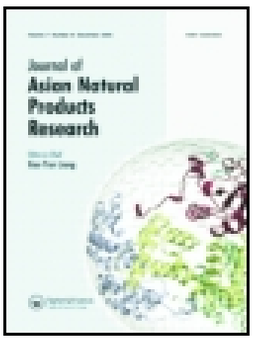

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Three new indole alkaloid derivatives from the roots of *Murraya paniculata*

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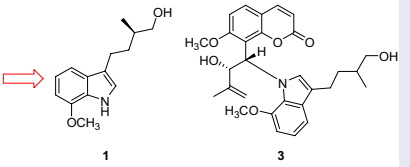
ABSTRACT

Three new indole alkaloid derivatives, named paniculidines D–F (**1**–**3**), and six known analogs (**4**–**9**) were isolated from the roots of *Murraya paniculata*. The structures were elucidated on the basis of comprehensive HRESIMS, UV, IR, and NMR spectroscopic data analysis and comparison with the data reported in literature. The absolute configurations of new compounds were assigned via the determination of specific optical rotation, Mosher's method, and ECD spectra. Compound **3** is the first heterodimer of C-N linked indole and coumarin derivatives.



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Rutaceae; *Murraya paniculata*; indole alkaloids; heterodimer

1. Introduction

The *Murraya* genus belongs to the Rutaceae family, including 14 species and 2 varieties all over the world. *Murraya paniculata* (L.) Jack, is a shrub distributed widely in India, Southeast Asia, and South China. The roots of *M. paniculata* have been used as a folk medicine for the treatment of gout, contusion, and bone ache [1]. Previous phytochemical investigations revealed that many bioactive compounds, such as indole alkaloids [1,2], coumarins [3–5], and flavonoids [6–8], were isolated from *M. paniculata*, with the activities of anti-inflammatory, anti-implantation, antidiarrhoeal, anti-diabetic, antioxidant, antinociceptive, antimicrobial, and anticancer effects [9–11].

Indole alkaloid derivatives are a type of very important heterocyclic compounds for the drug discovery and cell biology study. There has been an increasing interest in using the indole alkaloid derivatives as bioactive molecules against inflammation, microbes, cancer,

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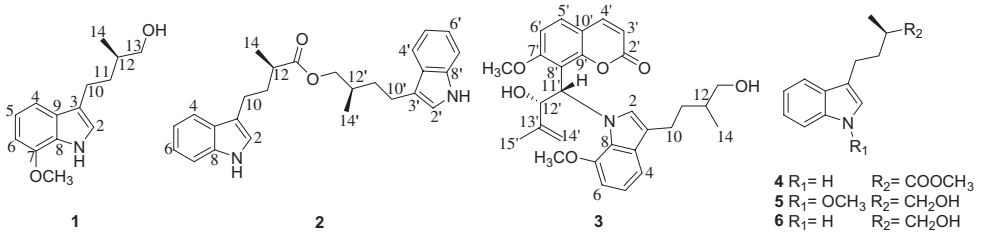

Figure 1. The structures of compounds **1–6**.

and various kinds of disorders in the human body [12]. As a continuation of a search for indole analogs from *Murraya* species, we report here the isolation and structural elucidation of three new indole alkaloids (**1**–**3**) and six known analogs (**4**–**9**) from the roots of *M. paniculata* (Figure 1).

2. Results and discussion

The 95% aqueous EtOH extract of the roots of *M. paniculata* was suspended in H_2O and partitioned successively with petroleum ether and $CHCl_3$. The $CHCl_3$-soluble portion was subjected repeatedly to silica gel and Sephadex LH-20 column chromatography (CC) followed by semipreparative RP-HPLC to afford three new indole alkaloid derivatives, named paniculidines D–F (**1**–**3**), and six known analogs, including paniculidines A–C (**4**–**6**) [1], tanakine (**7**) [13], indol-3-carbaldehyde (**8**) [14], and yuehchukene (**9**) [15].

