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TWO PROANTHOCYANIDINS FROM THE BARK OF *DALBERGIA MONETARIA*

DOMINGOS S. NUNES, ARMIN HAAG and HANS-JÜRGEN BESTMANN*

Institut für Organische Chemie der Universität Erlangen-Nürnberg, Henkestr. 42, 8520 Erlangen, F.R.G.

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Key Word Index—*Dalbergia monetaria*; Leguminosae–Papilionoideae; proanthocyanidin dimers.

Abstract—In a chemical investigation of the bark of *Dalbergia monetaria* the two new proanthocyanidins (2*R*,3*R*,4*R*)-3,3′,4′,7-tetrahydroxyflavan-(4β→8)-epicatechin and (2*R*,3*R*,4*R*)-3,4′,7-trihydroxyflavan-(4β→8)-epicatechin were isolated.

INTRODUCTION

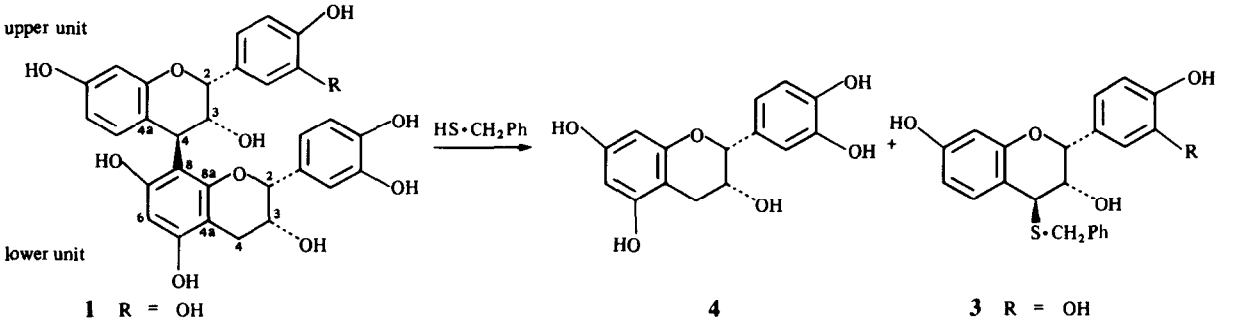
Earlier studies of the seed constituents of *Dalbergia monetaria* L. led to the isolation of isoflavonoids including rotenoids and rotenoid glucosides [1]. The decoction of the bark of this plant is traditionally utilized in Brazil, in the region of the Amazon River mouth, because of various alleged medicinal properties. The most widespread use of this popular preparation is for the daily wash of feminine genital parts, which is said to prevent infections and tumours and to recuperate the muscular elasticity after a delivery. As well as several other biological activities of dimeric and oligomeric proanthocyanidins, the positive effects of these compounds in the stabilization of collagen fibres has been long experimentally demonstrated [2].

We describe here the isolation and identification of two new dimeric proanthocyanidins from the bark of *Dalbergia monetaria*. This is the first report on the occurrence of these kinds of flavonoids in the genus *Dalbergia*.

RESULTS AND DISCUSSION

The ethyl acetate extract of the defatted bark was fractioned by a combination of polyamide and silica gel chromatography. Compounds **1** and **2** were separated from enriched fractions using a dry silica gel column and finally purified on Sephadex LH-20. The structure of both **1** and **2** is derived from their ^{1}H and ^{13}C NMR spectra, mass spectra of the respective acetyl, methyl and TMSi-derivatives, and from the identification of the reaction products of the original substances with benzylmercaptan/acetic acid in ethanol [3].

The ^{13}C NMR spectra of several procyanidins are well documented in the literature [4–8]. The ^{13}C NMR spectrum of **1** (CD_3OD, Table 1) shows the characteristic chemical shifts for two unsubstituted catechol B-rings (u = upper unit; l = lower unit): six aromatic methine carbons (C-2′u 115.1, C-2′l 115.6, C-5′u 115.9, C-5′l 116.0, C-6′u 119.7 and C-6′l 119.9 ppm), four hydroxy substituted carbons (C-3′u 145.3, C-3′l 145.4, C-4′u 145.5 and C-4′l 145.6 ppm) and two quaternary carbons (C-l′u 131.8 and C-1′l 132.2 ppm). Also characteristic of procyanidins, especially to procyanidins B-2 and B-5 [8], are the signals corresponding to the carbons of the heterocyclic aliphatic rings. Six aliphatic carbon signals are observed in the high field region of the ^{13}C NMR spectrum, of which four are methines bearing an oxygen atom (C-2l 79.5, C-2u 78.9, C-3u 72.3 and C-3l 66.5 ppm). The remaining sp^3 carbon



