Novel Flavonoids in Dragon's Blood of *Daemonorops draco*

by **Ken-ichi Nakashima**, **Naohito Abe**, **Fumiko Kamiya**, **Tetsuro Ito**, **Masayoshi Oyama**, and **Munekazu Iinuma***

Laboratory of Pharmacognosy, Department of Bioactive Molecules, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan
(phone: +81-58-2373931; fax: +81-58-2375979; e-mail: iinuma@gifu-pu.ac.jp).

The three novel methylene bis[flavonoids] **1**–**3**, the novel 2-flavene **4**, the new naturally occurring flavan **5**, and the new *retro*-dihydrochalcone **6** were isolated from dragon's blood of *Daemonorops draco*, together with seven known compounds. The structures were elucidated by extensive 1D- and 2D-NMR spectroscopic analysis.

Introduction. – 'Dragon's blood' is a common name of a red resin obtained from different genera such as *Daemonorops* (Arecaceae), *Dracaena* (Agavaceae), *Pterocarpus* (Leguminosae), and *Croton* (Euphorbiaceae). Each generous plant produces red pigments of dracorhodin [1], dracoflavylium [2], santalin A [3], and procyanidin B1 [4], respectively, which unequivocally identify the original source of the resin.

Chemical constituents of the dragon's blood derived from *Daemonorops draco* have particularly been studied to disclose the presence of novel secobiflavonoids [5], secotriflavonoids [6], and the precursors of the complex flavonoids, *C*-methylated flavans and/or chalcones. Pharmacological studies on the resin obtained from *D. draco* have so far revealed its antimicrobial [7], antiplatelet [8], and apoptotic activities [9].

In our successive research of the phytochemicals in secretes, we have isolated secobiflavonoids in farinose exudate of *Pentagramma triangularis* [10] and kamalachalcones in glandular hair of *Mallotus philippensis* [11], and the chemical constituents in the red resin originated from *D. draco* were investigated. Herein, the structures of three novel secobiflavonoids, daemonorols A–C[1]) (**1**–**3**), a novel 2-flavene, daemonorol D[1]) (**4**), a new naturally occurring flavan, daemonorol E[1]) (**5**), a new *retro*-dihydrochalcone, daemonorol F[1]) (**6**), and the seven known compounds **7**–**13** are discussed (*Fig. 1*).

Results and Discussion. – All compounds **1**–**13** were isolated from the acetone extract of *Daemonorops draco* resin by repeated column chromatography (CC), vacuum liquid chromatography (VLC), and prep. TLC.

Daemonorol A (**1**) was obtained as a colorless, optically active solid. It exhibited a UV absorption at 277 nm. The molecular formula was established as $C_{33}H_{32}O_6$ by HR-EI-MS showing M^+ at m/z 524.2207. The ^{1}H-NMR spectrum (*Table 1*) showed typical

