



Phenolics from *Maytenus senegalensis*

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Abstract

Two new methylated flavan-3-ol glucosides and a methylated proanthocyanidin were isolated from the MeOH extract of the stem-bark of *Maytenus senegalensis*, together with five known compounds. The structures of the new compounds were determined as: (–)-4'-methylepigallocatechin 5-*O*- β -glucopyranoside, (+)-4'-methylgallocatechin 3'-*O*- β -glucopyranoside and (–)-epicatechin (4 β → 8) (–)-4'-methylepigallocatechin by chemical and spectroscopic means. The MeOH and H₂O extracts showed moderate inhibitory effects against HIV-1 protease. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: *Maytenus senegalensis*; Celastraceae; Methylated flavan-3-ols; Proanthocyanidins

1. Introduction

The aqueous extract of the stem-bark of *Maytenus senegalensis* (Celastraceae) is an important herbal remedy in folk medicine in the Sudan. Its vernacular name is “Dabalab” and it has been widely used to treat tumors, dysentery and snake-bites. Most of the chemical work described in the literature has been confined to other *Maytenus* species (Kupchan & Smith, 1977; Brüning & Wagner, 1978; Shiota, Tamemura, Morita, Takeya & Itokawa, 1996), with little work on *M. senegalensis* (Tin-Wa, Farnsworth, Fong, Blomster, Troja'nek et al., 1971; Abraham, Troja'nek, Münzing, Fong & Farnsworth, 1971; Gómez-serranillos & Zaragoza, 1979; Delle Monache, Pomponi, Marin-Bettolo, Leoncio D'Albuquerque & Goncalves de Lima, 1976). (–)-4'-Methylepigallocatechin, (–)-epiafzelechin (4 β → 8) (–)-4'-methylepigallocatechin (ouratea-proanthocyanidin) and maytenonic acid have been isolated from this species (Brüning & Wagner, 1978; Abraham et al., 1971; Delle Monache et al., 1976). Ethanolic extracts of the stems of *M. senegalensis* demonstrated cytotoxic effects against carcinoma in cell cultures and leukemia in mice (Tin-Wa et al., 1971). Upon antiviral screening of medicinal plants,

MeOH and H₂O extracts of *M. senegalensis* showed moderate inhibitory effects against HIV-1 protease with IC₅₀ values of 104 and 88 μ g/ml respectively (Otake, Mori, Morimoto, Ueba, Sutardjo et al., 1995), whereas acetylpepstatin, as positive inhibitory control, showed an IC₅₀ of 0.24 μ M.

We describe here the isolation and structure elucidation of new methylated flavanol glucosides (**2**, **4**) and a methylated proanthocyanidin (**6**) from the MeOH extract of the stem-bark of *M. senegalensis*.

2. Results and discussion

The defatted MeOH extract of the stem-bark of *M. senegalensis* was partitioned between EtOAc and H₂O to give EtOAc-soluble and H₂O-soluble fractions. Repeated CC of the EtOAc-soluble fraction afforded five compounds (**1**, **3** and **5–7**) (Fig. 1). Likewise, the H₂O-soluble fraction afforded three compounds (**2**, **4** and **8**) (Fig. 1). The known compounds were (–)-4'-methylepigallocatechin (**1**) (Drewes & Mashibaye, 1993), (–)-epigallocatechin (**3**), epicatechin (4 β → 8) epigallocatechin (**5**) and epicatechin (4 β → 8) epicatechin (procyanidin B-2) (**7**) (Nonaka, Kawahara & Nishioka, 1983; Nonaka, Hsu & Nishioka, 1981; Porter, Newman, Foo, Wong & Hemingway, 1982; Hashimoto, Nonaka & Nishioka, 1989), and phloroglucinol 1-*O*- β -D-glucopyranoside (**8**), and identifi-

