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SECONDARY METABOLITES FROM *PODOCARPUS PARLATOREI* PILGER

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ABSTRACT

Phytochemical investigation on *Podocarpus parlatorei* Pilger led to the isolation of three biflavones together with three diterpenes. Their chemical structures were elucidated by spectroscopic analyses, primarily 1 and 2D NMR spectroscopy as well as high-resolution mass spectrometry. The isolated compounds are reported from this plant for the first time.

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RESUMEN

La investigación fitoquímica en *Podocarpus parlatorei* Pilger condujo al aislamiento de tres biflavonoides junto con tres diterpenos. Sus estructuras químicas fueron determinadas por análisis espectroscópicos, principalmente por NMR 1 y 2D, así como por espectrometría de masas de alta resolución. Los compuestos aislados se reportan en esta planta por primera vez.

INTRODUCTION

The genus Podocarpus compromises at least 107 species of shrubs and trees of the family Podocarpaceae, which are mainly distributed in the southern hemisphere [1]. These species have proven to be valuable plants for the discovery of natural products like terpenoids, nor-diterpenoid dilactones, flavonoids and biflavonoids [2].

Podocarpus parlatorei is a perennial native tree, which occurs naturally in Bolivia and Argentina [3]. It is distributed in the sub-Andean Amazonian Forest regions of Bolivia and is an important timber source in its native areas [4]. As part of our interest in phytochemical investigations of Bolivian plants, extracts of the leaves of *Podocarpus parlatorei* were fractionated and six natural products were isolated and characterized. All the identified compounds are know from previous reports, but were obtained from this plant for the first time.

RESULTS AND DISCUSSION

The ethanolic extract of the aerial parts of *P. parlatorei* was divided using liquid-liquid partition to afford a chloroform and a water-methanol fraction. The chloroform fraction was subsequently purified using a combination of vacuum liquid chromatography, column chromatography and size exclusion chromatography (Sephadex LH-20), to afford three biflavonoids **(1-3)** and three diterpenoids **(4-6)** (Figure 1). The structural elucidation of compounds was achieved on the basis of ^{1}H and ^{13}C NMR spectra, 2D COSY, NOESY, HMQC and HMBC experiments, and HR-ESI-MS.

The elemental composition of compound **(1)** was determined to be $C_{33}H_{24}O_{10}$, based on the 1D NMR spectra as well as HR-ESI-MS data (molecular ion peak at *m/z* 581.1453 $[M+H]^+$), indicating twenty-two degrees of unsaturation. The ^{1}H NMR spectrum (see Table 1) displays signals corresponding to twenty-four protons: three methoxy groups, two singlets at 13.05 and 12.91, which are characteristic of hydrogen-bonded hydroxyl groups (5-OH and 5''-OH), a broad hydroxy signal at δ 10.88 (1H, br), the remaining twelve signals appeared between δ 6.00 and 8.50 ppm.