1 R = OH
1a nona-acetate
1b nona-TMSi-derivative
1c heptamethylether (phenolic)
2 R = H
2a octa-acetate
2b octa-TMSI-derivative
2c hexamethylether (phenolic)

4

3 R = OH
5 R = H

Table 1. ^{13}C NMR data for compounds **1**–**7** (δ values)*

	1†	1c†	2†	2c†	3	4	5	6‡	7‡
sp^3 carbons									
C-2u	78.9	76.9	79.0	77.2	75.6	79.8	75.6	79.3	82.5
l	79.5	78.5	79.6	78.5					
C-3u	72.3	71.7	72.5	71.7	71.7	67.4	71.6	67.3	68.6
l	66.5	65.7	66.7	65.9					
C-4u	39.0	38.2	39.2	38.3	47.0	29.2	47.2	28.3	28.2
l	29.4	28.3	29.5	28.5					
A-ring carbons									
C-4au	117.3	116.2	117.2	116.3	111.7	100.0	111.7	100.0	100.8
l	100.7	101.7	100.9	101.8					
C-5u	130.4	129.0	130.7	129.1	128.0	157.6	128.0	157.5	157.3
l	156.1	153.7	156.2	153.8					
C-6u	109.0	107.7	109.1	107.8	110.1	95.8	110.2	95.8	95.5
l	97.0	89.6	97.0	89.8					
C-7u	156.4	158.8	156.6	158.9	158.6	157.9	158.6	157.8	157.5
l	156.9	157.8	157.0	157.9					
C-8u	103.5	100.6	103.6	100.7	103.7	96.4	103.7	96.3	96.3
l	108.6	110.3	108.8	110.3					
C-8au	156.1	158.0	156.2	158.1	156.9	157.3	156.9	157.3	156.7
l	155.4	154.6	155.5	154.9					
B-ring carbons									
C-1′u	132.2	131.3	131.9	130.8	131.7	132.2	131.0	132.2	132.2
l	131.8	130.4	131.6	130.4					
C-2′u	115.1	109.9	129.4	128.0	115.3	115.3	129.0	115.2	115.1
l	115.9	110.6	115.2	110.0					
C-3′u	145.3	148.7	115.7	113.8	145.7	145.7	115.8	145.6	145.9
l	145.4	148.8	145.5	148.8					
C-4′u	145.5	149.0	157.5	159.3	145.9	145.9	157.9	145.8	146.0
l	145.6	149.0	145.6	149.2					
C-5′u	115.6	111.4	115.7	113.8	115.9	115.8	115.8	115.9	116.1
l	116.0	111.4	115.9	111.5					
C-6′u	119.7	118.4	129.4	128.0	119.2	119.4	129.0	119.4	120.0
l	119.9	119.1	119.8	118.5					
Toluene–thiolyl carbons									
			C-1″		140.1		140.4		
			C-2″		129.9		130.0		
			C-3″		129.6		129.6		
			C-4″		133.6		133.6		
			C-5″		129.6		129.6		
			C-6″		129.9		130.0		
			S-CH_2		37.2		37.3		

*CD_3OD as solvent for phenols and $CDCl_3$ for methylethers.
‡Standards: **6**, (−)-epicatechin and **7**, (+)-catechin. u = upper unit, l = lower unit.
†Spectrum at 50°.

signals exhibit significant upfield shifts (39.0 and 29.4 ppm) and are attributed to C-4 of the upper and lower units, respectively.

The molecular ions obtained for the nona-acetate **1a** (*m/z* 940), the nona-TMSi-derivative **1b** (*m/z* 1210) and the heptamethylether **1c** (*m/z* 660) indicate that the dimeric structure contains one phenolic hydroxy group less than the B-procyanidins in the A-ring of the lower or the upper unit. The fragmentation pattern is in full agreement with the structure. The ^{1}H NMR spectrum of **1** showed the characteristic pattern for the methylene group of (−)-epicatechin as the lower unit (δ2.78, *br dd* and δ2.90, *br dd*, $J_{gem} = 16$ Hz).

Reaction of the dimer **1** with benzylmercaptan/acetic acid in ethanol yielded (−)-epicatechin (**4**) from the lower part and **3** as sole thioether from the upper part [3].

