Twelve benzene derivatives from *Clausena excavata*

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Abstract: A new phenethanol, (2'*R*)-4-(2', 3'-dihydroxy-3'-methyl-butanoxy)-phenethanol (**1**), along with other eleven known benzene derivatives (**2**−**12**) were isolated from the roots, stems and leaves of *Clausena excavata* (Rutaceae). Compounds **3** and **4** are new natural products, and compounds **5**−**8**, **10**−**12** were isolated from *C. excavata* for the first time. Their structures were elucidated on the basis of MS, 1D and 2D NMR spectroscopic analyses including HSQC, COSY and HMBC experiments. **1** was tested for its cytotoxicities against A549, HeLa and BGC-823 cancer cell lines, and antimicrobial activities against *Candida albicans* and *Staphylococcus aureus*. The results showed that **1** did not exhibit cytotoxic and antimicrobial activities.

Key words: *Clausena excavata*; phenethalol; benzene derivatives

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小叶臭黄皮中 12 个苯环衍生物

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摘要: 对小叶臭黄皮 (*Clausena excavata*) 根、茎和叶部位进行了化学成分研究, 经过一系列正相和反相色谱柱和高效液相色谱等现代分离技术, 分离得到 12 个苯环衍生物 (**1**～**12**), 并通过 MS、NMR、IR 等波谱学方法对这些化合物进行结构鉴定, 其中 (2'*R*)-4-(2', 3'-dihydroxy-3'-methyl-butanoxy)-phenethanol (**1**) 为一个新化合物, 化合物 **3** 和 **4** 为两个新天然产物, 化合物 **5**～**8**、**10**～**12** 均为首次从该植物中分离得到。测定了化合物 **1** 对 A549、HeLa 和 BGC-823 的细胞毒活性及其对 *Candida albicans*、*Staphylococcus aureus* 的抑菌活性, 结果显示化合物 **1** 没有细胞毒和抑菌活性。

关键词: 小叶臭黄皮; 苯乙醇; 苯环衍生物

In our previous studies[1, 2] on the chemical constituents of *Clausena excavata* Burm. f. (Rutaceae), which has been used as a folk medicine for treatment of dysentery, enteritis, and urethra infection[3, 4]. The isolation and structure elucidation of some carbazole alkaloids and coumarins from its roots, leaves and stems were reported. To continue our studies, the roots, stems and leaves of *C. excavata* were investigated. Herein, this paper described the isolation and structure elucidation of a new phenethanol, (2'*R*)-4-(2', 3'-dihydroxy-3'-methyl-butanoxy)-phenethanol (**1**), along with other eleven known benzene derivatives (**2**−**12**), and the evaluation of cytotoxic and antimicrobial activities of compound **1**. Compounds **3** and **4**

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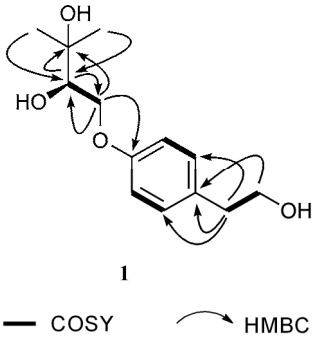
are new natural products, and compounds **5**−**8**, **10**−**12** were isolated from *C. excavata* for the first time.