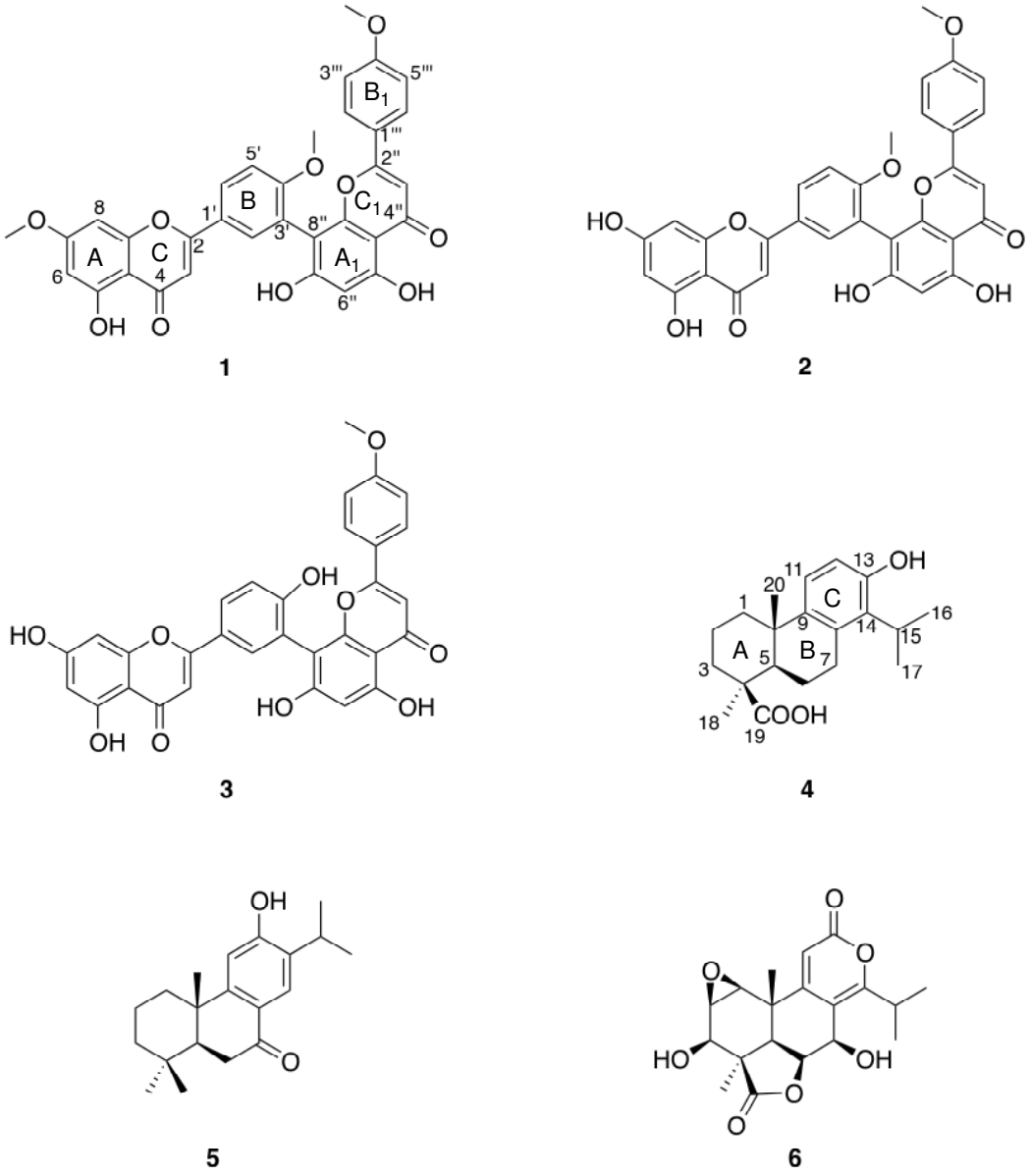

Figure 1. *Chemical structures of compounds (1-6).*

Moreover, the COSY and HMBC spectra suggest that the following proton systems are part of the structure: a tetra-substituted aromatic ring (A-ring) with a pair of *meta*-coupled protons at δ 6.36 (1H, d, *J*= 2.2; 6-H) and 6.79 (1H, d, *J*= 2.2; 8-H), a 1,3,4 tri-substituted ring (B-ring) at δ 7.37 (1H, d, *J*= 8.9), 8.08 (1H, d, *J*= 2.4) and 8.23 (1H, dd, *J*= 2.4, 8.9), a singlet at δ 7.00 (1H, s; 3-H), characteristic for a proton at C-3 in flavonoids, a penta-substituted aromatic ring (A_1-ring) with a single proton at δ 6.42 (1H, s; 6''-H), an AA'BB' aromatic spin system at δ 7.60 (2H, d, *J*= 9.0) and 6.93 (2H, d, *J*= 9.0) (B_1-ring), and a signal at δ 6.90 (1H, s) was attributed to 3''-H. Analysis of ^{13}C NMR spectrum and a combination of COSY, HMQC and HMBC experiments suggested that **1** is a biflavonoid linked between C-3' and C-8'', which was confirmed by HMBC correlations between 2'-H and C-8''. Therefore, the structure of **(1)** was determined to be 5,5'',7''-trihydroxy-4',4''',7-trimethoxy-3',8''-biflavone (sciadopitysin), previously isolated from *Taxus cuspidata* [5].

