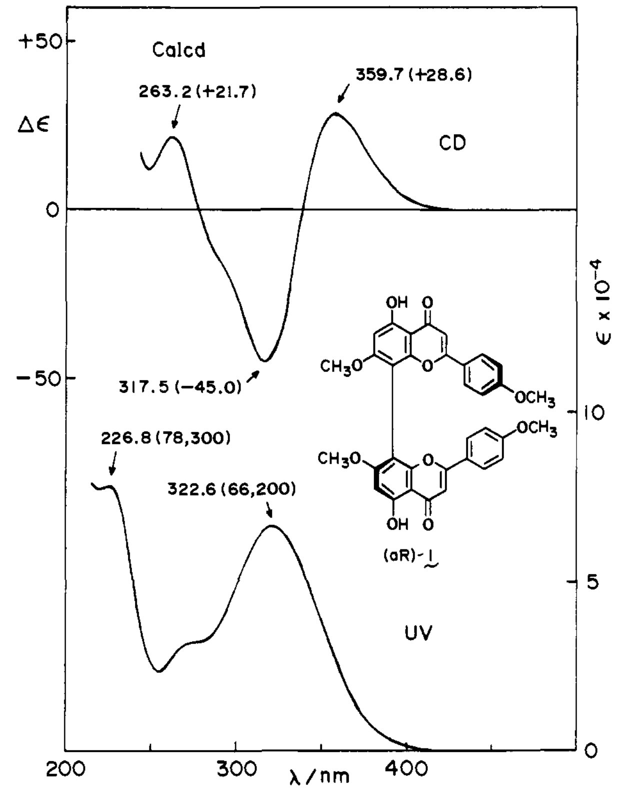

Figure 3. CD and UV spectral curves of 4′,4‴,7,7″-tetra-*O*-methylcupressuflavone ((*aR*)-**1**), calculated by the π-electron SCF-CI-DV MO method.

CD method has been successfully applied to various chiral natural products and synthetic compounds with twisted π-electron chromophores.[16-20]

Theoretical Calculation of CD and UV Spectra of Biflavone (−)-1 and Nonempirical Determination of Absolute Stereochemistry. The CD and UV spectral curves of (*aR*)-**1** were calculated by use of the π-electron SCF-CI-DV MO method,[9-11] and the atomic coordinates were obtained by molecular mechanics[8] calculation (Figure 3). The calculated UV spectrum curve exhibits three $\pi \rightarrow \pi^*$ bands: a broad and intense band at λ_{max} 322.6 nm (ϵ 66 200), a weak band appearing as a shoulder around 270 nm, and an intense band at 226.8 nm (ϵ 78 300). These calculated values agree well with the observed UV data of (−)-**1**: observed UV of (−)-**1**, λ_{max} 324.2 nm (ϵ 40 900), 273.0 nm (ϵ 41 400), and 225.8 nm (ϵ 51 800) (Figure 2). The pattern of the UV spectral curve of biflavone **1** was thus well reproduced by the theoretical calculation.

Table I. Calculated Dipole and Rotational Strengths of the Transitions of Biflavone ((*aR*)-(−)-**1**)

transition no.	wavelength (λ), nm	dipole strength ($10^{36}D$), cgs units	rotational strength ($10^{40}R$), cgs units
1	341.2	18.4	+681.0
2	338.8	29.8	−525.1
3	317.6	29.1	−1041.0
4	315.4	18.7	+899.3
5	305.7	0.3	−1.4
6	305.6	0.3	+5.1
7	301.0	0.1	−34.2
8	300.3	19.8	−24.5
9	274.6	15.4	−178.1
10	271.1	12.4	+207.9
11	259.9	6.1	+3.6
12	258.5	0.1	+7.4

