New Sesqui-neolignan from the Pericarps of *Illicium macranthum*

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A new triphenyl lignan, macranthol, was isolated from the pericarps of *Illicium macranthum* (Illiciaceae), a Chinese *Illicium* plant. The structure was deduced to be a trimer of C_6–C_3 units by the extensive application of two dimensional nuclear magnetic resonance spectroscopy, and by comparison with the structures of neolignan, honokiol and magnolol, which were isolated from Magnoliaceae plants.

Keywords *Illicium macranthum*; triphenyl neolignan; sesqui-neolignan; honokiol

As a continuation of our work on the toxic sesquiterpenes of *Illicium plants*,[1-4] we have isolated a new triphenyl lignan from the pericarps of *Illicium macranthum*, which is mainly distributed in the southern part of China and is regarded as toxic, though no toxic compound has been detected so far.

The crushed pericarps of *Illicium macranthum* collected in Yunnan were extracted with hot methanol the extract was dissolved in water, then partitioned between EtOAc and water. The EtOAc-soluble part was dissolved in *n*-hexane–EtOAc (2:1), and separated into the soluble and insoluble parts. Although sesquiterpene lactones were not detected in the insoluble part, a spot with strong ultraviolet (UV) absorption was seen on thin layer chromatography (TLC) of the soluble part. Repeated silica gel column chromatography of the soluble part yielded colorless crystals; this product was named macranthol (**1**).

Macranthol (**1**), $C_{27}H_{26}O_3$ (*m/z* 398), was positive to the $FeCl_3$ test and gave the tri-*O*-methoxy (**2**) (*m/z* 440) or tri-*O*-acetyl (**3**) (*m/z* 524) derivative on treatment with dimethyl sulfate–95% EtOH or dimethylaminopyridine (DMAP)–Ac_2O–pyridine, respectively. These results indicate that **1** has three phenolic hydroxy groups in the molecule.

In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum (see Table I) and the proton–proton two dimensional correlation spectroscopy (^{1}H–^{1}H 2D COSY) spectrum of **1**, three groups of aromatic ring (rings A, B and C) proton signals were seen, of which two were due to 1,3,4 trisubstituted rings and one to a 1,2,3,5 tetra-substituted ring. Three groups of α-propylene proton signals (groups A, B and C) were also seen. When compound **1** was hydrogenated over 5% palladium–carbon, it afforded a hexahydrogenated compound (**4**) (*m/z* 404), which supported the existence of the α-propylene moieties. These facts indicated that the three aromatic rings are linked linearly.

The linkages of the α-propylene groups to the benzene rings were deduced from the nuclear Overhauser effect (NOE) differential experiments. When the benzylmethylene proton signal (δ3.53) of group A was irradiated, the aromatic proton signal at δ 7.30, which was coupled only with the proton at the *meta* position, was enhanced by 7%. Moreover, the allyl groups B and C have protons on both of the *ortho* sides because the signals at δ 7.05, 7.06 on ring B and at δ 7.10, 7.15 on ring C were enhanced by 10% upon irradiation at the benzylmethylene proton signals of groups B and C, respectively.

These results suggested that **1** is a trimer of allylphenol (sesquilignan). Dimers of allylphenol (biphenyl neolignans) are already known: for example, magnolol and honokiol, which were obtained from the Magnoliaceae plants.[5]

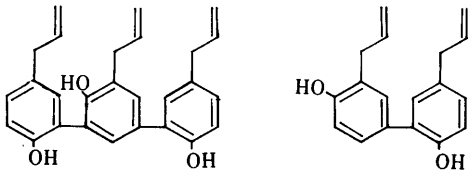
All correlations for the proton and carbon-13 signals were unambiguously assigned in the 2D ^{1}H–^{13}C COSY spectrum of **1**, and the other quaternary carbon signals were also assigned in the 2D long-range ^{1}H–^{13}C COSY spectrum of **1**, as shown in Fig. 2. Thus, it was concluded that both of the benzene rings B and C have 1-phenyl, 2-hydroxy, and 5-propylene substituents. The structure of ring A, in the middle of the molecule, was considered to involve 1,5-diphenyl, 3-allyl and 2- or 4-hydroxy substitutions, based on analysis of the aromatic proton signals and the 2D long-range ^{1}H–^{13}C COSY spectrum of **1**. The position of the hydroxy group on the aromatic ring A was deduced as 4 from the NOE experiment as mentioned above, and by comparison with the ^{13}C-NMR spectral data of honokiol and magnolol.[6]

