Two New Sesquiterpenoids from the Rhizomes of *Curcuma xanthorrhiza*

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Zedoardiol (**1**), a new furanoguaiane sesquiterpenoid, and 3,4-dihydroxybisabola-1,10-diene (**2**), a new naturally occurring bisabolane sesquiterpenoid, together with six known compounds, were isolated from *Curcuma xanthorrhiza* ROXB. Their structures were determined on the basis of comprehensive spectroscopic analyses, mainly 1D- and 2D-NMR, MS, IR and X-ray single-crystal diffraction. Herein, the isolation and structure elucidation of the compounds are described.

Introduction. – *Curcuma xanthorrhiza* ROXB. (Zingiberaceae), a well-known traditional medicinal plant used in Malaysia and Indonesia, has received attention for its biological features including anti-inflammatory [1] and anticancer activity [2], protective effect on liver damage [3], and prevention from neurodegenerative disorders [4]. Great efforts have been made to isolate and purify chemicals from this plant, leading to identification of some active compounds. Among these compounds, terpenoids and curcuminoids are the most abundant, and they possess biological activities [5][6]. For example, xanthorrhizol, a sesquiterpenoid obtained from *C. xanthorrhiza* displays potential anticancer and antifungal, as well as estrogenic activity [7–9]. As part of our studies on *C. xanthorrhiza*, we have previously reported the first isolation of four sesquiterpenoids from this species [10]. Continuation of our work on *C. xanthorrhiza* resulted in the isolation of a new furanoguaiane sesquiterpenoid, zedoardiol (**1**), and a new naturally occurring bisabolane sesquiterpenoid, bisabola-1,10-diene-3,4-diol (**2**), along with six known compounds, zedoarol (**3**), guaia-1(10),3,5,7(11),8-pentaene-2-on-12,8-olide (**4**; *Fig. 1*), zederone, curcumenone, vanillin, and dihydrocurcumin. Their structures were determined mainly by NMR and MS methods. For **1**, the X-ray single-crystal diffraction method was used to confirm its structure and relative configuration. Apart from the two new sesquiterpenoids **1** and **2**, this is also the first report for the isolation of zedoarol (a furanoguaiane; **3**) and vanillin from *C. xanthorrhiza.*

Results and Discussion. – Zedoardiol (**1**) was obtained as colorless needles (MeOH), and the molecular formula, $C_{15}H_{18}O_4$, was established by positive-ion-mode HR-ESI-MS (*m*/*z* 285.1100 ($[M+Na]^+$)), indicating seven degrees of unsaturation. Its IR spectrum showed absorptions for OH (3425 cm^{-1}) and conjugated C=O moieties (1653 cm^{-1}). Its ^1H- and ^{13}C-NMR data (*Table 1*) in conjunction with HMQC spectra revealed the presence of two sp^3 Me, three sp^3 CH_2, two sp^3 CH, two sp^2 CH, and six C_q-atoms, including one C=O C-atom (δ(C) 194.9 (C(6))), four sp^2 C-atoms, and one O-

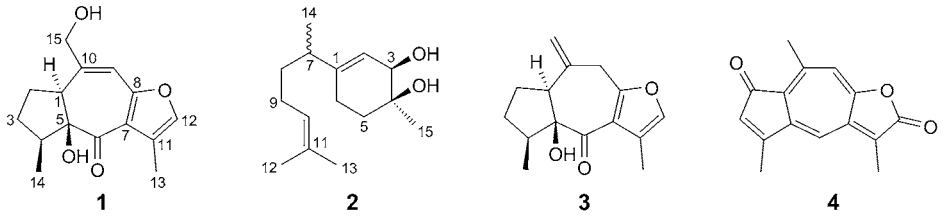

Fig. 1. *Sesquiterpenoids* **1**–**4** *isolated from* Curcuma xanthorrhiza *Roxb.*

