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Three new compounds from the bark of *Antiaris toxicaria*

Xiao-San Li[a,1], Jing-Jing Zhu[a,1], Huan Zhao[a], Shun-Lin Li[b], Xiao-Jiang Hao[b], Xin-Sheng Yao[a], Jin-Shan Tang[a,c,*]

[a] Institute of Traditional Chinese Medicine and Natural Products, College of Pharmacy, Jinan University, Guangzhou 510632, China
[b] State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China
[c] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

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ABSTRACT

Three new compounds, namely (+)-pranferol (**1**), antiarone M (**2**), and anticerol A (**3**), together with 9 known compounds, were obtained from the bark of *Antiaris toxicaria*. Their chemical structures were elucidated on the basis of spectroscopic methods including UV, IR, (HR) ESI–MS, ^{1}H, ^{13}C NMR, HSQC, ^{1}H-^{1}H COSY, HMBC and X-ray crystallographic technique. The absolute configurations of compounds **1** and **2** were determined by modified mosher method and CD spectrum.

1. Introduction

Antiaris toxicaria (Pers.) Lesh. (Moraceae), also known as "upas tree", is widely distributed throughout over tropic rain forest. Previous chemical investigations of this species have revealed that it was rich in cardiac glycosides, especially from its latex (Liu et al., 2013; Que et al., 2010) and seed (Zuo et al., 2013). Apart from the cardiac glycosides, prenylflavanones (Hano et al., 1990a,b; Hano et al., 1991; Que et al., 2009), phenylpropanoid and lignan derivatives (Jiang et al., 2009), and coumarin derivatives (Shi et al., 2014) were other kinds of components discovered from this plant, which exhibited anti-osteoporosis (Jiang et al., 2009) and antibacterial activities (Que et al., 2009).

In our search for anticancer agents from this plant, about 50 cardiac glycosides were isolated from the stem, latex, and bark of *A. toxicaria* by using bioassay and chemical guided fractionation (Jiang et al., 2008; Li et al., 2014; Liu et al., 2013). Herein, we reported the isolation and structural elucidation of three new (**1–3**) (Fig. 1) and 9 known compounds from the bark of *A. toxicaria*.

2. Results and discussion

Compound **1** was obtained as white amorphous powder. The HR–ESI–MS showed quasimolecular ion at *m/z* 289.1079 $[M+H]^+$ (calcd. for 289.1076), indicating the molecular formula of $C_{16}H_{16}O_5$ and accounting for 9 degrees of unsaturation. The IR spectrum of **1** displayed prominent absorption maxima at 3454, 1698, and 1628 cm^{-1}, indicating the presence of hydroxyl group (s), α,β-unsaturated lactone, conjugated carbonyl functionality. The UV absorptions at 204, 219, 249, 265, and 309 nm suggested that it was a coumarin derivative (Scott, 1964). The ^{1}H and ^{13}C NMR signals for **1** were assigned using 1D and 2D NMR experiments (Table 1). The ^{1}H NMR spectrum of **1** showed characteristic signals of psoralen (also known as furocoumarin) (Wulff et al., 1988) for two AB type system protons both at δ 6.31 (1H, d, *J* = 9.8 Hz, H-3), 8.32 (1H, d, *J* = 9.8 Hz, H-4) and δ 7.28 (1H, d, overlap, *J* = 2.5 Hz, H-9), 7.87 (1H, d, *J* = 2.5 Hz, H-10) as well as one aromatic proton at δ 7.28 (1H, s, overlap, H-8). In the ^{1}H-^{1}H COSY spectrum of **1**, successive correlations of protons at δ 4.68 (2H, m, H-1′), 4.06 (1H, m, H-2′), 2.10 (1H, m, H-3′), 1.14 (3H, d, *J* = 6.8 Hz, H-4′), and 1.20 (3H, d, *J* = 6.8 Hz, H-5′) revealed the presence of an 1,2-dioxyisopentyl group in the structure of **1**. Comparison of the ^{1}H and ^{13}C NMR data of **1** with that of (−)-pranferol revealed that they had the same planar structures (Kuznetsova et al., 1966; Shi et al., 2013). Key ^{1}H-^{1}H COSY and HMBC correlations (Fig. 2) together with X-ray Crystallographic analysis confirmed the deduction mentioned above (Fig. 3). Interestingly, the directions of specific rotation for

* Corresponding author. Fax: +86 20 85221559.
E-mail address: gztangjinshan@126.com (J.-S. Tang).
[1] Both authors contributed equally to this work.