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

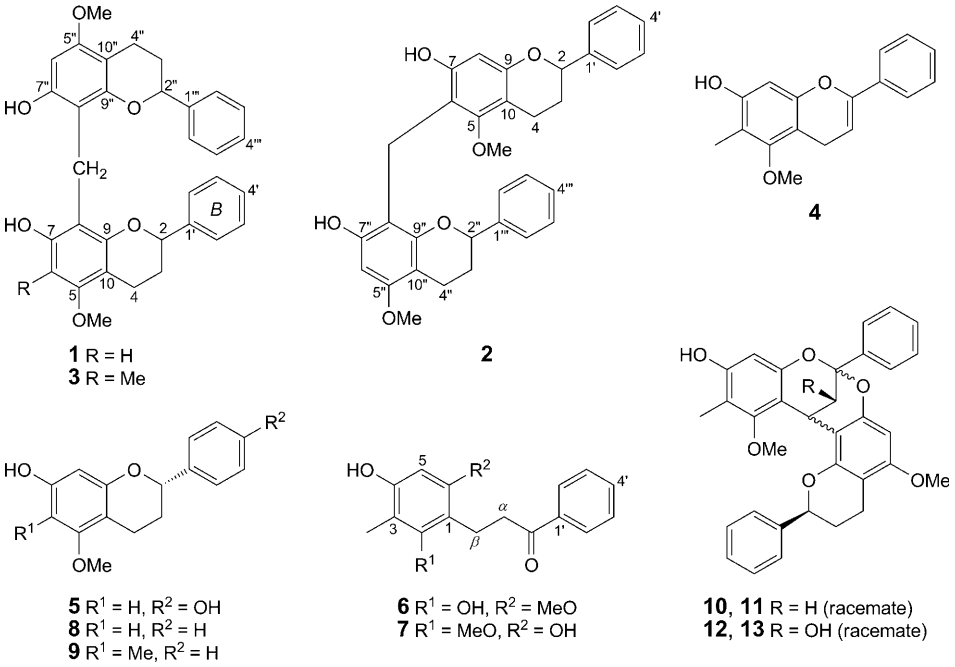

Fig. 1. *Compounds*[1]) *isolated from the resin of* Daemonorops draco

signals for five H-atoms at δ(H) 5.12 (*dd*, $J = 10.4$, 2.0 Hz, 1 H), 2.04–2.23 (*m*, 2 H), 2.73 (*ddd*, $J = 17.0$, 5.8, 3.4 Hz, 1 H), and 2.62 (*ddd*, $J = 17.0$, 10.8, 6.2 Hz, 1 H) which were assignable to H–C(2), CH_2(3), and CH_2(4) of a flavan skeleton. Furthermore, a Ph group (δ(H) 7.47 (br. *d*, $J = 7.8$ Hz, 2 H), 7.42 (br. *t*, $J = 7.8$ Hz, 2 H), and 7.35 (*dt*, $J =$ 7.8, 1.6 Hz, 1 H)) and an additional aromatic H-atom (δ(H) 6.06 (*s*)) were observed, as well as a MeO group (δ(H) 3.70 (*s*)) and an OH group (δ(H) 7.71 (*s*)). A fragment ion at *m*/*z* 104, caused by *retro-Diels–Alder* fragmentation, was attributed to C_6H_5–CH=CH_2^+ and demonstrated that **1** had an unsubstituted ring *B*. Thus, the MeO group and the OH group were supposed to be at ring *A*. The location of the MeO group was determined to be C(5) by the HMBCs between CH_2(4) at δ(H) 2.62 and 2.73 and C(5) at δ(C) 156.8, and between MeO at δ(H) 3.70 and C(5). Then, the OH group was estimated to be at C(7). In the HMQC spectrum, a remaining signal at δ(H) 3.77 (*s*, 2 H) was correlated with a signal at δ(C) 15.9 attributable to a CH_2 group, which was established by the DEPT spectrum. These findings suggested that the molecule consists of two equivalent flavan moieties connected symmetrically through the CH_2 group. The CH_2-bridge H-atoms at δ(H) 3.77 were coupled with C(7) at δ(C) 154.7 and C(9) at 151.6, in the HMBC spectrum, which demonstrated that the flavan moieties were connected at C(8) and C(8″). Consequently, the structure of daemonorol A (**1**) was determined as 8,8′-methylenebis[3,4-dihydro-5-methoxy-2-phenyl-2*H*-1-benzopyran-7-ol].

Daemonorol B (**2**), a colorless, optically active solid, exhibited an absorption at 281 nm in the UV spectrum. The molecular formula was determined to be $C_{33}H_{32}O_6$ by

Table 1. *^{1}H- and ^{13}C-NMR Spectral Data of* **1**[1])[a]). δ in ppm, J in Hz.

	δ(H)	δ(C)	HMBC
H–C(2,2″)	5.12 (*dd*, *J* = 10.4, 2.0)	79.3	C(4,4″), C(1′,1‴), C(2′,2‴), C(6′,6‴)
CH_2(3,3″)	2.04–2.23 (*m*)	29.1	C(2,2″), C(4,4″), C(10,10″), C(1′,1‴)
CH_2(4,4″)	2.62 (*ddd*, *J* = 17.0, 10.8, 6.2),	19.2	C(2,2″), C(3,3″), C(5,5″), C(9,9″), C(10,10″)
	2.73 (*ddd*, *J* = 17.0, 5.8, 3.4)		C(2,2″), C(3,3″), C(5,5″), C(9,9″), C(10,10″)
C(5,5″)		156.8	
H–C(6,6″)	6.06 (*s*)	93.0	C(7,7″), C(8,8″), C(10,10″)
C(7,7″)		154.7	
C(8,8″)		105.6	
C(9,9″)		151.6	
C(10,10″)		102.6	
C(1′,1‴)		140.3	
H–C(2′,6′,2‴,6‴)	7.47 (br. *d*, *J* = 7.8)	126.3	C(2,2″), C(4′,4‴)
H–C(3′,5′,3‴,5‴)	7.42 (br. *t*, *J* = 7.8)	128.7	C(3′,5′, 3‴,5‴), C(1′,1‴)
H–C(4′,4‴)	7.35 (*dt*, *J* = 7.8, 1.6)	128.4	C(2′,6′, 2‴,6‴)
Ar–*CH_2*–Ar	3.77 (*s*)	15.9	C(7,7″), C(8,8″), C(9,9″)
MeO–C(5,5″)	3.70 (*s*)	55.4	C(5,5″)
OH–C(7,7″)	7.71 (*s*)		C(6,6″), C(7,7″), C(8,8″)

[a]) Measured in $CDCl_3$ at 400 (^{1}H) and 100 MHz (^{13}C).