Paniculidine D (**1**) was obtained as a light brown oil, with $[\alpha]_D^{23}$ + 36.0 (*c* 0.10, MeOH). Its molecular formula was determined as $C_{14}H_{19}NO_2$ on the basis of a protonated ion at *m*/*z* 234.1495 $[M + H]^+$ in the positive HRESIMS and the ^{13}C NMR data. The UV spectrum showed a maximal absorption at 271 nm and the IR spectrum showed absorption bands for aromatic ring (1601, 1499, and 1452 cm^{-1}) functionality. The ^1H NMR data (Table 1) revealed the presence of a 3,7-disubstituted indole unit [δ_H 6.95 (1H, brs), 7.22 (1H, d, *J* = 7.8 Hz), 7.03 (1H, t, *J* = 7.8 Hz), 6.65 (1H, d, *J* = 7.8 Hz)], three methylene signals [δ_H 2.71–2.77, 2.81–2.87 (each 1H, m); 1.50–1.58, 1.82–1.89 (each 1H, m); 3.49 (1H, dd, *J* = 10.5, 6.5 Hz), 3.57 (1H, dd, *J* = 10.5, 5.7 Hz)], one methine signal [δ_H 1.70–1.77 (1H, m)], and one methyl signal [δ_H 1.02 (3H, d, *J* = 6.7 Hz)]. The NMR spectroscopic data of **1** were similar to those of paniculidine B (**5**) [1]. The main difference between these two compounds is the methoxy group in **5** shifts from the nitrogen atom to the C-7 position of the indole unit in **1**, deduced from the HMBC correlations between H-5 and C-7/C-9, H-6 and C-4/C-5/C-7/C-8, and OCH_3-7 and C-7 (Figure 2). The sign of the specific optical rotation of **1** is the same as that of **5**, whose configuration is 12*R*. Therefore, the structure of paniculidine D (**1**) was established as (2*R*)-methyl-4-(7′-methoxy-indole-3′-yl)-1-butanol.

Paniculidine E (**2**) was obtained as a light brown oil, with $[\alpha]_D^{23}$ + 22.5 (*c* 0.08, MeOH). Its positive mode HRESIMS showed a pseudomolecular ion at *m*/*z* 403.2377 $[M + H]^+$, which, in conjunction with the ^{13}C NMR data, established a molecular formula of $C_{26}H_{30}N_2O_2$. The ^1H NMR data (Table 1) revealed the presence of two 3-substituted indole units [δ_H 7.81 (1H, brs), 6.91 (1H, brs), 7.59 (1H, d, *J* = 7.8 Hz), 7.10 (1H, overlapped), 7.19 (1H, overlapped), 7.33 (1H, d, *J* = 8.1 Hz); 7.83 (1H, brs), 6.92 (1H, brs), 7.60 (1H, d, *J* = 7.8 Hz), 7.10 (1H, overlapped), 7.19 (1H, overlapped), 7.34 (1H, d, *J* = 8.1 Hz)], and two isopentenyl derivative

Table 1. ^{1}H and ^{13}C NMR spectral data of **1–3** (^{1}H: 500 MHz and ^{13}C: 125 MHz, in $CDCl_3$).

