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Constituents from the stems of *Actinodaphne lancifolia*

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Abstract

Two C_{16}-lactonic compounds, actinolides A−B (**1**–**2**), were isolated from the stems of *Actinodaphne lancifolia*, together with five known lactones (**3**–**7**) and three known lignans (**8**–**10**). Their structures were determined spectroscopically, which included 2D NMR spectroscopic analysis. © 2002 Published by Elsevier Science Ltd.

Keywords: *Actinodaphne lancifolia*; Lauraceae; Lactone; Methoxy-β-methyl-α,β-unsaturated butenolide; Lignan; Chemotaxonomy

1. Introduction

Actinodaphne lancifolia (Sieb. et Zucc.) Meissn is an evergreen tree in the family Lauraceae, which is distributed in the southern part of Korea, as well as in China and Japan. In the *Actinodaphne*, the root of *A. lancifolia* (Sieb. et Zucc.) Meissn. var. *sinensis* Allen. is a traditional Chinese medicine used for the treatment of stomachache, arthritis, overexertion, and edema (Kim et al., 1998). In this study, we have isolated seven lactones and three lignans from MeOH extract of the stems of *A. lancifolia*.

2. Results and discussion

Repeated column chromatography of the hexane- and EtOAc-soluble fractions of MeOH extract of *A. lancifolia* (stems) led to the isolation of seven lactonic compounds (**1**–**7**) and three lignans (**8**–**10**). Eight were known compounds, which were identified to be isolancifolide (**3**) (Tanaka et al., 1989a), lancifolide (**4**) (Tanaka et al., 1989a), secoisolancifolide (**5**) (Tanaka et al., 1989b), litsenolide C_1 (**6**) (Takeda et al., 1972), litsenolide C_2 (**7**) (Taketa et al., 1972), (±)-syringaresinol (**8**) (Deyama, 1983), (±)-de-4′-*O*-methylmagnolin (**9**) (Miyazawa et al., 1993) and lyoniresinol (**10**) (Shibuya et al., 1992; Lee et al., 2001) by comparing their spectral data with those that have been previously reported.

The molecular formula of actinolide A (**1**) was deduced to be $C_{16}H_{24}O_3$ based on the HR–FABMS, which indicated five degrees of unsaturation (Scheme 1). It exhibited two doublet signals at δ 5.83 ($J = 1.5$ Hz) and 1.89 ($J = 1.5$ Hz), which were assignable to an oxygenated vinyl moiety on the butenolide moiety in the ^{1}H NMR spectrum, compared with that of neomanoalide isolated from *Luffariella variabilis* (marine sponge) (de Silva and Scheuer, 1981). Its IR spectrum showed the presence of an α,β-unsaturated methyl-butenolide (1760 cm^{-1}) (de Silva and Scheuer, 1981). This observation was further supported by the ^{13}C NMR spectral assignments (a carbonyl carbon at δ 169.8, an olefinic carbon at δ 120.2, an olefinic quaternary carbon at δ 164.9, an oxygenated quaternary carbon at δ 111.1, and a methyl carbon at δ 12.7) coupled to DEPT and 2D NMR (COSY, HMQC, and HMBC) experiments. In addition, the ^{1}H NMR spectrum showed a methoxy group (δ_H, 3.11), which correlated with the oxygenated quaternary carbon at δ_C 111.1 (C-4) in the HMBC spectrum, and indicated the presence of γ-methoxy-β-methyl-α,β-unsaturated butenolide. This was further confirmed by the HMBC (Fig. 1) and EIMS spectra, which showed a prominent fragment ion peak at m/z 127 $[C_6H_7O_3]^+$ (Fig. 2). Furthermore, the terminal

