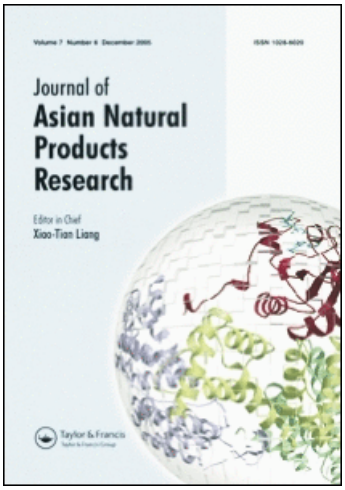

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

Four new compounds from the roots of *Uvaria macrophylla*

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To cite this Article Wang, Si , Zhang, Pei-Cheng , Chen, Ruo-Yun , Dai, Sheng-Jun , Yu, Shi-Shan and Yu, De-Quan(2005) 'Four new compounds from the roots of *Uvaria macrophylla*', Journal of Asian Natural Products Research, 7: 5, 687 — 694
To link to this Article: DOI: 10.1080/10286020412331286524
URL: http://dx.doi.org/10.1080/10286020412331286524

Journal of Asian Natural Products Research, Vol. 7, No. 5, October 2005, 687–694

Four new compounds from the roots of *Uvaria macrophylla*

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(Received 22 March 2004; revised 16 April 2004; in final form 19 April 2004)

Four new compounds, uvamalols A–C (**1**–**3**) and uvarimacrophin A (**4**), have been isolated from the roots of *Uvaria macrophylla*. Their structures have been elucidated by spectroscopic methods. The relative configurations of uvamalols A–C have been established by NOE experiments, and the relative stereochemistry of uvarimacrophin A inferred from the diagnostic NMR data by comparison with known model compounds.

Keywords: *Uvaria macrophylla*; Annonaceae; Uvamalols A, B and C; Uvarimacrophin A

1. Introduction

Uvaria macrophylla belongs to the genus *Uvaria* of the family Annonaceae, widely distributed in Hainan, Guangdong, and Guangxi provinces of southern China [1]. Acetogenins, alkaloids, dihydroflavonoids, polyoxygenated cyclohexenes and seco-cyclohexenes have been isolated from the genus *Uvaria* in our previous phytochemical investigations [2–7]. Here we describe the structural elucidation of three new polyoxygenated cyclohexenes, uvamalols A–C (**1**–**3**), and a new acetogenin, uvarimacrophin A (**4**), isolated from the title plant.

2. Results and discussion

Uvamalol A (**1**) has been isolated as a white powder. Its HR-EIMS gave a protonated molecular ion peak $[M + H]^+$ at *m/z* 385.1281, which is consistent with the molecular formula $C_{21}H_{20}O_7$.

The IR spectrum for **1** displays absorption bands attributable to hydroxyl (3506 and 3402 cm^{-1}), carbonyl (1714 and 1705 cm^{-1}) groups, and benzene ring (1601 and 1509 cm^{-1}). The ^1H NMR spectrum exhibits the presence of four oxygenated methine protons and a pair of germinal oxygenated methylene protons at δ 3.70–5.20 and an olefinic proton at δ 5.71 (1H, s).

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Journal of Asian Natural Products Research
ISSN 1028-6020 print/ISSN 1477-2213 online © 2005 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/10286020412331286524

In combination with the observed signals for two olefinic carbons at δ 136.8 and 128.6, and four oxygenated tertiary carbons at δ 71.0, 73.6, 75.8, and 78.7, as well as a secondary oxygenated carbon at δ 65.1 in the ^{13}C NMR spectrum, it is suggested that **1** is a polyoxygenated cyclohexene with a $\Delta^{1(6)}$ double bond [3,5]. In addition, the ten aromatic proton signals at δ 7.42–8.02 (10H, m), 14 carbon signals at δ 168.0, 167.3, 134.4, 134.1, 131.8, 131.3, 130.7 (2C), 130.6 (2C), 129.6 (2C), and 129.4 (2C) in the ^{1}H and ^{13}C NMR spectra, together with a basic peak at *m/z* 105 in the FABMS, indicate the presence of two benzoyl groups [5,7].