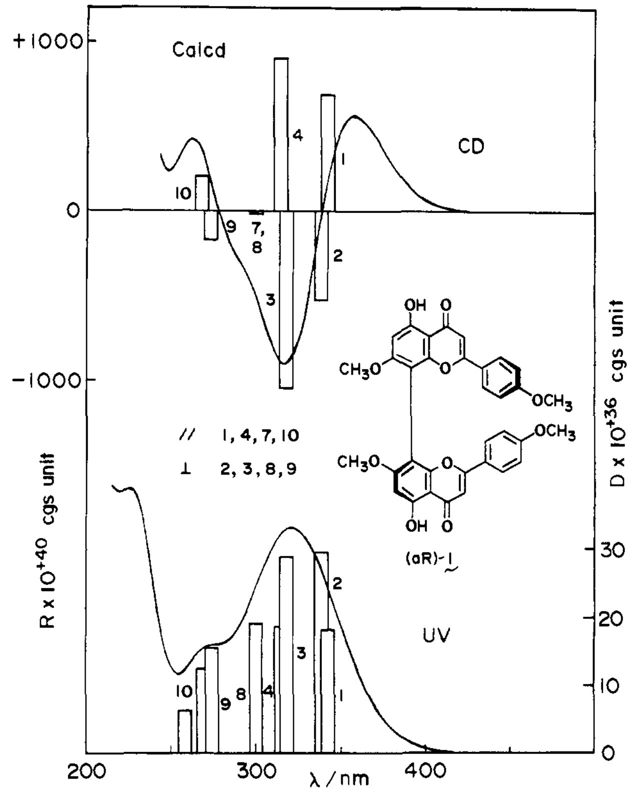

Figure 4. Rotational and dipole strengths of the transitions of biflavone, 4′,4‴,7,7″-tetra-*O*-methylcupressuflavone ((*aR*)-(−)-**1**), calculated by the π-electron SCF-CI-DV MO method. Transitions of nos. 1, 4, 7, and 10 are polarized along the C_2-symmetrical axis, while the transition moments of nos. 2, 3, 8, and 9 are perpendicular to the axis.

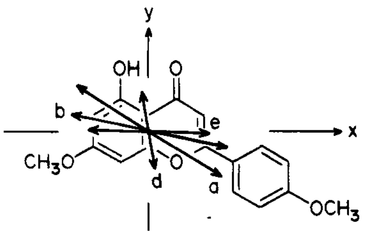

Figure 5. Calculated polarization and relative intensity of dipole strength of monomeric flavone **2**, calculated by the π-electron SCF-CI-DV MO method.

The CD spectral curve for (*aR*)-**1** was similarly calculated to give CD Cotton effects as shown in Figure 3. In the region of the first UV band, there were obtained a positive Cotton effect at λ_{ext} 359.7 nm ($\Delta\epsilon$ +28.6) and a negative one at λ_{ext} 317.5 nm ($\Delta\epsilon$ −45.0). For the second UV band, the calculation gave a negative Cotton effect which appeared as a shoulder around 290 nm and a positive one at λ_{ext} 263.2 nm ($\Delta\epsilon$ +21.7). These calculated CD values were in excellent agreement with those of observed CD data, including sign, intensity,[21] and position of Cotton effects (compare Figures 2 and 3): observed data of (−)-**1**, λ_{ext} 362.0 nm ($\Delta\epsilon$ +25.6), 326.2 (−54.4), a negative shoulder around 300 nm, and 267.5 (+21.3). Since the calculation was performed for the enantiomer of *aR* configuration, the absolute stereochemistry of the biflavone, (−)-4′,4‴,7,7″-tetra-*O*-methylcupressuflavone (**1**), was thus determined to be *aR* (or *M*

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(20) Gargiulo, D.; Derguini, F.; Berova, N.; Nakanishi, K.; Harada, N. *J. Am. Chem. Soc.* **1991**, *113*, 7046.

(21) The enantiomeric purity of the natural product (−)-**1** was checked by the ^{1}H NMR method using a chiral shift reagent and reported to be satisfactory; see ref 3.