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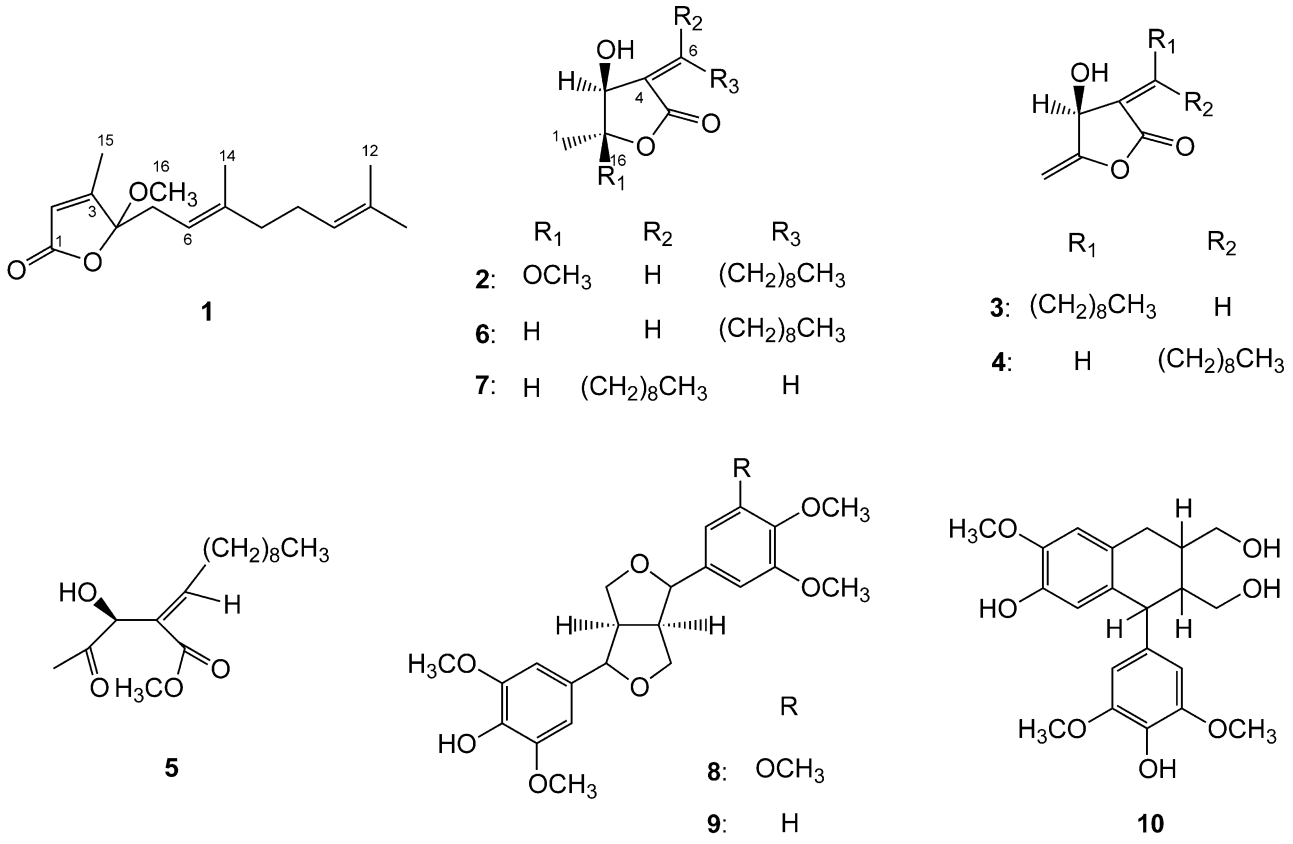

Scheme 1. Structures of compounds isolated from the stems of *Actinodaphne lancifolia*.

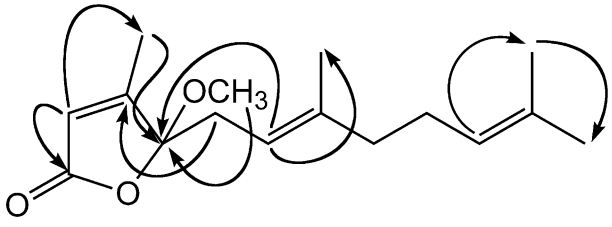

Fig. 1. Significant HMBC correlations for compound **1**.

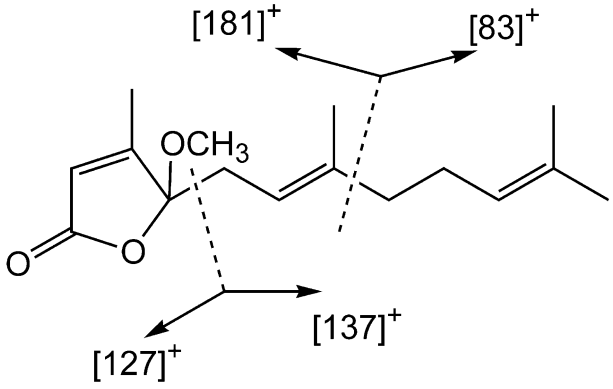

Fig. 2. Progressed mass fragmentation pattern of compound **1**.