Table 1: *^{13}C- and ^{1}H-NMR data of compounds 1, 2 and 3.*

Position	1[a]		2[b]		3[a]	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	-	-	-	-	-	-
2	163.6	-	164.6	-	163.8	-
3	103.9	7.00 s	104.1	6.72 s	103.0	6.83 s
4	182.0	-	183.4	-	181.7	-
5	161.1	-	163.4	-	161.4	-
6	98.2	6.36 d (2.2)	99.7	6.25 d (2.0)	98.8	6.18 d (2.0)
7	165.2	-	165.0	-	164.1	-
8	92.8	6.79 d (2.2)	94.8	6.53 d (2.0)	94.0	6.46 d (2.0)
9	157.4	-	158.9	-	157.4	-
10	104.8	-	105.3	-	103.7	-
1’	122.4	-	124.2	-	121.0	-
2’	130.9	8.08 d (2.4)	132.1	8.15 d (2.3)	131.4	7.99 d (2.2)
3’	121.6	-	122.8	-	119.9	-
4’	160.6	-	161.9	-	159.5	-
5’	111.8	7.37 d (8.9)	112.5	7.39 d (8.8)	116.2	7.16 d (8.6)
6’	128.4	8.23 dd (8.9, 2.4)	129.1	8.19 dd (8.7, 2.3)	127.9	8.01 dd (8.6, 2.2)
1’’	-	-	-	-	-	-
2’’	163.1	-	164.8	-	163.2	-
3’’	103.2	6.90 s	104.7	6.78 s	103.3	6.89 s
4’’	182.1	-	183.1	-	182.2	-
5’’	160.7	-	162.5	-	160.5	-
6’’	98.7	6.42 s	99.8	6.45 s	98.7	6.42 s
7’’	161.8	-	162.6	-	161.9	-
8’’	103.7	-	104.8	-	104.0	-
9’’	154.4	-	155.8	-	154.5	-
10’’	103.6	-	105.4	-	103.7	-
1’’’	122.8	-	124.2	-	123.0	-
2’’’	127.8	7.60 d (9.0)	128.8	7.67 d (9.0)	128.0	7.68 d (9.0)
3’’’	114.6	6.93 d (9.0)	115.3	6.94 d (9.0)	114.5	6.93 d (9.0)
4’’’	162.3	-	163.6	-	162.2	-
5’’’	114.6	6.93 d (9.0)	115.3	6.94 d (9.0)	114.5	6.93 d (9.0)
6’’’	127.8	7.60 d (9.0)	128.8	7.67 d (9.0)	128.0	7.68 d (9.0)
7-OMe	56.1	3.82 s	-	-	-	-
4’-OMe	55.5	3.75 s	56.4	3.87 s	-	-
4’’’-OMe	56.0	3.79 s	55.9	3.80 s	55.5	3.76 s
5-OH	-	12.91	-	12.99	-	12.97
5’’-OH	-	13.05		13.14	-	13.07
7’’-OH		10.88				

Spectra recorded in: [a]DMSO-d_6, [b]Acetone-d_6. * Overlapping. Assignments were based on COSY, HMQC, HMBC and NOESY experiments.

Compound **(2)** ($C_{32}H_{22}O_{10}$) and **(3)** ($C_{31}H_{20}O_{10}$) are biflavonoids with molecular mass ion peak at *m/z* 567.1290. $[M+H]^+$ and *m/z* 553.1161 $[M+H]^+$, respectively. The NMR features of **(2)** and **(3)** showed some similarities to those of **1** (Table 1). The analysis of ^{1}H NMR and HR-ESI-MS data showed that **(2)** has one methoxy group less than **(1)**, while **(3)** revealed the absence of two methoxy groups. Carbons and protons were assigned on the basis of 2D NMR data (COSY, HMQC and HMBC). Based on their data the structures were established as 5,5’’,7,7’’-tetrahydroxy-4’,4’’’-dimethoxy-3’,8’’-biflavone **(2)** (isoginkgetin) and 4’,5,5’’,7,7’’-pentahydroxy-4’’’-methoxy-3’,8’’-biflavone **(3)** (podocarpusflavone A). Compound **(2)** has previously been isolated from *Ginkgo biloba* [6], while **(3)** has been reported from *Podocalyx loranthoides* [7].