The ^{1}H and ^{13}C NMR spectra of **4** and of authentic (−)-epicatechin are superimposable. The ^{13}C NMR spectrum of the thioether **3** shows three A-ring methine signals at δ103.5, 110.1 and 128.0 attributed to C-8, C-6 and C-5, respectively. Similar chemical shifts for the A-ring methines of the upper unit of **1** are also observed at δ103.5, 109.0 and 130.4. The signals of quaternary carbon atoms at δ111.7 and 117.2 are attributed to C-4a in **3** and **1** respectively. The chemical shifts of C-2 in the thioether **3** (δ75.6) and in the upper unit of **1** (δ78.9) suggested (2,3-*cis*-3,4-*trans*)-isomerism.

Also favourable to this stereochemistry in the thioether

3 are the deshielding of H-2 (δ5.23, *s*) relative to H-2 in (−)-epicatechin (**4**) (δ4.80, *s*) and the signals corresponding to H-3 (δ3.8, *m*) and H-4 (δ3.97, *d*, J = 2 Hz).

The above considerations indicated for **1**, a (4β→6) or (4β→8) dimeric structure with (−)-epicatechin as the lower unit [3] and 3,3′,4′,7-tetrahydroxyflavan as the upper unit. The stereochemistry at C-4 was corroborated by a positive Cotton effect at 237 nm [3, 9], that defined for **1** the (4*R*)-configuration in terms of the aromatic quadrant rule [10].

As previously demonstrated for several methylethers of C-6 and C-8 substituted catechin derivatives [11–13], it is possible to differentiate between C-6 and C-8 substitution based on the chemical shifts of C-4a, C-6 and C-8 of the methylether. The values δ101.7, 89.6 and 110.3 respectively for the chemical shifts of these carbon atoms of the heptamethylether **1c** establish the presence of the C-4/C-8 linkage and so confirm **1** as a new profisetinidin, (2*R*,3*R*,4*R*)-3,3′,4′,7-tetrahydroxyflavan-(4β→8)-epicatechin.

The mass spectra of the acetyl, methyl and TMSi-derivatives of **2** showed the molecular ions *m/z* 882, 630 and 1122, respectively, indicating for compound **2** a structure with one hydroxy group less than in **1**. Again, the fragmentation pattern gives evidence for the structure.

The ^{13}C NMR spectrum of **2** clearly shows the chemical shifts for one 3′,4′-dihydroxy substituted B-ring (C-2′l 115.2, C-5′l 115.9 and C-6′l 119.8 ppm) and also for one *p*-hydroxy substituted B-ring (C-3′u and C-5′u 115.7 ppm; C-2′u and C-6′u 129.4 ppm), the remaining carbon atoms having shift values very similar to those observed for 1 (Table 1).

The ^{1}H NMR spectrum of **2** contained in the downfield aromatic region one A_2B_2 system (δ6.74, *d* and 7.26, *d*, J = 8 Hz). The cleavage of **2** with benzylmercaptan/HOAc produced again (−)-epicatechin (**4**) and a single thioether (**5**), which gave a negative Gibbs test [14]. Apart from the signals due to the B-ring carbon and hydrogen atoms, the ^{1}H and ^{13}C NMR spectra of **5** resemble those of the thioether **3**.

These data showed that **2** has (−)-epicatechin as the lower unit and 3,4′,7-trihydroxyflavan as the upper unit. The positive Cotton effect at 230 nm in the CD curve of **2** confirms the (4*R*)-configuration. The chemical shifts δ101.8, 89.8 and 110.3 for C-4a, C-6 and C-8 in the hexamethylether **2c** established for **2** the more commonly encountered C-4/C-8 linkage. We assign to this new proguibourtinidin the structure (2*R*,3*R*,4*R*)-3,4′,7-trihydroxyflavan-(4β→8)-epicatechin (**2**).

EXPERIMENTAL

Dalbergia monetaria L. was collected in Belém do Pará, Brazil, and a voucher specimen was deposited under number MG 110003 in the Herbarium of the Museu Paraense Emilio Goeldi.

Mps: uncorr. ^{1}H NMR spectra were determined at 399.4 MHz and ^{13}C NMR spectra at 100.4 MHz. Authentic samples of (−)-epicatechin (**6**) and (+)-catechin (**7**) were commercially available from Roth (F.R.G.).

