New Megastigmane Glucosides from *Excoecaria cochinchinensis* Lour. var. *cochinchinensis*

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Two new megastigmane glucosides, called excoecariosides A and B were isolated from the leaves of a medicinal Vietnamese plant, *Excoecaria cochinchinensis* Lour. var. *cochinchinensis* (Euphorbiaceae) together with seven known compounds. Their structures were elucidated by spectroscopic analyses and chemical reactions including the modified Mosher's method.

Key words *Excoecaria cochinchinensis*; Euphorbiaceae; megastigmane glucoside; excoecarioside

Excoecaria cochinchinensis Lour. var. *cochinchinensis* (Euphorbiaceae) (Vietnamese name: Don mat troi) is a small plant, about 1 m high and endemic to eastern Indochina.[1—3] Growing wild and also being cultivated as a medicinal and ornamental plant, the plant is characterized by the features that its leaves are nearly opposite, deep green above, and purple red beneath, and the margins denticulate.[1,2] Its leaves are usually used in a Vietnamese folk medicine to treat furuncles, pruritus, prolonged diarrhoea, urethrorrhagia, and dysentery.[2] Until now, there has been no information on glycosidic compounds from *E. cochinchinensis* var. *cochinchinensis*. This paper describes the isolation and structure elucidation of two new megastigmane glucosides (**3**, **4**), together with seven known compounds (**1**, **2**, **5**—**9**) from the leaves of the title plant.

The air-dried and powdered leaves of *E. cochinchinensis* var. *cochinchinensis* were extracted with MeOH at room temperature, and the successive partition of the concentrated MeOH extract between H_2O and organic solvents of increasing polarity, *n*-hexane, EtOAc, and 1-BuOH, gave three corresponding soluble fractions. The 1-BuOH-soluble fraction was subjected to a general separation procedure (see Experimental) to give compounds **1**—**9**.

Excoecarioside A (**3**), an amorphous powder, gave a molecular formula of $C_{19}H_{32}O_8$ at *m*/*z* 387.2028 ($[M-H]^-$) in the negative-ion high-resolution (HR)-FAB-MS. The IR spectrum indicated the presence of hydroxy (3368 cm^{-1}) and an α,β-unsaturated ketone (1643 cm^{-1}) group. The ^{1}H-, ^{13}C-NMR (Table 1), distortionless enhancement by polarization transfer (DEPT), and heteronuclear single quantum correlation (HSQC) spectra of **3** showed the presence of 13 carbons of a megastigmane skeleton and six carbons of β-glucopyranose [δ_C 104.3 (d), 77.8 (d), 77.6 (d), 74.8 (d), 71.3 (d), and 62.2 (t); anomeric proton: δ_H 4.15 (d, J=7.8 Hz)]. A similar

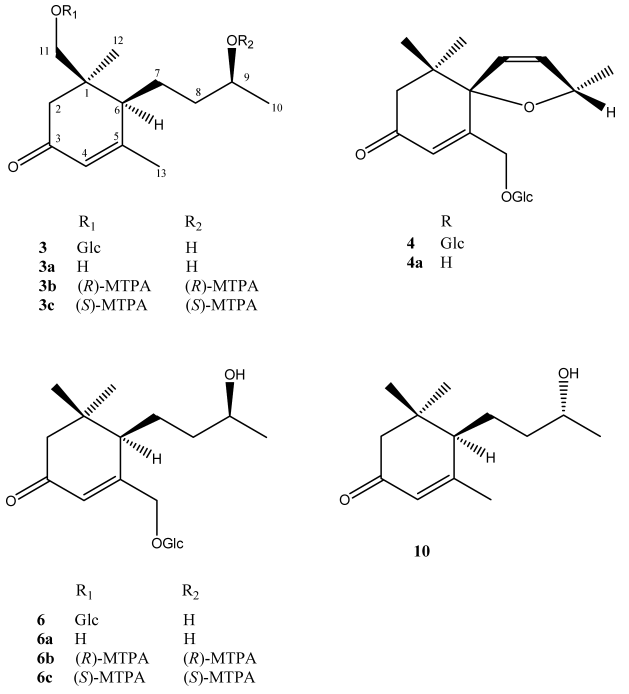

Fig. 1. Chemical Structures of Compounds **3**, **3a**—**c**, **4**, **4a**, **6**, **6a**—**c**, **10**, and **11**

Table 1. ^{1}H- and ^{13}C-NMR Spectroscopic Data of **3** and **4** (δ in ppm, J in Hz, CD_3OD)