The molecular formula of compound **(4)** ($C_{20}H_{28}O_3$) was established by ^{13}C NMR data (Table 2) and HR-ESI-MS (*m/z* 317.2130 $[M+H]^+$), which indicates seven degrees of unsaturation. The ^{13}C NMR spectrum suggest the presence of one carboxylic carbon and six carbon signals assigned to an aromatic ring, of which one signal was downshifted to δ 154.8 and should be an oxygenated aromatic carbon. These facts indicated that **(4)** is tricyclic. Its ATR-IR spectrum displayed bands for a hydroxy group at 3387, a carbonyl group at 1693 and aromatic double bonds at 1589 cm^{-1}. The ^{1}H NMR and 2D COSY spectrum showed that the following proton systems are present in the molecule: A

methine hydrogen of an isopropyl group at δ 3.24 (15-H) and two non-equivalent methyl doublets at δ 1.31 (16-H_3) and 1.32 (17-H_3). The aromatic region exhibited two *ortho*-coupled doublets at δ 6.52 (12-H) and 6.92 (11-H), which indicated the presence of a 1,2,3,4-tetrasubstituted aromatic ring. Three methylene groups assigned to ring A at δ 2.22/1.27 (1-H_2), 2.02/1.55 (2-H_2) and 2.21/1.08 (3-H_2) were identified, as well as a spin system consisting of a methine proton at δ 1.44 (5-H), a methylene group at δ 2.23/1.94 (6-H_2) and an additional methylene group at δ 2.92/2.61 (7-H_2). Besides the methyl groups of the isopropyl group, two methyl singlets resonating at δ 1.28 and δ 1.12 were assigned to C-18 and C-20, respectively. On the basis of HMBC spectrum, the methyl protons of isopropyl 16-H_3 and 17-H_3 exhibited correlations to C-14; and the hydrogen 12-H showed correlations to C-13, C-14 and C-9, which indicated that the isopropyl group was at carbon C-14 and the hydroxy group at C-13. Another further correlations were observed from 11-H to C-10 as well as to the aromatic carbons C-8 and C-13. On the ring A, the methyl at δ 1.28 (18-H_3) was located at C-4 via HMBC correlations to C-3, C-4, C-5 and the carboxylic carbon C-19. Furthermore, long-range correlations between the hydrogens at 3-H_2, 5-H, 18-H_3 and the carboxylic carbon C-19 showed that the carboxyl group was present at C-4. The methine proton 5-H exhibited correlations to C-4, C-6, C-7, C-9, C10, C-18 and C-20. Finally, the protons 20-H_3 showed correlations to C-1, C-5, C-9 and C-10. The relative stereochemistry of **(4)** was determined by the correlations present in a NOESY spectrum, and suggested that 5-Hα, 1-Hα (δ 1.25), 3-Hα (δ 1.08), 7-Hα (δ 2.61) and 18-H_3 are co-facial, while 20-H_3, 2-Hβ (δ 2.02) and 6-Hβ (δ 1.94) are on the opposite face. Thus, the structure of **(4)** was concluded to be identical to 4*β*-carboxy-19-nor-totarol, previously reported from *Podocarpus nagi* [8].