Results and discussion

(2'*R*)-4-(2', 3'-dihydroxy-3'-methyl-butanoxy)-phenethanol (**1**), $[\alpha]_D^{25.4}$ +2.06 (*c* 0.11, MeOH), was obtained as pale yellow oil. Its molecular formula was determined as $C_{13}H_{20}O_4$ by the HR-EI-MS at *m/z* 240.136 4 ($[M]^+$, Calcd. 240.136 2). The IR spectrum indicated the presence of OH at 3 406 cm^{-1}. Its ^1H NMR spectrum (Table 1) revealed that it contained one 1, 4-disubstituted benzene ring (δ_H 7.12, 2H, d, *J* = 7.5 Hz; 6.86, 2H, d, *J* = 7.5 Hz) and two CH_3 (δ_H 1.25, 3H, s; 1.21, 3H, s). The ^{13}C NMR spectrum (Table 1) showed a total of thirteen carbon signals corresponding to two CH_3, three CH_2, five CH and three C. The ^1H,^1H-COSY (Figure 1) correlations of H-2, 6/H-3, 5 and H-7/H-8 showed that **1** had a 1, 4-disubstituted benzene ring and a [-CH_2CH_2OH] moiety. The correlations of H-1'/(C-2', C-3'), H-2'/(C-1', C-3'), (H-4', H-5')/C-2' in the HMBC spectrum (Figure 1) and the correlation of H-1'/H-2' in the ^1H, ^1H-COSY spectrum indicated the presence of a [-$CH_2CH(OH)C(CH_3)_2OH$] unit. In addition, The correlations of H-1'/C-4 in the HMBC spectrum indicated that [-$CH_2CH(OH)C(CH_3)_2OH$] is attached to C-4. In the same spectrum, the correlations of H-7/C-1, C-2, C-6 and H-8/C-1 allowed the location of [-CH_2CH_2OH] at C-1. The optical rotation $[\alpha]_D^{25.4}$ 2.06 (*c* 0.11, MeOH) of **1** is opposite to the optical rotations of known compounds lenisin A ($[\alpha]_D^{30.3}$ −17.09) and lenisin C ($[\alpha]_D^{29.9}$ −27.41)[5]. It implied that the absolute configurations of **1** at C-2', and lenisin A and C at C-2' are different, because there is only one chiral carbon in them. For the absolute configuration of lenisin A and C at C-2' is *S*, that of **1** at C-2' should be *R*. Therefore, the structure of **1** was established to be a (2'*R*)-4-(2', 3'-dihydroxy-3'-methyl-butanoxy)-phenethanol and as shown in Figure 2. ^1H, ^{13}C NMR data of **1** see Table 1.



1

Figure 1 Key ^1H-^1H COSY, and HMBC correlations of compound **1**

Lenisin A (2): pale yellow oil, $[\alpha]_D^{22.9}$ −22.19 (*c* 0.21, MeOH); EI-MS *m/z* 296 $[M]^+$, $C_{16}H_{24}O_5$. ^1H NMR ($CDC1_3$, 400 MHz): δ_H 6.59 (2H, s, H-2, 6), 6.07 (1H, m, H-8), 5.18 (2H, m, H-9), 4.86 (1H, dd, *J* = 10.0, 3.2 Hz, H-1'a), 4.43 (1H, dd, *J* = 10.0, 8.2 Hz, H-1'b), 4.28 (1H, dd, *J* = 8.2, 3.2 Hz, H-2'), 3.72 (6H, s, $2CH_3$), 3.37 (2H, d, *J* = 6.7 Hz, H-7), 1.54 (3H, s, H-5'), 1.52 (3H, s, H-4'); ^{13}C NMR ($CDC1_3$, 100 MHz): δ_C 152.6 (s, 2×C-3, 5), 136.9 (s, C-1), 136.2 (d, C-8), 134.9 (s, C-4), 116.2 (t, C-9), 105.2 (d, 2×C-2, 6), 75.7 (d, C-2'), 75.4 (t, C-1'), 71.4 (s, C-3'), 55.9 (q, 2×OCH_3), 40.5 (t, C-7), 26.7 (q, C-5'), 24.9 (q, C-4')[5].

3-Methylbut-2-enyl-4-hydroxybenzoate (3): colorless oil, EI-MS *m/z* 206 $[M]^+$, $C_{12}H_{14}O_3$. ^1H NMR ($CDC1_3$, 400 MHz): δ_H 8.05 (2H, d, *J* = 8.8 Hz, H-2, 6), 6.94 (2H, d, *J* = 8.8 Hz, H-3, 5), 5.49 (1H, m, H-2'), 4.57 (2H, d, *J* = 6.7 Hz, H-1'), 1.75 (3H, s, H-4'), 1.64 (3H, s, H-5'); ^{13}C NMR ($CDC1_3$, 100 MHz): δ_C 171.9 (s, CO), 163.3 (s, C-4), 138.9 (s, C-3'), 132.3 (d, 2×C-2, 6), 121.5 (s, C-1), 118.9 (d, C-2'), 114.3 (d, 2×C-3, 5), 64.9 (t, C-1'), 25.8 (q, C-4'), 18.2 (q, C-5')[6].