C/H	**3**		**4**	
	C	H	C	H
1	41.3		42.7	
2a	44.1	2.33 d (16.8)	50.6	2.18 d (16.8)
b		2.33 d (16.8)		2.49 d (16.8)
3	201.4		201.3	
4	125.5	5.82 s	124.4	6.29 s
5	169.1		165.1	
6	46.1	2.35 m	79.1	
7a	26.2	1.65 m	130.0	5.83 s
b		1.75 m		
8a	39.2	1.56 m	137.1	5.82 d (4.4)
b		1.56 m		
9	68.5	3.70 m	68.7	4.31 m
10	24.3	1.15 d (6.1)	23.8	1.23 d (6.6)
11	76.4	3.70 m	23.4	0.99 s
12	23.1	1.12 s	24.1	1.04 s
13a	21.9	2.04 s	67.8	4.29 m
b				4.66 dd (17.6, 2.0)
1′	104.3	4.15 d (7.8)	103.7	4.27 d (7.8)
2′	74.8	3.15 m	75.0	3.27 m
3′	77.8	3.30 m	78.0	3.30 m
4′	71.3	3.30 m	71.6	3.28 m
5′	77.6	3.30 m	77.9	3.30 m
6′a	62.2	3.70 m	62.7	3.65 dd (12.0, 5.4)
b		3.86 br d (11.2)		3.85 dd (12.0, 2.2)

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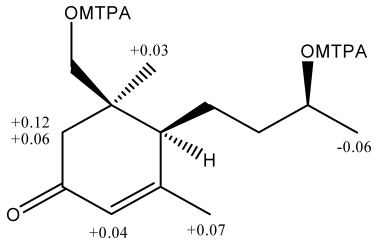

Fig. 2. $\Delta\delta_{S-R}$ Values (in ppm) Obtained for (*S*)- and (*R*)-MTPA Esters (**3b**, **c**) of **3a**

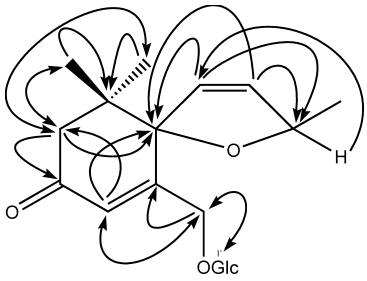

Fig. 3. HMBC Correlations of **4**

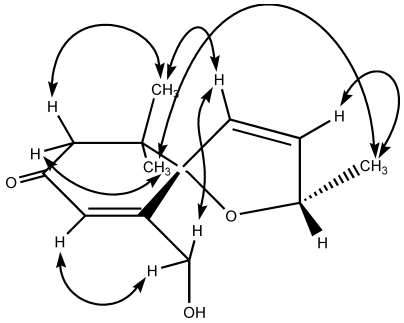

Fig. 4. Phase-Sensitive NOESY Correlations of **4a**

structure to blumenol C (**10**) was deduced by comparing the ^{13}C-NMR data of **3** with those of **10**,[4] except for a glucose-bearing hydroxymethylene group [δ_C 76.4 (t), δ_H 3.70 (2H, m)], which was positioned at either C-11 or C-12. The 6*S* configuration of **3** was determined by the extremes at 223 nm ($\Delta\varepsilon$ +1.39) and 244 nm ($\Delta\varepsilon$ +1.08) in the circular dichroism (CD) spectrum.[5] Enzymatic hydrolysis yielded D-glucose and the aglycone **3a**, called excoecariol A, whose structure was in agreement with the ^{1}H- and ^{13}C-NMR spectroscopic data (see Experimental). The nuclear Overhauser enhancement and exchange spectroscopy (NOESY) of **3a** showed a NOE between H_3-12 (δ_H 1.12) and Hα-6 (δ_H 2.15), hence the hydroxymethylene group was assigned in a β-orientation. Since stereoisomers of (9*R*) and (9*S*)-alcohols of megastigmane structures show essentially indistinguishable ^{13}C values,[5] the absolute configuration at C-9 of **3a** was determined to be *S* by the modified Mosher's method,[6] using the $\Delta\delta_{S-R}$ values obtained for (*S*)- and (*R*)-MTPA esters (**3b**, **c**) of **3a** (Fig. 2). Therefore, the structure of **3** was determined to be (6*S*,9*S*)-megastigman-3-on-4-ene-9,11-diol 11-*O*-β-D-glucopyranoside.

