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Chemical Studies on the Constituents of the Thymelaeaceous Plants. II.[1] Stereochemistry of Daphnodorin A and Daphnodorin B

KIMIYE BABA, KAZUO TAKEUCHI, MITSUNOBU DOI, MASATOSHI INOUE
and MITSUGI KOZAWA*

*Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara,
Osaka 580, Japan*

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The absolute configurations of daphnodorin A (**1**) and daphnodorin B (**2**) isolated from *Daphne odora* THUNB. (Thymelaeaceae) were studied, and **1** was assigned as C-2 (*S*), while **2** was assigned as C-2 (*R*), C-3 (*S*) on the basis of chemical transformations and spectral analyses. An X-ray analysis of daphnodorin A pentamethyl ether (**4**) was performed and two conformers (A and B) due to restricted rotation of the trioxy-benzoyl group were observed.

Keywords——*Daphne odora*; Thymelaeaceae; flavan; daphnodorin A; daphnodorin B; CD spectrum; X-ray analysis

In our preceding paper, we reported the isolation of three new flavans, daphnodorin A (**1**), daphnodorin B (**2**) and daphnodorin C (**3**), from the root and the bark of *Daphne odora* THUNB., together with several known coumarins,[2] and we elucidated the plane structures of **1** and **2**.[1] In the present paper, we report the absolute configuration at C-2 in **1**, and at C-2 and C-3 in **2**, and we present the result of an X-ray diffraction analysis of daphnodorin A pentamethyl ether (**4**).

Since compound **2** is a flavan bearing a hydroxyl group at C-3, the relative configuration of the C-ring should be the same as either that of catechin (2,3-*trans*) or that of epicatechin (2,3-*cis*). *d*-Catechin (**5**) and *l*-epicatechin (**6**) are distinguishable in terms of the signal patterns due to the protons at C-2, C-3 and C-4 in the proton nuclear magnetic resonance (^{1}H-NMR) spectra, and it is a characteristic feature that the proton signal at C-2 of **5** is observed as a doublet ($J=7.3$ Hz), while that of **6** appears as a singlet. The C-2, C-3 and C-4 proton signals of **2**, **5** and **6** are shown on the structures in Chart 1; the C-2 proton signal of **2** was observed as a doublet ($J=7.4$ Hz) at δ 4.57, coinciding very closely with that of **5**. Thus, the relative configuration between C-2 and C-3 of **2** was concluded to be *trans*.

The absolute configurations of **1** and **2** were determined as follows. Circular dichroism (CD) spectroscopic studies of the flavans including *d*-catechin (**5**) and *l*-epicatechin (**6**) have indicated that the Cotton effect ascribed to the A-chromophore in the range of 250—300 nm is available for determination of the absolute configuration at the C-2 position.[3] The CD spectra of **1**, **2**, **5** and **6** are shown in Fig. 1, and those of 3-*O*-acetyl-5,7,3′,4′-tetra-*O*-methyl-*d*-catechin (**7**), 3-*O*-acetyl-5,7,3′,4′-tetra-*O*-methyl-*l*-epicatechin (**8**) and **9** prepared from **2**, in Fig. 2. Since **1** and **2** showed nearly the same CD spectra, it is clear that the C-2 positions have the same orientations. Further, the Cotton effects ascribed to the A-chromophore in the range of 250—300 nm were both negative; the signs were the same as those of **5** and **6**, whose C-2 positions have *R*-configuration. However, it may not be appropriate to compare the CD spectra of **1** and **2** with those of **5** and **6**, because **1** and **2** contain the 2,4,6-trihydroxybenzoyl chromophore, which is non-coplanar with the flavan skeleton, and the CD spectra showed strong splitting of the Cotton effect in the neighborhood of the absorption band of A-chromophore (negative first Cotton: 327 nm, positive second Cotton: 299 nm). Thus, the CD spectrum of **9**, obtained by elimination of the 2,4,6-trihydroxybenzoyl group by cleavage of daphnodorin B pentamethyl ether with H_2SO_4 and AcOH, was compared with those of **7** and **8** prepared from **5** and **6**, respectively. As can been seen in Fig. 2, the CD spectrum of **9** did not show the split Cotton effect as seen in the spectra of **1** and **2**, but showed a negative Cotton effect ascribed to the A-chromophore, and this was shifted to longer wavelength as a result of