HR-EI-MS (M^+ at *m*/*z* 524.2205). The ^{1}H-NMR spectrum (*Table 2*) showed two series of H-atoms assignable to H–C(2,2″), CH_2(3,3″), and CH_2(4,4″) of the flavan moieties at δ(H) 5.14 (*dd*, *J* = 10.2, 2.2 Hz, 1 H), 4.97 (*dd*, *J* = 10.6, 2.2 Hz, 1 H), 2.71–2.80 (*m*, 3 H), 2.62 (*ddd*, *J* = 17.1, 10.7, 6.1 Hz, 1 H), 2.03–2.27 (*m*, 3 H), and 1.85–2.02 (*m*, 1 H). The spectrum also revealed two unsubstituted *B* rings (δ(H) 7.34–7.36 (*m*, 2 H), 7.33–7.34 (*m*, 2 H), 7.27–7.29 (*m*, 1 H), 7.45 (br. *d*, *J* = 7.6 Hz, 2 H), 7.39–7.42 (*m*, 3 H)), two additional aromatic H-atoms of the *A* rings (δ(H) 6.24 and 6.11 (2*s*)), two MeO groups (δ(H) 3.90 and 3.73 (2*s*)) and two OH groups (δ(H) 8.26 and 7.56 (2*s*)). In the case of **2**, the CH_2-bridge H-atoms were observed individually at δ(H) 3.80 and 3.67 (*d*, *J* = 15.6 Hz, each 1 H). By considering the above segments, **2** was predicted to be an isomer of **1**. The 5-methoxylated flavan moieties were deduced by the HMBCs between the MeO group at δ(H) 3.90 and C(5) at δ(C) 154.7, and between the other MeO group at δ(H) 3.73 and C(5″) at δ(C) 157.0 (*Fig. 2*). The interlinkage between C(6) and C(8″) through the CH_2 bridge was established by the essential correlations from the CH_2 H-atoms at δ(H) 3.67 and 3.80 to C(5) and/or C(7″) at δ(C) 154.7, C(7) at δ(C) 154.9, and C(9″) at δ(C) 151.3. As a MeO group resonates at a lower field when both *ortho*-positions are substituted, the downfield shift of MeO–C(5) (δ(C) 61.5) corroborated the idea that the CH_2 group was connected to C(6). Thus, the structure of daemonorol B (**2**) was determined as 6,8′-methylenebis[3,4-dihydro-5-methoxy-2-phenyl-2*H*-1-benzopyran-7-ol], the constitutional isomer of **1**.

Daemonorol C (**3**), a colorless, optically active solid, showed a UV absorption at 273 nm. The HR-EI-MS allowed to assign the molecular formula $C_{34}H_{34}O_6$ (M^+ at *m*/*z* 538.2362). The ^{1}H-NMR spectrum (*Table 2*) suggested the presence of two flavan moieties with unsubstituted *B* rings, two MeO groups (δ(H) 3.64 and 3.70 (2*s*)), two OH groups (δ(H) 7.70 and 7.79 (2*s*)), a Me group attached to an aromatic ring (δ(H)

Table 2. *^{1}H- and ^{13}C-NMR Spectral Data of* **2** *and* **3**[a]). δ in ppm, J in Hz.

	2[1])		**3**[1])	
	δ(H)	δ(C)	δ(H)	δ(C)
H–C(2)	4.97 (*dd*, *J* = 10.6, 2.2)	77.6	5.19 (*dd*, *J* = 9.7, 2.2)	79.2
CH_2(3)	1.85–2.02 (*m*), 2.03–2.27 (*m*)	29.6	2.09–2.24 (*m*)	29.1
CH_2(4)	2.71–2.80 (*m*)	19.9	2.72–2.88 (*m*)	18.9
C(5)		154.7		155.6
C(6)		111.3		111.5
C(7)		154.9		153.0
H–C(8) or C(8)	6.24 (*s*)	101.5		109.0
C(9)		154.4		149.2
C(10)		106.7		106.8
C(1′)		141.6		140.3
H–C(2′,6′)	7.33–7.34 (*m*)	125.9	7.44–7.46 (*m*)	126.3[b])
H–C(3′,5′)	7.34–7.36 (*m*)	128.5	7.40–7.44 (*m*)	128.7[c])
H–C(4′)	7.27–7.29 (*m*)	128.4	7.34–7.38 (*m*)	128.4
H–C(2″)	5.14 (*dd*, *J* = 10.2, 2.2)	79.3	5.14 (*dd*, *J* = 10.2, 2.2)	79.3
CH_2(3″)	2.03–2.27 (*m*)	29.1	2.09–2.24 (*m*)	28.9
CH_2(4″)	2.62 (*ddd*, *J* = 17.1, 10.7, 6.1), 2.71–2.80 (*m*)	19.1	2.58–2.73 (*m*)	19.8
C(5″)		157.0		156.8
H–C(6″)	6.11 (*s*)	93.3	6.07 (*s*)	92.9
C(7″)		154.7		154.8
C(8″)		105.3		105.2
C(9″)		151.3		151.6
C(10″)		102.8		102.6
C(1‴)		140.3		140.4
H–C(2‴,6‴)	7.45 (br. *d*, *J* = 7.6)	126.2	7.41–7.42 (*m*)	126.3[b])
H–C(3‴,5‴)	7.39–7.42 (*m*)	128.7	7.40–7.44 (*m*)	128.7[c])
H–C(4‴)	7.39–7.42 (*m*)	127.8	7.34–7.38 (*m*)	128.3
Ar–CH_2–Ar	3.67 (*d*, *J* = 15.6), 3.80 (*d*, *J* = 15.6)	16.9	3.80 (*s*)	16.3
MeO–C(5)	3.90 (*s*)	61.5	3.64 (*s*)	59.9
Me–C(6)			2.03 (*s*)	8.9
OH–C(7)	7.56 (*s*)		7.70 (*s*)	
MeO–C(5″)	3.73 (*s*)	55.4	3.70 (*s*)	55.3
OH–C(7″)	8.26 (*s*)		7.79 (*s*)	

[a]) Measured in $CDCl_3$ at 400 (^{1}H) and 100 MHz (^{13}C). [b])[c]) Overlapped signals.