In the HMBC spectrum, correlations of the proton signals at δ 4.98 (1H, d, J = 13.5 Hz) and 4.82 (1H, d, J = 13.5 Hz) with the carbonyl signal at δ 167.3 reveal that a benzoyl is attached to 7-OH, while correlations of the proton signals at δ 5.71 (1H, s) and 4.41 (1H, d, J = 8.0 Hz) with the carbon signal at δ 78.7, as well as the proton signal at δ 5.15 (1H, dd, J = 8.0, 11.0 Hz) with the carbonyl signal at δ 168.0, suggest that another benzoyl is linked to 4-OH (figure 1).

The relative stereochemistry of **1** was established by the inspection of NOE correlations and the observed coupling constants. The J values equal to or more than 8.0 Hz between H-2, H-3, H-4, and H-5 suggested that they each were all in trans relationship. This was also deduced by NOE difference experiments, the signals at δ 3.72 (H-3) and 5.71 (H-6) showed NOE enhancements when the proton at δ 4.41 (H-5) was irradiated, similarly the signal at δ 5.15 (H-4) also showed NOE enhancement when the proton at δ 4.30 (H-2) was irradiated.

Uvamalol B (**2**) was obtained as white crystals, its HR-EIMS revealed a quasi-molecular ion peak at *m/z* $[M + H]^+$ 443.1716, corresponding to the molecular formula $C_{24}H_{26}O_8$.

Absorption bands at 3249, 1730, 1600, 1495 cm^{-1} in the IR spectrum indicate the presence of hydroxyl, carbonyl, and benzene ring groups. Detailed examination of the ^{1}H and ^{13}C NMR spectra reveal the presence of benzoyl, (2-hydroxyl-5-methoxyl)benzyl, and acetyl functionalities [3,5,6]. The five aromatic protons at δ 7.58–8.01, together with the carbon signals at δ 165.9, 133.3, 129.7, 129.6, and 128.5, are ascribed to a benzoyl. The ABX system proton signals at δ 6.77 (1H, d, J = 8.0 Hz), 6.68 (1H, dd, J = 8.0, 3.0 Hz) and 6.63 (1H, d, J = 3.0 Hz), a methoxyl signal at δ 3.74 (3H, s) and a pair of methylene protons at δ 2.74 (1H, dd, J = 17.0, 7.0) and 3.07(1H, dd, J = 17.0, 7.0), as well as the carbon signals at δ 153.9, 147.4, 122.1, 117.5, 113.8, 113.4, 55.6, and 23.5, are characteristic of a (2-hydroxyl-5-methoxyl)benzyl unit [6]. Resonances for the protons at δ 2.10 (3H, s) and carbons at δ 20.9 and 172.0 are assigned to an acetyl. The remaining NMR signals (table 1) are closely comparable to those of polyoxygenated cyclohexenes with a $\Delta^{1(6)}$ double bond [3], in particular the signals for the proton at δ 2.67 (1H, dd, J = 7.0, 4.0) and its corresponding carbon signal at δ 35.2 suggest that C-3 in the cyclohexene unit does not bear oxygen. ^{1}H–^{1}H COSY correlations of the proton signals at δ 5.57 (H-5) with δ 4.08 (H-4), and δ 2.67 (H-3) with δ 4.08 (H-4), 2.74 (H-8) and 3.07 (H-8), indicate that the benzyl unit should be linked to

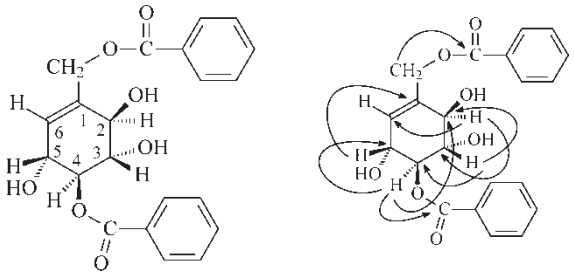

Figure 1. Structure and key HMBC correlations of uvamalol A (**1**).

Table 1. ^{1}H and ^{13}C NMR spectral data for **1** in CD_3OD, **2** and **3** in $CDCl_3$[a].