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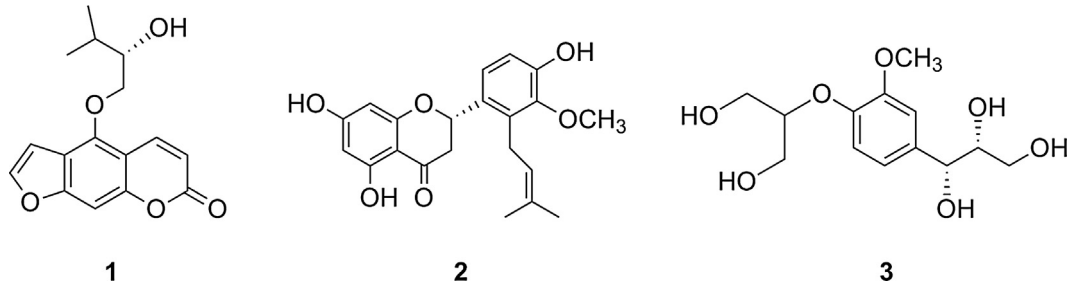

Fig. 1. Chemical structures of compounds 1–3.

Table 1
^{13}C and ^{1}H NMR spectral data of compounds **1–3** (δ in ppm, J in Hz).

No.	**1**[a] (pyridine-d_5)		**2**[a] (pyridine-d_5)		No.	**3**[b] (CH_3OH-d_4)	
	δ_C	δ_H	δ_C	δ_H		δ_C	δ_H
2	161.2	–	77.2	5.87, dd (13.2, 2.7)	1	138.2	–
3	113.2	6.31, d (9.8)	43.5	3.37, dd (17.2, 13.2) 2.93, dd (17.2, 2.7)	2	112.5	7.08, d (2.0)
4	140.1	8.32, d (9.8)	197.3	–	3	151.9	–
4a	107.8	–	103.2	–	4	148.3	–
5	150.9	–	165.6	–	5	118.7	7.06, d (8.0)
6	114.6	–	97.7	6.50, d (2.1)	6	120.7	6.91, dd (8.0, 2.0)
7	158.9	–	169.0	–	7	75.2	4.58, d (6.2)
8	94.4	7.28, s	96.5	6.42, d (2.1)	8	77.6	3.67, m
8a	153.7	–	164.7	–	9	64.4	3.51, m/3.40, m
9	106.2	7.28, d (2.5)			1′	83.2	4.21, m
10	146.0	7.87, d (2.5)			2′	62.2	3.76, m
1′	77.3	4.68, m	129.1	–	3′	62.2	3.76, m
2′	75.1	4.06, m	135.1	–	3-OMe	56.7	3.86, s
3′	32.0	2.10, m	147.5	–			
4′	20.0	1.14, d (6.8)	152.6	–			
5′	18.3	1.20, d (6.8)	116.2	7.25, d (8.5)			
6′			123.8	7.47, d (8.5)			
7′			26.0	3.78, m			
8′			124.7	5.32, t (6.6)			
9′			131.8	–			
10′			26.1	1.61, s			
11′			18.3	1.71, s			
3′-OMe			60.8	3.94, s			

The assignments of ^{1}H and ^{13}C NMR signals are based on HSQC, ^{1}H-^{1}H COSY, and HMBC experiments.
[a] ^{1}H for 400 MHz and ^{13}C for 100 MHz.
[b] ^{1}H for 500 MHz and ^{13}C for 125 MHz.

compound **1** and (−)-pranferol were opposite, which indicated that they were enantiomers (Kuznetsova et al., 1966). The absolute configuration of C-2′ for **1** was determined to be S configuration by the modified mosher method (Fig. 4). Thus, the structure of **1** was elucidated as 5-[(2S)-2-hydroxy-3-methylbutyloxy)]-psoralen named (+)-pranferol.