	1		**2**		**3**	
Position	δ_H (*J*, Hz)	δ_C	δ_H (*J*, Hz)	δ_C	δ_H (*J*, Hz)	δ_C
2	6.95, brs	120.7	6.91, brs	121.2	7.50, brs	124.4
3		117.3		116.0		117.2
4	7.22, d (7.8)	111.8	7.59, d (7.8)	119.0	7.13, d (7.9)	111.8
5	7.03, t (7.8)	119.6	7.10, overlapped	119.3	6.98, t (7.9)	119.5
6	6.65, d (7.8)	101.9	7.19, overlapped	122.1	6.69, d (7.9)	103.6
7		146.3	7.33, d (8.1)	111.2		147.7
8		126.9		136.5		127.8
9		128.9		127.6		129.9
10	2.81–2.87, m; 2.71–2.77, m	22.8	2.76–2.79, m	22.6	2.73–2.81, m; 2.63–2.71, m	22.8
11	1.82–1.89, m; 1.50–1.58, m	33.7	2.08–2.15, m; 1.79–1.88, m	34.3	1.76–1.85, m; 1.47–1.54, m	33.4
12	1.70–1.77, m	35.7	2.52–2.59, m	39.5	1.67–1.74, m	35.8
13	3.57, dd (10.5,5.7); 3.49, dd (10.5,6.5)	68.4		177.0	3.51–3.55, m; 3.43–3.49, m	68.4
14	1.02, d (6.7)	16.7	1.22, d (6.9)	17.4	0.98, d (6.7)	16.8
2′			6.92, brs	121.5		160.3
3′				116.7	6.22, d (9.5)	113.4
4′			7.60, d (7.8)	119.1	7.57, d (9.5)	143.8
5′			7.10, overlapped	119.3	7.34, d (8.7)	129.1
6′			7.19, overlapped	122.1	6.82, d (8.7)	108.3
7′			7.34, d (8.1)	111.2		161.0
8′				136.5		115.8
9′				127.6		153.7
10′			2.81–2.88, m; 2.76–2.79, m	23.0		113.4
11′			1.79–1.88, m; 1.58–1.64, m	32.6	7.41, d (10.0)	55.6
12′			1.88–1.95, m	33.9	5.47, d (10.0)	77.1
13′			3.97–4.04, m	69.2		144.3
14′			1.04, d (6.5)	17.0	4.93, s; 4.71, s	114.5
15′					1.78, s	16.8
OCH_3-7					4.07, s	55.9
OCH_3-7′					3.94, s	56.2
NH-1	8.18, brs		7.81, brs			
NH-1′			7.83, brs			

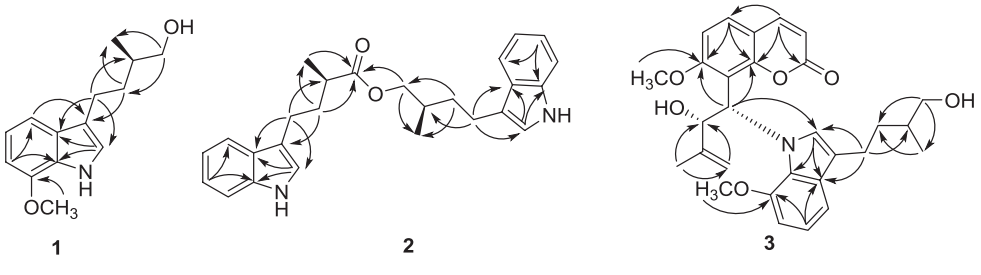

Figure 2. The key HMBC correlations of compounds **1–3**.

groups [δ_H 2.76–2.79 (2H, m), 1.79–1.88, 2.08–2.15 (each 1H, m), 2.52–2.59 (1H, m), 1.22 (3H, d, *J* = 6.9 Hz); 2.76–2.79, 2.81–2.88 (each 1H, m), 1.58–1.64, 1.79–1.88 (each 1H, m), 1.88–1.95 (1H, m), 3.97–4.04 (2H, m), 1.04 (3H, d, *J* = 6.5 Hz)]. These data, along with 26 carbon resonances in the ^{13}C NMR spectrum, suggested **2** to be a dimeric indole alkaloid composed of one 2-methyl-4-(3-indolyl)-butyric acid and one paniculidine C (**6**) units [1].

These two units were linked by an ester bond on the basis of the HMBC correlations of H-13′ and C-13/C-11′/C-12′/C-14′. The absolute configuration of **2** was deduced as (12*R*, 12′*R*) via alkaline hydrolysis and comparison of the specific optical rotation with those in literature [1]. Thus, the structure of paniculidine E (**2**) was elucidated as shown.