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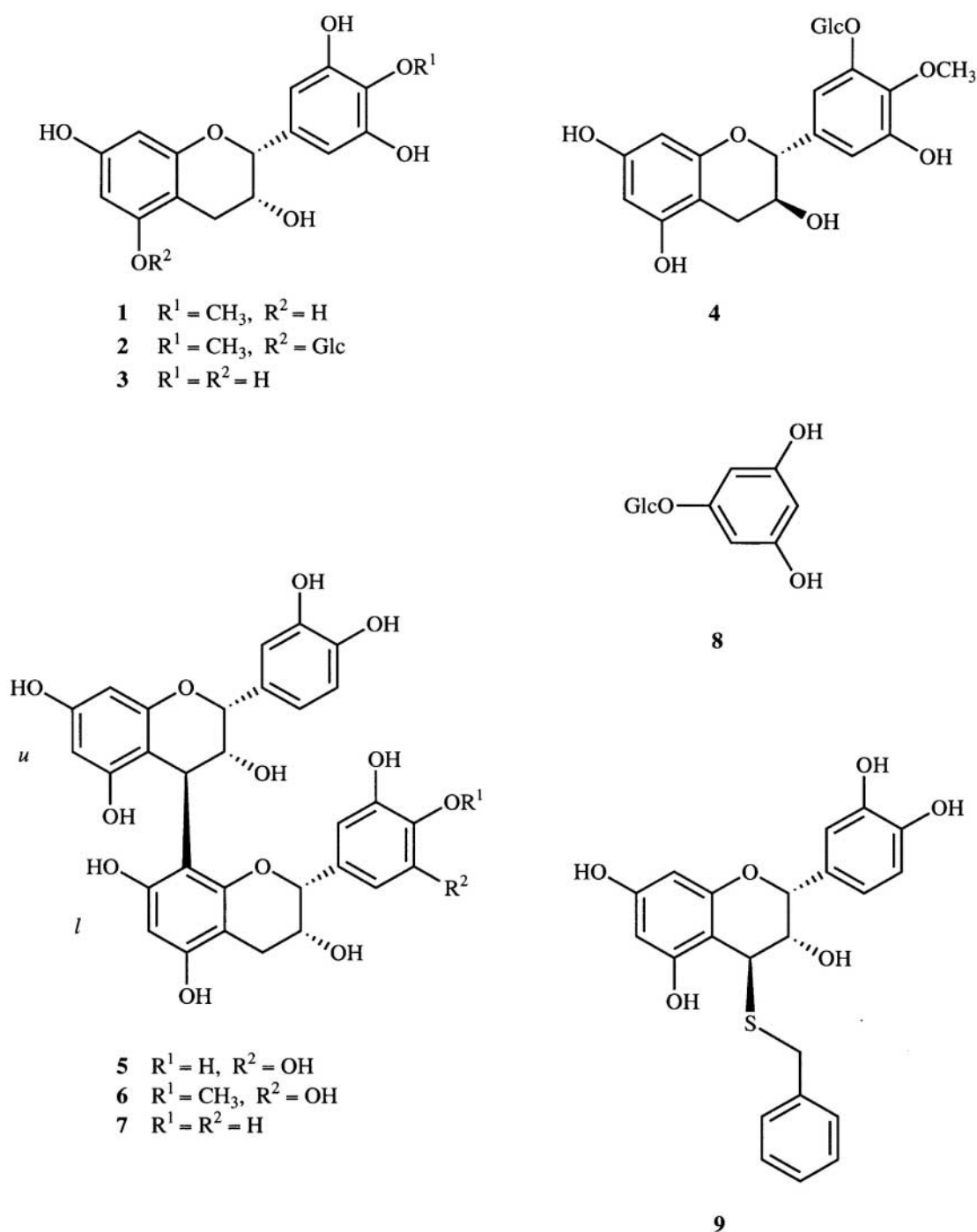


Fig. 1. Compounds 1–9.

cation of the three new compounds (**2**, **4** and **6**) are described below.