2.03 (*s*)), an aromatic H-atom (δ(H) 6.07 (*s*)), and a CH_2 bridge (δ(H) 3.80 (*s*)). The MeO–C(5) substitution was confirmed by the HMBCs between CH_2(4) at δ(H) 2.72–2.88 and C(5) at δ(C) 155.6, and between MeO at δ(H) 3.64 and C(5) (*Fig. 3*). The MeO–C(5″) substitution was determined by the HMBCs between CH_2(4″) at δ(H) 2.58–2.73 and C(5″) at δ(C) 156.8, and between MeO at δ(H) 3.70 and C(5″). The C(5) atom was also coupled with the aromatic Me group, which substantiated that the Me group was at C(6). Therefore, the CH_2 bridge was supposed to be at C(8). The cross-link between C(8) and C(8″) through the CH_2 bridge was established by the HMBCs from the CH_2 group at δ(H) 3.80 to C(7) at δ(C) 153.0, C(9) at δ(C) 149.2, C(7″) at δ(C) 154.8, and C(9″) at δ(C) 151.6. The structure of **3** was accordingly

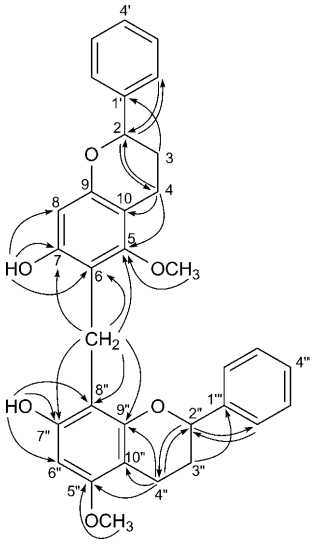

Fig. 2. *HMBCs* (H → C) *observed in* **2**[1])

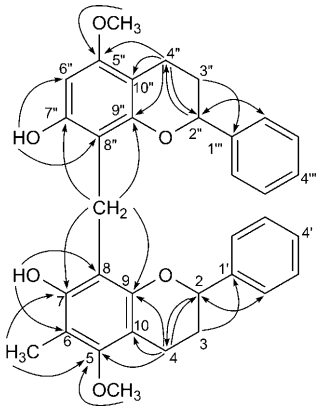

Fig. 3. *HMBCs* (H → C) *observed in* **3**[1])

established to be 8-[(3,4-dihydro-7-hydroxy-5-methoxy-2-phenyl-2*H*-1-benzopyran-8-yl)methyl]-3,4-dihydro-5-methoxy-6-methyl-2-phenyl-2*H*-1-benzopyran-7-ol.

Arnone et al. [6] have determined the configuration at C(2) of the monomeric flavans based on the CD spectrum. The CD spectra of **1**–**3**, however, showed no obvious *Cotton* effects. This result may be attributed to the chirality of the whole molecules. The absolute configurations at C(2) and C(2″) were tentatively assigned to be (*S*), judging from the fact that only (2*S*)-flavans have been reported from the resin of *D. draco* as well as from the (2*S*) configuration of **8** and **9** (see below).

Daemonorol D (**4**), a red solid, had the molecular formula $C_{17}H_{16}O_3$ (M^+ at *m*/*z* 268.1107). The ^{1}H-NMR spectrum (*Table 3*) suggested the presence of a Ph group (δ(H) 7.64 (br. *d*, *J* = 8.0 Hz, 2 H), 7.37 (br. *t*, *J* = 8.0 Hz, 2 H), and 7.32 (br. *t*, *J* = 8.0 Hz, 1 H)), an aromatic H-atom at δ(H) 6.33 (*s*), a MeO group at δ(H) 3.72 (*s*), an OH

Table 3. *^{1}H- and ^{13}C-NMR Spectral Data of* **4**[a]) *and* **5**[b]). δ in ppm, J in Hz.

