Constituents of Dragon's Blood. 5.[1] Dracoflavans B_1, B_2, C_1, C_2, D_1, and D_2, New A-Type Deoxyproanthocyanidins[2]

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From Dragon's Blood, a resin produced by plants of the genus *Daemonorops* (Palmae), six new A-type flavanoid deoxyproanthocyanidins have been isolated. Their structure and stereochemistry, established by chemical degradation and extensive NMR analysis, is consistent with a mechanism of formation common to other constituents of the resin, which involves oxidation of a 6-methylflavan to a quinonemethide, followed by coupling with another flavan moiety.

Dragon's Blood is a medieval name for the red resinous exudates of several very diverse kinds of plants used for dyeing and medicine.[3] However, at present, the only commercially available material is the East Asian resin obtained from some species of *Daemonorops* (Palmae). Two characteristics of the flavonoid constituents of this resin are the flavan or flavan-derived structure and the low number of hydroxy substituents either in ring A or C. Moreover, the structures of all the compounds so far isolated from the resin, including the well-known dracorhodins and dracorubins,[4−6] apparently derive from the oxidation of the two simplest components of the resin: 5-methoxyflavan-7-ol and 5-methoxy-6-methylflavan-7-ol;[7] or from the coupling of the former with the quinonemethide that is formed by oxidation of the latter.[1,2] Further components recently isolated include a benzodioxepine derivative,[8] a secobiflavanoid,[9] and a secotriflavanoid (dracoflavan A).[1]

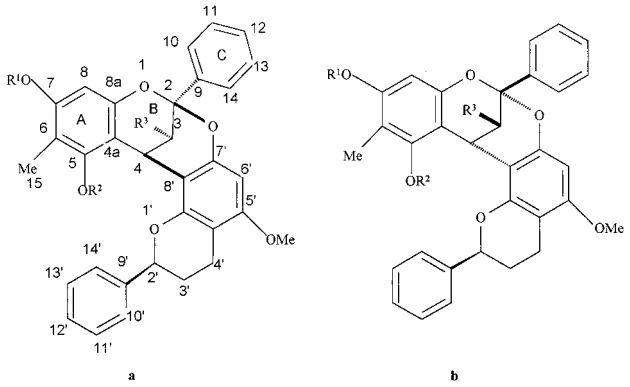
Further investigation of the resin resulted in the isolation of three new A-type deoxyproanthocyanidins **1**, **4**, and **7**, that we named dracoflavans B, C, and D.

Results and Discussion

Dracoflavan B (**1**) was obtained by extraction of the resin, followed by repeated chromatography on Si gel and appeared as an optically active white powder, mp 230−235 °C. The UV spectrum was consistent with a flavanoid structure. The compound analyzed for $C_{33}H_{30}O_7$, and EIMS ([M^+] = 538) confirmed the molecular formula, suggesting a biflavanoid structure. The formation of a monomethyl ether (**2**) and of a monomethyl ether−monoacetate (**3**) showed the presence of two OH groups, one phenolic and one alcoholic.

Chemical degradation with Zn and HCl of the methyl ether **2** (Scheme 1) afforded a mixture from which racemic 5,7-dimethoxy-6-methylflavan (**9**), (2*S*)-5-methoxyflavan-7-ol (**10**), and compounds **11** and **12** were isolated. Their formation is consistent with the structure **1** (apart from stereochemistry) for dracoflavan B, which was further confirmed by NMR data (see below).

Dracoflavan C (**4**) appeared very similar in structure to dracoflavan B, except for the lack of the alcoholic OH. MS and NMR spectra (see below) are consistent with this observation, supported by the formation of a monomethyl ether (**5**) and a phenolic monoacetate (**6**). Dracoflavan D (**7**) is an *O*-demethyl analogue of **4**, as it gives the methyl ether **5** by methylation and a diacetate (**8**) by acetylation.

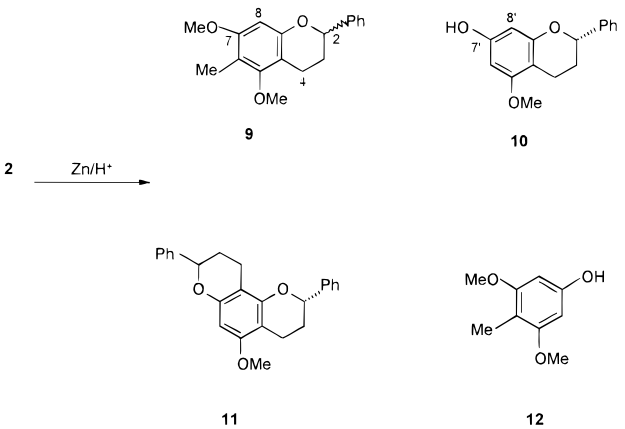


a **b**

1(a,b) R^1 = H; R^2 = Me; R^3 = OH
2(a,b) R^1 = Me; R^2 = Me; R^3 = OH
3(a,b) R^1 = Me; R^2 = Me; R^3 = OAc
4(a,b) R^1 = H, R^2 = Me; R^3 = H
5(a,b) R^1 = Me; R^2 = Me; R^3 = H
6(a,b) R^1 = Ac; R^2 = Me; R^3 = H
7(a,b) R^1 = R^2 = R^3 = H
8(a,b) R^1 = R^2 = Ac, R^3 =H