The assignments of the ^{1}H- and ^{13}C-NMR signals of the aromatic rings B and/or C were also supported by a

TABLE I. The ^{1}H-NMR Chemical Shifts of Macranthol (**1**)[a,b]

Proton No.		Proton No.		Proton No.	
2	73.0 (1H, d, J=2.2 Hz)	2′	—	2″	—
3	—	3′	6.89 (1H, d, J=9.2 Hz)	3″	6.96 (1H, d, J=8.1 Hz)
4	—	4′	7.05 (1H, dd, J=9.2, 2.2 Hz)	4″	7.15 (1H, dd, J=8.1, 2.2 Hz)
6	7.26 (1H, d, J=2.2 Hz)	6′	7.06 (1H, d, J=2.2 Hz)	6″	7.10 (1H, d, J=2.2 Hz)
7	3.53 (2H, br d, J=6.6 Hz)	7′	3.36 (2H, br d, J=6.6 Hz)	7″	3.35 (2H, br d, J=6.6 Hz)
8	6.07 (1H, ddd, J=17.2, 10.3, 6.6 Hz)	8′	5.95 (1H, ddd, J=16.9, 10.3, 6.6 Hz)	8″	5.97 (1H, ddd, J=16.9, 10.3, 6.6 Hz)
9a	5.20 (1H, dd, J=17.2, 1.5 Hz)	9a′	5.08 (1H, dd, J=16.9, 1.8 Hz)	9a″	5.08 (1H, dd, J=16.9, 1.8 Hz)
9b	5.15 (1H, dd, J=10.3, 1.5 Hz)	9b″	5.05 (1H, dd, J=10.3, 1.8 Hz)	9″	5.06 (1H, dd, J=10.3, 1.8 Hz)

a) Measured at 400 MHz in $CDCl_3$ solution. Chemical shifts are given on the δ (ppm) scale. *b*) Assignments were made on the basis of the ^{1}H–^{1}H COSY spectrum and NOE differential spectra (d, doublet; br, broad).



macranthol honokiol

Fig. 1

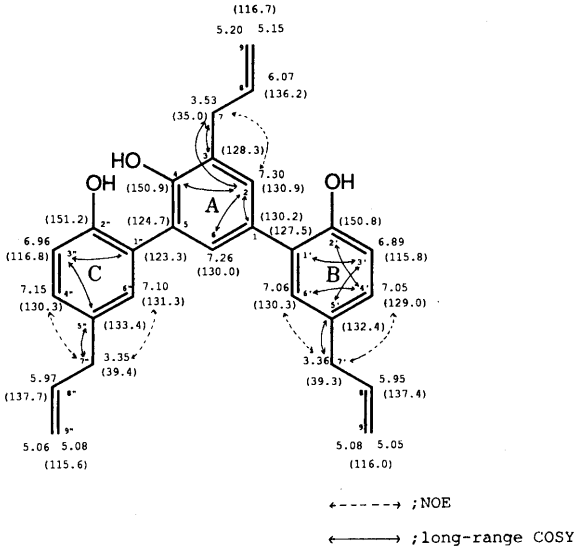


Fig. 2. Assignments of the ^1H- and ^{13}C-NMR (in Parentheses) Signals, and the ^1H–^{13}C Long-Range COSY, and NOE Correlations for Macranthol

comparison with the ^{13}C-NMR spectral data for honokiol. The aromatic rings A and B resemble the structure of honokiol, and the ^{13}C-NMR spectral data for honokiol were similar to those of the benzene rings A and B of compound **1** except for the signal at position 3, which corresponds to positon 5 in the structure of compound **1**.