The atmospheric pressure ionization (API) mass spectrum (positive ion mode) of **2** showed a molecular ion peak at m/z 483 $[\text{M} + \text{H}]^+$ consistent with the molecular formula $\text{C}_{22}\text{H}_{26}\text{O}_{12}$. The ^1H NMR spectrum showed signals characteristic for a flavan-3-ol skeleton with a phloroglucinol pattern for ring A (two doublets at δ 6.07 and 6.29, $J = 2.2$ Hz) and a pyrogallol pat-

tern for ring B (two protons as a singlet at δ 6.60), a sugar moiety (anomeric proton signal at δ 4.87), and a methoxy group (singlet at δ 3.80, 3H). The singlet at δ 4.84 (H-2) (C-2 at δ 79.3) and the multiplet at δ 4.20 (H-3) (C-3 at δ 66.7) are characteristic for the 2,3-*cis* configuration of the flavan-3-ol unit (Shen, Chang & Ho, 1993; Markham & Ternai, 1976). The fragment ion peak at m/z 321 $[\text{M} + \text{H} - 162]^+$ suggested a hexose unit which was identified as glucose by comparing

Table 1
¹³C NMR spectral data of compounds **1–4** and **8**

Position	1 ^a	2 ^b	3 ^a	4 ^a	8 ^a
1					160.8
2	79.6	79.3	79.8	82.1	96.7
3	67.3	66.7	67.4	68.4	160.0
4	29.1	28.8	29.1	27.6	98.0
4a	100.0	102.2	100.0	100.6	
5	157.9	158.1	157.9	157.7	160.0
6	96.3	97.8	96.3	96.4	96.7
7	157.5	157.6	157.6	157.5	
8	95.8	96.5	95.8	95.5	
8a	157.1	156.6	157.2	156.5	
1'	135.9	136.1	131.4	136.7	
2'	107.1	107.0	106.9	107.4	
3'	151.3	150.9	146.6	152.0	
4'	136.5	136.1	133.5	137.9	
5'	151.3	150.9	146.6	151.6	
6'	107.1	107.0	106.9	110.0	
1''		102.0		102.6	102.0
2''		74.6		74.8	74.7
3''		78.6		77.0	77.9
4''		71.3		71.0	71.3
5''		79.0		77.9	77.9
6''		62.7		61.5	62.5
OCH ₃	60.7	60.6		62.3	

Measured at 125 MHz (in CD₃OD^a and CD₃COCD₃–D₂O [2:1]^b)

the ¹³C NMR spectral data of the sugar carbons with those reported for methyl *O*-glucosides (Agrawal & Bansal, 1989). These findings suggested that **2** was the glucoside of **1** (Drewes & Mashibaye, 1993) (Table 1). This was further shown by enzymatic hydrolysis of **2**, which gave compound **1**. Significant HMBC correlations between C–5 (δ 158.1) and the proton signals at δ 4.87 (H–1'') and 6.29 (H–6), linked the glucose unit to C–5, whereas C–7 was correlated with both H–6 and H–8. Correlations between the carbon signal at δ 136.1 (C–4') and the proton signals at δ 3.80 (3H, *s*) and 6.60 (2H, *s*), placed the methoxyl group at C–4'. The coupling constant (*J* = 7.2 Hz, H–1'') was indicative of a β-anomeric configuration of the glucose unit. Thus, compound **2** was determined to be (–)-4'-methylgallo catechin 5-*O*-β glucopyranoside.