However, the NMR spectra of dracoflavan B showed a doubling of most signals. The possibility of hindered rotation of the two halves was not consistent with the fused structure of **1** and was ruled out by lack of coalescence of the double signals on heating. The product may thus constitute a mixture; this was confirmed when dracoflavan B was separated into two constituents

Scheme 1



9 **10**

11 **12**

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Table 1. ^{1}H-NMR Data for Compounds **1a**,**b**; **2a**,**b**; **4a**,**b**; **5a**,**b**; **6a**,**b**; and **8a**,**b**[a]

proton	1a	1b	2a	2b	4a	4b	5a	5b	6a	6b	8a	8b
3	4.16	4.22	4.21	4.27	2.24	2.28	2.27	2.24	2.32	2.35	2.34	2.36
4	4.68	4.73	4.77	4.79	4.69	4.76	4.72	4.75	4.77	4.88	4.28	4.52
8	6.40	6.37	6.48	6.46	(6.34)[b]	(6.32)	6.41	6.39	6.57	6.56	6.70	6.69
10	7.73	7.74	7.76	7.77	7.72	7.72	7.73	7.73	7.73	7.75	7.72	7.72
11	7.3−7.5	7.3−7.5	7.46	7.46	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.6	7.3−7.6
12	7.3−7.5	7.3−7.5	7.48	7.48	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.6	7.3−7.6
13	7.3−7.5	7.3−7.5	7.46	7.46	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.6	7.3−7.6
14	7.73	7.74	7.76	7.77	7.72	7.72	7.73	7.73	7.73	7.75	7.72	7.72
15	2.10	1.99	2.10	2.00	2.09	1.98	2.09	2.00	2.02	1.91	1.85	1.82
3-R	4.34	4.39	1.64	1.70	2.13	2.19	2.23	2.18	2.23	2.28	2.11	2.23
5-OR	3.54	3.37	3.50	3.33	3.52	3.37	3.49	3.33	3.56	3.43	1.60	1.60
7-OR	8.27	8.23	3.80	3.77	(8.31)	(8.27)	3.76	3.74	2.27	2.25	2.27	2.25
2′α	5.02	5.11	4.97	5.06	4.99	5.11	4.96	5.07	5.03	5.12	5.25	5.29
3′α	2.25	2.25	2.21	2.22	2.25	2.25	2.22	2.23	2.21	2.23	2.0−2.3	2.0−2.3
3′*β*	1.95	1.95	2.04	2.03	1.96	1.96	2.04	2.04	2.00	1.98	2.0−2.3	2.0−2.3
4′α	2.67	2.65	2.69	2.65	2.66	2.65	2.69	2.65	2.68	2.65	2.64	2.60
4′*β*	2.70	2.72	2.72	2.80	2.69	2.72	2.72	2.80	2.64	2.73	2.49	2.58
6′	6.18	6.17	6.18	6.17	(6.23)	(6.22)	6.24	6.23	6.27	6.26	6.23	6.22
10′	7.72	7.61	7.63	7.55	7.70	7.61	7.65	7.54	7.69	7.63	7.3−7.6	7.3−7.6
11′	7.3−7.5	7.3−7.5	7.42	7.43	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.6	7.3−7.6
12′	7.3−7.5	7.3−7.5	7.35	7.35	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.6	7.3−7.6
13′	7.3−7.5	7.3−7.5	7.42	7.43	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.5	7.3−7.6	7.3−7.6
14′	7.72	7.61	7.63	7.55	7.70	7.61	7.65	7.54	7.69	7.63	7.3−7.6	7.3−7.6
5′-OMe	3.77	3.76	3.75	3.75	(3.77)	(3.76)	3.76	3.75	3.80	3.81	3.77	3.76

[a] Chemical shifts obtained in acetone-d_6 for compounds **1a**,**b**; **4a**,**b**; **6a**,**b**; **8a**,**b** and in $CDCl_3$ for compounds **2a**,**b** and **5a**,**b**. [b] Similar values in parentheses exhibited by each pair of diastereoisomers may be interchanged.