	1		***2***		***3***	
Position	$\delta_H J$ *(Hz)*	δ_C	$\delta_H J$ *(Hz)*	δ_C	$\delta_H J$ *(Hz)*	δ_C
1		136.8		132.3		135.3
2	4.30, d (8.0)	73.6	4.77, s	70.8	4.57, s	67.7
3	3.72, dd (10.0, 8.0)	75.8	2.67, dd (7.0, 4.0)	35.2	5.42, dd (6.0, 4.0)	77.0
4	5.15, dd (10.0, 8.0)	78.7	4.08, dd (4.0, 5.5)	73.3	2.86, m	33.5
5	4.41, d (8.0)	71.0	5.57, d (5.5)	72.9	5.01, s	70.2
6	5.71, s	128.6	6.24, s	131.2	6.14, s	129.4
7	4.82, d (13.5)	65.1	4.76, d (12.0)	64.2	4.81, d (13.0)	64.7
7	4.98, d (13.5)		4.93, d (12.0)		5.18, d (13.0)	
8			2.74, dd (17.0, 7.0)	23.5	2.98, dd (16.5, 8.5)	23.6
8			3.07, dd (17.0, 7.0)		2.76, dd (16.5, 8.5)	
9				122.1		120.9
10				147.4		147.3
11			6.77, d (8.0)	117.5	6.77, d (7.0)	117.3
12			6.68, dd (8.0, 3.0)	113.8	6.66, dd (7.0, 2.5)	113.7
13				153.9		153.4
14			6.63, d (3.0)	113.4	6.56, d (2.5)	113.6
$1'$		168.0		165.9		166.6
$1''$		134.4		129.6		129.5
$2''$ ($6''$)	8.01, m	130.7	8.01, m	129.7	8.01, m	129.7
$3''$ ($5''$)	7.44, m	129.6	7.44, m	128.5	7.44, m	128.3
$4''$	7.58, m	131.8	7.58, m	133.3	7.57, m	133.3
$1'''$		167.3				166.6
$1''''$	8.02, m	134.1				129.6
$2''''$($6''''$)	7.46, m	130.6			8.03, m	129.7
$3''''$($5''''$)	7.60, m	129.4			7.46, m	128.4
$4''''$		131.3			7.59, m	133.3
AcO			2.10, s	20.9		
				172.0		
OCH_3			3.74, s	55.6	3.75, s	55.7

[a] Chemical shift values are in ppm, and *J* values in parentheses are in Hz. Assignments were confirmed by $^{1}H-^{1}H$ COSY, HSQC, and HMBC experiments.

C-3 (figure 2). HMBC correlations of the protons at δ 4.76 (H-7) and 4.91 (H-7) with the carbon signal at δ 165.9 (C-$1'$), and of the proton at δ 5.57 (H-5) with the carbon at δ 172.0, reveal that the benzoyl and acetyl are attached to 7-OH and 5-OH, respectively.

The relative stereochemistry of **2** was interpreted by the NOESY experiment. In the NOESY spectrum, the signal for the proton at δ 5.57 (H-5), correlating with protons at δ 2.74 (H-8), indicates that the benzyl and H-5 are on the same side of cyclohexene and axially

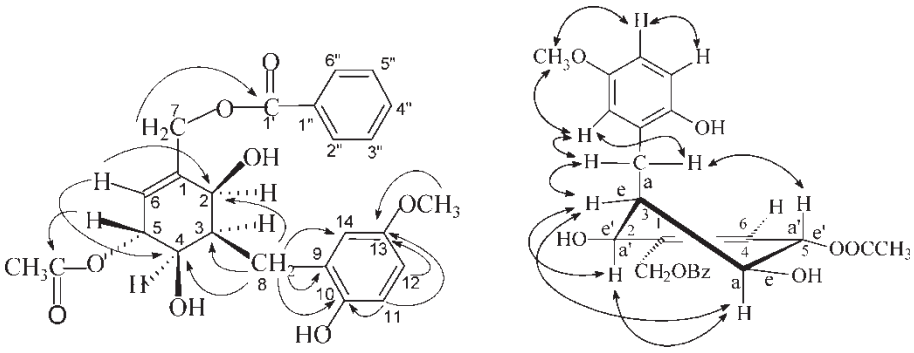

Figure 2. Key HMBC and NOE correlations of uvamalol B (**2**).

oriented; meanwhile, the signal for the proton at δ 2.67 (H-3) is correlated to the signals for the protons at δ 4.77 (H-2) and δ 4.08 (H-4), suggesting an equatorial bond for H-3, and axial bonds for H-2 and H-4 located on the other side of the cyclohexene.