Extraction and isolation. The bark (600 g) of *D. monetaria* was finely milled, defatted with hexane and percolated with Et_2O (3 × 3 l) and EtOAc (3 × 3 l). The combined EtOAc extract gave 39 g of a brown solid on evapn under red. pres. at 40°. This residue was dissolved in MeOH (150 ml), chromatographed on a column of polyamide (125 g, 85 × 3.5 cm, packed with H_2O), and eluted with H_2O–MeOH (7:3). Fractions of 11 were collected. TLC was carried out on Merck silica plates using EtOAc–MeOH–H_2O (80:13:11) (system A) and visualized by spraying with a soln of $FeCl_3$ 5% in MeOH. Fractions 9–16 (3.2 g) were rechromatographed on a column of silica gel (85 × 2.5 cm) with EtOAc giving a mixture (2.3 g) of **1** and **2**. The separation of the two compounds was achieved on a dry column of silica gel using Me_2CO–$CHCl_3$–MeOH–H_2O (12:9:2:1) (system B) as eluent. Final purification of the compounds on a column of Sephadex LH-20 (elution with Me_2CO) was necessary. TLC analyses were performed on silica plates using the systems A and B. HPLC quantitative analyses were carried out using a Chrompack LiChrosorb 10 RP18 column (250 × 4.6 mm) with a mixture of H_2O–MeOH–HOAc (40:10:1) as eluent and a flow rate of 1.5 ml/min.

(2R,3R,4R)-3,3′,4′,7-Tetrahydroxyflavan-(4β→8)-epicatechin (**1**). Pale yellow amorphous solid (580 mg), mp 185° dec., $[\alpha]_D^{20°}$ +39.7° (EtOH; *c* 0.14), λ_{max}^{MeOH} 281.9 nm, CD: $[\theta]_{290}$ = 0°, $[\theta]_{284}$ = +10 500°, $[\theta]_{277}$ = 0°, $[\theta]_{270}$ = −10 500°, $[\theta]_{262}$ = 0°, $[\theta]_{250}$ = +21 000°, $[\theta]_{237}$ = +126 300°, $[\theta]_{225}$ = +84 400°, ^{1}H NMR (Me_2CO-d_6): δ6.97 (*br s*, u 2′-H, l 2′-H), 6.75 (*br d*, $J_{6',5'}$ = 8.2 Hz, u 6′-H, l 6′-H), 6.71 (*d*, $J_{5',6'}$ = 8.2 Hz, u 5′-H, l 5′-H), 6.40–6.25 (*m*, u 5-H, u 6-H and u 8-H), 6.07 (*s*, l 5-H), 5.34 (*d*, $J_{2',3}$ = 2.4 Hz, l 2-H), 4.6 (*br, s*, u 2-H), 4.29 (*br s*, 13-H), 3.69 (*m*, u 3-H), 3.60 (*br s*, u 4-H), 2.90 (*br dd*, J_{H-H} = 16 Hz, l 4-H), 2.78 (*br d*, J_{H-H} = 16 Hz, l 4-H′). ^{13}C NMR: see Table 1.

Nona-acetate **1a** was obtained on acetylation of **1** (12 hr) with pyridine–Ac_2O, as a colourless amorphous substance, mp 123–124°, $[M]^+$ *m/z* 940.

Nona-TMSi-derivative **1b** was obtained by silylation of **1** with *N,O*-bis-(trimethylsilyl)-trifluoracetamide containing 1% trimethylchlorosilane, in pyridine under N_2 overnight. The reaction mixture was separated from the reagent and excess solvent under a stream of N_2. MS (direct inlet): *m/z* 1210 $[M]^+$.

Heptamethylether (**1c**). A mixture of 90 mg of **1**, dry K_2CO_3 (1.4 g) and Me_2SO_4 (0.9 ml) was refluxed for 4 hr with stirring. After removal of inorganic salts, the filtrate was concd to a syrup, which was chromatographed over silica gel. Elution with $CHCl_3$–MeOH (1%) gave the heptamethylether **1c** as a white amorphous powder (79 mg), mp 100–102°, $[M]^+$ *m/z* 660, ^{1}H NMR ($CDCl_3$, 50°): δ 7.01 (*d*, $J_{2',6'}$ 2 Hz, u = 2′-H), 6.96 (*dd*, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, u 6′-H), 6.89 (*br s*, l 2′-H), 6.80 (*d*, $J_{5',6'}$ = 8 Hz, u 5′-H), 6.80 (*d*, $J_{5,6}$ = 8 Hz, u 5-H), 6.74 (*br d*, $J_{5',6'} \approx J_{6',5'}$ = 8 Hz, l 5′-H and l 6′-H), 6.31 (*m*, u 6-H and u 8-H), 6.18 (*s*, l 6-H), 5.43 (*d*, $J_{2,3}$ = 2 Hz, l 2-H), 4.60 (*m*, u 2-H and u 3-H), 4.31 (*m*, l 3-H), 4.20 (*br s*, u 4-H), 2.95 (*d*, J_{H-H} = 17 Hz, l 4-H), 2.87 (*dd*, $J_{4,3}$ = 4.5 Hz, J_{H-H} = 17 Hz, l 4-H′). For ^{13}C NMR: see Table 1.