3-Methylbut-2-enyl 4-methoxybenzoate (4): colorless oil, ESI-MS *m/z* 243 $[M+Na]^+$, $C_{13}H_{16}O_3$, ^1H NMR (acetone-d_6, 400 MHz): δ_H 7.94 (2H, m, H-2, 6),

Table 1 ^1H, ^{13}C NMR data of **1** at 400 and 100 MHz, in CD_3OD, separately

No.	δ_H	δ_C	No.	δ_H	δ_C
1		132.4 (s)	1'	4.20 (1H, d, *J* = 9.4 Hz)	70.5 (t)
2	7.12 (1H, d, *J* = 7.5 Hz)	130.9 (d)		3.87 (1H, d, *J* = 9.4 Hz)	
3	6.86 (1H, d, *J* = 7.5 Hz)	115.6 (d)	2'	3.71 (1H, br. s)	77.7 (d)
4		159.0 (s)	3'		72.8 (s)
5	6.86 (1H, d, *J* = 7.5 Hz)	115.6 (d)	4'	1.25 (3H, s)	26.7 (q)
6	7.12 (1H, d, *J* = 7.5 Hz)	130.9 (d)	5'	1.21 (3H, s)	25.0 (q)
7	2.74 (2H, t, *J* = 7.1 Hz)	39.4 (t)			
8	3.67 (2H, t, *J* = 7.1 Hz)	64.5 (t)			

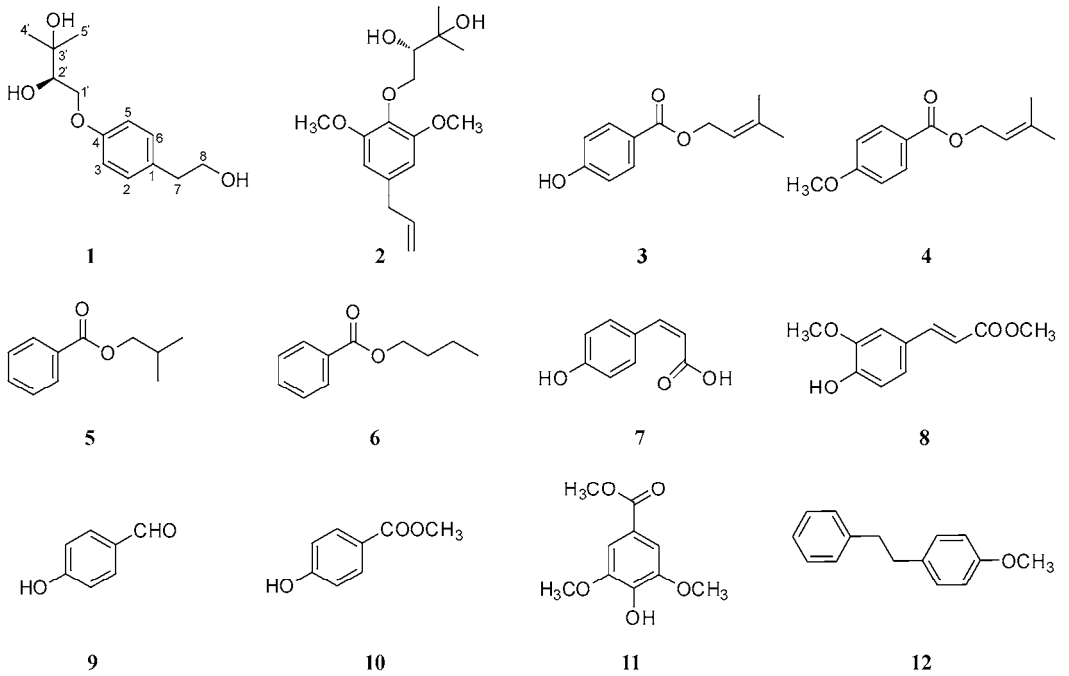


Figure 2 Structures of compounds **1**−**12**

7.01 (2H, m, H-3, 5), 5.46 (1H, m, H-2'), 4.63 (2H, d, J = 6.6 Hz, Hz, H-1'), 3.82 (3H, s, 4-OCH_3), 1.75 (3H, s, H-4'), 1.73 (3H, s, H-5'); ^{13}C NMR (acetone-d_6, 100 MHz): δ_C 166.8 (s, C=O), 163.7 (s, C-4), 138.5 (s, C-3'), 132.1 (d, 2×C-2, 6), 123.2 (s, C-1), 120.4 (d, C-2'), 115.2 (d, 2×C-3, 5), 65.6 (t, C-1'), 51.9 (4-OCH_3), 25.7 (q, C-4'), 18.1 (q, C-5')[7].