Uvamalol C (**3**) was isolated as an oil, and its molecular formula was assigned as $C_{29}H_{28}O_8$ on the basis of its HR-FABMS ($[M - H_2O]^+$ *m/z* 486.1678).

A preliminary examination of the spectral data of **3** suggested that this compound is very similar to **2**, both having a polyoxygenated cyclohexene moiety, a (2-hydroxy-5-methoxyl)benzyl unit and a benzoyl group [3,5–7]. However, there are some significant differences between the two compounds: **3** has one benzoyl more than **2** and no acetyl group, moreover, the chemical shifts of the cyclohexene proton signals in **3** are apparently different from those in **2**, indicating that the benzyl unit is not substituted to C-3. In the $^1H-^1H$ COSY spectrum, the proton signal at δ 2.86 (H-4) is correlated to the protons at δ 5.42 (H-3), 2.98 (H-8), and 2.76 (H-8). The HMBC experiment clearly exhibited long-range correlations of the protons at δ 2.98 (H-8) and 2.76 (H-8) with the carbons at δ 77.0 (C-3), 33.5 (C-4), and 70.2 (C-5), and the proton at δ 6.14 (H-6) with the carbons at δ 70.2(C-5) and 33.5(C-4) (figure 3). These findings reveal that the benzyl unit is linked to C-4.

In the NOE spectrum, significant cross peaks of H-4 with H-5 and H-3 suggest an equatorial bond for H-4 and axial bonds for H-3 and H-5 on the same side of the hexene ring; a cross peak of H-2 with H-8 reveals that the benzyl unit and H-2 are both axially oriented on the other side of the hexene ring.

Uvarimacrophin A (**4**) was isolated as a waxy solid, and its molecular formula was determined as $C_{39}H_{70}O_7$ by HR-FABMS ($[M + H]^+$ *m/z* 651.5179).

A prominent IR carbonyl absorption at 1755 cm^{-1} suggests the presence of an unsaturated γ-lactone, which is confirmed from the NMR spectra, showing diagnostic signals at δ 6.95 (1H, H-35), 4.99 (1H, H-36), 1.41 (3H, H-37) and δ 173.8 (C-1), 148.8 (C-35), 134.3 (C-2), 77.3 (C-36), 19.2 (C-37) [4,8]. Both the IR carbonyl absorption band at 1720 cm^{-1} and the resonance for the protons at δ 2.06 (3H, s) and the carbons at δ 171.5, and 21.2 reveal the presence of an acetoxyl group, which is also supported by the fragment ion at *m/z* 591 ($[MH - HOAc]^+$) in the FABMS spectrum [4,8]. Proton signals at δ 5.11 (1H, H-17), 3.86 (1H, H-18), 3.82 (1H, H-21), and 3.42 (1H, H-22), and the corresponding carbon signals at δ 71.6 (C-17), 82.2 (C-18), 82.9 (C-21), and 74.1 (C-22), are characteristic for mono-THF acetogenin with one flanking hydroxyl and another flanking acetoxyl [4,8]. In addition, successive losses of two H_2O units from the fragment ($[MH - HOAc]^+$) in the FABMS indicates the presence of another hydroxyl group.

The locations of the THF ring, the two hydroxyls and the acetoxyl along the aliphatic chain in **4** were determined by analysis of the EIMS of **4** and **4a** (figure 4). EIMS of **4**/**4a** gave fragment

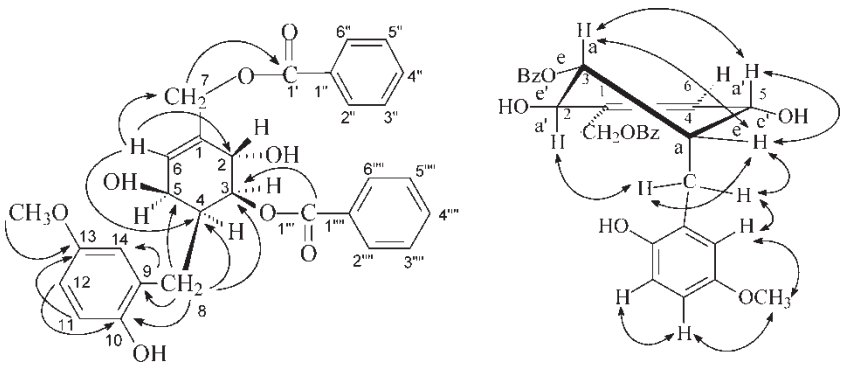

Figure 3. Key HMBC and NOE correlations of uvamalol C (**3**).