Compound **2** was obtained as white amorphous powder. The HR–ESI–MS showed quasimolecular ion at m/z 371.1496 $[M+H]^+$ (calcd. for 371.1495), indicating the molecular formula of $C_{21}H_{22}O_6$ and accounting for 11 degrees of unsaturation. The IR spectrum showed absorption bands at 3446 cm^{-1} and 1639 cm^{-1}, indicating the existence of hydroxyl group and conjugated carbonyl functionality. The UV spectrum exhibited the maxima absorption at 205, 228, 289 and 331 nm, suggesting that it was a flavonoid derivative (Scott, 1964). The ^{1}H and ^{13}C NMR signals for **2** were assigned using 1D and 2D NMR experiments (Table 1). The ^{1}H NMR spectrum of **2** revealed the presence of an 1,2,3,5-tetrasubstituted benzene ring proton signals at δ_H 6.50 (1H, d, J = 2.1 Hz, H-6) and 6.42 (1H, d, J = 2.1 Hz, H-8), an 1,2,3,4-tetrasubstituted benzene ring proton signals at δ_H 7.25 (1H, d, J = 8.5 Hz, H-5′)

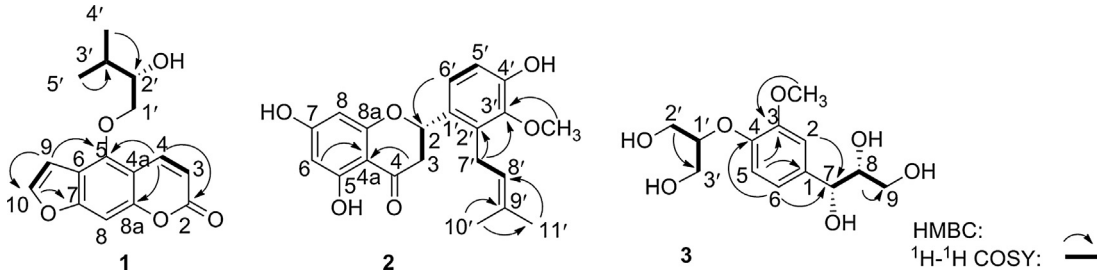

Fig. 2. Key ^{1}H-^{1}H COSY and HMBC correlations of compounds 1–3.

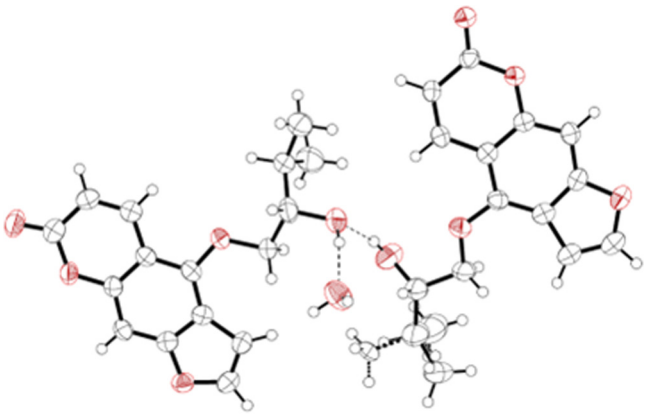

Fig. 3. Plot of the X-ray crystallographic data of 1.