bearing sp^3 C_q-atom (83.7 (C(5))). In its HMBC spectra, the strong correlations of the signals at δ(H) 2.23 (*s*, H–C(13)) and 7.16 (*s*, H–C(12)) with that at δ(C) 120.0 (C(7)), of the signals at δ(H) 6.73 (*s*, H–C(9)) and 7.16 (*s*, H–C(12)) with that at δ(C) 156.3 (C(8)), of the signals at δ(H) 2.23 (*s*, H–C(13)) and 7.16 (*s*, H–C(12)) with that at δ(C) 123.0 (C(11)), together with the correlation of the signal at δ(H) 2.23 (*s*, H–C(13)) with that at δ(C) 139.4 (C(12)) indicated the presence of a methylated furan ring with the linkage of C(8) to C(12) *via* an O-atom, and of the Me(13) group on C(11). The presence of an olefinic H-atom (δ(H) 6.73 (H–C(9))) and the fragment O–CH_2(15)–C(10)–CH(9) were identified on the basis of the HMBC cross-peaks δ(H) 4.29, 4.40 (*d*, H–C(15))/δ(C) 115.8 (C(9)); δ(H) 6.73 (*s*, H–C(9)), 4.29, 4.40 (*d*, H–C(15))/δ(C) 143.3 (C(10)), and δ(H) 6.73 (*s*, H–C(9))/δ(C) 65.5 (C(15)). Another atom linked to C(9) was C(8), as determined by the HMBC δ(H) 6.73 (*s*, H–C(9))/δ(C) 156.3 (C(8)). Two connected CH_2 groups (CH_2(2) and CH_2(3)) were deduced from signals at δ(H) 2.00–2.07, 2.11–2.18 (*m*, 2 H), 1.50–1.56, 1.91–1.96 (*m*, 2 H), and their ^{1}H,^{1}H-COSY correlations (*Fig. 2*). A five-membered ring constituted of C(1), C(2), C(3), C(4), and C(5) was evidenced by the following correlations (*Fig. 2*): δ(H) 3.16 (*t*, H–C(1)), 1.50–1.56, 1.91–1.96 (*m*, CH_2(3))/δ(C) 24.1 (C(2)); δ(H) 3.16 (*t*, H–C(1)), 2.59–2.64 (*m*, H–C(4))/δ(C) 30.1 (C(3)); δ(H) 2.00–2.07, 2.11–2.18 (*m*, CH_2(2)), 1.50–1.56, 1.91–1.96 (*m*, CH_2(3))/δ(C) 83.7 (C(5)). The Me group (δ(H) 1.17 (*d*, Me(14))) was linked to C(4) (δ(C) 39.2) according to its *doublet* signal and HMBCs: δ(H) 1.17 (*d*, Me(14))/δ(C) 30.1 (C(3)), 39.2 (C(4)), 83.7 (C(5)). The position of C=O (C(6)) was established by the weak HMBC: δ(H) 3.16 (*t*, H–C(1))/δ(C) 194.9 (C(6)). X-Ray single-crystal diffraction data further confirmed unambiguously the structure of **1** and revealed its relative configuration as shown in *Fig. 3*.

Table 1. *^{1}H- and ^{13}C-NMR Data* (600 and 150 MHz, resp., $CDCl_3$) *of* **1**. δ in ppm, *J* in Hz. Atom numbering as indicated in *Fig. 1.*

Position	δ(H)	δ(C)	Position	δ(H)	δ(C)
1	3.16 (*t*, *J* = 9.0)	48.5	8		156.3
2	2.00–2.07 (*m*), 2.11–2.18 (*m*)	24.1	9	6.73 (*s*)	115.8
			10		143.3
3	1.50–1.56 (*m*), 1.91–1.96 (*m*)	30.1	11		123.0
			12	7.16 (*s*)	139.4
4	2.59–2.64 (*m*)	39.2	13	2.23 (*s*)	9.8
5		83.7	14	1.17 (*d*, *J* = 6.0)	14.4
6		194.9	15	4.29, 4.40 (2*d*, ^2J = 13.8)	65.5
7		120.0			