Excoecarioside B (**4**) was obtained as a syrup with a molecular formula of $C_{19}H_{28}O_8$ at *m/z* 383.1729 ([M−H]$^-$) in the negative-ion high-resolution (HR)-FAB-MS. The IR spectrum indicated the presence of hydroxy (3372 cm^{-1}) and an α,β-unsaturated ketone (1650 cm^{-1}) group. The ^{1}H-, ^{13}C-NMR (Table 1), and DEPT spectra characterized **4** as a megastigmane glucoside. Two tertiary methyl groups [δ_H 0.99 (s), 1.04 (s)], a glucose-bearing hydroxymethylene group [δ_H 4.29 (m) and 4.66 (dd, *J*=17.6, 2.0 Hz)], and an α,β-unsaturated ketone group [δ_C 201.3 (s), 165.1 (s), and 124.4 (d); δ_H 6.29 (s)] and β-glucopyranose [δ_C 103.7 (d), 78.0 (d), 77.9 (d), 75.0 (d), 71.6 (d), and 62.7 (t), anomeric proton: δ_H 4.27 (d, *J*=7.8 Hz)] were assigned for the structure of **4**. Enzymatic hydrolysis released the aglycone **4a**, which showed a chemical shift of H-4 [δ_H 6.07 (s)] characteristic of the presence of the hydroxymethylene at C-13,[7] and D-glucose. Full ^{1}H- and ^{13}C-NMR assignments of **4a**, named excoecariol B, are listed in Experimental. The position of the sugar moiety was determined at C-13 on the basis of the heteronuclear multiple bond correlations (HMBC) of **4** between H-1′ (δ_H 4.27) and C-13 (δ_C 67.8), between H_2-13 (δ_H 4.29, 4.66) and C-4 (δ_C 124.4), C-5 (δ_C 165.1) and C-1′ (δ_C 103.7), and between H-4 (δ_H 6.29) and C-13 (Fig. 3). The C-6 side chain formed an epoxy ring between C-6 and C-9 in accordance with the number of double bond equivalence (6) and remarkable small coupling constants of H-7 and H-8 [δ_H 5.83 (s), 5.82 (d, *J*=4.4 Hz)]. Thus **4** was deduced to have a spirocyclic structure of a theaspirone.[8] The relative stereochemistry of **4** was determined using the phase-sensitive NOESY spectrum of **4a** (Fig. 4). NOEs from H-7 (δ_H 5.71) to H_3-11 (δ_H 0.91) and Ha-13 (δ_H 4.08), and from H_3-10 (δ_H 1.14) to H_3-12 (δ_H 0.95) are indicative of the 6α,9α stereochemistry of the epoxy ring and α-orientation of the methyl group at C-10. Therefore, the structure of **4** was determined to be 6α,9α-epoxymegastigman-3-on-4-ene 13-*O*-β-D-glucopyranoside. Since the first report on theaspirones from black tea essential oil in 1968,[9] this work is the first isolation of a theaspirone glucopyranoside from Nature.

Compound **6** showed identical ^{1}H- and ^{13}C-NMR spectroscopic data and HR-FAB-MS as those of glochidionionoside B, previously isolated from *Glodichion zeylanicum*.[5] Of two chiral centers at C-6 and C-9, the configuration at C-6 was determined to be *R* by the same extremes as those of glochidionionoside B in the CD spectrum. Due to the ambiguity caused by the small values of the optical rotations of **6** {$[\alpha]_D^{25}$ +7.5° (*c*=0.53, MeOH)} and glochidionionoside B {$[\alpha]_D^{28}$ +7.4° (*c*=1.22, MeOH)} we verified the configuration at C-9. The modified Mosher's method was applied for the aglycone (**6a**) of **6**,[6] indicating the same distribution of positive and negative $\Delta\delta_{S-R}$ values of (*S*)- and (*R*)-MTPA esters of **6a** (data not shown) as those reported for (*S*)- and (*R*)-MTPA esters of the aglycone of glochidionionoside B. Thus the 9*R* stereochemistry and the identity of **6** with glochodionionoside B were proved.