Table 2. ^{1}H-NMR Coupling Constants for Compounds **1a**,**b**; **2a**,**b**; **4a**,**b**; **5a**,**b**; **6a**,**b**; and **8a**,**b**

	J/Hz											
	1a	1b	2a	2b	4a	4b	5a	5b	6a	6b	8a	8b
3a,3b					13.2	13.2	13.2	13.2	13.3	13.4	13.3	13.3
3a,4	3.4	3.4	3.5	3.5	3.1	3.1	3.1	3.1	3.2	3.2	3.4	3.5
3a,OH-3	5.5	5.5	6.1	6.1								
3b,4					3.1	3.1	3.1	3.1	3.1	3.1	3.2	3.0
2′α,3′α	2.2	2.3	2.3	2.3	2.2	2.4	2.2	2.4	2.1	2.5	3.9	2.9
2′α,3′*β*	10.5	10.5	10.7	10.6	10.6	10.5	10.6	10.5	10.4	10.4	7.4	8.6
3′α,3′*β*	*a*	*a*	13.6	13.7	*a*	*a*	*a*	*a*	13.6	13.7	*a*	*a*
3′α,4′α	*a*	6.0	5.9	6.3	*a*	6.1	*a*	6.1	6.2	6.0	*a*	7.8
3′α,4′*β*	*a*	3.2	3.4	2.7	*a*	3.1	*a*	2.9	3.2	3.0	*a*	5.5
3′*β*,4′α	*a*	11.0	10.5	11.6	*a*	11.1	*a*	11.1	10.6	11.2	*a*	7.8
3′*β*,4′*β*	*a*	6.2	7.0	5.7	*a*	6.2	*a*	6.0	6.5	6.0	*a*	5.5
4′α,4′*β*	*a*	16.8	16.9	16.8	*a*	16.8	*a*	16.8	16.9	16.8	*a*	16.8

[a] Not assigned.

(dracoflavans B_1 and B_2, **1a** and **1b**) by preparative HPLC using a chiral column (see Experimental Section). A similar separation was obtained for dracoflavan C acetate, showing dracoflavan C to consist of two constituents [dracoflavan C_1 (**4a**) and dracoflavan C_2 (**4b**)]. The resonances of the two components of **1** and **4** could be distinguished in ^{1}H and ^{13}C NMR spectra, allowing the structural assignment to be performed on the mixtures.

The ^{1}H-NMR spectra of both **1a,b** (Tables 1 and 2) showed the majority of the resonances arising from the flavan moieties **9** and **10**, except for those attributable to H-2 and OMe-7 in **9** and to H-8′ and OH-7′ in **10**. Moreover, they contained signals due to the presence of a >C(4)H−C(3)HOH fragment in place of the corresponding $-CH_2CH_2-$ unit of ring B of **9**, and of an OH located at C-7, as evidenced by the NOE observed between H-8 and OH-7 (7.5%). These findings, combined with a detailed analysis of the ^{13}C-NMR spectra of **1a**,**b** (Table 3) indicated that the two flavan moieties are linked together via C(4)−C(8′) and C(2)−O−C(7′) bonds. In fact, in both compounds, the proton assigned to H-4 presented two- or three-bond C,H couplings ranging between 4 and 6.5 Hz not only with C-4a and C-8a, but also with C-7′, C-8′ and C-8a′, and the chemical shift values of C-2 (δ_C = 99.74 and 99.64) imply that these carbons bear an additional oxygen atom with respect to **9**.

Comparison of the ^{1}H- and ^{13}C-NMR spectra of **1a** and **1b** with those of **4a** and **4b** (Tables 1−3 and Experimental Section) showed a close similarity among the four compounds, the only significant difference being the presence in **4a**,**b** of a C(3)-H_2 group (^2J = 13.2 Hz) in place of a C(3)HOH unit. Here again the NOE observed between H-8 and OH-7 (10.5%) indicated that the phenolic OH group is located at C-7.

Dracoflavan D (**7**) has the only OMe group allocated at C-5′, since the *ortho*-positioned H-6′ does not undergo a downfield shift by acetylation to **8**. The assignment of the signals of **8a** and **8b**, respectively (Table 1), is based on the broadening of H-3 at 2.23 ppm, H-4 and H-2′ in the monoacetates, so that we tentatively assigned these protons to compound **8b**, as the presence of an OAc group at C-5 causes in this diastereoisomer diminished mobility of the two flavanoid moieties.

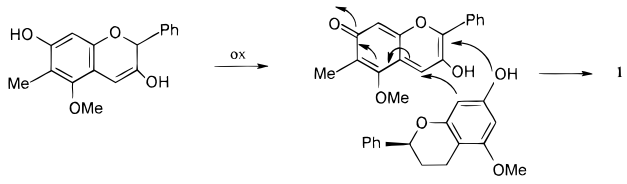
NOE difference experiments permitted us to assign the absolute configuration to the chiral centers in compounds **1a**,**b** and **4a**,**b**, provided that the absolute configuration of C-2′ is *S*, which is the usual configuration at this stereocenter in the natural compounds. This assignment was confirmed by the isolation of only 2-(*S*)-**10** in high yield in the reductive degradation of