Table 2: *^{13}C- and ^{1}H-NMR data of compounds 4, 5 and 6.*

Position	4[a]		5[a]		6[b]	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1α	41.8	1.25 *	39.1	1.52 m*	56.9	3.56 d (4.5)
1β		2.22 *		2.28 m		-
2α	21.5	1.55 m	19.9	1.68 m	50.6	3.32 *
2β		2.02 m		1.83 m*		-
3α	38.9	1.08 td (13.5, 4.3)	42.5	1.31 td (13.5, 3.9)	66.4	4.23 dd (5.9, 5.0)
3β		2.21*		1.54 m*		-
4	44.9	-	34.2		49.0	
5	53.8	1.44 dd (11.2, 1.2)	51.1	1.84 m*	49.8	2.05 d (6.8)
6α	22.8	2.23*	36.8	2.61*	72.2	4.88 dd (8.5, 6.8)
6β		1.94 m		2.59*		-
7α	31.4	2.61 ddd (16.6,12.6,	200.9	-	58.7	5.21 dd (8.5, 4.5)
7β		6.3)		-		-
		2.92 dd (16.7, 4.8)				
8	134.7	-	124.0	-	111.3	-
9	141.1	-	158.4	-	165.0	-
10	39.7	-	37.4	-	36.9	-
11	125.0	6.92 d (8.6)	110.4	6.76 s	105.8	6.27 s
12	115.5	6.52 d (8.6)	162.4	-	161.2	-
13	154.8	-	134.6	-	-	-
14	132.1	-	127.0	7.79 s	169.4	-
15	28.9	3.24 m	27.8	3.22 septet (6.9)	28.5	3.27 septet (6.8)
16	20.8	1.31 d (7.1)	22.8	1.20 d (6.9)	20.1	1.20 d (6.8)
17	20.7	1.32 d (7.1)	22.7	1.21 d (6.9)	20.3	1.17 d (6.8)
18	29.4	1.28 s	33.0	1.03 s	176.8	
19	181.8	-	21.7	0.95 s	25.5	1.31 s
20	23.9	1.12 s	23.5	1.23 s	18.3	1.33 s
					3-OH	5.29 d (5.0)
					7-OH	5.78 d (4.5)

Spectra recorded in: [a]Methanol-d_4, [b]DMSO-d_6. * Overlapping. Assignments were based on COSY, HMQC, HMBC, DEPT and NOESY experiments.

The elemental composition of **(5)**, $C_{20}H_{28}O_2$, was determined by HR-ESI-MS (*m/z* 301.2179 $[M+H]^+$). Its ATR-IR spectrum displayed bands for a hydroxy group at 3237, a carbonyl at 1648 and aromatic double bonds at 1592 cm^{-1}. As with **(4)**, compound **(5)** is a tricyclic natural product with seven degrees of unsaturation, including one aromatic ring and one carbonyl group, which is conjugated with the aromatic ring. The ^{1}H NMR spectrum (Table 2)

showed the presence of three methyl groups at δ 0.95 (19-H_3), 1.03 (18-H_3) and 1.23 (20-H_3), one isopropyl group consisting of a methine proton at δ 3.21 (15-H) and two methyl doublets at δ 1.20 (16-H_3) and 1.21 (17-H_3). Furthermore, two aromatic singlets at δ 6.76 (11-H) and 7.79 (14-H), which apparently are situated in positions 1 and 4 in the aromatic ring. In addition to this, three methylene groups at δ 2.28/1.52 (1-H_2), 1.83/1.68 (2-H_2) and 1.54/1.31 (3-H_2) and a second order system at δ 2.61/2.59 (6-H_2) and 1.84 (5-H) can be observed. From the HMBC data, the position of the carbonyl function was placed at C-7 by correlations between 14-H as well as 6-H_2 and C-7. The isopropyl and hydroxy groups are located at C-13 and C-12, respectively, by the correlations observed from 14-H to C-15, C-9, C-12 and from 11-H to C-8, C-13 and C-12. All these results indicated that the structure of **(5)** was identical to 12-hydroxyabieta-8,11,13-triene-7-one (sugiol), previously reported from *Podocarpus nagi* [8].