As expected, macranthol is optically active, although the optical rotation value is very small (+2°), suggesting that the benzene rings are mutually sterically hindered in the molecule of **1**. This compound is considered to be one of the sesquineolignans.

Experimental

The melting point was determined on a Yanagimoto micro hot stage and is uncorrected. Optical rotation was measured with a JASCO DIP-181 polarimeter. The infrared (IR) spectrum was taken on a JASCO IR-810 spectrometer. NMR spectra were recorded on JEOL FX-90Q and GX-400 instruments using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were taken on a JEOL JMS-DX-303 spectrometer. UV absorption maxima were measured on a Hitachi 323 spectrometer. Merck silica gel 60 (particle size 0.063—0.200 nm) was used for column chromatography.

Extraction and Separation The pericarps (1.8 kg) of *Illicium macranthum* were collected at Yunnan in China. Dried material was crushed and extracted with hot MeOH. The extract was concentrated to dryness and the residue was suspended in H_2O, then extracted with *n*-hexane, EtOAc, and 1-BuOH, successively. The EtOAc extract (49.5 g) was extracted with *n*-hexane–EtOAc (2 : 1) at room temperature, and the soluble part was chromatographed repeatedly on a silica gel column with the solvent system of $CHCl_3$–MeOH (95 : 5). Macranthol was obtained as colorless needles (217 mg) from *n*-hexane–EtOAc (9 : 1).

Macranthol (**1**): Colorless needles, mp 140—141 °C, $[\alpha]_D^{18}$ +2° (c=0.31, EtOH). EI-MS m/z: 398. *Anal.* Calcd for $C_{27}H_{26}O_3$: C, 81.38; H, 6.58. Found: C, 81.23; H, 6.66. IR (KBr): 3210 (OH), 1640, 1608 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 222 (4.72×10^4), 181 sh (2.46×10^4), 197 (1.36×10^4).

Methylation of 1 Dimethyl sulfate (0.3 ml) was added to a solution of **1** (20 mg) in 95% EtOH, then alkalized with 4 N NaOH, and stirred for 3 h at room temperature. The reaction mixture was acidified with 2N HCl, and extracted with Et_2O. The Et_2O extract was washed with water and dried over anhydrous Na_2SO_4, then evaporated to dryness. The residue was subjected to column chromatography on silica gel (*n*-hexane–$CHCl_3$) to give trimethoxymacranthol (**2**), as an oily compound (5 mg). A colorless oil, EI-MS m/z: 440 (M^+), δ ($CDCl_3$, 90 MHz)$_{ppm}$; 3.39, 3.77, 3.78 (each 3H, s), 3.35 (4H, br d, J=6.8 Hz), 3.55 (2H, br d, J=6.6 Hz), 4.90—5.22 (6H, m), 5.71—6.29 (3H, m), 6.80—7.37 (8H, m).

Acetylation of 1 A solution of **1** (10 mg) in pyridine (1 ml), 4-(dimethylamino)pyridine (2 mg), and Ac_2O (1 ml) was stirred for 5 h at room temperature. The reaction mixture was evaporated, and chromatographed on silica gel to give the triacetate (**3**) (11 mg). A colorless oil. EI-MS m/z: 524 (M^+), δ ($CDCl_3$, 90 MHz)$_{ppm}$; 2.07 (6H, s), 2.10 (3H, s), 3.37—3.42 (6H, m), 4.90—5.21 (6H, m), 5.70—6.18 (3H, m), 6.85—7.38 (8H, m).

Catalytic Hydrogenation of 1 A solution of **1** (52 mg) in EtOH (10 ml) containing Pd–black (6 mg) was stirred under an H_2 atmosphere at room temperature for 7 h. The reaction mixture was filtered. The filtrate was evaporated *in vacuo*, and the residue was chromatographed on silica gel (*n*-hexane–$CHCl_3$ (1 : 5)) to give the hydrogenated compound (**4**) (51 mg) as a colorless oil. EI-MS m/z: 404 (M^+), δ ($CDCl_3$, 90 MHz)$_{ppm}$; 0.84—1.08 (9H, m), 1.42—1.90 (6H, m), 2.45—2.78 (6H, m), 6.78—7.24 (8H, m).

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