and 7.47 (1H, d, J = 8.5 Hz, H-6′), and a methoxy proton signal at δ_H 3.94 (3H, s, 3′-OCH_3). In addition, an isoprenyl group proton signals were also observed at δ 1.61 (3H, s, CH_3-10′), 1.71 (3H, s, CH_3-11′), 3.78 (2H, m, H-7′) and 5.32 (1H, t, J = 6.6 Hz, H-8′) in the ^{1}H NMR spectrum of **2**, which was confirmed by the ^{1}H-^{1}H COSY correlation between H-7′ (δ_H 3.78, 2H, m) and H-8′ (δ_H 5.32, 1H, t, 6.6) as well as the HMBC correlations from the methyl proton at δ_H 1.61 (3H, s, H-10′) to δ_C 124.7 (C-8′), 131.8 (C-9′), and 18.3 (C-11′). The HMBC correlation from δ_H 3.94 (3H, s, 3′-OCH_3) to δ_C 147.5 (C-3′) indicated that the methoxy group was linked to C-3′ of B ring. The HMBC correlations from δ_H 3.78 (2H, m, H-7′) to δ_C 135.1 (C-2′) and 147.5 (C-3′) attached the isoprenyl group to the C-2′ of B ring. Hence, the planar structure of **2** was determined and key ^{1}H-^{1}H COSY and HMBC correlations were shown in Fig. 2. The absolute configuration of C-2 was determined to be S configuration by a negative cotton effect at 289 nm and a positive cotton effect observed at 331 nm in the circular dichroism (CD) spectrum of **2** (Fig. 5) (Antus et al., 1994) (Shi et al., 2014). Thus, compound **2** was established as (2S)-4,5,7-trihydroxy-3′-methoxy-2′-prenylflavanone named antiarone M.

Compound **3** was obtained as colorless oil. The HR-ESI–MS spectrum showed quasimolecular ion at m/z 311.1110 $[M+Na]^+$ (calcd. for 311.1107), indicating its molecular formula of $C_{13}H_{20}O_7$ containing 4 degrees of unsaturation. The ^{1}H and ^{13}C NMR signals for **3** were assigned using 1D and 2D NMR experiments (Table 1). The ^{1}H NMR spectrum of **3** revealed three ABX aromatic proton signals at δ 7.08 (1H, d, J = 2.0 Hz, H-2), 6.91 (1H, dd, J = 8.0, 2.0 Hz, H-6), 7.06 (1H, d, J = 8.0 Hz, H-5) and a methoxyl proton signal at δ 3.86 (3H, s, 3-OCH_3). Meanwhile, the ^{1}H NMR spectrum of **3** showed the presence of a glycerol fragment signals at δ 4.58 (1H, d, J = 6.2 Hz, H-7), 3.67 (1H, m, H-8), and 3.51 (1H, m, H-9a)/3.40 (1H, m, H-9b), which was linked to C-1 of the benzene ring based on the HMBC correlations from δ_H 7.08 (1H, d, J = 2.0 Hz, H-2) and 6.91 (1H, dd, J = 8.0, 2.0 Hz, H-6) to δ_C 75.2 (C-7). The long-range HMBC correlations from the

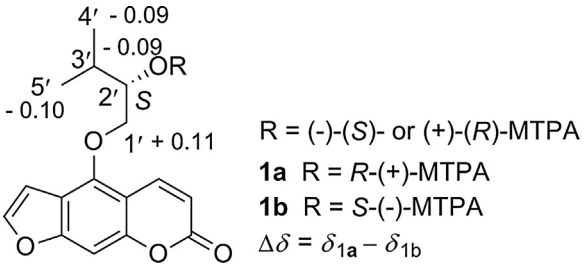

Fig. 4. Determination of the absolute configuration of (+)-pranferol.

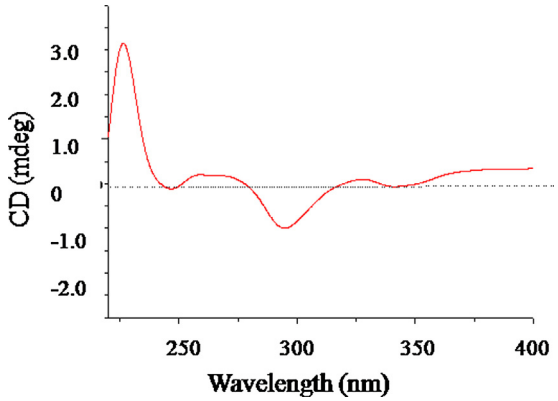

Fig. 5. CD spectrum for compound 2.