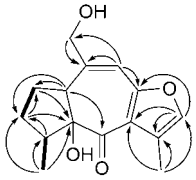

Fig. 2. *Key HMBCs* (H → C) *and* $^1H,^1H$*-COSY* (—) *Correlations of* **1**

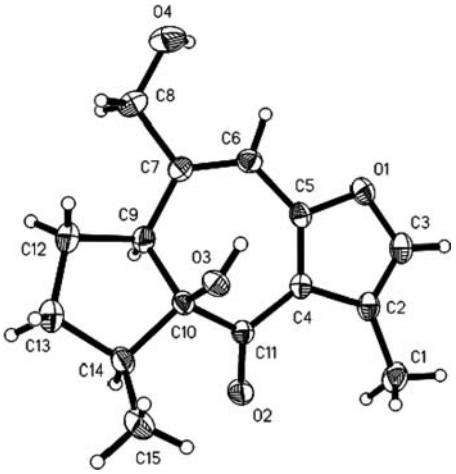

Fig. 3. *ORTEP Structure of* **1**

Bisabola-1,10-diene-3,4-diol (**2**) was obtained as pale yellow oil. Based on HR-ESI-MS (*m*/*z* 261.1826 ($[M+Na]^+$)), the molecular formula was established as $C_{15}H_{26}O_2$, requiring three degrees of unsaturation. Its ^{13}C-NMR spectrum (*Table 2*) exhibited 15 C-atom signals with four at low field (δ(C) 144.9 (C(1)), 122.3 (C(6)), 124.4 (C(10)), and 131.5 (C(11))) indicating the presence of two C=C bonds. The molecular formula and the presence of two C=C bonds evidenced that **2** is a monocyclic sesquiterpenoid. The signals at δ(C) 72.3 and 74.7 were characteristic of two C-atoms with OH substituents. The HMQC spectrum ($CDCl_3$) of **2** indicated four Me (δ(C) 17.7 (C(12)), 19.7 (C(14)), 21.0 (C(15)), and 25.7 (C(13))), four sp^3 CH_2 (23.9 (C(6)), 33.5 (C(5)), 35.2 (C(8)), and 26.1 (C(9))), two sp^3 CH (74.7 (C(3)) and 39.8 (C(7))), two sp^2 CH groups (122.3 (C(2)) and 124.4 (C(10))), and three C_q-atoms (144.9 (C(1)), 72.3 (C(4)), and 131.5 (C(11))). In the ^{1}H-NMR spectrum of **2**, four signals attributable to Me groups were observed as a *doublet* at δ(H) 1.01 ($^3J = 7.2$, Me(14)), and three *singlet*s at 1.20 (Me(15)), 1.59 (Me(12)), and 1.68 (Me(13)). The last two resonances were assigned to olefinic Me groups on C(11) based on their HMBCs with the C-atom signals at δ(C) 131.5 (C(11)) and 124.4 (C(10)). The HMBCs of the signals at δ(H) 1.20 (*s*, Me(15)) with those at δ(C) 72.3 (C(4)), 33.5 (C(5)), and 74.7 (C(3)) revealed that the Me group (C(15)) was attached to C(4). The strong ^{1}H,^{1}H-COSY correlations δ(H) 1.01 (*d*, Me(14))/2.11 (H–C(7)) indicated the position of the Me group (C(14)) at C(7). The structure of **2** was established as bisabola-1,10-diene-3,4-diol based on the key HMBCs (*Fig. 4*). The obvious NOESY correlation Me(15)/H–C(3) evidenced the *cis*-orientation of the OH groups at C(3) and C(4) on the six-membered ring in a half-chair

Table 2. *^{1}H- and ^{13}C-NMR Data* (600 and 150 MHz, resp., $CDCl_3$) *of* **2**. δ in ppm, J in Hz. Atom numbering as indicated in *Fig. 1*.