Table 3. ^{13}C-NMR Data for Compounds **1a**,**b** in Acetone-d_6

	1a				**1b**			
carbon	δ_C		^1J(C,H)/Hz	$^{>1}J$(C,H)/Hz	δ_C		^1J(C,H)/Hz	$^{>1}J$(C,H)/Hz
2	99.74	S m			99.64	S m		
3	68.00	D br s	149		68.00	D br s	149	
4	29.82	D br s	141.5		29.82	D br s	141.5	
4a	109.44	S ddd		7 (H-3), 6.5 (H-4), 5.5 (H-8)	109.24	S ddd		7 (H-3), 6.5 (H-4), 5.5 (H-8)
5	159.10	S m			159.00	S m		
6	(111.46)[a]	S dq		6 (H-8), 6 (H_3-15)	(111.57)	S dq		6 (H-8), 6 (H_3-15)
7	(155.84)	S br dq		3.5 (H-8), 4 (H_3-15)	(155.78)	S br dq		3.5 (H-8), 4 (H_3-15)
8	99.51	D br s	159		99.51	D br s	159	
8a	151.82	S dd		4 (H-4), 5 (H-8)	151.56	S dd		4 (H-4), 5 (H-8)
9	140.87	S br t		7 (H-11 and -13)	140.78	S br t		7 (H-11 and -13)
10	127.90	D t	163	6 (H-12 and -14)	127.90	D t	163	6 (H-12 and -14)
11	128.44	D d	160	7 (H-13)	128.44	D d	160	7 (H-13)
12	(128.27)	D t	160	7.5 (H-10 and -14)	(128.27)	D t	160	7.5 (H-10 and -14)
13	128.44	D d	160	7 (H-11)	128.44	D d	160	7 (H-11)
14	127.90	D t	163	6 (H-10 and -12)	127.90	D t	163	6 (H-10 and -12)
15	9.19	Q br s	127.5		9.15	Q br s	127.5	
5-OMe	(60.94)	Q s	143.5		(60.52)	Q s	143.5	
2′	(78.87)	D m	145.5		(78.12)	D m	145.5	
3′	30.51	T m	130.5		30.33	T m	130.5	
4′	20.80	T m	131		20.18	T m	131	
4′a	104.74	S m			104.58	S m		
5′	157.93	S dtq		4 (H-6′), 3.5 (H_2-4′), 4 (H_3-15′)	157.79	S dtq		4 (H-6′), 3.5 (H_2-4′), 4 (H_3-15′)
6′	91.79	D br s	161		91.79	D br s	161	
7′	152.41	S dd		4.5 (H-4), 5.5 (H-6′)	152.19	s dd		4.5 (H-4), 5.5 (H-6′)
8′	108.22	S br dd		6.5 (H-4), 5 (H-6′)	108.22	S br dd		6.5 (H-4), 5 (H-6′)
8′a	153.13	S dt		4 (H-4), 3.5 (H_2-4′)	152.53	S dt		4 (H-4), 3.5 (H_2-4′)
9′	143.31	S br dt		3.5 (H-2′), 7.5 (H-11′ and -13′)	142.77	S br t		3.5 (H-2′), 7.5 (H-11′ and -13′)
10′	127.20	D dt	160	4 (H-2′), 7 (H-12′ and -14′)	126.86	D dt	159.5	4 (H-2′), 7 (H-12′ and -14′)
11′	(128.90)	D d	160.5	8 (H-13′)	(129.04)	D d	160.5	8 (H-13′)
12′	(129.18)	D t	160.5	7.5 (H-10′ and -14′)	(129.18)	D t	160.5	7.5 (H-10′ and -14′)
13′	(129.90)	D d	160.5	8 (H-11′)	(129.04)	D d	160.5	8 (H-11′)
14′	127.20	D dt	160	4 (H-2′), 7 (H-10′ and -12′)	(126.86)	D dt	159.5	4 (H-2′), 7 (H-10′ and -12′)
5′-OMe	55.75	Q s	143.5		55.75	Q s	143.5	

[a] Similar values in parentheses may be interchanged.

Scheme 2



the mixture **2**. Moreover, the resin contains only 2*S*-5-methoxyflavan-7-ol, from which **1** is deemed to be formed. The coupling constants observed between H-2′ and H_2-3′ (Table 2) indicate that the preferred conformation assumed by the heterocyclic ring B′ is a half-chair with the C-2′ phenyl group pseudoequatorial (see also Vivas *et al.*[10]). In fact, significant NOEs were observed in **1b** and **4b** between the 5-OMe protons and H-2′ (3%), whereas only small enhancements (<0.5%) were observed for the corresponding proton signals in **1a** and **4a**. Models of the two epimers possibly deriving from the coupling shown in Scheme 2 and with the C-2′-phenyl group pseudoequatorial were built using the DISCOVER program included in the INSIGHTII package (Biosym Technologies). Inspection of these models (Figure 1) confirmed that in compounds **1b** and **4b** the 5-OMe group is spatially much closer to H-2′ than in **1a** and **4a**, respectively. As the above-mentioned NOEs are the same for **1a** and **4a**, the two compounds, as well as **1b** and **4b**, must have the same configuration at carbons 2 and 4.