aromatic proton at δ_H 7.06 (1H, d, J = 8.0 Hz, H-5) and methoxyl proton at δ_H 3.86 (3H, s) to δ_C 151.9 (C-3) indicated that the methoxy group was linked to C-3 of **3** (Fig. 2). The ^{1}H-^{1}H COSY correlations of oxygenated methylene protons at H-2′ (δ_H 3.76, overlap, 2H, m) and H-3′ (δ_H 3.76, overlap, 2H, m) with H-1′ (δ_H 4.21, 1H, m) indicated the presence of an 1,3-diol-2-oxyl group in the structure of **3**. Analysis of ^{1}H and ^{13}C data indicated that the structure of **3** was similar to that of guaiacyl glycerol excepted for an extra 1,3-diol-2-oxyl group instead of a hydroxyl group (OH) at C-4 in **3** (Jong et al., 2009; Liu et al., 2007). In the HR-ESI-MS^2 spectrum of **3**, the fragment ion at m/z 235.0319 $[M - C_3H_8O_2 + Na]^+$ confirmed the presence of 1,3-diol-2-oxyl group in the structure of **3**. The *threo* configuration of C-7 and C-8 in **3** was defined on the basis of the coupling constant (J value) of 6.2 Hz between H-7 and H-8 (Huang et al., 2012) (Li and Seeram, 2011) (Kijima et al., 1998) and comparison of the ^{1}H and ^{13}C NMR data with that of 1-(4-hydroxy-3-methoxy)-phenyl-2-[4-(1,2,3-trihydroxy-propyl)-2-methoxy]-phenoxy-1,3-propandiol (Della Greca et al., 1998). Therefore, the structure of **3** was elucidated as (7R*, 8R*)-4-1′,3′-diol-2′-oxyl guaiacyl glycerol named anticerol A.

The other nine known compounds were identified as xanthyletin (**4**) (Hong et al., 2012), seselin (**5**) (Hong et al., 2012), umbelliferone (**6**) (Olennikov et al., 2012), 7-demethylsuberosine (**7**) (Kang et al., 2001), 8-hydroxy-7-methoxy-6-prenylcoumarin (**8**) (Filho et al., 1972), vaginol (**9**) (Zou et al., 2005), antiarsin B (**10**) (Jiang et al., 2009), antiarone K (**11**) (Shi et al., 2014), and antiarone F (**12**) (Hano et al., 1990a) by comparison of their physical and spectroscopic properties with those reported in the literatures.

3. Experimental

3.1. General experimental procedures

Optical rotations were obtained on a P-1020 digital polarimeter (Jasco Corporation). UV spectra were measured on a JASCO V-550 UV/vis spectrophotometer. IR spectra were recorded on a JASCO FTIR-480 plus spectrometer. CD spectra were obtained on a Jasco J-810 spectropolarimeter at room temperature. A single-crystal X-ray diffraction was measured on Agilent SuperNova. NMR spectra were measured on Bruker AV 400 and 500 instruments. Chemical shifts were given in ppm (δ) relative to chemical shifts of solvent resonances (pyridine-d_5: 7.58 and 135.9 ppm) and (methanol-d_4: 3.31 and 49.1 ppm). HR–ESI–MS spectra were obtained on a Micromass Q-TOF mass spectrometer. HPLC was performed on a cosmosil C_{18} column (4.6 × 250 mm, 5 μm) and a HPLC system equipped with a Dionex Ultimate 3000 pump, a Dionex Ultimate 3000 diode array detector, a Dionex Ultimate 3000 column compartment and a Dionex Ultimate 3000 autosampler (Dionex, USA). Semipreparative HPLC was performed on a Shimadzu LC-6AD liquid chromatograph with SPD-20A Detector, using an ODS column [YMC-Pack ODS-A](UV detection wavelength: 220 and 254 nm). Open column chromatography (CC) was performed using silica gel (200–300 mesh, Qingdao Haiyang Chemical Group Corp., Qingdao), ODS (50 μm, YMC), and Sephadex LH-20 (Pharmacia). TLC analysis was performed on pre-coated silica gel GF254 plates (Qingdao Haiyang Chemical Group Corp., Qingdao).