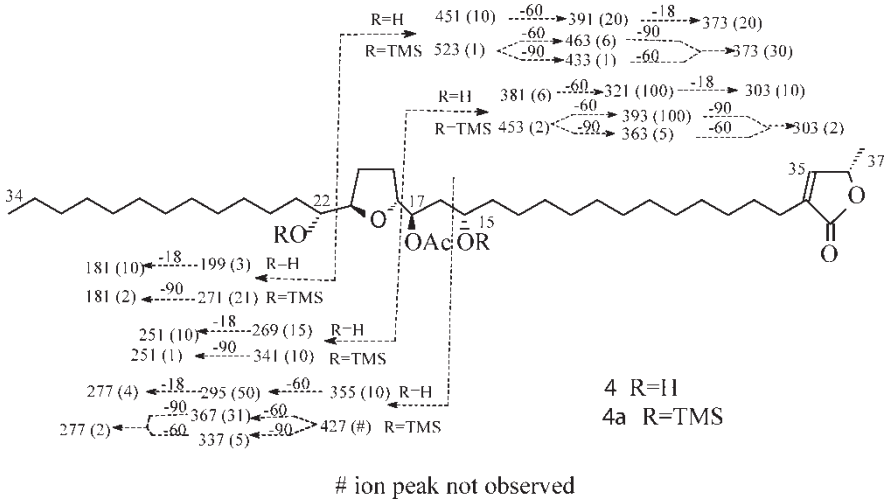

Figure 4. Structure of uvarimacrophin A (**4**) and diagnostic EIMS fragment ions (*m/z*) of **4** and **4a**.

ions at *m/z* 295/367, 381/453, and 453/523, which clearly show the position of the THF ring between C-18 and C-21, two hydroxyls at C-15 and C-22, and the acetoxyl at C-17 [4]. Correlation of the proton at δ 3.38 (H-15) with that at δ 5.11 (H-17) through H-16 (δ 1.54) in the ^{1}H–^{1}H COSY spectrum substantiates the location of the isolated hydroxyl at C-15; meanwhile, a significant cross peak between the proton at δ 5.11(H-17) and the carbonyl carbon at δ 171.5 in an HMBC experiment also demonstrates that the acetoxyl is linked to C-17.

Based on the foregoing discussion, the diagnostic NMR data is closely similar to those of calaminstrin B, except for the signals of H-22 and C-22, indicating that the relative stereochemistries at C-15, C-17, C-18, and C-21 were the same as those of the corresponding carbons in calaminstrin B [4]. Further comparison with diagnostic chemical shifts of a pair of model mono-THF compounds with adjacent hydroxyls in *threo* and *erythro* configurations suggested that the relative stereochemistry between C-21 and C-22 was *threo*, which is evident from the characteristic NMR signals for H-21 at δ 3.82 and C-22 at δ 74.1 [8,9].

The results of the present investigation suggest that uvamalols B and C are a new type of polyoxygenated hexene; its skeleton includes two moieties, a seven carbon cyclohexene unit and a seven carbon benzyl unit, which are linked through a carbon–carbon bond. Interestingly, in combination with our previous investigation, macrophyllols A and B also contain the (2-hydroxy-5-methoxyl)benzyl unit [2,6] — how is the same structural unit attached to two different types of compounds? It is worth exploring the biogenetic pathway of these compounds.

3. Experimental

3.1 General experimental procedures

Melting points were determined on an XT-4 micro-melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer 683 FT infrared spectrometer. UV spectra were obtained on a Shimadzu UV-240 instrument. NMR spectra were run on a Varian INOVA-500 NMR spectrometer with TMS as internal standard. EIMS were obtained on a VG ZAB-2F mass

spectrometer and ESIMS, FABMS, HR-EIMS and HR-FABMS were performed on an Autospec-Utima ETOF Spec mass spectrometer. HPLC separations were conducted on a TSP 3200 pump system equipped with a TSP 3200 UV detector and with a Waters μ-Bondapak C-18 Hyperprep. Column: 10 μm, 25 mm i.d. 250 mm long. Compounds were detected by UV radiation at 254 nm.