Paniculidine F (**3**) was obtained as a light yellow oil. Its molecular formula was assigned as $C_{29}H_{33}NO_6$ based on the ^{13}C NMR spectroscopic data and a pseudomolecular ion at *m*/*z* 492.2379 $[M + H]^+$ was observed in the positive mode HRESIMS. The ^1H NMR data (Table 1) indicated the presence of a 7-methoxy-8-isopentenyl coumarin moiety similar to auraptenol [16] [δ_H 6.22 (1H, d, *J* = 9.5 Hz), 7.57 (1H, d, *J* = 9.5 Hz), 6.82 (1H, d, *J* = 8.7 Hz), 7.34 (1H, d, *J* = 8.7 Hz), 3.94 (3H, s)], and an indole unit similar to compound **1** [δ_H 6.69 (1H, d, *J* = 7.9 Hz), 6.98 (1H, t, *J* = 7.9 Hz), 7.13 (1H, d, *J* = 7.9 Hz), 7.50 (1H, brs)]. These two units were linked through N-C-11′ deduced from the HMBC correlations of H-11′ and C-2/C-8/C-7′/C-8′/C-9′/C-12′.

The coupling constant between H-11′ and H-12′ (*J* = 10.0 Hz) indicated that **3** is a *threo* isomer. The absolute configuration of C-12′ was determined as *S* by the Mosher's method (Figure 3), and the absolute configuration of C-11′ was deduced as *S*. Moreover, the ECD spectrum of **3** was calculated using the TDDFT method at the B3LYP/6-31G(d) level, which is a powerful tool and widely used for the determination of absolute configuration of natural products [17]. The calculated ECD spectrum of (11′*S*,12′*S*)-**3** agreed well with the experimental one (Figure 4). Therefore, the absolute configuration of **3** was assigned as (11′*S*,12′*S*), and the structure of paniculidine F (**3**) was elucidated as shown.

The roots of *M. paniculata* have been used as a folk medicine for the treatment of inflammation-related diseases. Thus, in our study, all the isolates were tested for their inhibition activities on NO production stimulated by lipopolysaccharide in BV-2 microglial cells. However, these compounds showed no inhibitory effect at the concentration of 100 μM.

3. Experimental

3.1. General experimental procedures

Specific optical rotation data were acquired on a Rudolph Autopol III automatic polarimeter (Rudolph Research, Fairfield, New jersey, U.S.A.). UV spectra were recorded on a Shimadzu UV-2450 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). IR spectra

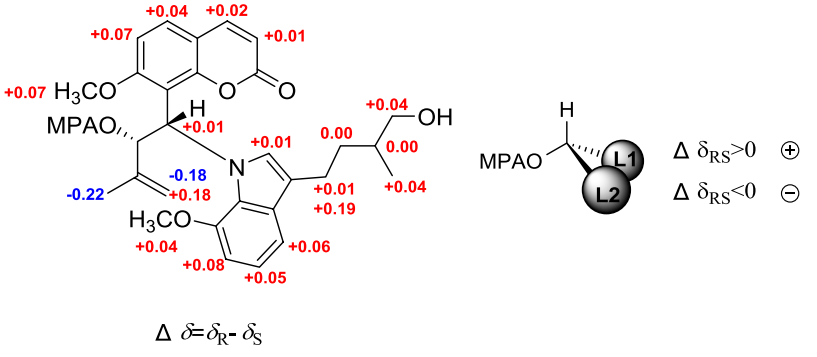

Figure 3. $\Delta\delta = \delta_R - \delta_S$ values obtained from the ^1H NMR spectra of the MPA esters of **3**.