3.2. Plant material

The bark of *A. toxicaria* was collected from *Xishuangbanna* Tropical Botanical Garden, Chinese Academy of Sciences, Yunnan province, P.R. China in March 2011. The plant was authenticated by Professor Yu Chen of Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (ANTO201103) was deposited in the Institute of Traditional Chinese Medicine & Natural Products, Jinan University.

3.3. Extraction and isolation

The back of *A. toxicaria* (3.25 kg) was extracted by 95% (v/v) ethanol–water (4 × 30 L) under reflux condition for 2 h every time. The combined ethanol extracts were concentrated under vacuum to obtain the crude extract (135.0 g). The crude extract was subjected to open silica gel CC (f 3.3 × 53 cm) using a $CHCl_3$–MeOH gradient to give 12 fractions (C.1–C.12). Fraction C.4 (18.0 g) was chromatographed over ODS (f 3.3 × 25 cm) MPLC using MeOH–H_2O gradient to give 12 subfractions (C.4-1 ∼ C.4-12). Subfraction C.4-2 (132.8 mg) was subjected to semipreparative RP-HPLC using 35% MeOH–H_2O (v/v) at flow rate of 3.0 mL/min to afford compound **6** (t_R = 24.0 min, 18.7 mg). Subfraction C.4-3 (58.0 mg) was applied to semipreparative RP-HPLC using 35% MeOH-H_2O (v/v) at flow rate of 3.0 mL/min to obtain compound **9** (t_R = 15.0 min, 10.6 mg). Subfraction C.4-6 (85.2 mg) was applied to semipreparative RP-HPLC using 60% MeOH–H_2O (v/v) at flow rate of 3.0 mL/min to obtain compounds **1** (t_R = 20.0 min, 7.3 mg), **4** (t_R = 20.0 min, 4.5 mg), and **5** (t_R = 23.5 min, 4.1 mg). Subfraction C.4-7 (78.0 mg) was applied to semipreparative RP-HPLC using 65% MeOH–H_2O (v/v) at flow rate of 3.0 mL/min to obtain compounds **7** (t_R = 19.0 min, 30.9 mg) and **8** (t_R = 21.0 min, 6.7 mg). Subfraction C.4-8 (109.3 mg) was applied to semipreparative RP-HPLC using 63% MeOH–H_2O (v/v) at flow rate of 3.0 mL/min to obtain compounds **2** (t_R = 31.0 min, 7.6 mg) and **11** (t_R = 36.0 min, 12.4 mg). Subfraction C.4-9 (454.9 mg) was subjected to ODS (f 3.5 × 13 cm) MPLC eluting with MeOH–H_2O gradient to give 5 subfractions (C4-9-1 ∼ C4-9-7). Subfraction C.4-9-3 was applied to semipreparative RP-HPLC using 72% MeOH-H_2O (v/v) at flow rate of 3.0 mL/min to obtain compound **12** (t_R = 18.0 min, 12.0 mg). Fraction C.8 (3.33 g) was subjected to ODS (f 3.5 × 13 cm) MPLC eluting with MeOH–H_2O gradient to give 5 subfractions (C.8-1 ∼ C.8-5). Subfraction C.8-4 (31.6 mg) was applied to semi-preparative RP-HPLC using 30% MeOH-H_2O (v/v) at flow rate of 3.0 mL/min to obtain compound **10** (t_R = 21.0 min, 13.8 mg). Fraction C11 was subjected to ODS (f 3.3 × 25 cm) MPLC eluting with MeOH–H_2O gradient to give 8 subfractions (C.11-1 ∼ C.11-8). Subfraction C.11-1 (882.0 mg) was applied to preparative RP-HPLC using 7% MeOH–H_2O (v/v) at flow rate of 3.0 mL/min to obtain compound **3** (t_R = 8.0 min, 2.7 mg).