Compound **4** was assigned the molecular formula C₂₂H₂₆O₁₂ on the basis of the API-mass spectrum (*m/z* at 483 [M + H]⁺). The doublet (*J* = 7.5 Hz) at δ 4.82 (H–2) and carbon signals at δ 68.4 (C–3) and 82.1 (C–2) (Table 1) suggested a flavan-3-ol skeleton with 2,3-*trans* configuration (Porter et al., 1982). Signals characteristic for a hexose moiety (anomeric proton at δ 4.68, fragment ion at *m/z* 321 [M + H – 162]⁺) and a methoxyl group (δ 3.84, 3H, *s*) were also observed in the ¹H NMR spectrum (see experimental). The hexose moiety was identified as glucose with the β-anomeric configuration (*J* = 6.8 Hz) (Agrawal & Bansal, 1989),

whereas enzymatic hydrolysis of **4** afforded (+)-4'-methylgallo catechin (Plazzo De Mello, Petereit & Nahrstedt, 1996). The downfield shift of C–3' (δ 152.0) and the upfield shift of C–2' (107.4), when compared with that of C–6' (110.0), suggested glycosylation at C–3' (Table 1). This was further confirmed by the HMBC correlations C–3' (δ 152.0) with H–1'' (δ 4.68) and H–2' (6.61). Long range correlations C–4' (δ 137.9) with the methoxy protons (δ 3.84) and H–2', connected the methoxy group to C–4'. From these data, compound **4** was determined to be (+)-4'-methylgallo catechin 3'-*O*-β-glucopyranoside.

The positive ion API-mass spectrum of **6** revealed a molecular ion peak at *m/z* 631 [M + Na]⁺ consistent with the molecular formula C₃₁H₂₈O₁₃. The NMR data of **6** showed features characteristic for flavan-ols of proanthocyanidin dimers similar to that of **5** (Table 2) (Nonaka et al., 1981; Porter et al., 1982; Hashimoto et al., 1989), and a methoxyl group (δ_H 3.76/δ_C 60.7). A pair of singlets at δ 4.58 and 5.10 of H–2 and that of multiplets at δ 3.91 and 4.29 of H–3, were characteristic for two flavan-3-ol units with epicatechin stereochemistry (C2, C3: *cis*) (Nonaka et al., 1981; Nonaka, Kawahara & Nishioka, 1982). The broad singlets at δ 5.98 and 6.02 were assigned for H–8 (upper = *u*) and H–6*u*, respectively, and the singlet at δ 5.91 was assigned for H–6 (lower = *l*). The singlet at δ 6.71 (2H) suggested a pyrogallol hydroxylation of

Table 2
¹³C NMR spectral data of compounds 5–7^a

Position	5	6	7
2(<i>u</i>)	77.0	76.9	77.1
3(<i>u</i>)	73.4	73.1	73.4
4(<i>u</i>)	37.1	36.9	37.1
4a(<i>u</i>)	100.5	100.4	100.5
5(<i>u</i>)	158.2	158.1	158.3
6(<i>u</i>)	97.3	96.5	96.3
7(<i>u</i>)	157.8	157.6	157.8
8(<i>u</i>)	96.1	96.1	96.2
8a(<i>u</i>)	156.3	156.3	156.4
1'(<i>u</i>)	131.1	132.2	132.0
2'(<i>u</i>)	115.2	115.1	115.2
3'(<i>u</i>)	145.5	145.4	145.6
4'(<i>u</i>)	145.8	145.7	145.8
5'(<i>u</i>)	115.9	115.8	115.9
6'(<i>u</i>)	119.2	119.2	119.4
2(<i>l</i>)	78.8	79.2	78.8
3(<i>l</i>)	66.7	66.6	66.9
4(<i>l</i>)	29.8	29.7	29.7
4a(<i>l</i>)	100.5	100.4	100.5
5(<i>l</i>)	158.2	158.1	158.3
6(<i>l</i>)	97.5	97.3	96.5
7(<i>l</i>)	157.8	157.6	157.8
8(<i>l</i>)	106.8	106.8	107.3
8a(<i>l</i>)	156.3	156.3	156.4
1'(<i>l</i>)	132.5	135.8	132.5
2'(<i>l</i>)	106.8	106.8	115.9
3'(<i>l</i>)	146.6	151.1	145.6
4'(<i>l</i>)	133.4	136.1	145.8
5'(<i>l</i>)	146.4	151.1	115.2
6'(<i>l</i>)	106.8	106.8	119.4
–OCH ₃		60.7	