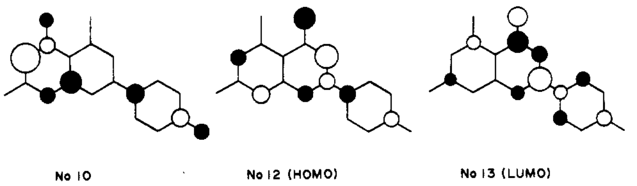

Figure 6. Calculated molecular orbital distribution of monomeric flavone **2**.

helicity) in a theoretical and nonempirical manner.

Circular Dichroic Power Due to Atropisomerism of Biflavone. The calculated CD and UV spectral data were analyzed in detail to clarify the mechanism of CD and UV activity. As shown in Table I and Figure 4, there are 12 $\pi \rightarrow \pi^*$ transitions above 250 nm. The electric transitions of nos. 1, 4, 7, 10, and 12 are polarized along the C_2-symmetrical axis, while those of nos. 2, 3, 8, 9, and 11 are polarized perpendicular to the axis. In the region of 400–300 nm, electric transitions of nos. 1, 2, 3, and 4 make a dominant contribution to CD and UV spectra. Analysis of calculation results revealed that transitions nos. 1 and 2 were, to a first approximation, exciton-coupled partners as seen from the opposite signs of their rotational strengths. These transitions are composed of transition *a* of the monomeric flavone chromophore **2** (Figure 5). The transition moment of the monomeric transition *a* is almost parallel to the long axis of the *p*-methoxycinnamoyl moiety. For determination of the nature of the transition *a*, molecular orbital distribution was investigated.

The most dominant excitation configuration contained in transition *a* is HOMO (no. 12) → LUMO (no. 13), the MO distributions of which are illustrated in Figure 6. The HOMO is mainly distributed in the *p*-methoxycinnamoyl part. Therefore, it may be concluded that transitions nos. 1 and 2 are composed of exciton coupling between the long axes polarized transitions of two *p*-methoxycinnamoyl chromophores. However, transitions nos. 1 and 2 deviate from pure exciton coupling, because the rotational strength of transition no. 1 ($R = +681 \times 10^{-40}$ cgs unit) is larger than that of transition no. 2 ($R = -525 \times 10^{-40}$ cgs unit). In the ideal case of exciton coupling, the rotational strengths of two exciton transitions should be opposite in sign but equal in absolute value to each other. The imbalance of rotational strengths produces the positive Cotton effect at 359.7 nm.

It was found that transitions nos. 3 and 4 were exciton-coupled partners. These transitions are composed of the monomeric transition *b*, the transition moment of which is inclined as shown in Figure 5. The major excitation configuration of transition *b* is MO (no. 10) → LUMO (no. 13), and the MO (no. 10) is delocalized over the molecule (Figure 6). It is thus difficult to assign transition *b* to a specific moiety of the chromophore. Since the rotational strength of transition no. 3 ($R = -1041 \times 10^{-40}$ cgs unit) is larger than that of its exciton-coupled partner no. 4 ($R = +899 \times 10^{-40}$ cgs unit), summation of the two rotational strengths gives rise to the negative Cotton effect at 317.5 nm. It was thus clear that the bisignate Cotton effects at 359.7 and 317.5 nm originate from the composition of two pairs of exciton coupling transition: one pair of transitions nos. 1 and 2 and a second pair of transitions nos. 3 and 4. Hence, it is now obvious that the CD exciton chirality method cannot be applied in a straightforward way to these Cotton effects. For determination of the absolute stereochemistry of biflavone **1**, theoretical calculation of the CD curve is needed as described above.