The molecular formula of compound (**6**) was established to be $C_{19}H_{22}O_7$ from the $[M+H]^+$ ion peak at *m/z* 363.1450 determined by HR-ESI-MS and the 1D NMR data (Table 2), which indicate nine degrees of unsaturation. The ATR-IR spectrum displayed bands at 3444, 1770 and 1714 cm^{-1}, which are indicative of hydroxy, γ-lactone and δ-lactone moieties, respectively. The ^1H NMR spectrum showed the presence of two methyl singlets at δ 1.31 and 1.33, they were assigned to C-18 and C-20, respectively; one singlet olefinic proton at δ 6.27 (11-H). Furthermore, two protons at δ 3.56 (1-H) and 3.32 (2-H), correlated in the HMQC spectrum with carbons at δ 56.9 and 50.6, respectively, which allowed the establishment of the presence of an epoxy ring located at C-1/C-2 based on the HMBC correlations from 1-H to C-2, C-3, C-9 and C-10, and correlations from 2-H to C-1, C-3, and C-4. Three spin systems were evident in the COSY spectrum: correlations between two methyl doublets at δ 1.20 (16-H) and 1.17 (17-H), attributed to an isopropyl group, and the isopropyl methine proton at δ 3.27 (15-H), which appeared as a septet; the proton signal at δ 3.32 (2-H) correlated with 3.56 (1-H) and 4.23 (3-H), which coupled with the hydroxy proton at δ 5.29 (3-OH); the proton signal at δ 4.88 (6-H) coupled with 2.05 (5-H) and 5.21 (7-H), which correlated with the hydroxy proton at δ 5.78 (7-OH). HMBC correlations: from 11-H to C-8, C-12, C-14; as well as 7-H to C-9 and C-14; and from 15-H to C-8 and C-14 confirmed the assignment of δ-lactone ring carbons. The location of the γ-lactone between C-19 and C-6 were by correlations observed in the HMBC spectrum between 18-H_3 and C-19, and between 7-H, 5-H and C-6. The NOESY spectrum exhibited correlations between 5-H, 6-H, 7-H and 18-H_3, suggesting the β-orientation of the γ-lactone and the hydroxy group at δ 5.78 (7-OH). NOESY correlations between 1-H, 2-H, 3-H and 18-H_3 suggest that the hydroxy group at δ 5.29 (3-OH) was β-oriented, as well as the epoxy group. Hence, compound **(6)** was concluded to be a nor-diterpene dilactone type-A, known as nagilactone C [9, 10]. Compound **(6)** has previously been isolated from *Podocarpus nagi* [9]

EXPERIMENTAL

General experimental procedures

The optical rotation was measured with a Perkin-Elmer 341 polarimeter at 20 °C. HR-ESI-MS spectra were recorded with a Waters Q-TOF Micro system spectrometer, using H_3PO_4 for calibration and as internal standard. ATR-IR spectrum was obtained with a Bruker-Alpha-P spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were measured with a Bruker DRX spectrometer; the spectra were recorder in DMSO-d_6 (solvent residual signals at δ_H 2.50 and δ_C 39.52), acetone-d_6 (solvent residual signals at δ_H 2.05 and δ_C 29.84) and methanol-d_4 (solvent residual signals at δ_H 3.31 and δ_C 49.00). The chemical shift (δ) are given in ppm, and coupling constants (*J*) in Hz. Vacuum liquid chromatography (VLC) was carried out using TLC grade silica gel (Merck), while column chromatography (CC) were run on silica gel 60 (230-400 mesh, Merck) and Sephadex LH-20. TLC analyses were carried out on silica gel GF_{254} precoated plates (Merck); chromatograms were visualized under a UV lamp and by spraying with vanillin (6%)-sulfuric acid (1.5%)-ethanol solution, followed by heating.

Plant material

The aerial parts of *P. parlatorei* Pilger were collected from south of Cochabamba-Bolivia at 2900 meters above sea level in April 2008. A voucher specimen (MZ-3007) was deposited at the National Herbarium "Herbario Nacional Martín Cárdenas" at Cochabamba-Bolivia