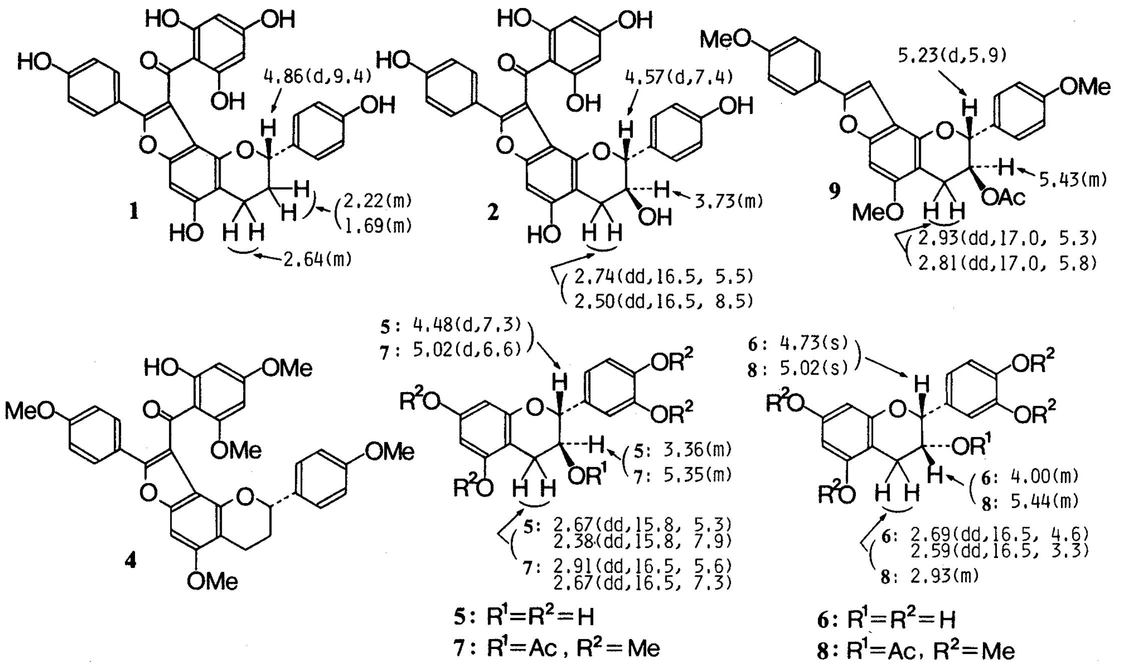


Chart 1

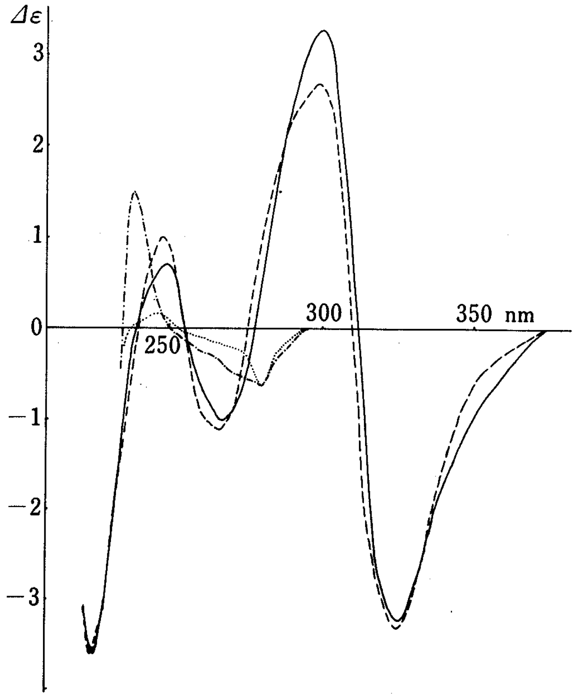


Fig. 1. CD Spectra of **1**, **2**, **5** and **6** in MeOH
——, **1**; – – – –, **2**; ------, **5**; – - – - –, **6**.