Transitions nos. 7 and 8 at 301 and 300 nm, respectively, make little contribution to CD activity, although transition no. 8 is strongly allowed in the UV transition (Figure 4). These transitions are composed of the monomeric flavone transition *d* which is polarized almost along the *y* axis (Figure 5). Thus, the transition moment is almost parallel to the 8–8″ bond, and therefore the CD activity of transitions nos. 7 and 8 is weak. In fact, the rotational strengths of these calculated transitions are small: no. 7, $R = -34 \times 10^{-40}$ cgs unit; no. 8, $R = -25 \times 10^{-40}$ cgs unit.

The analysis of the negative CD shoulder at 290 nm and positive Cotton effect at 263.2 nm is a little simpler than the case of the Cotton effects at 359.7 and 317.5 nm. Transitions nos. 9 and 10, which are exciton coupled partners, are responsible for these Cotton effects (Figure 4). Transitions nos. 9 and 10 are composed of the monomeric flavone transition *e* which is polarized along the *x* axis (Figure 5). The main excitation configuration of transition *e* is MO (no. 10) → LUMO (no. 13). Since the transition *e* is perpendicular to the 8–8″ bond and the two component transitions *e* of exciton coupling constitute a counterclockwise twist for the *aR* absolute configuration, exciton Cotton effects of negative chirality would be expected. In accordance with this expectation, the CD calculations gave a negative CD shoulder at 290 nm and a positive Cotton effect at 263.2 nm. The analysis of CD Cotton effects around 290–260 nm thus confirmed the *aR* absolute configuration of biflavone (−)-**1** determined by the π-electron SCF-CI-DV MO method.

Concluding Remarks

The absolute stereochemistry of biflavone (−)-**1**, a natural atropisomer, was first determined to be *aR* by theoretically calculated CD spectra. It is worth noting that the theoretical calculation of CD and UV spectra by means of the π-electron SCF-CI-DV MO method is more useful in this case than is the CD exciton chirality method, because the π-electron chromophore of **1** is too complex for application of the exciton method. The calculated CD data were in excellent agreement with observed CD data. Analysis of the theoretical results revealed that, unlike the usual cases where the exciton CD Cotton effects are composed of one pair of exciton coupling, the bisignate Cotton effects of **1** at 359.7 and 317.5 nm were composed of two pairs of exciton coupling. Therefore, it should be emphasized that bisignate CD Cotton effects are not always due to pure exciton coupling. Care is required in the interpretation of such bisignate CD Cotton effects. This work provides a nonempirical method for determining the absolute stereochemistry of molecular asymmetry due to the atropisomerism of biflavone. This theoretical approach should be a promising tool for determination of the absolute stereochemistry of various optically active natural and synthetic compounds.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were obtained as KBr disks by using a JEOL JIR-100 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-600 spectrometer at 600.1 and 150.9 MHz settings, respectively. The assignment of the proton and carbon signals was performed by the ^{1}H NOESY, heteronuclear gated decoupling ^{13}C NMR, ^{1}H–^{13}C COSY, and long range ^{1}H–^{13}C COSY (COLOC) measurements. All NMR data are reported in ppm (δ) downfield from tetramethylsilane. Optical rotation $[\alpha]_D$ was measured on a JASCO DIP-360 spectropolarimeter. UV and CD spectra were recorded on JASCO Ubest-50 and JASCO J-400X spectrometers, respectively. MS spectra was obtained with a JEOL JMS DX-300/JMA-3100/3500 spectrometer by the electron ionization procedure (70 eV). The purity of the title compound was shown to be ≥95% by ^{1}H NMR, TLC, and HPLC.