^a Measured in CD₃OD at 100 MHz.

ring B, similar to that of **2**, while an ABX-like spin system at δ 6.66, 6.73 and 6.89 suggested a B-ring of catechol pattern. Twin carbon signals at δ 29.7 and 36.9 assigned for the lower (*l*) and upper (*u*) C–4, respectively. From these findings, **6** was determined to be composed of epicatechin, epigallocatechin units and a methoxy group. The position of a carbon–carbon linkage between the two flavan units was determined by comparison of the NMR data of **6** with those of **5**. A singlet at δ 4.65 ascribed for H–4*u* and a carbon shift at δ 76.9 (C–2*u*) are characteristic for the β -linkage of the two flavan units (Nonaka et al., 1982; Morimoto, Nonaka, Chen & Nishioka, 1988). The relatively upfield shifts of C–4*l* (at δ 29.7), C–8*l* (δ 106.8) and H–2*l* (δ 4.58) and the downfield shift of H–2*u* (δ 5.1) suggested a 4 β $\rightarrow$ 8 linkage, as the most frequently encountered C–4/C–8 bonds in proanthocyanidins (Morimoto et al., 1988). On thiolytic degradation using benzylmercaptan and acetic acid, **6** produced **1** and compound **9** (Nonaka, Nishioka, Nagasawa & Oura, 1981). Accordingly, the structure of **6** was determined to be (–)-epicatechin (4 β $\rightarrow$ 8) (–)-4'-methylepigallocatechin.

3. Experimental

3.1. General

Optical rotations were taken with a JASCO DIP-360 automatic polarimeter. UV: MeOH (UV-2200, SHIMADZU, Japan). IR: KBr (FT/IR-230, JASCO, Japan). NMR spectra were measured with a VARIAN UNITY 500 (¹H–, 500 MHz; ¹³C–, 125 MHz) or a JEOL JNA-LA 400WB-FT (¹H–, 400 MHz; ¹³C–, 100 MHz) spectrometers. The atmospheric pressure ionization (API) mass spectra were measured with a PE SCIEX API III biomolecular mass analyzer. TLC: precoated silica gel 60 F₂₅₄ and RP-18 F₂₅₄S plates (0.25 mm, MERCK) developed with solvent system, A (benzene–ethyl formate–formic acid, 1:7:1), and B (acetonitrile–0.1% trifluoroacetic acid/H₂O, 3:7), respectively. Detection of the spots: by UV and anisaldehyde/H₂SO₄ and ferric chloride reagents. CC: Sephadex LH-20 (PHARMACIA, Sweden), Diaion HP-20 and MCI gel CHP-20P (MITSUBISHI, Tokyo, Japan) and Silica gel 60 (70–230 mesh, MERCK). MPLC: LiChroprep RP-18 (size A, MERCK).

3.2. Isolation of 1–8

The powdered stem-bark (2.8 kg) of *M. senegalensis*, collected in December 1995 from Arkowit district, East of Sudan, was extracted with MeOH (2*l* $\times$ 2) at room temp. and then by reflux (1.5*l* $\times$ 2). The MeOH was concentrated to 300 ml and shaken with hexane (600 ml). The MeOH layer was then evaporated under red. press., suspended in H₂O (500 ml) and shaken with an equal volume of EtOAc. The EtOAc layer was evaporated to dryness to give the EtOAc-soluble fraction (10.5 g) which was further fractionated by CC/ Sephadex LH-20 (EtOH, H₂O to MeOH) to give 6 fractions. CC/silica gel (CHCl₃–MeOH, 8:2) of fr. 2 afforded **1** (1.87 g). CC/MCI gel (30% aq. MeOH) of fr. 3 followed by silica gel CC (eluted with CHCl₃–MeOH–H₂O, 6:4:1) gave **5** (80 mg) and **7** (29 mg). Similarly, fr. 4 afforded **3** (24 mg) and **6** (186 mg).