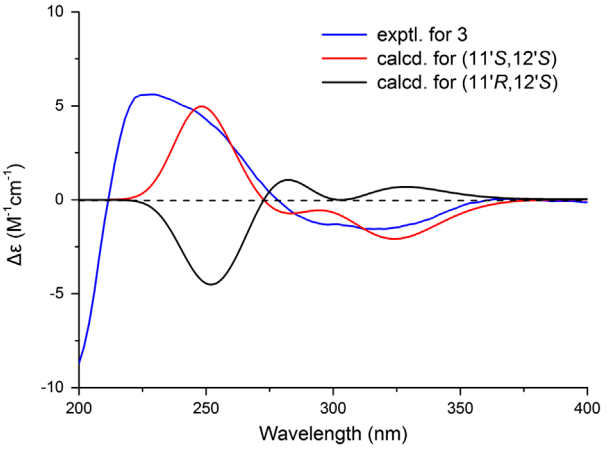

Figure 4. Calculated and experimental ECD spectra of **3**.

were recorded on a Thermo Nicolet Nexus 470 FT-IR spectrometer (Thermo Nicolet, Vernon Hills, Illinois, U.S.A.). ECD data were acquired on a JASCO 810 CD spectrophotometer (Jasco Corporation, Tokyo, Japan). NMR spectra were recorded on a Varian INOVA-500 NMR spectrometer (Agilent Technologies, Santa Clara, California, U.S.A.), using $CDCl_3$ as solvent and the chemical shifts were referenced to the solvent residual peak. HRESIMS experiments were measured on a Waters Xevo G2 Q-TOF mass spectrometer (Waters MS Technologies, Manchester, UK). Silica gel (100–200 mesh or 200–300 mesh, Qingdao Marine Chemical Co. Ltd., China) and Sephadex LH-20 (Amersham Biosciences, Sweden) were used for open CC. Preparative HPLC were carried out using a Agilent Zorbax Eclipse XDB-C_{18} column (9.4 × 250 mm, 5 μm) on an Agilent 1260 system (Agilent Technologies Inc., Santa Clara, California, U.S.A.) with a DAD detector. Fractions and compounds were monitored at 210 nm and 330 nm. TLC analyses were carried out on the pre-coated silica gel GF_{254} plates (Qingdao Marine Chemical Co. Ltd., China). Spots were visualized under the UV lights (254 and 365 nm). All the solvents used for isolation were of analytical grade and the solvents used for HPLC were of HPLC grade.

3.2. Plant material

The roots of *Murraya paniculata* were collected from Lihu Township, Guangxi Province, China, in June 2015, and were identified by Prof. Peng-Fei Tu. A voucher specimen (No. MP201506) has been deposited at the Herbarium of the Peking University Modern Research Center for Traditional Chinese Medicine.

3.3. Extraction and isolation

The roots of *M. paniculata* (9.3 kg) were extracted three times with 95% aqueous EtOH at room temperature. The extract was evaporated under reduced pressure, and the residue (500 g) was suspended in H_2O and partitioned successively with petroleum ether and $CHCl_3$. The $CHCl_3$ extract (150 g) was subjected to silica gel CC and eluted with a stepwise gradient of petroleum ether–EtOAc (7:3, 3:2, 2:3, 1:4, and 0:1, v/v) to afford nine fractions (A–I).