Isolation and Identification of (−)-4′,4‴,7,7″-Tetra-*O*-methylcupressuflavone (1). The petrol extract of the leaves of *G. mangostana*, after solvent fractionation followed by column chromatography on silica gel, gave an oily mass on elution with benzene. Preparative TLC (silica gel G, benzene/acetone 3:1) of this fraction followed by crystallization from acetone/benzene gave yellow needle-shaped crystals. The material was identified as the title compound **1** by a direct comparison with an authentic sample isolated from *A. cookii*: mp 156–157 °C; IR (KBr) ν_{max} 2939, 2843, 1651, 1599, 1591, 1510, 1487, 1427, 1373, 1336, 1263, 1240, 1207, 1180, 1122, 1030, 833, 577 cm^{-1}; ^{1}H NMR (600.1 MHz, CDCl$_3$) δ 3.799 (6 H, s, 7- and 7″-OCH$_3$), 3.823 (6 H, s, 4′- and 4‴-OCH$_3$), 6.587 (2 H, s, 6- and 6″-H), 6.595 (2 H, s, 3- and 3″-H), 6.665 (4 H, d, J = 9.0 Hz, 3′-, 5′-, 3‴-, and 5‴-H), 7.428 (4 H, d, J = 9.0 Hz, 2′-, 6′-, 2‴-, and 6‴-H), 13.219 (2 H, s, 5- and 5″-OH); ^{1}H NMR NOESY (600.1 MHz, CDCl$_3$), data for the half monomer unit, 6-H/7-OCH$_3$, 3-H/2′-H, 2′-H/3′-H, 3′-H/4′-OCH$_3$; heteronuclear gated decoupling ^{13}C NMR (150.9 MHz, CDCl$_3$) δ 55.50 (q, J = 145 Hz, 4′- and 4‴-OCH$_3$), 56.24 (q, J = 145 Hz, 7- and 7″-OCH$_3$), 95.33 (dd, J = 161, 7 Hz, 6- and 6″-C), 99.56 (d, J = 6 Hz, 8- and 8″-C), 103.57 (d, J = 167 Hz, 3- and 3″-C), 105.32 (ddd, J = 4, 4, 4 Hz, 4a- and 4a″-C), 114.59 (dd, J = 162, 5 Hz, 3′-, 5′-, 3‴-, and 5‴-C), 123.34 (td, J = 8, 2 Hz, 1′- and 1‴-C), 127.63 (dd, J = 161, 7 Hz, 2′-, 6′-, 2‴-, and 6‴-C), 154.71 (s, 8a- and 8a″-C), 162.65 (m, 4′- and 4‴-C), 162.70 (dd, J = 5, 5 Hz, 5- and 5″-C), 163.39 (m, 7- and 7″-C), 163.96 (td, J = 5, 5 Hz, 2- and 2″-C), 182.95 (br s, $W_{1/2}$ = 5 Hz, 4- and 4″-C); ^{1}H–^{13}C COSY (600 MHz, $CDCl_3$), data for the half monomer unit, 7-OCH_3/7-OCH_3, 4′-OCH_3/4′-OCH_3, 6-H/6-C, 3-H/3-C, 3′-H/3′-C, 2′-H/2′-C; long range ^{1}H–^{13}C COSY (COLOC, 600 MHz, $CDCl_3$), data for the half monomer unit, 7-OCH_3/7-C, 4′-OCH_3/4′-C, 6-H/8-C, 6-H/4a-C, 6-H/5-C, 6-H/7-C, 3-H/4a-C, 3-H/2-C, 3-H/4-C, 3′-H/5′-C, 3′-H/1′-C, 2′-H/6′-C, 2′-H/4′-C, 2′-H/2-C, 5-OH/6-C, 5-OH/4a-C, 5-OH/5-C; $[\alpha]^{27}_D$ −25.3° (c 0.3, MeOH); UV (EtOH) λ_{max} 324.2 nm (ϵ 40 900), 273.0 (41 400), 225.8 (51 800); CD (EtOH) λ_{ext} 362.0 nm ($\Delta\epsilon$ +25.6), 326.2 (−54.4), 267.5 (+21.3); MS m/z 594 (M^+, relative intensity 100), 433 (2), 297 (16), 135 (16), 77 (1); HRMS calcd for $C_{34}H_{26}O_{10}$ 594.152 58, found 594.152 99.