	4[1])		**5**[1])	
	δ(H)	δ(C)	δ(H)	δ(C)
C(2) or H–C(2)		148.6	4.87 (*dd*, *J* = 2.4, 10.0)	78.0
H–C(3) or CH_2(3)	5.51 (*t*, *J* = 4.0)	96.4	1.86–1.98 (*m*), 2.04–2.15 (*m*)	30.2
CH_2(4)	3.48 (*d*, *J* = 4.0)	19.9	2.53–2.61 (*m*), 2.61–2.69 (*m*)	20.0
C(5)		156.9		159.5
C(6) or H–C(6)		112.0	6.05 (*d*, *J* = 2.2)	96.7
C(7)		153.5		157.7[d])
H–C(8)	6.33 (*s*)	99.4	5.97 (*d*, *J* = 2.2)	92.2
C(9)		150.7		157.4
C(10)		106.0		102.7
C(1′)		134.5		133.9
H–C(2′,6′)	7.64 (br. *d*, *J* = 8.0)	124.4	7.26 (*d*, *J* = 8.4)	128.2
H–C(3′,5′)	7.37 (br. *t*, *J* = 8.0)	128.3[c])	6.84 (*d*, *J* = 8.4)	115.9
H–C(4′) or C(4′)	7.32 (br. *t*, *J* = 8.0)	128.3[c])		157.8[d])
MeO–C(5)	3.72 (*s*)	60.2	3.75 (*s*)	55.6
Me–C(6)	2.14 (*s*)	8.5		
OH–C(7)	4.88 (br. *s*)		8.13 (br. *s*)	
OH–C(4′)			8.34 (br. *s*)	

[a]) Measured in $CDCl_3$ at 400 (^{1}H) and 100 MHz (^{13}C). [b]) Measured in (D_6)acetone at 400 (^{1}H) and 100 MHz (^{13}C). [c]) Overlapping signals. [d]) Interchangeable signals.

group at δ(H) 4.88 (br. *s*), an aromatic Me group at δ(H) 2.14 (*s*), a CH_2 group at δ(H) 3.48 (*d*, *J* = 4.0 Hz), and a vicinal olefin H-atom at δ(H) 5.51 (*t*, *J* = 4.0 Hz). The olefinic H–C(3) showed essential HMBCs (*Fig. 4*) with C(1′) at δ(C) 134.5 and C(10) at δ(C) 106.0, which suggested that **4** was a 2-flavene derivative. The 7-hydroxy-5-methoxy-6-methyl substitution at the *A* ring was established by the following HMBCs: CH_2(4)/C(5), MeO–C(5)/C(5), Me–C(6)/C(5), and Me–C(6)/C(7). Therefore, the structure of **4** was determined as 5-methoxy-6-methyl-2-flaven-7-ol. The reduction with Pd/C and H_2 gas produced a known compound, (2*S*)-5-methoxy-6-methylflavan-7-ol (**9**), which certified the unusual flavonoid framework of **4**.

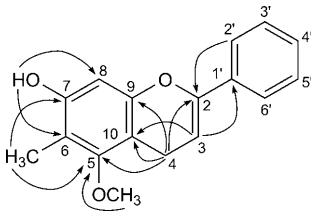

Fig. 4. *HMBCs* (H → C) *observed in* **4**[1])

Daemonorol E (**5**), a colorless, weakly optically active solid, had a molecular formula $C_{17}H_{18}O_4$ as deduced by HR-EI-MS (M^+ at *m*/*z* 272.1044). In the ^{1}H-NMR spectrum (*Table 3*), a *dd* at δ(H) 4.87 (*dd*, *J* = 10.0, 2.4 Hz, 1 H) and four *m* (each 1 H) ranging from δ(H) 1.86 to 2.69 were preferably assigned to H–C(2), CH_2(3), and

CH_2(4) of a flavan skeleton. A 4-oxygenated Ph group, appearing characteristically, at δ(H) 7.26 and 6.84 (*d*, $J = 8.4$ Hz, each 2 H), existed in the molecule. Besides the *m*-coupled H-atoms at δ(H) 6.05 and 5.97 (*d*, $J = 2.2$ Hz), a MeO group at δ(H) 3.75 (*s*), and two OH groups at δ(H) 8.34 and 8.13 (2 br. *s*) were observed. Two significant fragments at *m*/*z* 153 and 120 caused by a *retro-Diels–Alder* cleavage in the EI-MS indicated that one of the OH groups and a MeO group had to be positioned at the *A* ring, and the other OH group at the *B* ring. Therefore, the *B* ring moiety was a 4′-hydroxyphenyl substituent. The location of the MeO group was confirmed to be at C(5) by the essential HMBCs CH_2(4)/C(5) and MeO/C(5) (*Fig. 5*). The structure of **5** was consequently determined to be 4′-hydroxy-5-methoxyflavan-7-ol. The absolute configuration at C(2) of **5** was determined to be (*S*) since a negative *Cotton* effect ($\Delta\varepsilon - 0.93$) was observed at 281 nm in the CD spectrum [12].

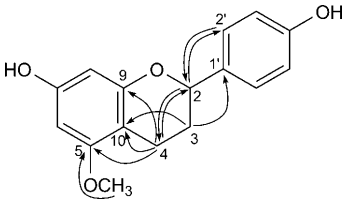

Fig. 5. *HMBCs* (H → C) *observed in* **5**[1])

Daemonorol F (**6**), a colorless solid, showed the M^+ at *m*/*z* 286.1211 in the HR-EI-MS and was assigned the molecular formula $C_{17}H_{18}O_4$. The ^{1}H-NMR spectrum (*Table 4*) exhibited a pair of mutually coupled H-atoms at δ(H) 3.39 (br. *t*, $J = 6.0$ Hz, 2 H) and

Table 4. *^{1}H- and ^{13}C-NMR Spectral Data of* **6**[1])[a]). δ in ppm, *J* in Hz.