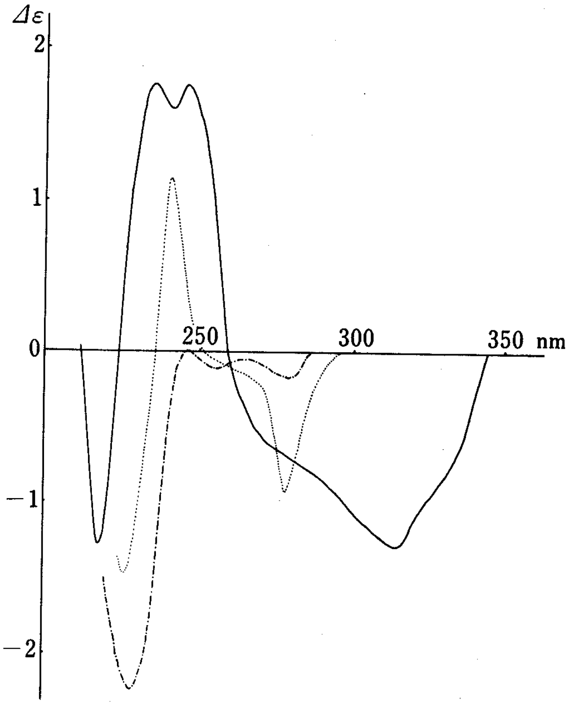


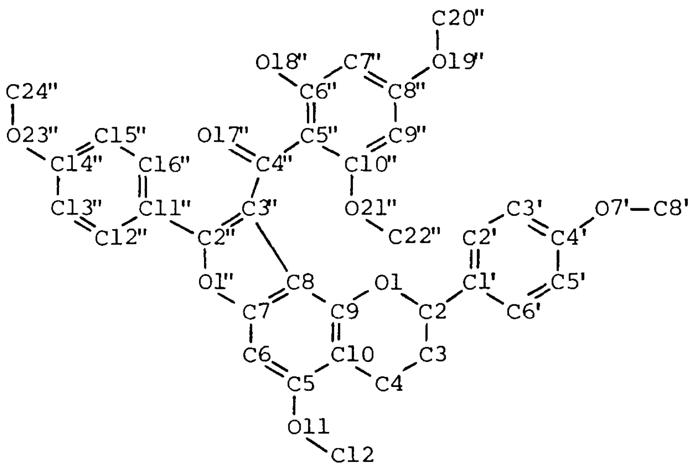
Fig. 2. CD Spectra of **7**, **8** and **9** in Dioxane
------, **7**; – - – - –, **8**; ——, **9**.

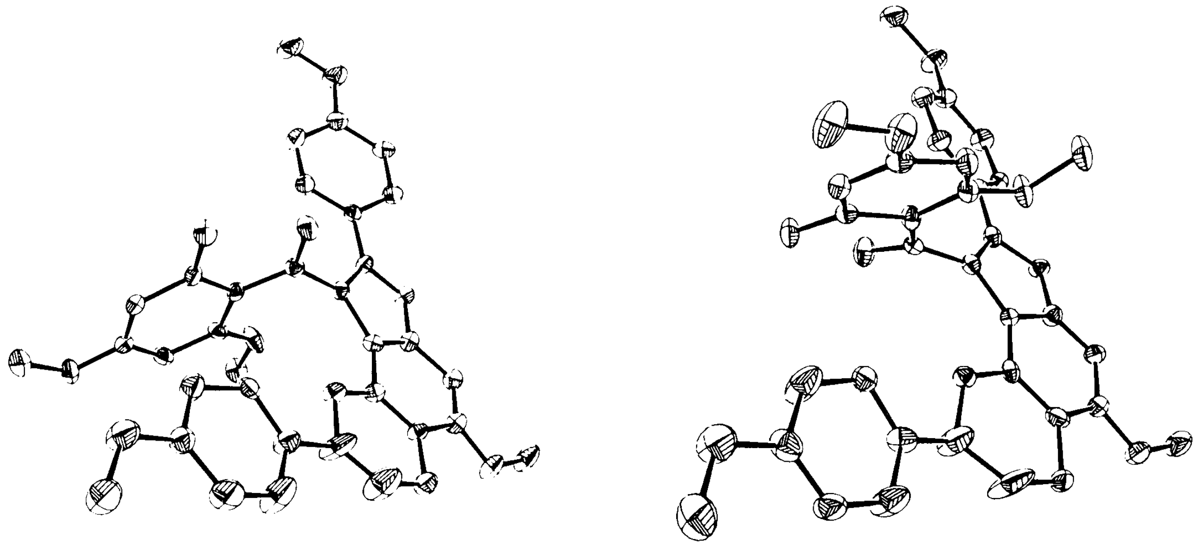
TABLE I. Atomic Parameters ($\times 10^4$) of Nonhydrogen Atoms for 4 with Anisotropic Temperature Factors