Isobutyl benzoate (5): colorless oil, EI-MS *m/z* 178 $[M]^+$, $C_{11}H_{14}O_2$, ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.10 (2H, m, H-2, 6), 7.91 (2H, m, H-3, 5), 7.63 (1H, m, H-4), 4.45 (2H, d, J = 6.6 Hz, H-1'), 2.41 (1H, m, H-2'), 1.36 (6H, d, J = 6.7 Hz, 2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 167.7 (s, CO), 132.3 (s, C-1), 130.9 (d, C-4), 130.8 (d, 2×C-2, 6), 128.8 (d, 2×C-3, 5), 71.8 (t, C-1'), 27.7 (d, C-2'), 19.1 (q, 2×CH_3)[8].

Butyl benzoate (6): colorless oil, EI-MS *m/z* 178 $[M]^+$, $C_{11}H_{14}O_2$, ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.72 (2H, m, H-2, 6), 7.53 (2H, m, H-3, 5), 7.67 (1H, m, H-4), 4.31 (2H, t, J = 6.7 Hz, H-1'), 1.72 (2H, m, H-2'), 1.45 (2H, m, H-3'), 0.98 (3H, t, J = 7.4 Hz, 4'-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 167.7 (s, CO), 132.2 (s, C-1), 130.9 (d, C-4), 130.2 (d, 2×C-2, 6), 128.8 (d, 2×C-3, 5), 65.5 (t, C-1'), 30.5 (t, C-2'), 19.1 (t, C-3'), 13.7 (q, C-4')[9, 10].

(*Z*)-3-(4'-Hydroxyphenyl)acrylic acid (7): pale yellow oil, ESI-MS *m/z* 187 $[M+Na]^+$, $C_9H_8O_3$. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 7.59 (1H, d, J = 15.9 Hz, H-3), 7.44 (2H, J = 8.5 Hz, H-2', 6'), 6.80 (2H, J = 8.5 Hz, H-3', 5'), 6.27 (1H, d, J = 15.9 Hz, H-2); ^{13}C NMR (CD_3OD, 100 MHz): δ_C 171.1 (s, C-1), 161.2 (s, C-4'), 146.7 (d, C-3), 131.1 (d, 2×C-2', 6'), 127.2 (s, C-1'), 116.8 (d, 2×C-3', 5'), 115.6 (d, C-2)[11].

(*E*)-Methyl 3-(4-hydroxy-3-methoxyphenyl)acrylate (8): pale yellow oil, ESI-MS *m/z* 231 $[M+Na]^+$, $C_{11}H_{12}O_4$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.61 (1H, d, J = 15.9 Hz, H-1'), 7.06 (1H, dd, J = 8.2, 1.8 Hz, H-5), 7.01 (1H, d, J = 1.8 Hz, H-3), 6.91 (1H, d, J = 8.2 Hz, H-6), 6.26 (1H, d, J = 15.9 Hz, H-2'), 3.91 (3H, s, 2-OCH_3), 3.79 (3H, s, 3'-OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 167.7 (s, CO), 147.9 (s, C-2), 146.7 (s, C-4), 144.9 (d, C-1'), 126.8 (s, C-1), 123.0 (d, C-5), 115.1 (d, C-6), 114.7 (d, C-2'), 109.3 (d, C-3), 55.9 (q, 2-OCH_3), 51.6 (q, 3'-OCH_3)[12].

4-Hydroxybenzaldehyde (9): colorless oil, ESI-MS *m/z* 145 $[M+Na]^+$, $C_7H_6O_2$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.86 (1H, CHO), 7.81 (2H, d, J = 8.5 Hz, H-2, 6), 6.97 (2H, d, J = 8.5 Hz, H-3, 5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 191.6 (s, CHO), 162.1 (s, C-4), 132.9 (d, 2×C-2, 6), 130.2 (s, C-1), 116.4 (d, 2×C-3, 5)[13].