	δ(H)	δ(C)	HMBC
C(1)		109.3	
C(2)		155.0	
C(3)		105.0	
C(4)		154.2	
H–C(5)	6.02 (*s*)	92.1	C(1), C(3), C(4), C(6)
C(6)		157.3	
C(1′)		137.0	
H–C(2′,6′)	7.97 (br. *d*, $J = 8.0$)	129.4	C(2′,6′), C(4′), C=O
H–C(3′,5′)	7.43 (br. *t*, $J = 8.0$)	129.3	C(3′,5′), C(1′)
H–C(4′)	7.55 (br. *t*, $J = 8.0$)	134.6	C(2′,6′)
$CH_2(\alpha)$	3.39 (br. *t*, $J = 6.0$)	40.1	C(1), C=O, C(β)
$CH_2(\beta)$	2.95 (br. *t*, $J = 6.0$)	17.7	C(1), C(2), C(6), C=O, C(α)
C=O		204.5	
OH–C(2)	8.70 (*s*)		C(1), C(2), C(3)
Me–C(3)	2.12 (*s*)	8.9	C(2), C(3), C(4)
OH–C(4)	4.85 (*s*)		C(3), C(4), C(5)
MeO–C(6)	3.75 (*s*)	56.3	C(6)

[a]) Measured in $CDCl_3$ at 400 (^{1}H) and 100 MHz (^{13}C).

2.95 (br. *t*, *J* = 6.0 Hz, 2 H), assignable to the $CH_2(\alpha)$ and $CH_2(\beta)$ groups of a dihydrochalcone skeleton. A Ph group (δ(H) 7.97 (br. *d*, *J* = 8.0 Hz, 2 H), 7.43 (br. *t*, *J* = 8.0 Hz, 2 H), and 7.55 (br. *t*, *J* = 8.0 Hz, 1 H)), an aromatic H-atom (δ(H) 6.02 (*s*)), a MeO group (δ(H) 3.75 (*s*)), two OH groups (δ(H) 8.70 and 4.85 (2*s*), and an aromatic Me group (δ(H) 2.12 (*s*)) were also present. In the HMBC spectrum, the aromatic H-atoms at δ(H) 7.97 were correlated with a C=O group at δ(C) 204.5, which indicated that **3** is a *retro*-dihydrochalcone derivative. The $CH_2(\beta)$ H-atoms were correlated with C(2) at δ(C) 155.0 and C(6) at 157.3. The latter C-atom had a correlation with the MeO H-atoms. Thus, a 2,4-dihydroxy-6-methoxy substitution in the second ring derived from the malonate pathway was demonstrated. The location of the aromatic Me group at C(3) was confirmed by the HMBCs Me/C(4) and C(2). Finally, the structure of **6** was determined to be α,β-dihydro-2,4-dihydroxy-6-methoxy-3-methylchalcone.

The other, known compounds were characterized as α,β-dihydro-4,6-dihydroxy-2-methoxy-3-methylchalcone (**7**) [13], (2*S*)-5-methoxyflavan-7-ol (**8**) [14], (2*S*)-5-methoxy-6-methylflavan-7-ol (**9**) [14], and dracoflavans B_1 (**10**), B_2 (**11**), C_1 (**12**), and C_2 (**13**) [15] by comparison of the spectral data with the literature values. Compounds **10**/**11** and **12**/**13** were obtained as racemates of the two corresponding isomers.

The present study revealed the following new findings. The occurrence of secobiflavonoids is very limited in nature being present only in *Pentagramma triangularis* [10], *Bosistoa brassii* [16], and *Blutaparon portulacoides* [17]. To the best of our knowledge, daemonorols A–C (**1**–**3**) are the first compounds composed of two flavan units and cross-linked through a CH_2 group. The framework of a 2-flavene (=2-phenyl-4*H*-1-benzopyran) in daemonorol D (**4**) is the first observation as a natural product, although the synthesis of **4** has been reported in [18]. Daemonorol E (**5**) has been previously synthesized [19]; however, this is the first report of its isolation from a natural source and of its detailed spectral data. Daemonorol F (**6**) is an isomer of **7**, suggesting that 8-methylated flavans were plausible precursors of **1**–**3**.

Experimental Part

General. Column chromatography (CC): silica gel *60* (SiO_2; 70–230 mesh; *Merck*), *Chromatorex DMS* (100–200 mesh; *Fuji Silysia Chemicals*), or *Sephadex LH-20* (*GE Healthcare Bio-sciences*). Vacuum liquid chromatography (VLC): SiO_2 *60 H* (*Merck*). TLC: SiO_2 *60* F_{254} and SiO_2 *RP-18* F_{254S} (both *Merck*). Optical rotation: *Jasco-P-1020* polarimeter. CD Spectra: *Jasco-J-820P* spectropolarimeter; λ_{ext} ($\Delta\varepsilon$) in nm; at 25°. UV Spectra: *Shimadzu-UV-3100* spectrophotometer; λ_{max} (log ε) in nm. NMR Spectra: *Jeol-JNM-AL-400* spectrometer equipped with field-gradient system; δ in ppm rel. to Me_4Si; *J* in Hz. MS: *Jeol-JMS-DX-300* spectrometer; in *m*/*z* (rel. %).