Gallic acid (**1**) and (−)-shikimic acid (**2**) were determined by direct comparison ($[\alpha]_D$ and NMR) with the authentic samples. Comparison of ^{1}H- and ^{13}C- NMR spectroscopic data with those reported in the literature determined *p*-hydroxybenzoic acid (**5**),[10] kaempferol 3-*O*-β-D-glucopyranoside (**7**),[11] kaempferol 3-*O*-β-D-galactopyranoside (**8**),[12] and kaempferol 3-*O*-α-L-rhamnopyranoside (**9**).[13]

Experimental

General Procedure Optical rotations were measured on a Union Giken PM-101 digital polarimeter at 25 °C. FT-IR spectra were recorded on a Horiba FT-710 spectrophotometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were obtained on a JEOL JNM α-400 NMR spectrometer. Negative-ion and positive-ion HR-FAB-MS were measured on a JEOL SX-102 mass spectrometer with PEG-400 and PEG-600, respectively, as the calibration matrix. HPLC was carried out with a JASCO PU-1580 pump and UV-2075 Plus detector (set at 254 nm) on YMC ODS columns (150×4.6 mm i.d. in analytical and 150×20 mm i.d. in preparative scales) at the corresponding flow rates of 0.5 and 5 ml/min. Diaion HP-20 (Mitsubishi), silica gel 60 (0.063—0.200 mm, Merck) and reversed-phased octadecyl silica (ODS) gel (YMC) were used for open column chromatography (CC). TLC was carried out on Merck TLC glass plates (silica gel 60 F_{254}), and detected by spraying with 10% H_2SO_4 in 50% EtOH, followed by heating on a hot plate at 200 °C. β-Glucosidase from almond, (*R*)-(+)- and (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acids (MTPA) were from Nacalai Tesque (Japan). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) was from Cica (Japan). 4-Dimethylaminopyridine (4-DMAP) was from Wako (Japan).

Plant Material Leaves of *E. cochinchinensis* var. *cochinchinensis* were collected in September 2003 in Hanoi, Vietnam. Identification was carried out by Dr. Tran Ngoc Ninh of the Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology Hanoi, Vietnam. A voucher specimen (HCTN No. 903) is deposited in the Herbarium of the Institute of Ecology and Biological Resources.

Extraction and Isolation The air-dried and powdered leaves of *E. cochinchinensis* var. *cochinchinensis* (2.5 kg) were extracted three times with MeOH by percolation at room temperature. The combined extracts were concentrated under reduced pressure and the obtained MeOH extract was suspended in H_2O and extracted with *n*-hexane, EtOAc, and 1-BuOH, successively. Three corresponding soluble fractions were obtained with the respective weights of 179 g, 49 g, and 57 g. The 1-BuOH-soluble fraction was divided into fractions I—VI by Diaion HP-20 CC by eluting with H_2O, MeOH–H_2O (20%, 40%, 60%, 80%, and 100%). The separation procedure for fractions II—IV is as follows: 1) CC on silica gel using $CHCl_3$–MeOH solvent systems; 2) CC on ODS gel using MeOH–H_2O, from 20 to 40%, as solvent systems, and 3) preparative ODS HPLC using CH_3CN–H_2O, 15% (HPLC solvent system I) or MeOH–H_2O, 40% (HPLC solvent system II). Compounds **1** (240 mg), **2** (744 mg), **3** (13.6 mg), and **4** (60 mg) were isolated from fraction II (31.9 g), **5** (3.4 mg) and **6** (5.3 mg) from fraction III (4.8 g) using HPLC solvent system 1. Compounds **7** (44.5 mg), **8** (22.1 mg), and **9** (55.6 mg) were isolated from fraction IV (6.3 g) using HPLC solvent system 2.

Excoecarioside A (**3**): Amorphous powder. $[\alpha]_D^{25}$ −10.3° (c=1.36, MeOH). IR ν_{max} (film) cm^{-1}: 3368, 2966, 2931, 2884, 1643, 1377, 1077, 1044. CD (MeOH): $\Delta\varepsilon$ (nm): +1.39 (223), +1.08 (244), −0.83 (292), −0.03 (328) (c=4.25×10^{-3} M). ^{1}H- and ^{13}C-NMR: see Table 1. Negative-ion HR-FAB-MS: *m/z* 387.2028 $[M-H]^-$ (Calcd for $C_{19}H_{31}O_8$: 387.2019).

Excoecarioside B (**4**): Syrup, $[\alpha]_D^{25}$ +29.3° (c=0.82, MeOH). IR ν_{max} (film) cm^{-1}: 3372, 2965, 2931, 2878, 1650, 1077, 1041. CD (MeOH): $\Delta\varepsilon$ (nm): +7.53 (234), −0.61 (328) (c=5.18×10^{-4} M). ^{1}H- and ^{13}C-NMR: see Table 1. Negative-ion HR-FAB-MS: *m/z* 383.1729 $[M-H]^-$ (Calcd for $C_{19}H_{27}O_8$: 383.1706).