The aqueous layer was concentrated and passed through a column of Diaion HP-20. Elution was started with H₂O, 50% MeOH and then MeOH. CC of the 50% MeOH eluate (30 g) over Sephadex LH-20 (EtOH, H₂O to MeOH) gave five fractions, fr. I–V. Repeated CC of fr. II over Sephadex LH-20 (70% EtOH), silica gel (CHCl₃–MeOH–H₂O) afforded **8** (36 mg). Likewise, repeated CC of fr. III over Sephadex LH-20, silica gel and then MPLC (system B) gave **2** (35 mg) and **4** (18 mg). CC/ Sephadex LH-20 of fr. IV gave additional amount of **1** (115 mg).

3.3. (–)-4'-Methylepigallocatechin 5-O- β -glucopyranoside (**2**)

Light brown amorphous powder, (R_f 0.53, in solvent system B). $[\alpha]_D -13.1^\circ$ (MeOH, c 0.15). UV λ_{max} nm (log ϵ): 210 (4.59), 230 *sh* (4.14), 270 (3.41). IR ν_{max} cm^{-1} : 3400 (OH), 1610 (arom. C=C). 1H -NMR (400 MHz, CD_3COCD_3/D_2O , [2:1]) δ : 2.94 (1H, *dd*, $J = 16.4, 4.6$ Hz, H-4*ax*, as in CD_3OD), 2.90 (1H, *dd*, $J = 16.4, 4.1$ Hz, H-4*eq*, as in CD_3OD), 3.34–3.84 (6H, H-2'' ~ H-6''), 3.80 (3H, *s*, OMe), 4.20 (1H, *m*, H-3), 4.84 (1H, *s*, H-2), 4.87 (1H, *d*, $J = 7.2$ Hz, H-1''), 6.07 (1H, *d*, $J = 2.2$ Hz, H-8), 6.29 (1H, *d*, $J = 2.2$ Hz, H-6), 6.60 (2H, *s*, H-2' and H-6'). ^{13}C -NMR (Table 1). API-MS (positive ion mode) m/z (rel. int.%): 505 $[M + Na]^+$ (49), 483 $[M + H]^+$ (17) and 321 $[M + H - Glc]^+$ (44).

3.4. Enzymatic hydrolysis of **2**

Glucoside **2** (5 mg) was dissolved in 50 mM NaOAc buffer (pH 5.0) and incubated with crude naringinase (Sigma Chemical Co.) at 40°C for 48 h. The ethyl acetate-soluble portion of the mixture was purified over Sephadex LH-20 (EtOH) to afford (–)-4'-methylepigallocatechin **1** (2 mg), $[\alpha]_D -23.2^\circ$ (EtOH, c 0.1). Lit. (Delle Monache et al., 1976): $[\alpha]_D -60.0^\circ$ (EtOH, c 1.0). The 1H -NMR spectral data were consistent with reported values (Drewes & Mashibaye, 1993).

3.5. (+)-4'-Methylgallocatechin 3'-O- β -glucopyranoside (**4**)