Plant Material. The resin of *Daemonorops draco* (270 g) was purchased from *Matsuura Yakugyo* (Nagoya; Japan) in 2006. A voucher specimen was deposited with the Gifu Pharmaceutical University, Gifu, Japan.

Extraction and Isolation. The resin was thoroughly dissolved in acetone. The filtered soln. was concentrated to yield an extract (252 g), part of which (250 g) was subjected to CC (SiO_2, hexane/AcOEt, finally acetone): *Fractions A–F. Frs. A* (with hexane/AcOEt 10:1), *D* (with hexane/AcOEt 3:1), and *F* (with acetone) were not further separated. *Fr. B* (with hexane/AcOEt 8:1) was separated by CC (*Chromatorex DMS*, MeOH/H_2O 2:3 → 1:0). The resulting fractions abundant in flavonoids were further purified by CC (*Sephadex LH-20*, MeOH) and VLC (SiO_2, benzene): **1** (3.4 mg), **3** (2.3 mg), and

5 (49.0 mg). *Fr. C* (with hexane/AcOEt 5:1) was separated by CC (*Chromatorex DMS*, MeOH/H_2O 2:3 → 1:0). The resulting fractions were further purified by CC (*Sephadex LH-20*, MeOH) and VLC (SiO_2, hexane/benzene 5:1 → 1:1): **1** (230.6 mg), **2** (4.3 mg), **5** (18.7 mg), **8** (153.2 mg), and **9** (100.6 mg). *Fr. E* (with hexane/AcOEt 1:1) was separated by CC (*Chromatorex DMS*, MeOH/H_2O 2:3 → 1:0). The fractions containing flavonoids were purified by CC (*Sephadex LH-20*, MeOH) and VLC (SiO_2, benzene/EtOH 40:1 → 1:1) and subsequently by prep. TLC (benzene/EtOH 20:1): **4** (40.0 mg), **6** (32.2 mg), and **7** (48.0 mg) in pure forms, and **10**/**11** (21.7 mg) and **12**/**13** (23.7 mg) as mixtures of the corresponding isomers. TLC: detection by 10% H_2SO_4 soln. made **1**–**4** orange, and, on the contrary, **5** and **6** yellow.

Daemonorol A (=*8,8′-Methylenebis[3,4-dihydro]-5-methoxy-2-phenyl-2*H-*1-benzopyran-7-ol*; **1**): Colorless solid. $[\alpha]_D^{25} = -118$ ($c = 0.1$, $CHCl_3$). UV ($CHCl_3$): 277 (3.52). ^{1}H- and ^{13}C-NMR: *Table 1*. EI-MS: 524 (56, M^+), 505 (16), 420 (28), 401 (8), 316 (8), 269 (100), 256 (43), 165 (44), 104 (50). HR-EI-MS: 524.2207 (M^+, $C_{33}H_{32}O_6^+$; calc. 524.2199).

Daemonorol B (=*6,8′-Methylenebis[3,4-dihydro]-5-methoxy-2-phenyl-2*H-*1-benzopyran-7-ol*=*6-[(3,4-Dihydro-7-hydroxy-5-methoxy-2-phenyl-2*H-*1-benzopyran-8-yl)methyl]-3,4-dihydro-5-methoxy-2-phenyl-2*H-*1-benzopyran-7-ol*; **2**): Colorless solid. $[\alpha]_D^{25} = -116$ ($c = 0.1$, $CHCl_3$). UV ($CHCl_3$): 281 (3.63). ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 524 (37, M^+), 420 (8), 401 (8), 269 (100), 256 (54), 165 (34), 104 (42). HR-EI-MS: 524.2205 (M^+, $C_{33}H_{32}O_6^+$; calc. 524.2199).

Daemonorol C (=*8-[(3,4-Dihydro-7-hydroxy-5-methoxy-2-phenyl-2*H-*1-benzopyran-8-yl)methyl]-3,4-dihydro-5-methoxy-2-phenyl-2*H-*1-benzopyran-7-ol*; **3**): Colorless solid. $[\alpha]_D^{25} = -85$ ($c = 0.1$, $CHCl_3$). UV ($CHCl_3$): 273 (3.82). ^{1}H- and ^{13}C-NMR: *Table 2*. EI-MS: 538 (80, M^+), 434 (8), 282 (88), 269 (100), 256 (40), 179 (28), 165 (60), 152 (24), 104 (82). HR-EI-MS: 538.2362 (M^+, $C_{34}H_{34}O_6^+$; calc. 538.2355).

Daemonorol D (=*5-Methoxy-6-methyl-2-phenyl-4*H-*1-benzopyran-7-ol*; **4**): Red solid. UV (MeOH): 316 (3.07), 283 (3.65), 228 (4.26). ^{1}H- and ^{13}C-NMR: *Table 3*. EI-MS: 268 (100, M^+), 252 (16), 237 (12), 191 (20). HR-EI-MS: 268.1107 (M^+, $C_{17}H_{16}O_3^+$; calc. 268.1100).