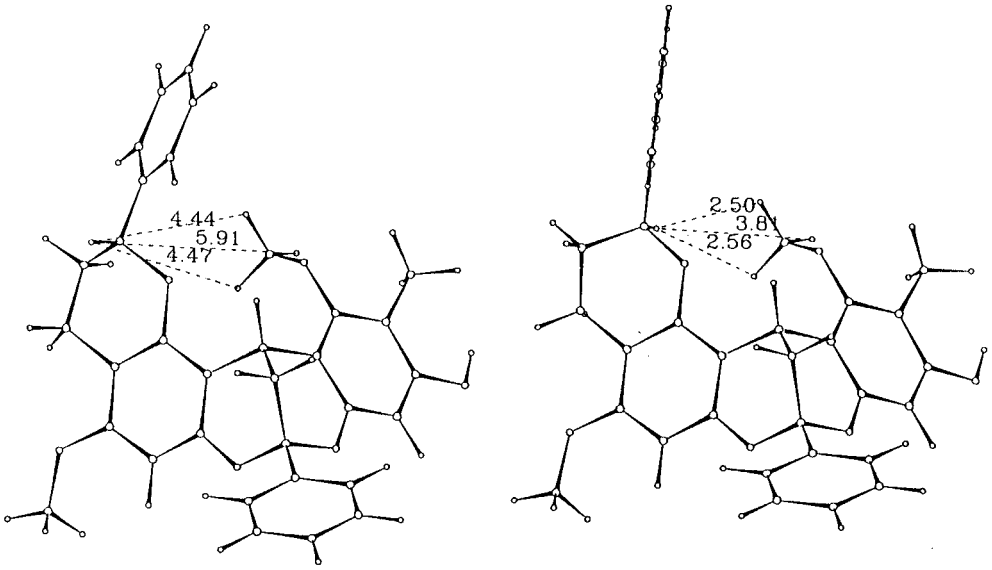
The 3,4-*trans* configuration of the substituents on ring B of **1a**,**b** appears from the observation of significant NOEs[11] between H-3 and H-6′, and between H-8 and OH-3 (see Experimental Section). It follows that **1a** must have the 2*S*,3*R*,4*R*,2′*S* and **1b** the 2*R*,3*S*,4*S*,2′*S* configuration. However, because of the priority rules, this becomes 2*R*,4*R*,2′*S* for **4a** and **7a** and 2*S*,4*S*,2′*S* for **4b** and **7b**.

The likely mode of formation of dracoflavans B, C, and D is consistent with the oxidation process that gives rise to the other constituents of the resin,[2] that is, oxidation of a 5-methoxy-6-methylflavan-7-ol to the corresponding quinonemethide and nucleophilic attack of carbon 8 of 5-methoxyflavan-7-ol onto carbon 4 of the quinonemethide, followed by ring closure of the 7-OH onto carbon 2 of the quinonemethide (Scheme 2). This process could give rise to two diastereoisomers, depending on the face of attack in the first step. In the case of **1**, the intermediacy of a flav-2-en-3-ol (Scheme 2) seems likely, as the configuration at C-3 is opposite in the two diastereoisomers **1a** and **1b**, most probably as a consequence of the OH group being pushed into the direction opposite to that of the attack of the second flavan moiety.

The mixture **1a**,**b** was subjected to selected pharmacological tests at the dosage of 100 mg/kg ip. Tests showed significant antiinflammatory activity in the carrageenin-induced paw edema of the rat [average reduction of the edema 45% with respect to the controls (10 rats) treated with 5% gum arabic], inhibition of bradykinin-induced capillary permeability in the rat (average 35%, 10 rats), and an increase (average 11.0%, 8 rats) of capillary resistance in starving rats.

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler apparatus and are uncorrected. IR and UV spectra (EtOH) were recorded with a Perkin-Elmer 177 instrument and a JASCO Uvidec-510 spectrophotometer, respectively; optical rotations



4a **4b**

Figure 1. Models of **4a** and **4b**, featuring the distances (Å) between H-2′ and the protons of 5-OMe. For sake of better comparison between the structures of dracoflavans C_1 and C_2, the model **4a** shows, in fact, the enantiomer of the corresponding natural product.

($CHCl_3$), on a JASCO Dip-181 polarimeter; mass spectra, on a Finnigan-MAT TSQ70 spectrometer. NMR spectra were acquired on a Bruker AC 250L spectrometer operating at 250.1 MHz for ^1H and 62.9 MHz for ^{13}C; chemical shifts are in parts per million (δ) from $SiMe_4$ as internal standard, and J values are in Hz. TLC and PLC were performed with Merck HF_{254} Si gel. The separation and purity of the compounds were determined by HPLC analysis using a Merck−Hitachi L6000 apparatus equipped with a Daicel chiralcel OD 0.45 × 25 cm column with hexane−iPrOH as eluent (a), flow rate $cm^3\ min^{-1}$ (fr) , retention time (t_R).