geranyl fragment of **1** was established by the presence of two olefinic protons (δ 4.85 and 4.93) and three vinyl methyl groups (δ 1.51, 1.55 and 1.60) in the ^{1}H NMR spectrum (Table 1), considering which remain degrees of unsaturations (Culioli et al., 1999; Valls et al., 1995). This was further confirmed by fragment ions at m/z 137 $[C_{10}H_{17}]^+$ and 181 $[M-C_6H_{11}]^+$ in the EIMS spectrum. The two partial structures were linked using an HMBC experiment. Long-range correlations between δ_H 2.45 and 2.68 (H-5)/δ_C 164.9 (C-3), and δ_H 4.85 (H-6)/δ_C 111.1 (C-4) confirmed that the geranyl moiety was linked to the γ-methoxy-β-methyl-α,β-unsaturated butenolide by C-4.

The *E* configuration of the double bond of the isoprenoid chain was verified by the position of the C-14 methyl signal observed above δ 20 in the ^{13}C NMR spectrum (de Silva and Scheuer, 1980; Valls et al., 1986).

The presence of γ-methoxy-β-methyl-α,β-unsaturated butenolide group included in the isoprenoid unit may be the first observation as a secondary metabolite of the plant. However, the absolute configuration at C-4 remained unidentified. Therefore, the structure of actinolide A (**1**) was determined to be (4ξ)-4-(3,7-dimethyl-2,6-octadienyl)-4-methoxy-3-methylbut-2-enolide.

Actinolide B (**2**) was isolated as a colorless oil and established to have a molecular formula of $C_{16}H_{28}O_4$ by HR–FABMS. The UV absorption at 265 nm and the IR band at 1750 cm^{-1} suggested the presence of a conjugated γ-lactone group. The ^{1}H NMR spectrum of **2**

Table 1
NMR spectral data of compound **1**[a] ($CDCl_3$, ^1H; 300 MHz, ^{13}C; 75 MHz)

C	^1H NMR	^{13}C NMR
1	–	169.8
2	5.83, *d* (1.5)[b]	120.2
3	–	164.9
4	–	111.1
5	2.68, *dd* (15.0, 7.5) 2.45, *dd* (15.0, 6.6)	34.1
6	4.85, *dt* (7.5, 6.6)	115.0
7	–	140.3
8	1.96, *m*	26.4
9	1.92, *m*	39.7
10	4.93, *t* (6.2)	123.9
11	–	131.5
12	1.51, *s*	17.6
13	1.60, *s*	25.6
14	1.55, *s*	16.3
15	1.89, *d* (1.5)	12.7
16	3.11, *s*	50.5

[a] All the measurements were done in $CDCl_3$.
[b] *J* values (Hz) are given in parentheses.

showed signals for an olefinic proton at δ 4.47 and an oxygenated methylene at δ 6.37 (*td*, $J = 7.7$, 1.2 Hz). The ^{13}C NMR spectrum of **2** contained 16 resonance peaks, including a lactone carbonyl carbon at δ 167.6, olefinic carbons at δ 150.4 and 128.8, and a methyl group at δ 14.1 (Table 2). These spectral features were similar to those of a known lactonic compound, lancifolide (**4**). In comparison with **4**, compound **2** had an oxygen-bearing quaternary carbon at δ 109.0, a methoxyl at δ 50.4 and a methyl carbon at δ 16.2 but lacked a pair of methylene carbons at δ 157.6 and 90.3 (C-1 and C-2) in the ^{13}C NMR spectrum. It could be deduced that **2** had methoxyl and methyl groups at C-2 in place of the methylene. The position of these groups was established by HMBC. The methyl signal at δ_H 1.54 was correlated with an oxygen bearing quaternary carbon at δ_C 109.0 and a methine carbon at δ_C 75.7 (C-3). The former carbon also correlated with the signal at δ_H 4.47 (H-3). Furthermore, the methoxyl signal at δ_H 3.36 also correlated with the C-2 carbon signal (δ_C 109.0) (Fig. 3).