Position	δ(H)	δ(C)	Position	δ(H)	δ(C)
1		144.9	9	1.69–1.71 (*m*), 1.89–1.91 (*m*)	26.1
2	5.36 (br. *s*)	122.3	10	5.08 (*t*, *J* = 6.0)	124.4
3	4.05 (br. *s*)	74.7	11		131.5
4		72.3	12	1.59 (*s*)	17.7
5	1.70–1.73 (*m*)	33.5	13	1.68 (*s*)	25.7
6	2.00–2.04 (*m*)	23.9	14	1.01 (*d*, *J* = 7.2)	19.7
7	2.08–2.13 (*m*)	39.8	15	1.20 (*s*)	21.0
8	1.27–1.33 (*m*), 1.37–1.43 (*m*)	35.2			

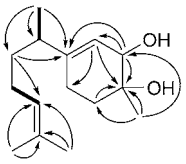

Fig. 4. *Key HMBCs* (H → C) *and ^{1}H,^{1}H-COSY* (—) *Correlations of* **2**

conformation (*Fig. 5*). This compound was prepared and described in a conference abstract [11] without any structural information.

On the basis of NMR and MS data, or comparison with reference compounds, zedoarol [12], guaia-1(10),3,5,7(11),8-pentaene-2-on-12,8-olide [13], zederone [14], curcumenone [15], dihydrocurcumin [16], and vanillin [17] were identified.

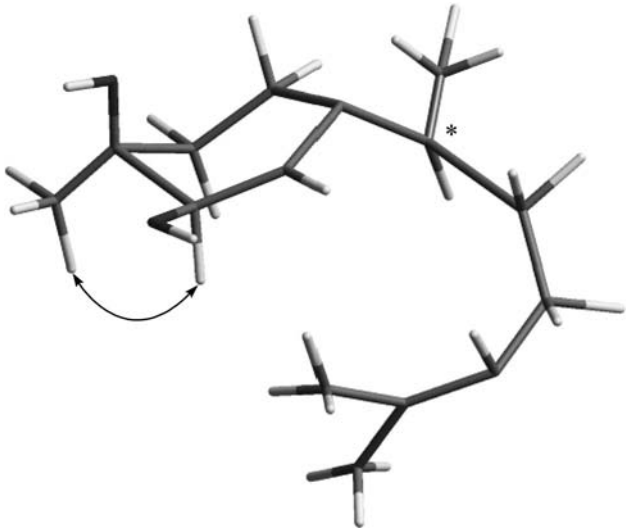

Fig. 5. *ChemDraw 3D model showing key NOESY* (H ↔ H) *correlations of* **2** (the configuration of the C-atom marked with * is assumed.)

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Experimental Part

General. Reagents and solvents used were mostly of anal. grade. TLC: Silica-gel F_{254} plates (SiO_2; *Qingdao Haiyang Chemical Factory*, Qingdao, P. R. China). Column chromatography (CC): SiO_2 (200–300 and 300–400 mesh, *Qingdao Haiyang Chemical Factory*), *Sephadex LH-20* (20–100 μm, *GE Healthcare*, Sweden), and reversed-phase (RP) gel *ODS-A-HG* (12 nm–50 μm, *YMC*, Japan). HPLC: *Agilent 1200 G1322A* degasser, *Agilent 1200 G1311A* quaternary pump, *Agilent 1100 G1315D* DAD detector, *ZORBAX SB-C*$_{18}$ 5 μm column (9.4 × 250 mm and 4.6 × 250 mm; *Agilent Technologies*). IR Spectra: *Avatar-360-ESP* spectrophotometer (*Thermo Nicolet*); KBr tablets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker-Avance-600* spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-ESI-MS: *LTQ-Orbitrap XL*; in m/z.

Plant Material. *C. xanthorrhiza* ROXB. rhizome material (origin, Indonesia) was purchased from *Dixa*, CH-St. Gallen, and was identified by Prof. *Lan Xiang*. A voucher specimen has been deposited with the School of Pharmaceutical Sciences, Shandong University, Jinan, P. R. China.