Isolation and Purification of Dracoflavans B, C, and D (1a,b, 4a,b, 7a,b). Finely powdered "Dragon's Blood" resin [commercial batches of the resin imported from Singapore (so called Indian resin) by Ghezzi snc, via Volta 16, Milano] (100 g) was extracted in a Soxhlet apparatus first with hexane, and then with EtOAc; the EtOAc extract, after flash chromatography with hexane−Et_2O (2:1), afforded a mixture of dimeric flavanoids that were further purified by repeated column chromatography and PLC. Owing to the complexity of the purification from the other flavanoids and terpenoids,[1] we report the R_f values in hexane−EtOAc (2:1).

Dracoflavans B (1a,b) (150 mg): R_f 0.3, obtained as white crystals, $[\alpha]_D$ −21° (*c* 0.6); UV λ_{max} (ϵ) 214 (29 400) and 280 (1600) nm; IR (nujol) ν_{max} 3300 (OH), 1620, 1400 cm^{-1}; *anal.* calcd for $C_{33}H_{30}O_7$, C 73.59%, H 5.61%; found C 73.4%, H 5.7%; EIMS *m*/*z* 538 $[M]^+$ (5%), 283 (100), 281 (97); the dracoflavans B (**1a**) and (**1b**) were separated by HPLC on Chiralcel OD, a = 70:30, fr = 0.8, t_R = 8.4 (50%) and 13.2 (50), respectively; **1a**, as a solid, mp 224 °C (Et_2O−hexane); $[\alpha]_D$ +12.6° (*c* 0.05); **1b**, mp 170 °C; $[\alpha]_D$ −76.4° (*c* 0.06); the ^1H- and ^{13}C-NMR data are reported in Tables 1, 2, and 3.

1a: selected NOE experiments (acetone-d_6); {H-3} enhanced H-4 (9.5%), H-10 and H-14 (3%), OH −3 (8%) and H-6′ (0.5%); {H-4} enhanced H-3 (10%), OH-3 (3%), OMe −5 (2%), H-10′ and H-14′ (1%); {H-8} enhanced OH-3 (3%) and OH-7 (7.5%); {OMe-5} enhanced H-4 (9.5%), H_3-15 (2.5%), H-2′ (<0.5%), H-10′ and H-14′ (2.5%); {H-6′} enhanced OMe-5′ (3.5%).

1b: the NOEs exhibited by H-3, H-4, H-8, and H-6′ were very similar to those of **1a**, while {OMe-5} enhanced H-2′ (3%) together with H-4 (9.5%), H_3-15 (2.5%), H-10′ and H-14′ (1.5%).

Dracoflavan B Monomethyl Ethers (2a,b). Methylation (MeI, K_2CO_3, acetone) of **1a**,**b** (100 mg) gave the monomethylethers **2a**,**b**; mp 218−220 °C (Et_2O−hexane); UV λ_{max} (ϵ) 212 (52 000), 273 (2300), 283 (sh, 2100); *anal.* calcd for $C_{34}H_{32}O_7$, C 73.89%, H 5.84%, found C 73.7%, H 5.7%; EIMS *m*/*z* 552 $[M]^+$, 297 and 296.

Compounds 2a,b: **2a**, mp 135−140 °C, $[\alpha]_D$ +51.4° (*c* 0.1); **2b**, mp 122−130 °C, $[\alpha]_D$ −87° (*c* 0.2) may be isolated by HPLC: eluent (a) = 90:1, fr = 0.8, t_R = 9.0 (48%) and 14.5 (50), respectively. The ^1H-NMR data are listed in Tables 1 and 2.

Acetylation of 3a,b: **2a**,**b** (10 mg) with Ac_2O (0.2 mL) in dry pyridine for 30 min at room temperature and evaporation of the mixture gave the monomethyl ether monoacetates **3a**,**b**; EIMS *m*/*z* 594 $[M]^+$, 534 $[M^+ - 60]$, 490, 297 and 296; δ_H (DMSO-d_6) 7.8−7.2 (2 × 10 H, m, ArH), 6.49 and 6.47 (2 × 1H, br s, H-8), 6.19 (2 × 1H, br s, H-6′), 5.29 and 5.25 (2 × 1H, d, J = 3.5 Hz, H-3), 5.03 and 4.95 (2 × 1H, m, H-2′), 4.69 and 4.63 (2 × 1H, d, J = 3.5 Hz, H-4), 3.70, 3.68, 3.66, and 3.65 (2 × 6H, s, 7- and 5′-OMe), 3.32 and 3.19 (2 × 3H, s, 5-OMe), 2.7−2.3 (2 × 2H, m, H_2-4′), 2.2−1.7 (2 × 2H, m, H_2-3′), 1.95 and 1.85 (2 × 3H, br s, H_3-15), 1.65 and 1.62 (2 × 3H, s, 3-OAc).