3.2 Plant material

Roots of *Uvaria macrophylla* were collected in Jianfengling, Hainan Province, China, in December 2000 and identified by Professor Shi-Man Huang. A voucher specimen (No. 62161) has been deposited in the Herbarium of Institute of Materia Medica, Chinese Academy of Medical Sciences.

3.3 Extraction and isolation

Dried, ground roots (10.0 kg) were extracted with 95% EtOH to afford 1.4 kg of a residue on removal of solvent under reduced pressure. The EtOH extract was partitioned between H_2O and $CHCl_3$, giving a water-soluble fraction I (294 g) and a chloroform-soluble fraction II (230 g) as well as an insoluble fraction III (800 g). Fraction II was first dissolved in 90% MeOH and then defatted with light petroleum to give a methanol-soluble fraction IV (175 g). Fraction IV was subjected to column chromatography on silica gel, eluting with a gradient of light petroleum–acetone, and the eluate collected in 1000 mL fractions (fractions 1–110). Fractions 36–42 + 68–74 and 43–53 showed the presence of polyoxygenated cyclohexenes and acetogenins, respectively, as detected by TLC with a 10% H_2SO_4 alcohol solution containing 0.5% vanillin as spray agent. Fractions 36–42 and 68–74 were mixed and evaporated *in vacuo*, yielding 15.2 g of a residue. The residue was further subjected to column chromatography on silica gel (600 g) eluted with light petroleum–EtOAc (6:4 → 3:7) in 250 mL fractions (fractions 1–36). Eluted subfractions 9 and 23 contained compounds **2** and **1** + **3**, respectively. Subfraction 9 was further purified by preparative TLC with light petroleum–$CHCl_3$–EtOAc (3:1:2) to give 6.8 mg of **2** ($R_f = 0.61$). Subfraction 23 (8.0 mg) showed a single spot on normal phase TLC, but the NMR spectrum revealed a mixture of two compounds in a ratio of 2:1, therefore this fraction was subjected to semipreparative reversed-phase HPLC (flow rate = 1.0 mL min^{-1}) with MeOH–H_2O (75:25) to afford 5.0 mg of **1** ($t_R = 5.37$ min) and 1.5 mg of **3** ($t_R = 6.35$ min). The combined fractions 43–53, containing acetogenins, was repeatedly chromatographed on a silica gel column, alternately eluted with light petroleum–Me_2CO (8:1) and light petroleum–EtOAc (5:1), to yield 15.0 mg of **4**.

3.3.1 Uvamalol A. White powder, mp 136–138°C; $[\alpha]_D^{23}$ − 78 (*c*0.24, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3506 (OH), 3402 (OH), 1714 (C═O), 1705 (C═O), 1601, 1509, 1450, 1315, 1279, 1120, 1070, 1007, 960, 866, 708; UV (MeOH) λ_{max} (nm) (log ϵ): 230 (4.12), 205 (3.04); ^1H ($CDCl_3$, 500 MHz) and ^{13}C ($CDCl_3$, 125 MHz) NMR, see table 1; FABMS *m/z*: 385 (16), 367 (52), 179 (18), 167 (15), 154 (30), 149 (5), 136 (34), 105 (100), 95 (95), 69 (51), 55 (70); HR-FABMS *m/z*: 385.1281 $[M + H]^+$ (calcd for $C_{21}H_{21}O_7$, 385.1287).

3.3.2 Uvamalol B. White crystals, mp 150–151°C; $[\alpha]_D^{23}$ − 275 (*c*0.05, MeOH); IR(KBr) ν_{max} (cm^{-1}): 3429 (OH), 3062, 2935, 2881, 1730 (C═O), 1712, 1600, 1495, 1431, 1377,

1327, 1277, 1250, 1205, 1120, 1045, 1032, 945, 926, 858, 816, 712; UV (MeOH) λ_{max} (nm) (log ϵ): 382 (2.82), 287 (3.76), 230 (4.32); ^{1}H ($CDCl_3$, 500 Hz) and ^{13}C ($CDCl_3$, 125 MHz) NMR, see table 1; EIMS *m/z* 424 (40), 364 (1), 334 (2), 302 (3), 260 (5), 242 (100), 211 (2), 181 (2), 136 (43), 105 (90), 91 (2), 77 (42), 51 (12); HR-FABMS *m/z*: 443.1716 $[M + H]^+$ (calcd for $C_{24}H_{26}O_8$, 443.1706).