Yellowish amorphous powder, (R_f 0.71, in solvent system B). $[\alpha]_D -15.2^\circ$ (MeOH, c 0.15). UV λ_{max} nm (log ϵ): 210 (4.53), 230 *sh* (3.98), 280 (2.9). IR ν_{max} cm^{-1} : 3400 (OH), 1610 (arom. C=C). 1H -NMR (500 MHz, CD_3OD) δ : 2.51 (1H, *dd*, $J = 16.4, 7.2$ Hz, H-4*ax*), 2.72 (1H, *dd*, $J = 16.4, 5.3$ Hz, H-4*eq*), 3.23 (1H, *m*, H-5''), 3.42 (1H, *m*, H-4''), 3.44 (1H, *m*, H-3''), 3.74 (1H, *m*, H-2''), 3.70–3.74 (2H, *m*, H-6''), 3.84 (3H, *s*, OMe), 3.99 (1H, *m*, H-3), 4.68 (1H, *d*, $J = 6.8$ Hz, H-1''), 4.82 (1H, *d*, $J = 7.5$ Hz, H-2), 5.91 (1H, *d*, $J = 2.2$ Hz, H-8), 5.94 (1H, *d*, $J = 2.2$ Hz, H-6), 6.61 (1H, *d*, $J = 1.9$ Hz, H-2'), 6.71 (1H, *d*, $J = 1.9$ Hz, H-6'). ^{13}C -NMR (Table 1). API-MS (positive ion mode) m/z (rel. int.%): 505 $[M + Na]^+$ (73), 483 $[M + H]^+$ (12) and 321 $[M + H - Glc]^+$ (10).

3.6. Enzymatic hydrolysis of **4**

Glucoside **4** (5 mg) was treated as for **2** to afford (+)-4'-methylgallocatechin (**2** mg), $[\alpha]_D +10^\circ$ (50% Me_2CO , c 0.12). Lit. (Plazzo De Mello et al., 1996): $[\alpha]_D +28^\circ$ (50% Me_2CO), c 0.2). The 1H -NMR spec-

tral data were consistent with reported values (Plazzo De Mello et al., 1996).

3.7. (–)-Epicatechin (4 $\beta \rightarrow 8$) (–)-4'-methylepigallocatechin (**6**)

Light brown amorphous powder, (R_f 0.29, in solvent system A). $[\alpha]_D +22.7^\circ$ (MeOH, c 0.72). UV λ_{max} nm (log ϵ): 220 (4.3), 280 (3.39). IR ν_{max} cm^{-1} : 3360 (OH), 1610 (arom. C=C). 1H -NMR (400 MHz, CD_3OD) δ : 2.82 (2H, *m*, H-4 l), 3.76 (3H, *s*, $-OCH_3$), 3.91 (1H, *br s*, H-3 u), 4.29 (1H, *br s*, H-3 l), 4.58 (1H, *br s*, H-2 l), 4.65 (1H, *br s*, H-4 u), 5.10 (1H, *br s*, H-2 u), 5.91 (1H, *br s*, H-6 l), 5.98 (1H, *br s*, H-6 u), 6.02 (1H, *br s*, H-8 u), 6.66 (1H, *br s*, H-6' u), 6.71 (2H, *s*, H-2' l , H-6' l), 6.73 (1H, *br s*, H-5' u), 6.89 (1H, *br s*, H-2' u). ^{13}C -NMR (Table 2). API-MS (positive ion mode) m/z (rel. int.%): 631 $[M + Na]^+$ (10) and 609 $[M + 1]^+$ (27). [u = upper; l = lower]

3.8. Thiolytic of compound **6**

A mixture of **6** (24 mg) in ethanol (3 ml), benzylmercaptan (0.5 ml) and acetic acid (0.5 ml) was stirred under argon at 50–60°C for 48 h. The mixture was evaporated under red. pres. and chromatographed over Sephadex LH-20 (benzene–EtOH) to afford **1** and (–)-epicatechin-4 β -benzylthioether **9**, $[\alpha]_D -28.9^\circ$ (Me_2CO , c 0.15). Lit. (Nonaka et al., 1981): $[\alpha]_D -28^\circ$ (Me_2CO , c 1.0). API-MS (positive ion mode) m/z (rel. int.%): 413 $[M + 1]^+$ (64). The 1H NMR spectral data were in agreement with lit. values (Nonaka et al., 1981).

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