Table 2
NMR spectral data of compound **2**[a] ($CDCl_3$, ^1H: 300 MHz, ^{13}C: 75 MHz)

C	^1H NMR	^{13}C NMR
1	1.54, *s*	16.2
2	–	109.0
3	4.47, *s*	75.7
4	–	128.8
5	–	167.6
6	6.37, *td* (7.7, 1.2)[b]	150.4
7	2.62, *m*	28.0
8–14	1.26∼1.30, *br s*	31.8, 29.5, 29.4 29.2, 28.7, 22.6
15	0.80, *t* (6.7)	14.1
16	3.36, *s*	50.4

[a] All the measurements were done in $CDCl_3$.
[b] *J* values (Hz) are given in parentheses.

The geometry of the trisubstituted double bond conjugated to a lactone carbonyl group had a β-*trans* proton (cisoid enone system) which was deduced from the ^1H NMR chemical shift of olefinic β-proton in **2** (δ 6.37), compared to that of **3** (δ 7.08) and **4** (δ 6.69). The remaining structure of **2**, except for the β-hydroxy-γ-methyl-γ-methoxyl-α,β′-unsaturated-γ-lactone moiety, was clarified from observations in the ^{13}C NMR spectrum which showed the presence of a long methylene chain, a *n*-nonyl group consisting of eight methylene groups and one methyl group. The determination of the absolute configuration of at C-3 was examined by a modification of Mosher's method (Dale and Mosher, 1973; Min et al., 2000). Under the standard reaction conditions with (*R*)-MTPA and (*S*)-MTPA in the presence of 1-ethyl 3-(3-dimethylaminopropyl)-carbodiimide·HCl (EDC·HCl) and 4-dimethylaminopyridine (4-DMAP), **2** gave 3-(*R*)-MTPA ester (**2a**) and 3-(*S*)-MTPA ester (**2b**), respectively. As shown in Fig. 4, the proton signals assigned for H-1 and H-16 in the (*S*)-MTPA ester (**2b**) were observed at lower field compared to those of the (*R*)-MTPA ester (**2a**), while the proton signal due to H-6 in the former ester was observed at a higher field compared to that in the latter ester (Fig. 4). Therefore, the absolute stereochemistry of the asymmetric carbon at C-3 was concluded to be *R*. This was further supported by the chemical shift of C-3 (δ_H 4.47, δ_c 75.7) in the NMR spectra, which resembles that of litsenoside A1 isolated from *Litsea japonica* (Lauraceae) (Takeda et al., 1972). In addition, the configuration of C-2 was also confirmed to have the *R* form by NOE observed between H-3 (δ 4.47) and H_3-1 (δ 1.54) in the NOESY spectrum (Fig. 3). Consequently, the structure of actinolide B (**2**) was determined to be (2*R*,3*R*)-4-decylidene-2-hydroxy-3-methoxy-3-methylbutanolide.

3. Experimental

3.1. General

Optical rotation: Jasco DIP-1000 Digital Polarimeter; UV: UV-2200 UV–vis recording spectrophotometer (Shimadzu, Japan); IR: Jasco Report-100 spectrophotometer; NMR: Bruker DMX 300 spectrometer; EIMS: JMS-AX 505 HAD at an ionization voltage of 70 eV; Positive mode HR–FABMS: JMS-AX 110/110A (Jeol, Japan); column chromatography: silica gel 60 (70–230 and 230–400 mesh, Merck) and YMC-GEL ODS-A (12 nm, S-75 μm, YMC); TLC and preparative TLC: pre-coated silica gel 60 F_{254} and RP-18 F_{254s} (Merck).

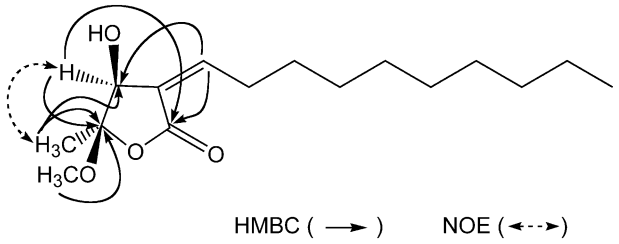

Fig. 3. Significant HMBC and NOE (in NOESY spectrum) correlations for compound **2**.

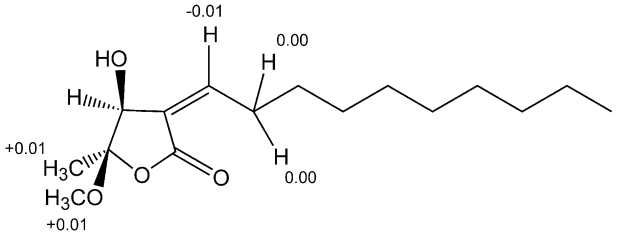

Fig. 4. Chemical shift differnence for the (*S*)-MTPA ester (**2b**) and (*R*)-MTPA ester (**2a**) in ppm at 500 MHz.