Cleavage of the benzylmercaptan of **1** as well as the isolation of the reaction products were carried out as described in the literature [3] for procyanidin B-2. 180 mg of **1** were added to 2 ml benzylmercaptan and 1 ml HOAc, and the mixture heated under reflux with N_2 protection for 24 hr. Chromatography of the reaction mixture on a Sephadex LH-20 column using $CHCl_3$–PrOH (4:1) led to the isolation of the compounds **3** and **4**. (2*R*,3*S*,4*S*)-4-Benzylthioflavan-3,3′,4′,7-tetraol (**3**) was obtained as a white amorphous solid (85 mg), mp 103–105°, $[\alpha]_D^{20°}$ −17.1° (EtOH; *c* 1.4), ^{1}H NMR (CD_3OD): δ7.42–7.22 (*m*, benzyl 5 H), 6.95 (*d*, $J_{2',6'}$ = 1.8 Hz, 2′-H), 6.91 (*d*, $J_{5,6}$ = 8 Hz, 5-H), 6.76 (*d*, $J_{5',6'}$ = 8 Hz, 5′-H), 6.71 (*dd*, $J_{6',5'}$ = 8 Hz, $J_{5',6'}$ = 8 Hz, 6′-H), 6.34 (*dd*, $J_{6,5}$ = 8 Hz, $J_{6,8}$ = 2.4 Hz, 6-H), 6.29 (*d*, $J_{8,6}$ = 2.4 Hz, 8-H), 5.23 (*br s*, 2-H), 3.97 (*br s*, 3-H), 3.90 (*dd*, J_{H-H} = 16 Hz, S-CH_2), 3.80 (*br s*, 4-H). ^{13}C NMR: see Table 1. (−)-Epicatechin (**4**), amorphous solid (36 mg), mp and mmp 235–236°, ^{1}H NMR (CD_3OD): δ6.97 (*d*, $J_{2',6'}$ = 1.8 Hz, 2′-H), 6.79 (*dd*, $J_{6',5'}$ = 8 Hz, $J_{6',2'}$ = 1.8 Hz, 6′-H), 6.75 (*d*, $J_{5',6'}$ = 8 Hz, 5′-H), 5.93 (*d*, $J_{8,6}$

= 2.5 Hz, 8-H), 5.91 (*d*, $J_{6,8}$ = 2.5 Hz, 6-H), 4.80 (*br s*, 2-H), 4.17 (*m*, 3-H), 2.86 (*dd*, $J_{4,3}$ = 4.6 Hz, J_{H-H} = 16 Hz, 4-H), 2.73 (*dd*, $J_{4,3}$ = 2.7 Hz, J_{H-H} = 16 Hz, 4-H). ^{13}C NMR: see Table 1.

(2R,3R,4R)-3,4',7-*Trihydroxyflavan*-(4β→8)-*epicatechin* (**2**). Pale yellow amorphous solid (198 mg), mp 178° dec., $[\alpha]_D^{20°}$ +66.6° (EtOH; *c* 0.27), λ_{max}^{MeOH} 281.5 nm, CD: $[\theta]_{295}$ = 0°, $[\theta]_{285}$ = +13 650°, $[\theta]_{279}$ = 0°, $[\theta]_{273}$ = −13 650°, $[\theta]_{267}$ = 0°, $[\theta]_{250}$ = +21 310°, $[\theta]_{230}$ = +136 500°, $[\theta]_{225}$ = +98 300°, ^{1}H NMR (Me_2CO-d_6): δ 7.26 (*d*, $J_{2',3'} = J_{6',5'}$ = 8 Hz, u 2'-H and u 6'-H), 6.97 (*br s*, 1 2'-H), 6.85 (*br d*, $J_{6',5'}$ = 8.4 Hz, 1 6'-H), 6.79 (*d*, $J_{5',6'}$ = 8.4 Hz, 1 5'-H), 6.74 (*d*, $J_{5',6'} = J_{3',2'}$ = 8 Hz, u 5'-H and u 3'-H), 6.40–6.25 (*m*, u 5-H, u 6-H and u 8-H), 6.07 (*s*, 1 5-H), 5.29 (*d*, $J_{2,3}$ = 2.4 Hz, 1 2-H), 4.60 (*br s*, u 2-H), 4.27 (*br s*, 1 3-H), 3.68 (*m*, u 4-H and u 3-H), 2.90 (*br dd*, J_{H-H} = 16 Hz, 1 4-H), 2.78 (*br d*, J_{H-H} = 16 Hz, 1 4-H'). ^{13}C NMR: see Table 1.