Extraction and isolation

The dried and pulverized whole plant material of *P. parlatorei* (300 g) was extracted with ethanol. The solvent was recovered *in vacuo* to yield a crude extract (10 g). A volume of methanol-water (5:1) was added to the crude extract and the mixture was agitated thoroughly to form a suspension, which was extracted with chloroform three times (A, B and C). After evaporation, the fraction A was subject to VLC eluted with heptane-ethyl acetate gradient to give seven fractions (A1-A7). The compound (**5**) (5 mg) was purified from fraction A3 by CC using a mixture of heptane-ethyl acetate (80:20) as a solvent. Fraction A4 was applied to repeated silica gel VLC (chloroform-methanol (80:20) and chloroform) and CC on Sephadex LH-20 (chloroform-methanol (50:50)) to yield compound (**4**) (5 mg). Fraction C was subject to VLC on silica gel eluted with chloroform-methanol to give two main fractions C1 and C2. Fraction C1 (1.4 g) was subject to CC on Sephadex LH-20 eluted with chloroform-methanol (50:50) to give eight fractions (1-8). Fraction 1 (140 mg) was precipitated with methanol to give compound (**6**) (5 mg). Fraction 2 (200 mg) was precipitated with methanol to give compound (**3**) (3 mg). Fraction 3 (380 mg) was precipitated with methanol to give compound (**1**) (7 mg). Finally, fraction 8 was washed with cold acetone and filtered to yield compound (**2**) (1.5 mg).

5,5'',7''-trihydroxy-4',4''',7-trimethoxy-3',8''-biflavone (sciadopitysin) ***(1).*** Yellow powder. mp 285-288 °C. ^{1}H NMR (DMSO-d_6 400 MHz) and ^{13}C NMR (DMSO-d_6 100 MHz), see Table 1. HRMS-ESI *m/z* 581.1453 $[M+H]^+$. Calculated for $C_{33}H_{24}O_{10}$, 581.1448.

5,5'',7,7''-tetrahydroxy-4',4'''-dimethoxy-3',8''-biflavone (isoginkgetin) ***(2).*** Yellow powder. mp 202-204 °C. ^{1}H NMR (acetone-d_6 400 MHz) and ^{13}C NMR (acetone-d_6 100 MHz), see Table 1. HRMS-ESI *m/z* 567.1290 $[M+H]^+$. Calculated for $C_{32}H_{22}O_{10}$, 567.1291.

4',5,5'',7,7''-pentahydroxy-4'''-methoxy-3',8''-biflavone (podocarpusflavone A) ***(3).*** Yellow powder. mp 240-242 °C. ^{1}H NMR (DMSO-d_6 400 MHz) and ^{13}C NMR (DMSO-d_6 100 MHz), see Table 1. HRMS-ESI *m/z* 553.1161 $[M+H]^+$. Calculated for $C_{31}H_{20}O_{10}$, 553.1135.

4β-carboxy-19-nor-totarol ***(4).*** Yellow oil. $[\alpha]_D^{20}$ + 119 (*c* 0.38, MeOH). ATR-IR ν_{max} 3387, 2954, 2872, 1693, 1589, 1448, 1357, 1274, 1183 cm^{-1}. ^{1}H NMR (methanol-d_4 400 MHz) and ^{13}C NMR (methanol-d_4 100 MHz), see Table 2. HRMS-ESI *m/z* 317.2130 $[M+H]^+$. Calculated for $C_{20}H_{28}O_3$, 317.2117.

12-Hydroxyabieta-8,11,13-triene-7-one (sugiol) ***(5).*** White, amorphous solid. mp 290-292 °C. $[\alpha]_D^{20}$ + 20 (*c* 0.06, MeOH). ATR-IR ν_{max} 3237, 2955, 2929, 2863, 1648, 1592, 1303, 1268 cm^{-1}. ^{1}H NMR (methanol-d_4 400 MHz) and ^{13}C NMR (methanol-d_4 100 MHz), see Table 2. HRMS-ESI *m/z* 301.2179 $[M+H]^+$. Calculated for $C_{20}H_{28}O_2$, 301.2168.

Nagilactone C ***(6).*** White, amorphous powder. mp 300-305 °C. $[\alpha]_D^{20}$ + 5 (*c* 0.88, DMSO). ATR-IR ν_{max} 3444, 3274, 2249, 2122, 1770, 1714, 166, 1050, 1007, 820, 758 cm^{-1}. ^{1}H NMR (DMSO-d_6 400 MHz) and ^{13}C NMR (DMSO-d_6 100 MHz), see Table 2. HRMS-ESI *m/z* 363.1450 $[M+H]^+$. Calculated for $C_{19}H_{22}O_7$, 363.1444.

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