3.2. Plant material

A. lancifolia was collected in May 2000, at Jeju Island (Korea) and a voucher specimen (NDC-356A) is deposited in the Immunomodulator Research Laboratory, Korea Research Institute of Bioscience and Biotechnology.

3.3. Extraction and isolation

Air-dried stems of *A. lancifolia* (30 kg) were finely ground and extracted at room temperature with 90% MeOH in H_2O (90 l) for 1 month, and the MeOH solution was evaporated to dryness in vacuo. The resulting MeOH extract (6 kg) of the *A. lancifolia* was partitioned between water (16 l) and hexane (35 l) and then further extracted with EtOAc (54 l). The hexane-soluble fraction (1.4 kg) was loaded onto a silica gel column, which was eluted with hexane:EtOAc (50:1→1:1, v/v) to give six fractions (fr. 1∼fr. 6). Silica gel column chromatography of fr. 2 with a solvent mixture of hexane:$CHCl_3$:EtOAc (step-gradient system, 15:1:1 → 10:1:1, v/v) yielded five sub-fractions (fr. 21∼fr. 25). Among these fractions, preparative-TLC (MeOH:H_2O = 8:2, v/v) of fr. 21 afforded **1** (60 mg) and column chromatography of fr. 24 over silica gel column chromatography (step-gradient system, *n*-hexane:$CHCl_3$:EtOAc = 10:1:0.1 → 5:1:0.1, v/v) yielded **2** (30 mg). Combined frs. 22 and 23 were applied to preparative-TLC (hexane:$CHCl_3$:MeOH = 2:1:0.1 and MeOH:water = 8:2, v/v) to yield **3** (400 mg), **4** (20 mg) and **5** (75 mg), respectively. Column chromatography of fr. 3 over silica gel with a isocratic solvent system of $CHCl_3$:acetone (50:1, v/v) gave three sub-fractions (fr. 31–33). Among these fractions, column chromatography of fr. 31 over RP-18 column chromatography (MeOH:water = 6:4 → 8:2, v/v) and preparative-TLC (hexane:$CHCl_3$:EtOAc = 9:8:3 and hexane:acetone = 5:1, v/v) resulted in **6** (100 mg) and **7** (90 mg). On the other hand, repeated column chromatography of the EtOAc-soluble fraction (155 g) on silica gel and reverse phase ODS, followed by preparative-TLC (silica gel, hexane:$CHCl_3$:MeOH = 1:1:0.5 and RP-18, MeOH:H_2O = 4.5:5.5, v/v) yielded **8** (20 mg), **9** (30 mg) and **10** (150 mg).

3.4. Actinolide A (*1*)

Colorless oil. $[\alpha]_D^{26.5}$ [+5.1° ($CHCl_3$, *c* 0.33); UV λ_{max} ($CHCl_3$) nm:263; IR ν_{max} (CCl_4) cm^{-1}:1750 (C = O); ^1H and ^{13}C NMR: see Table 1; EIMS (rel. int.) *m/z*: 264$[M]^+$ (5), 181 (2), 137 (12), 127 (100); HR-FABMS *m/z*: 287.1628 ($[M+Na]^+$, calc. for $C_{16}H_{24}O_3Na$ 287.1623).

3.5. Actinolide B (*2*)

Colorless oil. $[\alpha]_D^{25}$ +14.7° ($CHCl_3$, *c* 1.00); UV λ_{max} ($CHCl_3$) nm: 265; IR ν_{max} (CCl_4) cm^{-1}: 3430 (OH), 1750 (C = O); ^1H and ^{13}C NMR: see Table 2; positive FABMS *m/z*: 307 $[M+Na]^+$, 285 $[M+H]^+$; HR-FABMS *m/z*: 285.2063 ($[M+H]^+$, Calcd for $C_{16}H_{29}O_4$ 285.2066).