Glochidionionoside B (**6**): Amorphous powder, $[\alpha]_D^{25}$ +7.5° (c=0.53, MeOH). IR ν_{max} (film) cm^{-1}: 3367, 2962, 2931, 2877, 1649, 1371, 1076, 1044. CD (MeOH): $\Delta\varepsilon$ (nm): +0.77 (218), +1.32 (242), −0.24 (290), +0.07 (328) (c=1.30×10^{-4} M). ^{1}H- and ^{13}C-NMR: see ref. 5. Negative-ion HR-FAB-MS: *m/z* 387.2061 $[M-H]^-$ (Calcd for $C_{19}H_{31}O_8$: 387.2019).

Enzymatic Hydrolysis of Excoecarioside A (3) Excoecarioside A (**3**) (12.6 mg) was hydrolyzed with β-glucosidase (20 mg) in 2 ml of H_2O at 37 °C for 30 h. The reaction mixture was concentrated and then subjected to silica gel CC eluting with $CHCl_3$ (50 ml), $CHCl_3$–MeOH (19 : 1, 100 ml; 9 : 1, 100 ml; 17 : 3, 100 ml; and 7 : 3, 100 ml) to give an aglycone, **3a** (2.7 mg) and D-glucose (3.2 mg). D-Glucose: $[\alpha]_D^{25}$+50.8° (c=0.32, H_2O, 24 h after being dissolved in H_2O).

Excoecariol A (**3a**): Colorless syrup, $[\alpha]_D^{25}$ −14.8° (c=0.27, MeOH). IR ν_{max} (film) cm^{-1}: 3420, 2965, 2930, 2871, 1658, 1378, 1122, 1019. ^{1}H-NMR (CD_3OD) δ: 0.97 (3H, s, Me-12), 1.06 (3H, d, J=6.1 Hz, Me-10), 1.42 (1H, m, H-8a), 1.52 (1H, m, H-8b), 1.55 (1H, m, H-7a), 1.64 (1H, m, H-7b), 1.94 (3H, s, Me-13), 2.09 (1H, d, J=17.8 Hz, H-2a), 2.15 (1H, t, J=4.9 Hz, H-6), 2.22 (1H, d, J=17.8 Hz, H-2b), 3.20 (2H, m, 2H-11), 3.60 (1H, q, J=6.1 Hz, H-9), 5.72 (1H, s, H-4). ^{13}C-NMR (CD_3OD) δ: 22.1 (C-12), 23.5 (C-13), 24.6 (C-10), 26.8 (C-7), 39.6 (C-8), 42.2 (C-1), 44.1 (C-2), 46.4 (C-6), 68.6 (C-9), 69.4 (C-11), 125.9 (C-4), 169.0 (C-5), 201.6 (C-3). Negative-ion HR-FAB-MS: *m/z* 225.1469 $[M-H]^-$ (Calcd for $C_{13}H_{21}O_3$: 225.1491).

Preparation of (*R*)- and (*S*)-MTPA Esters (3b, c) from Excoecarinol A (3a) A solution of **3** (2.0 mg) in 1 ml of dehydrated CH_2Cl_2 was reacted with (*R*)-MTPA (50 mg) in the presence of EDC (28.8 mg) and 4-DMAP (31.5 mg) and the resulting mixture was occasionally stirred at 25 °C for 24 h. After the addition of 1 ml of each of H_2O and CH_2Cl_2, the solution was washed successively with 5% HCl, $NaHCO_3$-saturated H_2O and brine. The organic layer was dried over Na_2SO_4 and then evaporated under reduced pressure. The residue was purified by silica gel CC ($CHCl_3$ and $CHCl_3$–$(CH_3)_2CO$, 19 : 1) to give the ester, **3b** (2.0 mg). Using a similar procedure, **3c** (1.0 mg) was prepared from **3a** (0.91 mg) with (*S*)-MTPA (25.3 mg), EDC (23.2 mg), and 4-DMAP (12.2 mg).

Excoecariol A (*R*)-MTPA Ester (**3b**): Amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, Me-12), 1.32 (3H, d, J=6.3 Hz, Me-10), 1.46—1.70 (4H, m, 2H-7, 2H-8), 2.02 (1H, d, J=17.3 Hz, H-2a), 2.09 (1H, m, H-6), 2.10 (3H, s, Me-13), 2.20 (1H, d, J=17.3 Hz, H-2b), 3.42—3.53 (2H, m, 2H-11), 3.47 (3H, s, –OMe), 3.50 (3H, s, –OMe), 5.08 (1H, m, H-9), 5.74 (1H, br s, H-4), 7.19—7.48 (10H, m, aromatic protons). Positive-ion HR-FAB-MS: *m/z* 681.2302 $[M+Na]^+$ (Calcd for $C_{33}H_{36}O_7F_6Na$: 681.2263).