3.3.3 Uvamalol C. Oil, mp 150–151°C; $[\alpha]_D^{23}$ −97 (*c*0.07, MeOH); IR (film) ν_{max} (cm^{-1}): 3469 (OH), 3062, 2924, 2854, 1716 (C═O), 1601, 1452, 1369, 1315, 1269, 1176, 1070, 1026, 806, 710, 687; UV (MeOH) λ_{max} (nm) (log ϵ): 203 (4.16), 228 (4.04), 290 (3.87), 358 (2.95); ^{1}H ($CDCl_3$, 500 MHz) and ^{13}C ($CDCl_3$, 125 MHz) NMR, see table 1; FABMS *m/z*: 486 ($[M - H_2O]^+$, 1), 159 (5), 147 (30), 123 (25), 105 (42), 81 (65), 69 (87), 55 (100); HR-FABMS *m/z*: 486.1643 $[M - H_2O]^+$ (calcd for $C_{29}H_{26}O_7$, 486.1678).

3.3.4 Uvarimacrophin A. Wax, $[\alpha]_D^{23}$ +31 (*c* 0.08, MeOH); IR(film) ν_{max} (cm^{-1}): 3469 (OH), 2924, 1852, 1757 (C═O), 1739 (C═O), 1466, 1373, 1317, 1244, 1177, 1074, 1026, 955, 879, 719; ^{1}H ($CDCl_3$, 500 MHz) δ (ppm): 2.27 (H-3, t, $J = 6.8$ Hz), 1.10–1.60 (H-4-14 and H-23-33, m), 3.38 (H-15, m), 1.55 (H-16, m), 5.11 (H-17, m), 3.86 (H-18, m), 1.92–1.64 (H-19-20, m), 3.82 (H-21, m), 3.42 (H-22, m), 0.87 (H-34, t, $J = 6.8$ Hz), 6.95 (H-35, d, $J = 1.5$ Hz), 4.99 (H-36, dq, $J = 1.5, 6.8$ Hz), 1.41 (H-37, d, $J = 6.8$ Hz), 2.06 (CH_3CO, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 173.8 (C-1), 134.3 (C-2), 25.1 (C-3), 22.6–38.7 (C-4-14, 19-20, and 23-33), 70.0 (C-15), 25.3 (C-16), 71.6 (C-17), 82.2 (C-18), 82.9 (C-21), 74.1 (C-22), 14.1 (C-34), 148.8 (C-35), 77.3 (C-36), 19.2 (C-37), 171.5 (CH_3CO), 21.2 (CH_3CO); FABMS *m/z*: 651 ($[M + H]^+$, 70), 591 ($[M + H - HOAc]^+$, 92), 573 ($[M + H - HOAc - H_2O]^+$, 80), 555 ($[M + H - HOAc - 2H_2O]^+$, 100), 537 (31), 451 (12), 387 (4), 374 (10), 321 (20), 295 (20), 277 (3), 239 (10), 209 (4), 161 (3), 149 (15), 109 (50), 95 (72), 81 (80), 69 (100); EIMS data see figure 4. HR-FABMS *m/z*: 651.5179 $[M + H]^+$ (calcd for $C_{39}H_{71}O_7$).

3.3.5 TMSi Derivative (4a). A small amount (0.5 mg) of **4** was treated with *N*,*O*-bis(trimethylsilyl)-acetamide-pyridine and heated at 70°C for 30 min to yield a tri-TMSi derivative (**4a**). The mixture was used directly to measure EIMS; for EIMS fragments of **4a**, see figure 4.

Acknowledgements

This research was supported by National Project 973 (G1998051120). The authors acknowledge the Department of Instrumental Analysis, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College for measuring the UV, IR, NMR, and MS data. We also thank Professor Shi-Man Huang for the plant identification.

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