Atom	x	y	z	B_{eq}
Molecule-A				
O(1)	2779 (2)	1369 (2)	661 (6)	3.5 (2)
C(2)	2846 (4)	2026 (4)	67 (15)	7.3 (5)
C(3)	3404 (5)	2397 (5)	449 (16)	8.1 (6)
C(4)	4146 (3)	2093 (4)	1028 (10)	4.1 (3)
C(5)	4775 (3)	1034 (3)	2238 (9)	3.4 (2)
C(6)	4776 (3)	410 (3)	2772 (8)	3.4 (2)
C(7)	4058 (3)	108 (3)	2503 (8)	3.0 (2)
C(8)	3425 (3)	410 (3)	1850 (8)	3.0 (2)
C(9)	3452 (3)	1070 (3)	1244 (8)	3.0 (2)
C(10)	4109 (3)	1385 (3)	1477 (8)	3.1 (2)
O(11)	5410 (2)	1389 (2)	2218 (7)	4.7 (2)
C(12)	6082 (4)	1034 (4)	2969 (13)	5.9 (4)
C(1)′	2051 (4)	2310 (3)	−478 (10)	4.2 (3)
C(2)′	1413 (3)	1985 (3)	−255 (7)	3.1 (2)
C(3)′	697 (4)	2216 (4)	−1031 (11)	4.5 (3)
C(4)′	636 (4)	2859 (4)	−1618 (9)	3.9 (3)
C(5)′	1255 (5)	3201 (4)	−1651 (14)	6.3 (4)
C(6)′	1952 (5)	2958 (4)	−1086 (15)	7.3 (5)
O(7)′	−76 (3)	3071 (3)	−2215 (8)	6.1 (3)
C(8)′	−179 (4)	3729 (4)	−2916 (13)	6.3 (4)
O(1)″	3974 (2)	−523 (2)	3051 (6)	3.2 (1)
C(2)″	3209 (3)	−602 (3)	2847 (8)	2.9 (2)
C(3)″	2838 (3)	−65 (3)	2044 (7)	2.7 (2)
C(4)″	2023 (3)	50 (3)	1676 (8)	2.9 (2)
C(5)″	1585 (3)	62 (3)	−85 (7)	2.6 (2)
C(6)″	861 (3)	292 (3)	−383 (8)	2.9 (2)
C(7)″	431 (3)	423 (3)	−2042 (8)	3.2 (2)
C(8)″	737 (3)	235 (3)	−3420 (8)	3.1 (2)
C(9)″	1415 (3)	−39 (3)	−3222 (8)	3.3 (2)
C(10)″	1856 (3)	−129 (3)	−1544 (7)	2.8 (2)
C(11)″	2963 (3)	−1250 (3)	3379 (7)	2.7 (2)
C(12)″	3485 (4)	−1616 (3)	4569 (9)	3.6 (3)
C(13)″	3297 (4)	−2226 (4)	5138 (9)	3.9 (3)
C(14)″	2551 (4)	−2446 (4)	4540 (9)	4.2 (3)
C(15)″	2034 (3)	−2088 (4)	3312 (10)	4.1 (3)
C(16)″	2253 (4)	−1492 (3)	2786 (9)	3.7 (3)
O(17)″	1741 (2)	175 (2)	2880 (5)	3.7 (2)
O(18)″	548 (2)	475 (2)	946 (5)	4.1 (2)
O(19)″	370 (2)	265 (3)	−5107 (5)	4.2 (2)
C(20)″	−364 (4)	590 (5)	−5431 (10)	5.3 (4)
O(21)″	2532 (2)	−423 (3)	−1289 (5)	4.5 (2)
C(22)″	2789 (4)	−682 (4)	−2709 (9)	4.1 (3)
O(23)″	2392 (3)	−3028 (3)	5330 (8)	5.8 (2)
C(24)″	1704 (4)	−3300 (5)	4741 (12)	6.1 (4)
Molecule-B				
O(1)	2227 (2)	2710 (2)	4247 (5)	2.9 (1)
C(2)	2228 (4)	2009 (5)	4432 (16)	7.4 (5)
C(3)	1577 (5)	1726 (5)	4677 (21)	11.7 (8)
C(4)	828 (3)	1994 (3)	4064 (10)	3.9 (3)
C(5)	229 (3)	3059 (3)	2957 (9)	3.7 (3)
C(6)	224 (3)	3731 (3)	2341 (9)	3.7 (3)
C(7)	889 (3)	3990 (3)	2398 (8)	3.2 (2)
C(8)	1594 (3)	3675 (3)	3115 (8)	2.7 (2)