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Total Synthesis of (+)-Jatrophone

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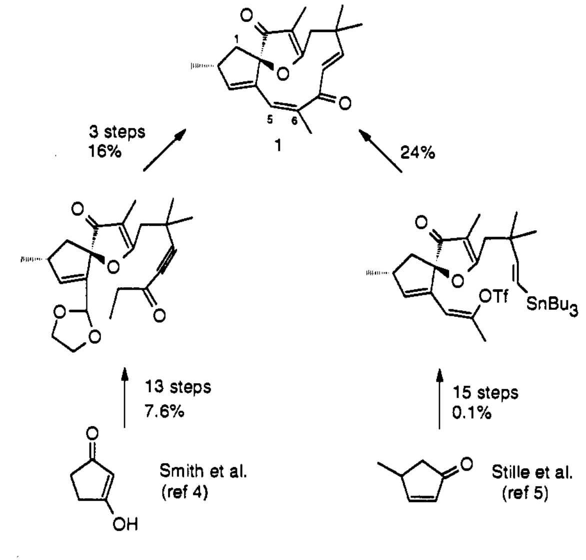
Abstract: The first total synthesis of optically active (+)-jatrophone is described. A convergent sequence provides the natural enantiomer in just 12 steps from (R)-(+)-3-methyladipic acid. Key steps include formation of the jatrophone C-ring through a Wadsworth–Horner–Emmons variant, a Pd-catalyzed cross-coupling that incorporates the C5–C6 double bond with the required Z-stereochemistry, and formation of the macrocycle by condensation of an acetylenic aldehyde. This sequence provides a short, efficient, and stereocontrolled route to the complex diterpenoid (+)-jatrophone.

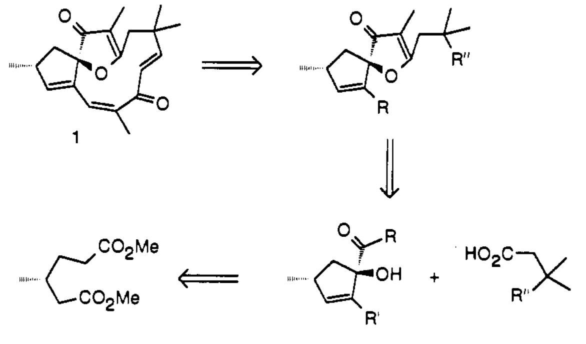
In 1970, Kupchan et al. first reported the isolation and characterization of the macrocyclic diterpenoid jatrophone (**1**),[1] a novel natural product with a new carbon skeleton and an unusual array of functionality. Significant antileukemic activity was reported for this compound, and subsequent studies unveiled that biological nucleophiles were trapped by a novel transannular cyclization.[2] In the intervening years a number of jatrophane diterpenoids have been characterized, including the kansuinines,[3a] the esulones,[3b,c] and euphornin[3d] and the euphoscopins,[3e] but as the prototypical jatrophane diterpenoid, jatrophone retains a special prestige.

The combination of an interesting skeleton and significant biological activity has stimulated several efforts to synthesize jatrophone. Despite the problems posed by the presence of two stereogenic centers, four carbon–carbon double bonds (including two that can isomerize), and an 11-membered ring, two successful routes to racemic jatrophone have been published.[4,5] While the two approaches differ substantially, both encountered significant difficulties with formation of the macrocyclic ring (Scheme I). In Smith's approach,[4] an aldol-type reaction was used to form the C5–C6 double bond in 23% yield. In the more recent example from Stille's laboratories,[5] a Pd-catalyzed carbonylation was employed to form both the C6–C7 and C7–C8 bonds in 24% yield. While these transformations did allow assembly of the natural product in both cases, it was tempting to speculate that a more efficient procedure could be found. Furthermore, the significant biological activity of the natural product places a premium on routes that would afford optically active materials.[6]

Scheme I



Scheme II



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