3.6. (*R*)-MTPA ester (*2a*) from actinolide B (*2*)

A solution of **2** (5.0 mg, 17.6 μM) in CH_2Cl_2 (2.0 ml) was treated with (*R*)-MTPA (20.0 mg, 85.7 μM) in the presence of EDC·HCl (16.5 mg, 85.7 μM) and 4-DMAP (6.1 mg, 50.0 μM) (Yoshikawa et al., 1999). After stirring under reflux for 3 h, the mixture was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was successively washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and NaCl, then dried over $MgSO_4$ powder and filtered. Removal of the solvent from the filtrate under reduced pressure furnished a residue which was purified by preparative thin layer chromatography (hexane·EtOAc, 3:1) to give 3-(*R*)-MTPA ester (**2a**, 5.5 mg) as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.56 (3H, *s*, H-1), 6.64 (1H, *s*, H-3), 6.80 (1H, *td*, *J* = 15.9, 7.2 Hz, H-6), 2.11 (2H, *m*, H-7), 0.81 (3H, *t*, *J* = 6.6 Hz, H-15), 3.14 (3H, *s*, H-16).

3.7. (*S*)-MTPA ester (*2b*) from actinolide B (*2*)

A solution of **2** (5.0 mg, 17.6 μM) in CH_2Cl_2 (2.0 ml) was treated with (*S*)-MTPA (20.0 mg, 85.7 μM) in the presence of EDC·HCl (16.5 mg, 85.7 μM) and 4-DMAP

(6.1 mg, 50.0 μM). Workup as described above gave the 3-(*S*)-MTPA ester (2b, 4.6 mg) as a colorless oil. ^{1}H NMR ($CDCl_3$):δ 1.57 (3H, *s*, H-1), 6.64 (1H, *s*, H-3), 6.79 (1H, *td*, J = 16.2, 7.2 Hz, H-6), 2.11 (2H, *m*, H-7), 0.81 (3H, *t*, J = 6.6 Hz, H-15), 3.15 (3H, *s*, H-16).

3.8. Isolancifolide (**3**)

Colorless oil. $[\alpha]_D^{25}$ −59.0° ($CHCl_4$, *c* 0.5); UV λ_{max} ($CHCl_3$) nm: 266; IR ν_{max} (CCl_4) cm^{-1}: 3600, 3400 (OH), 1780 (C = O), 1685, 1670; positive FABMS *m*/*z*:253 $[M+1]^+$.

3.9. Lancifolide (**4**)

Colorless oil. $[\alpha]_D^{25}$ −49.0° ($CHCl_4$, *c* 0.58); UV λ_{max} ($CHCl_3$) nm: 262; IR ν_{max} (CCl_4) cm^{-1}: 3580, 3400 (OH), 1780 (C = O), 1680; positive FABMS *m*/*z*: 253 $[M+1]^+$.

3.10. Secoisolancifolide (**5**)

Colorless oil. $[\alpha]_D^{25}$ +102.7° ($CHCl_4$, *c* 0.49); UV λ_{max} ($CHCl_3$) nm: 259; IR ν_{max} (CCl_4) cm^{-1}: 3475 (OH), 1730 (C = O), 1720, 1650; positive FABMS *m*/*z*: 285 $[M+1]^+$.

3.11. Litsenolide C_1 (**6**)

Colorless oil. $[\alpha]_D^{25}$ −9.4° ($CHCl_3$, *c* 0.61); UV λ_{max} ($CHCl_3$) nm: 221; IR ν_{max} (CCl_4) cm^{-1}: 3600, 3400 (OH), 1755 (α,β-unsaturated-γ-lactone), 1650 (C = O).

3.12. Litsenolide C_2 (**7**)

Colorless oil. $[\alpha]_D^{25}$ −45.2° ($CHCl_3$, *c* 0.98); UV λ_{max} ($CHCl_3$) nm: 219; IR ν_{max} (CCl_4) cm^{-1}: 3600, 3400 (OH), 1755 (α,β-unsaturated-γ-lactone), 1678 (C = O).

3.13. (±)-Syringaresinol (**8**)

Amorphous powder. $[\alpha]_D^{26.5}$ −0.7° (MeOH, *c* 0.06); EIMS *m*/*z*:418 $[M]^+$.

3.14. (±)-de-4′-O-Methylmagnolin (**9**)

Amorphous powder. $[\alpha]_D^{26.5}$ −3.5° (MeOH, *c* 0.25); EI-MS *m*/*z*: 402 $[M]^+$.

3.15. Lyoniresinol (**10**)

Amorphous powder. $[\alpha]_D^{26.5}$ +1.3° (MeOH, *c* 1.0); EIMS *m*/*z*: 420 $[M]^+$.

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