Dracoflavans C (4a,b) (25 mg): R_f 0.5, isolated as a solid mp 90−95 °C, $[\alpha]_D$ −14° (*c* 0.1); UV λ_{max} (ϵ) 213 (55 000), 275 (sh, 2200), and 283 (2500) nm; IR (nujol) ν_{max} 3400 (OH),1630, and 1460 cm^{-1}; *anal.* calcd. for $C_{33}H_{30}O_6$, C 75.84%, H 5.79%; found C 75.7%, H, 5.8%; EIMS *m*/*z* 522 $[M]^+$, 491, 418, 387, 322, 267 and 201. Compounds **4a** and **4b** may be separated by HPLC: eluent (a) = 95:1, fr = 1, t_R = 27.12 (57%) and 42.00 (43), respectively; ^1H-NMR values in Tables 1 and 2 were taken on the mixture; δ_C NMR (acetone-d_6) 157.77 and 157.63 (C-5 and -7); 156.07 and 155.99 (C-5′); 153.08, 152.98, 152.77, 152.43, 152.28 and 152.04 (C-8a, -7′, and -8′a); 143.50, 143.21, 142.92, 129.30, 129.11, 128.99, 128.33, 127.31, 126.93, and 126.54 (ArC of rings

at C-2 and -2′); 112.42 and 112.28 (C-4a); 111.45 and 111.28 (C-6); 108.90 and 108.83 (C-8′); 104.63 and 104.48 (C-4′a); 99.66 and 99.56 (C-8); 99.12 and 98.98 (C-2); 92.31 and 92.26 (C-6′); 78.93 and 78.14 (C-2′); 61.04 and 60.65 (OMe-5); 55.78 (OMe-5′); 35.37 and 35.27 (C-3); 30.62 (C-3′); 21.92 (C-4); 20.68 and 20.19 (C-4′); and 9.16 (C-15).

4a: selected NOE experiments (acetone-d_6); {H-8}enhanced OH-7 (10.5%); {OMe-5} enhanced H-4 (8%), H_3-15 (2.5%), H-2′ (<0.5%) and H-10′ and H-14′ (2.5%); {H-6′} enhanced OMe-5′ (3.5%); and {OMe-5′} enhanced H-6′ (20.5%).

4b: the NOEs exhibited by H-8, H-6′ and OMe-5′ very similar to those of **4a**, while {OMe-5} enhanced H-2′ (3%) together with H-4 (7.5%), H_3-15 (2.5%), H-10′ and H-14′ (1.5%).

Dracoflavan C Monomethyl Ethers (5a,b). Methylation (MeI, K_2CO_3, acetone) of **4a**,**b** (10 mg) gave **5a**,**b** as a solid: mp 240−242 °C, (Et_2O); $[\alpha]_D$ −50.4° (*c* 0.06); UV λ_{max} (ϵ) 210 (23 600), 275 (1400), and 284 (sh, 1100) nm; EIMS *m*/*z* 536 $[M]^+$ (65%), 505 $[M^+ - 31]$ (87), 432$[M^+ - 104]$ (50), 401 (100), 281 (28), and 265 (45).

Dracoflavan C Monoacetates (6a,b). Acetylation of **4a,b** (50 mg) was performed with Ac_2O (0.5 mL) in dry pyridine (0.25 mL) for 1 h at room temperature. PLC of the residue in hexane−EtOAc (2:1) gave **6a**,**b** as a solid, mp 130−135 °C; $[\alpha]_D$ −17° (*c* 0.05); UV λ_{max} (ϵ) 207 (58 000), 273 (sh, 2300) and 282 (sh, 2100) nm; IR (nujol) ν_{max} 1770 (Ac) cm^{-1}; *anal.* calcd for $C_{35}H_{32}O_7$, C 74.45%, H 5.71%; found C 74.3%, H 5.6%; EIMS *m*/*z* 564 $[M]^+$, 522 $[M^+ - 42]$, 505, 491, 418, 401, 369, 341, 265, and 254; HPLC (a) = 95:5, fr = 1, **6a** t_R = 10.6 (60%) and **6b** 12.8 (40%). Compounds **6a** and **6b** were separated by PLC using CH_2Cl_2−hexane (10:1.5) as eluent (three runs); **6a** has mp 112−115 °C, $[\alpha]_D$ +44.8° (*c* 0.05) and **6b** mp 185−190 °C, $[\alpha]_D$ −65° (*c* 0.05); the purity of compounds was checked by HPLC. The ^{1}H-NMR data are reported in Tables 1 and 2.