3.3.1. (+)-Pranferol (*1*)

White amorphous powder (MeOH); $[\alpha]_D^{26}$ + 8.2 (*c* 0.7, MeOH); IR (KBr) ν_{max} 3454, 2925, 1698, 1628, 1468, 1086 cm^{-1}; UV (MeOH) λ_{max}: 204, 219, 249, 265, 309 nm; ^{1}H and ^{13}C NMR data (see Table 1); ESI–MS m/z 289.3 $[M + H]^+$, 311.2 $[M + Na]^+$; HR–ESI–MS (positive-ion mode) m/z 289.1079 $[M + H]^+$ (calcd. for C_{16} H_{17} O_5, 289.1076).

3.3.2. antiarone M (*2*)

White amorphous powder (MeOH); $[\alpha]_D^{26}$ − 29.1 (*c* 0.5, MeOH); IR (KBr) ν_{max}: 3446, 2931, 1639, 1531, 1079 cm^{-1}; UV λ_{max} (MeOH): 205, 228, 289, 331 nm; CD λ_{max} (MeOH) nm ($\Delta\varepsilon$): 289 (−5.57), 331 (+0.82); ^{1}H and ^{13}C NMR data (see Table 1); ESI–MS m/z 371.5 $[M + H]^+$, 369.7 $[M - H]^-$; HR–ESI–MS (positive-ion mode) m/z 371.1496 $[M + H]^+$ (calcd. for $C_{21}H_{23}O_6$, 371.1495).

3.3.3. Anticerol A (*3*)

Colorless oil; $[\alpha]_D^{26}$ − 8.2 (*c* 0.7, MeOH); IR (KBr) ν_{max}: 3414, 2926, 1646, 1512, 1042 cm^{-1}; UV λ_{max} (MeOH): 203, 228, 277 nm; ^{1}H and ^{13}C NMR data (see Table 1); ESI–MS m/z 311.3 $[M + Na]^+$, 287.4 $[M - H]^-$; HR–ESI–MS (positive-ion mode) m/z 311.1110 $[M + Na]^+$ (calcd. for $C_{13}H_{20}O_7Na$, 311.1107).

*3.3.4. X-ray Crystallographic analysis of (+)-pranferol (**1**)*

Upon crystallization from MeOH using the vapor diffusion method, needles of **1** were obtained. Data were collected using a Sapphire CCD with a graphite monochromated Cu Kα radiation, λ = 1.54184 Å at 293 K. Crystal data: $2C_{16}H_{16}O_5 \cdot H_2O$, $M = 594.59$, orthorhombic, space group $P1211$; unit cell dimensions were determined to be $a = 6.6061$ (4) Å, $b = 20.4665$ (8) Å, $c = 10.8230$ (5) Å, $\alpha = 90.00°$, $\beta = 97.908$ (5)°, $\gamma = 90.00°$, $V = 1449.39$ (13) Å^3, $Z = 2$, $Dx = 1.362$ g/cm^3, F (000) = 628, μ (Cu Kα) = 0.861 mm^{-1}. 19,375 reflections were collected until $\theta_{max} = 61.18°$, in which independent unique 4282 reflections were observed [$F^2 > 4\sigma(F^2)$]. The structure was solved by direct methods using the SHELXS-97 program, and refined by the SHELXL-97 program and full-matrix least-squares calculations (Dolomanov et al., 2009). In the structure refinements, nonhydrogen atoms were placed on the geometrically ideal positions by the "ride on" method. Hydrogen atoms bonded to oxygen were located by the structure factors with isotropic temperature factors. The final refinement gave $R = 0.0508$, $R_W = 0.1396$, $S = 1.010$, and Flack = 0.2 (3). Further details can be obtained via CCDC. CCDC 1018582 contains the supplemen-tary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*3.3.1. Preparation of (R)-(**1a**) and (S)-(**1b**) MTPA esters*

A solution of **1** (0.5 mg) in pyridine-d_5 (0.5 mL) was treated with (S)-(+)-MTPA chloride (15 μL) under an atmosphere of nitrogen in an NMR tube. The mixture was stirred at room temperature for 4 h to obtain the (R)-(+)-MTPA ester (**1a**). The same procedure was used to prepare the (S)-(−)MTPA ester (**1b**) with (R)-(−)MTPA chloride.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytol.2015.06.006.

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