Methyl 4-hydroxybenzoate (10): colorless oil, ESI-MS *m/z* 175 $[M+Na]^+$, $C_8H_8O_3$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.95 (2H, d, J = 8.2 Hz, H-2, 6), 6.87 (2H, d, J = 8.2 Hz, H-3, 5), 3.89 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 167.2 (s, CO), 160.1 (s, C-4), 131.9 (d, 2×C-2, 6), 122.4 (s, C-1), 115.2 (d, 2×C-3, 5), 52.1 (q, OCH_3)[14].

Methyl syringate (11): colorless oil, ESI-MS *m/z* 235 $[M+Na]^+$, $C_{10}H_{12}O_5$. ^{1}H NMR ($CDCl_3$, 400 MHz):

δ_H 7.32 (2H, s, H-2, 6), 5.95 (1H, br s, OH-4), 3.93 (6H, s, 2×MeO-3, 5), 3.89 (3H, s, $COOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 121. 2 (s, C-1), 166.9 (s, CO), 146. 7 (s, 2×C-3, 5) , 139. 3 (s, C-4), 106. 8 (d, 2×C-2, 6), 56.5 (q, 2×MeO-3, 5), 52.1 (q, $COOCH_3$)[15].

1-Methoxy-4-phenethylbenzene (12): pale yellow oil, EI-MS *m/z* 212 $[M]^+$, $C_{15}H_{16}O$. ^1H NMR ($CDC1_3$, 400 MHz): δ_H 7.69 (2H, d, *J* = 7.3 Hz, H-3', 5'), 7.48 (1H, t, *J* = 7.3 Hz, H-4'), 7.40 (2H, d, *J* = 7.3 Hz, H-2', 6'), 7.08 (2H, d, *J* = 8.4 Hz, H-3, 5), 6.86 (2H, d, *J* = 8.4 Hz, H-2, 6), 3.80 (3H, s, OCH_3), 3.68 (2H, t, *J* = 6.5 Hz, H-2"), 2.87 (2H, t, *J* = 6.5 Hz, H-1"); ^{13}C NMR ($CDC1_3$, 100 MHz): δ_C 158.3 (s, C-1), 143.9 (s, C-1'), 134.6 (s, C-4), 131.4 (d, 2×C-3, 5), 129.7 (d, 2×C-3', 5'), 128.5 (d, 2×C-2', 6'), 126.8 (d, C-4'), 114.1 (d, 2×C-2, 6), 55.2 (q, OCH_3), 41.3 (t, C-2"), 34.7 (t, C-1')[16].

Compound **1** was tested for its cytotoxic activities against A549, Hela and BGC-823 cancer cell lines, and antimicrobial activities against *Candida albicans* and *Staphylococcus aureus*[17]. The results showed that **1** did not exhibit cytotoxic and antimicrobial activities.

Experiment section

General experiment procedures Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401-A spectrophotometer. IR spectra were recorded with a Tensor 27 FT-IR spectrometer with KBr pellets. The ^1H and ^{13}C NMR spectra were acquired with a Bruker AM-400 (^1H: 400 MHz, ^{13}C: 100 MHz) or DRX-500 (^1H: 500 MHz, ^{13}C: 125 MHz) spectrometer in acetone-d_6 or CD_3OD with TMS as the internal standard at room temperature. MS were recorded on an API QSTAR Pular-1 mass spectrometer. Column chromatography (CC) was performed on silica gel (100−200 mesh, 200−300 mesh, and 10−40 μm, Qingdao Marine Chemical, Inc., China) and Lichroprep RP-18 gel (40−63 mm, Merck, Darmstadt, Germany). TLC was carried out on precoated silica gel GF_{254} glass plates (Qingdao Marine Chemical, Inc., China) and chromogenic agent (5% H_2SO_4-dehydrated alcohol). Semi-preparative HPLC was performed on an Agilent 1100 apparatus equipped with a UV detector and an YMC-Pack ODS-A (YMC, 1×15 cm) column at a flow rate of 2 mL·min^{-1}.