Dracoflavans D (7a,b) (9 mg): R_f 0.4 as a solid, mp 225−230 °C; UV λ_{max} (ϵ) 210 (58 000), 275 (4650), and 285 (4300) nm; EIMS *m*/*z* 508 $[M]^+$; methylation of **7a**,**b** (5 mg) (see above) gave **5a**,**b**, also obtained by methylation of dracoflavans C.

Dracoflavan D Diacetates (8a,b). Acetylation of **7a**,**b** (10 mg) gave **8a**,**b** as a solid, mp 183−185 °C (Et_2O−hexane); $[\alpha]_D$ −60.3° (*c* 0.14); *anal.* calcd for $C_{36}H_{32}O_8$, C 72.96%, H 5.44%; found C 72.8%, H 5.3%; EIMS *m*/*z* 592 $[M]^+$(12%), 533 (63), 488 $[M^+ - 104]$ (87), 429 (95), 387 (100), 265 (50), and 253 (30); HPLC: (a) = 90:10, fr = 0.5, t_R = 17.1 (68%) and 19.1 (27). The compounds were not separated, and the ^{1}H-NMR analysis was performed on the mixture.

Degradation of Dracoflavan B Methyl Ethers (2a,b). To **2a**,**b** (150 mg) dissolved in a solution of concd. HCl in MeOH (1:2) (10 mL), an excess of Zn powder was added, and the mixture was refluxed for 6 h. After removal of the solvent, H_2O was added, and the residue was neutralized and extracted twice with EtOAc. Flash chromatography of the mixture with hexane−EtOAc (4:1) and PLC in the same solvent gave compounds **9**−**12**.

5,7-Dimethoxy-6-methylflavan (9) (10 mg): identified by comparison with a sample obtained by methylation of the natural (2*S*)-compound;[7] oil, $[\alpha]_D$ −13.5° (*c* 0.6); EIMS *m*/*z* 284 $[M]^+$; chiral HPLC, (a) = 95:5, fr = 0.5 and t_R = 9.8; **9**, 9.8 (31%) and 10.5(66); δ_H ($CDCl_3$) 7.6−7.2 (5H, m, ArH), 6.30 (1H, br s, H-8), 4.99 (1H, dd, *J* = 9.5, 3.7 Hz, H-2), 3.75 and 3.71 (6H, s, 2 × OMe), 3.0−2.6 (2H, m, H_2-4), 2.3−1.8 (2H, m, H_2-3), and 2.08 (3H, br s, Me-6).

(2*S*)-5-Methoxyflavan-7-ol (10) (15 mg): was identified by direct comparison (TLC, EIMS, $[\alpha]_D$, NMR) with an authentic sample[7] and confirmed by chiral HPLC.

Compound 11 (40 mg): solid, mp 110−115 °C, $[\alpha]_D$ −35° (*c* 0.3); IR (liquid film) ν_{max} 1640, 1610, 1470, and 1450 cm^{-1}; *anal.* calcd for $C_{25}H_{24}O_3$, C 80.62%, H 6.49%; found C 80.4%, H 6.3%; EIMS *m*/*z* 372 $[M]^+$ (55%), 268 $[M^+ - 104$, RDA] (44), 177 (50), 104 (100), and 91 (20); chiral HPLC: (a) = 95:5, fr = 0.5, t_R = 11.5 (33%) and 12.7 (66); δ_H ($CDCl_3$) 7.5−7.2 (10H, m, ArH), 6.14 (1H, br s, H-6), 5.00 (2H, m, 2 × OCHPh), 3.77 (3H, s, OMe-5), 2.9−2.5 and 2.3−1.8 (8H, m, 4 × CH_2).

2,4-Dimethoxy-3-methylphenol (12) (2 mg): was isolated as a solid; EIMS *m*/*z* 168 $[M]^+$; δ_H ($CDCl_3$) 6.07 (2H, br s, ArH), 4.52 (1H, br signal, OH), 3.76 (6H, s, 2 × OMe) and 2.01 (3H, br s, Me).

Biological Assay. The mixture **1a**,**b** was first subjected to the standard Irwin test in the mouse at doses of 100−300−1000 mg/kg. No death was observed even at the highest dosage. Therefore, the mixture was tested for antiinflammatory activity employing the carrageenin-induced rat paw assay at the dosage of 100 mg/kg ip, according to the procedure of Winter *et al.*,[12] using 10 Charles River rats weighing 135 ± 15 g, starving from the preceding evening. Control rats were treated with 5% gum arabic under the same conditions. The inhibition of bradikynin-induced capillary permeability in the rat was measured according to the procedures of Udaka *et al.*[13] and Conti *et al.*,[14] using Morini rats weighing 220 ± 20 g, starving from 18 h before the experiment. The activity on the capillary resistance in the rat was measured according to the procedure of Charlier *et al.*,[15] using 10 Morini rats weighing 180−200 g.

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