TABLE I. (continued)

Atom	x	y	z	B_{eq}
C(9)	1564 (3)	3018 (3)	3591 (7)	2.6 (2)
C(10)	873 (4)	2703 (3)	3529 (9)	3.8 (3)
O(11)	−416 (2)	2709 (2)	2811 (7)	4.8 (2)
C(12)	−1093 (4)	3033 (5)	2233 (13)	5.8 (4)
C(1)′	2982 (4)	1762 (3)	5309 (9)	3.8 (2)
C(2)′	3588 (3)	2180 (3)	5697 (8)	3.5 (2)
C(3)′	4250 (4)	1898 (5)	6096 (14)	7.0 (4)
C(4)′	4372 (4)	1241 (4)	6689 (10)	4.9 (3)
C(5)′	3776 (4)	850 (4)	6491 (13)	5.6 (4)
C(6)′	3067 (4)	1116 (4)	5817 (14)	6.7 (4)
O(7)′	5085 (3)	1030 (3)	7209 (8)	6.6 (3)
C(8)′	5151 (4)	348 (5)	7758 (13)	7.0 (5)
O(1)″	1035 (2)	4597 (2)	1825 (5)	3.1 (1)
C(2)″	1794 (3)	4699 (3)	2179 (7)	2.9 (2)
C(3)″	2144 (3)	4148 (3)	2936 (7)	2.8 (2)
C(4)″	2951 (3)	4064 (3)	3337 (7)	2.6 (2)
C(5)″	3391 (3)	4028 (3)	5077 (8)	2.8 (2)
C(6)″	4147 (3)	3774 (3)	5397 (8)	3.0 (2)
C(7)″	4557 (3)	3710 (3)	6993 (8)	3.2 (2)
C(8)″	4270 (3)	3888 (3)	8411 (8)	3.2 (2)
C(9)″	3552 (3)	4166 (3)	8175 (9)	3.5 (2)
C(10)″	3148 (3)	4225 (3)	6613 (8)	3.2 (2)
C(11)″	1983 (3)	5327 (3)	1621 (9)	3.3 (2)
C(12)″	2720 (3)	5585 (3)	2206 (9)	3.8 (3)
C(13)″	2916 (4)	6186 (4)	1510 (10)	4.1 (3)
C(14)″	2423 (4)	6555 (3)	387 (9)	3.7 (3)
C(15)″	1702 (4)	6308 (3)	−100 (9)	3.9 (3)
C(16)″	1492 (3)	5735 (3)	496 (8)	3.1 (2)
O(17)″	3264 (2)	4037 (3)	2053 (6)	4.2 (2)
O(18)″	4471 (2)	3616 (2)	4082 (6)	3.9 (2)
O(19)″	2466 (2)	4504 (3)	6277 (5)	4.0 (2)
C(20)″	2240 (4)	4821 (5)	7718 (9)	5.0 (3)
O(21)″	4628 (2)	3792 (3)	10077 (6)	4.9 (2)
C(22)″	5346 (4)	3558 (6)	10402 (11)	6.0 (4)
O(23)″	2559 (3)	7142 (3)	−294 (7)	5.3 (2)
C(24)″	3316 (5)	7391 (5)	188 (12)	5.9 (4)