Plant material The roots, stems and leaves of *C. excavata* were collected at Xishuangbanna, Yunnan Province, P. R. China, in August 2010, which were identified by Prof. Yu-min Shui of Kunming Institute of Botany. A voucher specimen (No.2010813) has been deposited in the State Key Laboratory of Phytochemistry and plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and isolation The air-dried and powdered stems and leaves of *C. excavata* (32 kg) were extracted by refluxing 95% methanol three times (35 L×3). The methanol extract was submitted to the liquid-liquid fractionation with the solvents petroleum ether (PE), AcOEt, and BuOH. The EtOAc soluble fraction (1.1 kg) was applied to silica gel (100−200 mesh) column chromatography, eluting with PE/acetone (10∶1−0∶1) to yield 5 fractions (Fr. 1−Fr. 5). Fr. 2 (33 g) by silica gel (200−300 mesh) column chromatography eluted with PE/acetone (5∶1) gave sub-fractions (Fr. 2.1 to Fr. 2.4). Further separation of Fr. 2.2 (0.9 g) was subjected to a reversed-phase column (RP-18) eluting with MeOH−H_2O (30%−90%) to afford 5 subfractions (Fr. 2.2.1−Fr. 2.2.5). Fr. 2.2.2 (81 mg) was subjected to semipreparative reversed-phase HPLC (75% MeOH-H_2O) to give **12** (17 mg), **10** (11 mg) and **8** (9 mg). Fr. 3 (52 g) was subjected to silica gel (200−300 mesh) column chromatography eluted with PE/acetone (4∶1) gave sub-fractions (Fr. 3.1 to Fr. 3.5). Fr. 3.1 (0.8 g) was subjected to a reversed-phase column (RP-18) eluting with MeOH-H_2O (30%−90%) to afford 4 subfractions (Fr. 3.1.1−Fr. 3.1.4). Fr. 3.1.3 (90 mg) was subjected to semipreparative reversed-phase HPLC (65% MeOH-H_2O) to give **9** (10 mg), **11** (8 mg) and **2** (10 mg). Fr. 5 (21 g) was subjected to silica gel (200−300 mesh) column chromatography eluted with PE/acetone (2∶1) gave sub-fractions (Fr. 5.1 to Fr. 5.3). Fr. 5.3 (120 mg) was subjected to a reversed-phase column (RP-18) eluting with MeOH-H_2O (30%−90%) to afford 3 subfractions (Fr. 5.3.1−Fr. 5.3.3). Fr. 5.3.3 (32 mg) was subjected to semipreparative reversed-phase HPLC (50% MeOH-H_2O) to give **3** (8 mg), **7** (6 mg) and **1** (16 mg).

The air-dried and powdered roots of *C. excavata* (13 kg) were extracted with 95% EtOH under reflux for three times. The filtrates were combined and evaporated to a small volume, followed by successive partition with petroleum ether (PE), EtOAc and BuOH. The EtOAc soluble fraction (600 g) was applied to silica gel (200−300 mesh) column eluting gradiently with $CHCl_3$-MeOH (10∶0, 9∶1, 8∶2, 7∶3, 1∶1, 0∶1), to give six fractions, A−F. The separation of fraction C (18 g) over silica gel column was eluted with

PE−acetone (10∶1−1∶2) to yield fractions C1−C6. Fraction C2 (1.1 g) was subjected to a silica gel column eluted with PE−acetone (5∶1−1∶1) to give four subfractions (C2-1−C2-4). C2-4 (65 mg) was subjected to semipreparative reversed-phase HPLC (55% MeOH-H_2O) to give **6** (9 mg), **5** (14 mg) and **4** (20 mg).

(2'*R*)-4-(2', 3'-dihydroxy-3'-methyl-butanoxy)-phenethanol (**1**): pale yellow oil, $[\alpha]_D^{25.4}$ +2.06 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ε): 201 (4.07), 224 (4.12), 276 (3.37) nm; IR (KBr): ν_{max} 3 406, 2 971, 2 936, 2 879, 1 612, 1 513, 1 462, 1 384, 1 299, 1 245, 1 177, 1 096, 1 042, 827 cm^{-1}; ^1H NMR (400 Hz, CD_3OD) and ^{13}C NMR (100 Hz, CD_3OD): See Table 1; ESI-MS: *m/z* 263 $[M+Na]^+$; HR-EI-MS: *m/z* 240.136 4 ($[M]^+$, $C_{13}H_{20}O_4$, Calcd. 240.136 2).

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