Octa-acetate **2a** was obtained as described above for **1a**, mp 125–126°, $[M]^+$ *m/z* 882.

Octa-TMSi-derivative **2b** was obtained as described above for **1b**, $[M]^+$ *m/z* 1122.

Hexamethylether (**2c**). Methylation of 65 mg of **2** in a similar manner to **1** gave the hexamethylether **2c** as a white amorphous solid (49 mg), mp 97.5–99°, M^+ *m/z* 630, ^{1}H NMR ($CDCl_3$, 50°): δ 7.35 (*d*, $J_{6',5'} = J_{2',3'}$ = 8 Hz, u 6'-H and u 2'-H), 6.88 (*br s*, $J_{2',6'}$ = 2 Hz, u 2'-H), 6.84 (*d*, $J_{5',6'} = J_{3',2'}$ = 8 Hz, u 5'-H and u 3'-H), 6.79 (*d*, $J_{5,6}$ = 8 Hz, u 5-H), 6.74 (*br d*, $J_{5',6'} = J_{6',5'}$ = 8 Hz, 1 5'-H and 1 6'-H), 6.30 (*m*, u 6-H and u 8-H), 6.17 (*s*, 1 6-H), 5.44 (*d*, $J_{2,3}$ = 2 Hz, 1 2-H), 4.59 (*m*, u 2-H and u 3-H), 4.32 (*m*, 1 3-H), 4.23 (*br s*, u 4-H), 2.95 (*d*, J_{H-H} = 17 Hz, 1 4-H), 2.87 (*dd*, $J_{4,3}$ = 4.5 Hz, J_{H-H} = 17 Hz, 1 4-H'). ^{13}C NMR: see Table 1.

Cleavage with benzylmercaptan of 90 mg of **2** and the isolation procedure were performed in a similar manner to that described above for **1**. (2*R*,3*S*,4*S*)-4-Benzylthioflavan-3,4',7-triol (**5**) was obtained as a white amorphous solid (26 mg), mp 86–87°, $[\alpha]_D^{20°}$ −23.3° (EtOH; *c* 1.2), ^{1}H NMR (CD_3OD): δ 7.42–7.20 (*m*, benzyl 5 H), 7.23 (*d*, $J_{2',3'} = J_{6',5'}$ = 8.5 Hz, 2'-H and 6'-H), 6.92 (*d*, $J_{5,6}$ = 8.5 Hz, 5-H), 6.78 (*d*, $J_{5',6'} = J_{3',2'}$ = 8.5 Hz, 3'-H, 5'-H), 6.35 (*dd*, $J_{6,5}$ = 8.5 Hz, $J_{6,8}$ = 2.4 Hz, 6-H), 6.30 (*d*, $J_{8,6}$ = 2.4 Hz, 8-H), 5.29 (*br s*, 2-H), 3.96 (*br s*, 3-H), 3.94 (*dd*, J_{H-H} = 13.1 Hz, S-CH_2), 3.83 (*br s*, 4-H). ^{13}C NMR: see Table 1.

(−)-Epicatechin obtained from **2** was identified by ^{1}H NMR, mp and mmp 235–236°.

The Gibbs test [14] on **5** was performed as follows: 1.0 mg of **5** dissolved in pyridine (1.0 ml) was treated with a 2% soln of 2,6-dichlorobenzoquinonechloroimide in pyridine (1.0 ml) and the mixture diluted to 100 ml with borate buffer (pH 9.2). The absorption spectrum was measured after 10 min and showed no maximum in the region 500–700 nm.

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