molecule-A molecule-B

Fig. 3

the condensation with the α-phenylfuran. On the other hand, the CD spectra of **7** and **8** showed negative Cotton effects similar to those of **5** and **6**. From above results, the absolute configurations of **1** and **2** were assigned as C-2(*S*) and C-2(*R*), C-3(*S*), respectively.

In order to clarify the stereostructure, X-ray diffraction analysis of daphnodorin A pentamethyl ether (**4**) was carried out. Single crystals of **4** were grown from a hexane–AcOEt solution by slow evaporation. Preliminary oscillation and Weisenberg photographs were taken in each case to establish the crystal symmetry and space group. Determination of cell constants and X-ray intensity data were performed on an AFC-5 instrument (Rigaku Denki) equipped with a graphite monochromator. The obtained crystal data were as follows: monoclinic, $P2_1$, $a=18.474$ (7), $b=20.232$ (4), $c=7.932$ (2) Å, $\beta=102.29$ (4)°, $V=2890$ (1) Å^3 and $Z=4$. The density of 1.369 (3) Mg/m^3 was determined by the flotation method using aqueous potassium iodate solution. In total, 4856 independent reflections ($F_o>0.0$) within $\sin\theta/\lambda$ less than 0.588 Å^{-1} were collected with Cu-K_α radiation at the rate of 8°/min. The four standard reflections monitored at 100 reflection intervals showed no evidence of structural deterioration during data collection. All reflections were corrected for Lorentz and polarization effects; no absorption corrections were applied. Numerical calculations for structure determinations and refinements were carried out using the UNICS library of crystallographic programs (Crystallographic Research Center, Institute for Protein Research of Osaka University).

The structure of **4** was solved by the direct method using the MULTAN program.[4] Electron density maps calculated by using the normalized structure factors (E) located 82 nonhydrogen atoms, which were computed with the phase set having the highest figure of merit using 452 reflections with $|E|>1.679$. The remaining atoms were found by weighted Fourier synthesis. The structure was refined by a block-diagonal least-squares procedure, minimizing the quantity $\Sigma w(|F_o|-|F_c|)^2$ with weight w equal to $1/(\sigma(F_o)^2+F_{\max}F_o+F_{\min}F_o^2)$. The final refinement was computed with a weighting scheme of the following form; $w=0.0$ for $F_o=0.0$ and $F_{\max}=-0.20199$, $F_{\min}=0.1547$ for $F_o>0.0$. All heavy atoms were refined with anisotropic temperature factors, while isotropic temperature factors were used for the hydrogen atoms, calculated in their stereochemically expected positions. The final R value was 0.093. The obtained atomic parameters of **4** are listed in Table I, and the molecular structures are illustrated in Fig. 3.

From the above results, it became evident that in the crystal state, compound **4** had two conformers (A and B) due to restricted rotation of the 2,4,6-trioxybenzoyl group. In the preceding paper,[1] we reported that in the ^{1}H-NMR spectrum of **4**, the signals arising from the benzene protons of 2,4,6-trioxybenzoyl group were observed as doublets coupled with $J=2.3$ Hz by measurement at 70 °C, while broad signals were seen at room temperature. These characteristics of the benzene protons of the 2,4,6-trioxybenzoyl group in the ^{1}H-NMR spectrum are considered to be related to the steric hindrance of this group.