Excoecariol A (S)-MTPA Ester (**3c**): Amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s, Me-12), 1.26 (3H, d, J=6.4 Hz, Me-10), 1.53—1.77 (4H, m, 2H-7, 2H-8), 2.14 (1H, d, J=17.6 Hz, H-2a), 2.16 (1H, m, H-6), 2.17 (3H, s, Me-13), 2.26 (1H, d, J=17.6 Hz, H-2b), 3.42 (6H, s, –OMe×2), 3.49 (1H, d, J=8.0, 2.0 Hz, H-11a), 3.55 (1H, d, J=8.0 Hz, H-11b), 5.08 (1H, qui, J=6.4 Hz, H-9), 5.78 (1H, br s, H-4), 7.19—7.45 (10H, m, aromatic protons). Positive-ion HR-FAB-MS: *m/z* 681.2288 $[M+Na]^+$ (Calcd for $C_{33}H_{36}O_7F_6Na$: 681.2263).

Enzymatic Hydrolysis of Excoecarioside B (4) Excoecarioside B (**4**) (20 mg) was hydrolyzed with β-glucosidase (24 mg) in 2 ml of H_2O at 37 °C for 30 h. The reaction mixture was concentrated and then workup in a similar manner to that for **3a** gave an aglycone, **4a** (3.1 mg) and D-glucose (3.7 mg). D-Glucose: $[\alpha]_D^{25}$+49.3° (c=0.37, H_2O, 24 h after being dissolved in H_2O).

Excoecariol B (**4a**): Colorless syrup, $[\alpha]_D^{25}$ +48.4° (c=0.31, MeOH). IR ν_{max} (film) cm^{-1}: 3367, 2966, 2931, 2875, 1656, 1070. ^{1}H-NMR (CD_3OD) δ: 0.91 (3H, s, Me-11), 0.95 (3H, s, Me-12), 1.14 (3H, d, J=6.4 Hz, Me-10), 2.09 (1H, d, J=16.8 Hz, H-2a), 2.40 (1H, d, J=16.8 Hz, H-2b), 4.08 (1H, dd, J=18.6, 1.7 Hz, H-13a), 4.20 (1H, m, H-9), 4.23 (1H, d, J=18.6, 1.7 Hz, H-13b), 5.70 (1H, d, J=3.4 Hz, H-8), 5.71 (1H, s, H-7), 6.07 (1H, s, H-4). ^{13}C-NMR (CD_3OD) δ: 23.4 (C-12), 23.8 (C-10), 42.8 (C-1), 50.7 (C-2), 61.4 (C-13), 68.7 (C-9), 79.3 (C-6), 123.1 (C-4), 130.3 (C-7), 136.9 (C-8), 166.8 (C-5), 201.5 (C-3). Negative-ion HR-FAB-MS: *m/z* 221.1201 $[M-H]^-$ (Calcd for $C_{13}H_{17}O_3$: 221.1178).

Enzymatic Hydrolysis of 6 Compound **6** (5.8 mg) was hydrolyzed with β-glucosidase (15 mg) in 2 ml of H_2O at 37 °C for 30 h. The usual workup gave an aglycone, **6a** (3.5 mg) and D-glucose (2.2 mg). D-Glucose: $[\alpha]_D^{25}$ +40.8° (c=0.22, H_2O, 24 h after being dissolved in H_2O). The ^{1}H-NMR (CD_3OD) of **6a** was compatible with that of glochidionionol B.[5]

Preparation of (*R*)- and (*S*)-MTPA Esters (6b, c) from 6a Usual esterification procedure gave **6b** (2.8 mg) from **6a** (1.7 mg), (*R*)-MTPA (37.3 mg), EDC (36.6 mg), and 4-DMAP (19.2 mg), and **6c** (1.6 mg) from **6a** (1.8 mg), (*S*)-MTPA (54.8 mg), EDC (36.6 mg), and 4-DMAP (15.9 mg). The ^{1}H- and ^{13}C-NMR ($CDCl_3$) of **6b**, **c** were compatible with those of (*R*)-MTPA and (*S*)-MTPA esters of glochidionionol B.[5]

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