Fraction A (10 g) was separated on silica gel CC eluting with petroleum ether–acetone (10:1, 4:1, v/v) to afford six subfractions (A1–A6). Subfractions A4 (2 g) and A5 (2 g) were further chromatographed over Sephadex LH-20 eluting with CH_2Cl_2–MeOH (1:1, v/v) to afford Frs. A4-5 (0.3 g) and A5-4 (0.5 g), respectively, which were further purified by semipreparative RP-HPLC using a mobile phase of MeCN–H_2O (70:30, v/v, 2 ml/min) to give **9** (7 mg, t_R 35.6 min) and **2** (5 mg, t_R 17.9 min), respectively. Fraction B (15 g) was separated on silica gel CC eluting with petroleum ether–acetone (4:1, v/v) to afford six fractions (B1–B6). Subfraction B1 (3 g) was further chromatographed over Sephadex LH-20 (CH_2Cl_2–MeOH, 1:1, v/v) and ODS (MeOH–H_2O, 7:3, v/v) to afford Fr. B1-5-31 (0.6 g), which was further purified by semipreparative RP-HPLC using a mobile phase of MeCN–H_2O (70:30, v/v, 2 ml/min) to give **4** (28 mg, t_R 31.3 min) and **5** (21 mg, t_R 24.4 min). Fraction C (18 g) was separated on silica gel CC (CH_2Cl_2–acetone, 1:0–100:1, v/v) to afford four fractions (C1–C4). Subfraction C3 (5 g) was chromatographed successively on silica gel (petroleum ether–acetone, 3:1, v/v) and Sephadex LH-20 (CH_2Cl_2–MeOH, 1:1, v/v) CC to afford Fr. C3-2-5 (2 g), which was further purified by semipreparative RP-HPLC using a mobile phase of MeCN–H_2O (35:65, v/v, 2 ml/min) to give **1** (11 mg, t_R 39.0 min) and **6** (13 mg, t_R 34.5 min). Fraction D (30 g) was separated on silica gel (petroleum ether–acetone, 7:3, v/v) and Sephadex LH-20 (CH_2Cl_2–MeOH, 1:1, v/v) CC to afford Fr. D3-4-1 (1 g), which was further separated by preparative TLC (petroleum ether–acetone, 3:2, v/v) to give **7** (3 mg) and **8** (3 mg). Fraction E (30 g) was separated on silica gel (petroleum ether–acetone, 3:2, v/v) and Sephadex LH-20 (CH_2Cl_2–MeOH, 1:1, v/v) CC to afford Fr. E4-3-3 (2 g), which was further purified by semipreparative RP-HPLC using a mobile phase of MeCN–H_2O (40:60, v/v, 3 ml/min) to give **3** (3 mg, t_R 60.5 min).

3.3.1. Paniculidine D (1)

Light brown oil, $[\alpha]_D^{23}$ + 36.0 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 222 (4.40), 271 (3.55) nm; IR (KBr) ν_{max} 3399, 2918, 2851, 1713, 1601, 1578, 1499, 1452, 1374, 1259, 1034 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 234.1495 $[M + H]^+$ (calcd for $C_{14}H_{20}NO_2$, 234.1494).

3.3.2. Paniculidine E (2)

Light brown oil, $[\alpha]_D^{23}$ + 22.5 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 203 (4.52), 223 (4.69), 282 (3.96) nm; IR (KBr) ν_{max} 3400, 2918, 2851, 1713, 1604, 1456, 1361, 1222, 1026, 530 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 403.2377 $[M + H]^+$ (calcd for $C_{26}H_{30}N_2O_2$, 403.2386).

3.3.3. Paniculidine F (3)

Light yellow oil, $[\alpha]_D^{23}$ + 17.5 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.68), 299 (4.03), 326 (3.98) nm; IR (KBr) ν_{max} 3445, 2918, 2850, 1735, 1713, 1604, 1363, 1029, 905, 836, 578 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 492.2379 $[M + H]^+$ (calcd for $C_{29}H_{34}NO_6$, 492.2386).

3.4. Determination of absolute configuration of compound 2

Compound **2** (1.3 mg) and K_2CO_3 (2.2 mg) were dissolved in MeOH (2 ml) for 4 h at 80 °C. The reaction product was acidized with 0.1 M HCl and then extracted with CH_2Cl_2 for three