Daemonorol E (=*(2*S*)-3,4-Dihydro-2-(4-hydroxyphenyl)-5-methoxy-2*H-*benzopyrane-7-ol*; **5**): Colorless solid. $[\alpha]_D^{25} = -85$ ($c = 0.1$, MeOH). UV (MeOH): 281 (3.83), 230 (4.69). CD ($c = 0.01$, MeOH): 281 (−0.93). ^{1}H- and ^{13}C-NMR: *Table 3*. EI-MS: 272 (100, M^+), 153 (93), 120 (60). HR-EI-MS: 272.1044 (M^+, $C_{17}H_{18}O_4^+$; calc. 272.1049).

Daemonorol F (=*3-(2,4-Dihydroxy-6-methoxy-3-methylphenyl)-1-phenylpropan-1-one*; **6**): Colorless solid. UV (MeOH): 279 (3.16), 238 (3.98). ^{1}H- and ^{13}C-NMR: *Table 4*. EI-MS: 286 (60, M^+), 267 (8), 256 (7), 167 (100), 154 (71), 137 (11), 105 (33), 77 (22). HR-EI-MS: 286.1211 (M^+, $C_{17}H_{18}O_4^+$; calc. 286.1205).

Catalytic Hydrogenation of **4**. A mixture of **4** (3.5 mg) and 5% Pd/C (7 mg) in EtOH (6 ml) was stirred under H_2 at r.t. overnight. The mixture was filtered, the filtrate concentrated, and the residue purified by prep. TLC (benzene/AcOEt 10:1): 1.0 mg of reduced product. The product was identified as *(2*S*)-5-methoxy-6-methylflavan-7-ol* (=*(2*S*)-3,4-dihydro-5-methoxy-6-methyl-2-phenyl-2*H-*1-benzopyran-7-ol*) by comparison with the ^{1}H-NMR data and R_f value on TLC (benzene/AcOEt 10:1) of **9**.

REFERENCES

[1] H. Brockmann, H. Junge, *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 751.
[2] M. J. Melo, M. Sousa, A. J. Parola, J. S. Seixas de Melo, F. Catarino, J. Marcalo, F. Pina, *Chem.–Eur. J.* **2007**, *13*, 1417.
[3] J. Kinjo, H. Uemura, T. Nohara, M. Yamashita, N. Marubayashi, K. Yoshihira, *Tetrahedron Lett.* **1995**, *36*, 5599.
[4] E. Risco, F. Ghia, R. Vila, J. Iglesias, E. Alvarez, S. Canigueral, *Planta Med.* **2003**, *69*, 785.
[5] L. Merlini, G. Nasini, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1570.
[6] A. Arnone, G. Nasini, L. Merlini, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2637.
[7] G. S. R. Rao, M. A. Gerhart, R. T. Lee III, L. A. Mitscher, S. Drake, *J. Nat. Prod.* **1982**, *45*, 646.
[8] W. J. Tsai, H. T. Hsieh, C. C. Chen, Y. C. Kuo, C. F. Chen, *Eur. J. Pharmacol.* **1998**, *346*, 103.
[9] M. Xia, M. Wang, S. Tashiro, S. Onodera, M. Minami, T. Ikejima, *Biol. Pharm. Bull.* **2005**, *28*, 226.

[10] M. Iinuma, Y. Kakuto, N. Tanida, T. Tanaka, F. A. Lang, *Phytochemistry* **1997**, *44*, 705.
[11] M. Furusawa, Y. Ido, T. Tanaka, T. Ito, K. Nakaya, I. Iliya, M. Oyama, M. Iinuma, Y. Shirataki, Y. Takahashi, *Helv. Chim. Acta* **2005**, *88*, 1048.
[12] S. Antus, T. Kurtan, L. Juhasz, L. Kiss, M. Hollosi, Z. S. Majer, *Chirality* **2001**, *13*, 493.
[13] C. C. Shen, S. Y. Tsai, S. L. Wei, S. T. Wang, B. J. Shieh, C. C. Chen, *Nat. Prod. Res.* **2007**, *21*, 377.
[14] G. Cardillo, L. Merlini, G. Nasini, *J. Chem. Soc. C* **1971**, 3967.
[15] A. Arnone, G. Nasini, O. Vajna de Pava, *J. Nat. Prod*. **1997**, *60*, 971.
[16] I. C. Parsons, A. I. Gray, P. G. Waterman, T. G. Hartley, *J. Nat. Prod*. **1993**, *56*, 46.
[17] D. B. De Oliveira, A. Paula de Almeida, G. L. De, B. A. Simoes, C. Auvin, C. R. Kaiser, S. S. Costa, *Planta Med*. **2003**, *69*, 382.
[18] G. A. Reynolds, J. A. Vanallan, *J. Org. Chem*. **1967**, *32*, 3616.
[19] G. Baudouin, F. Tillequin, M. Koch, M. Vuilhorgne, J. Y. Lallemand, H. Jacquemin, *J. Nat. Prod*. **1983**, *46*, 681.

Received March 12, 2009