Experimental

The ^{1}H-NMR spectra were taken with a Varian XL-300 spectrometer with tetramethylsilane an internal standard. The CD spectra were recorded with a JASCO J-500 spectropolarimeter. The cell constants and intensity data were collected on a Rigaku Denki AFC-5 diffractometer. The physicochemical and spectral data (except for the CD data) of **1**, **2**, **4** and **9** were reported in a previous paper.[1]

Daphnodorin A (1)——CD ($c=5.13\times10^{-5}$, MeOH) $\Delta\varepsilon^{23}$: 0 (373), -3.2 (327) (negative max.), 0 (312), 3.3 (299) (positive max.), 0 (278), -1.0 (267) (negative max.), 0 (255), 0.7 (250) (positive max.), 0 (239), -3.6 (227) (negative max.).

Daphnodorin B (2)——CD ($c=4.24\times10^{-5}$, MeOH) $\Delta\varepsilon^{23}$: 0 (373), -3.3 (327) (negative max.), 0 (310), 2.7 (298) (positive max.), 0 (276), -1.1 (267) (negative max.), 0 (255), 1.0 (248) (positive max.), 0 (240), -3.6 (226) (negative max.).

Compound 9——CD ($c=5.69\times10^{-5}$, dioxane) $\Delta\varepsilon^{23}$: 0 (344), -0.6 (338), -1.28 (315) (negative max.), -0.7 (275), 0 (258), 1.8 (245) (positive max), 1.6 (241), 1.8 (234) (positive max.), 0 (224), -1.3 (218), 0 (212).

***d*-Catechin (5)**——CD ($c=2.48\times10^{-4}$, MeOH) $\Delta\varepsilon^{23}$: 0 (296), -0.3 (285), -0.6 (280) (negative max.), -0.3 (275), 0 (253), 0.1 (246) (positive max.), 0 (238).

***l*-Epicatechin (6)**——CD ($c=7.58\times10^{-5}$, MeOH) $\Delta\varepsilon^{23}$: 0 (296), -0.6 (280) (negative max.), -0.5 (270), 0 (250), 1.5 (238) (positive max.), 0 (235).

3-*O*-Acetyl-5,7,3′,4′-tetra-*O*-methyl-*d*-catechin (7)——^{1}H-NMR ($CDCl_3$) δ: 6.92 (1H, dd, $J=2.0$, 8.6 Hz), 6.89 (1H, d, $J=2.0$ Hz), 6.83 (1H, d, $J=8.6$ Hz), 6.18 (1H, d, $J=2.6$ Hz), 6.10 (1H, d, $J=2.6$ Hz), 5.35 (1H, m), 5.02 (1H, d, $J=6.6$ Hz), 3.87, 3.86, 3.78, 3.77 (each 3H, s), 2.91 (1H, dd, $J=16.5$, 5.6 Hz), 2.67 (1H, dd, $J=16.5$, 7.3 Hz), 1.95 (1H, s). CD ($c=1.08\times10^{-4}$, dioxane) $\Delta\varepsilon^{23}$: 0 (296), -0.9 (278) (negative max.), -0.2 (270), 0 (251), 1.2 (240) (positive max.), 0 (236), -1.5 (226) (negative max.).

3-*O*-Acetyl-5,7,3′,4′-tetra-*O*-methyl-*l*-epicatechin (8)——^{1}H-NMR ($CDCl_3$) δ: 7.04 (1H, d, $J=2.0$ Hz), 6.97 (1H, dd, $J=2.0$, 8.6 Hz), 6.86 (1H, d, $J=8.6$ Hz), 6.21 (1H, d, $J=2.0$ Hz), 6.12 (1H, d, $J=2.0$ Hz), 5.44 (1H, m), 5.02 (1H, s), 3.91, 3.89 (each 3H, s), 3.79 (6H, s), 2.93 (2H, m), 1.93 (1H, s). CD ($c=1.08\times10^{-4}$, dioxane) $\Delta\varepsilon^{23}$: 0 (286), -0.2 (280) (negative max.), -0.06 (265), -0.1 (256) (negative max.), 0 (246), -2.2 (229) (negative max.).

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References and Notes

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