times. After being concentrated to dryness, the organic residue was separated by semipreparative HPLC [1.0 ml/min, MeCN/0.1%HCOOH–H_2O (45:55)] to yield 2-methyl-4-(3-indolyl)-butyric acid (**a**), and paniculidine C (**b**) (each 0.3 mg) at 11.3 min and 12.7 min, respectively. The structures of compounds **a** and **b** were identified by LC-MS (Figure S25, Supporting Information) under the following conditions: an Agilent 1260 chromatograph equipped with an Agilent Zorbax SB-Aq RP C_{18} column (4.6 × 250 mm, 5 μm); column temperature: 35 °C; mobile phase: 0–30 min MeCN/0.1%HCOOH–H_2O (10:90–100:0); flow rate: 1.0 ml/min; UV detection wavelength: 210 nm. The molecular weights of **a** and **b** were *m*/*z* 217 and 203, respectively. The signs of the specific optical rotation of **a** [$[\alpha]_D^{25}$ + 46.7 (*c* 0.03, MeOH)] and **b** [$[\alpha]_D^{25}$ + 53.3 (*c* 0.03, MeOH)] were the same as that of **6**. Hence, the absolute configuration of **2** was deduced as (12*R*, 12′*R*).

3.5. Preparation of the (R)- and (S)-MPA esters of 3

Compound **3** (1.0 mg) was dissolved in 350 μl of CH_2Cl_2, and DCC (0.8 mg), DMAP (0.5 mg), and (*R*)-MPA (0.6 mg) were then added sequentially. The reaction mixture was stirred for 16 h at room temperature. The crude products were separated by semipreparative HPLC [1.0 ml/min, MeCN/H_2O (80:20)] to yield the (*R*)-MPA ester **3*r*** at 6.5 min. In a similar manner, (*S*)-MPA ester **3*s*** was prepared by semipreparative HPLC [1.0 ml/min, MeCN/H_2O (80:20)] at 6.7 min, from the reaction of **3** (1.0 mg) with (*S*)-MPA.

(*R*)-MPA ester (**3*r***): ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.55 (1H, d, *J* = 9.3 Hz, H-4′), 7.46 (1H, d, *J* = 10.2 Hz, H-11′), 7.43 (1H, s, H-2), 7.37 (1H, d, *J* = 8.7 Hz, H-5′), 7.04 (1H, d, *J* = 7.8 Hz, H-4), 6.99 (1H, t, *J* = 7.8 Hz, H-5), 6.86 (1H, d, *J* = 8.7 Hz, H-6′), 6.73 (1H, d, *J* = 7.8 Hz, H-6), 6.22 (1H, d, *J* = 9.3 Hz, H-3′), 4.89 (1H, s, H-14′), 4.64 (1H, s, H-14′), 4.12 (3H, s, OCH_3-7), 4.07 (1H, m, H-13), 3.99 (3H, s, OCH_3-7′), 3.93 (1H, m, H-13), 2.61 (1H, m, H-10), 2.53 (1H, m, H-10), 1.80 (1H, m, H-11), 1.73 (1H, m, H-12), 1.67 (3H, s, H-15′), 1.62 (1H, m, H-11), 0.88 (3H, d, *J* = 6.6 Hz, H-14). (*S*)-MPA ester (**3*s***): ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.53 (1H, d, *J* = 9.6 Hz, H-4′), 7.45 (1H, d, *J* = 10.2 Hz, H-11′), 7.42 (1H, s, H-2), 7.32 (1H, d, *J* = 8.7 Hz, H-5′), 6.98 (1H, d, *J* = 7.7 Hz, H-4), 6.94 (1H, t, *J* = 7.7 Hz, H-5), 6.79 (1H, d, *J* = 8.7 Hz, H-6′), 6.65 (1H, d, *J* = 7.7 Hz, H-6), 6.21 (1H, d, *J* = 9.6 Hz, H-3′), 5.07 (1H, s, H-14′), 4.46 (1H, s, H-14′), 4.08 (3H, s, OCH_3-7), 4.03 (1H, m, H-13), 3.92 (3H, s, OCH_3-7′), 3.99 (1H, m, H-13), 2.60 (1H, m, H-10), 2.34 (1H, m, H-10), 1.80 (1H, m, H-11), 1.73 (1H, m, H-12), 1.62 (1H, m, H-11), 1.45 (3H, s, H-15′), 0.84 (3H, d, *J* = 6.7 Hz, H-14).

Disclosure statement

No potential conflict of interest was reported by the authors.

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