Extraction and Isolation. The dried and powdered material (5.0 kg) of *C. xanthorrhiza* ROXB. was percolated three times with 95% EtOH at r.t. The residue (193.0 g) was suspended in H_2O, and then extracted with petroleum ether (PE; 3 × 500 ml), AcOEt (3 × 500 ml), and BuOH (0.5 × 500 ml), successively. The PE-soluble part (330 g) was subjected to CC (SiO_2 (200–300 mesh; 105 g), 8 × 70 cm; PE/AcOEt 100:0 to 0:100): *Frs. 1–15*. *Fr. 4* (8.92 g) was submitted to MPLC (*ODS-A-HG* (12 nm–50 μm); MeOH/H_2O 3:7 to 0:10): zederone (33 mg). *Fr. 5* (1.82 g) was separated by repeated CC (SiO_2 (200–300 mesh); PE/AcOEt 98:2 to 1:1)): **3** (12 mg). *Frs. 6–8* and *Frs. 9–11* were separated by RP-CC (MeOH/H_2O 3:7 to 10:0), CC (*Sephadex LH-20*; MeOH/H_2O), and HPLC (MeOH/H_2O), resp.: **1** (11 mg), **2** (9 mg), **4** (4.2 mg), vanillin (5.0 mg), curcumenone (3.6 mg). *Fr. 12* was subjected to CC (*Sephadex LH-20*; MeOH/H_2O): dihydrocurcumin (7.7 mg).

Zedoardiol (= rel-*(4a*R,*5*R,*7a*R*)-5,6,7,7a-Tetrahydro-4a-hydroxy-8-(hydroxymethyl)-3,5-dimethylazuleno[6,5-*b*]furan-4(4a*H*)-one*; **1**). Colorless needles (MeOH). IR: 3529, 3425, 2953, 2875, 1653, 1597, 1546, 1418, 1376, 1278, 1067, 967. ^{1}H- and ^{13}C-NMR: *Table 1*. HR-ESI-MS: 285.1100 ($[M+Na]^+$, $C_{15}H_{18}NaO_4^+$; calc. 285.1103), 245.1173 ($[M-OH]^+$, $C_{15}H_{17}O_3^+$; calc. 245.1178).

Bisabola-1,10-diene-3,4-diol (= rel-(*1*R,*2*S*)-1-Methyl-4-(6-methylhept-5-en-2-yl)cyclohex-3-ene-1,2-diol*; **2**). Pale-yellow oil. ^{1}H- and ^{13}C-NMR: *Table 2*. HR-ESI-MS: 261.1826 ($[M+Na]^+$, $C_{15}H_{26}NaO_2^+$; calc. 261.1830), 238.2166 (M^+, $C_{15}H_{26}O_2^+$; calc. 238.1933).

X-Ray Crystal-Structure Determination of Zedoardiol[1]). A colorless platelet crystal with dimensions of 0.47 × 0.25 × 0.05 mm^3 was used for data collection on a *Bruker APEX2* CCD area-detector diffractometer equipped graphite-monochromated MoK_α radiation (λ = 0.71069 Å) and operating in ω scan technique for data collection at 293(2) K. The determination of lattice parameters, integration of the intensities, correction for *Lorentz* and polarization effects, and cell refinement was performed with APEX2 Software Suite (*Bruker*, 2009). The structure was solved by direct methods using SIR 97 program (*Altomare*, 1999) and refined by SHELXL-97 program (*Sheldrick*, 1997). Crystal data: a = 5.4612(8) Å, b = 13.158(2) Å, c = 17.948(3) Å; V = 1289.7(3) $Å^3$; Z = 4; D_x = 1.351 g cm^{-3}; space group: $P2_12_12_1$. Refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 2976/0/176; goodness-of-fit on F^2: 1.055; final R indices [$I > 2\sigma(I)$]: R^1 = 0.0397, wR^2 = 0.1035; R indices (for all data): R^1 = 0.0508, wR^2 = 0.1109; largest diff. peak and hole: 0.260 and −0.194 e $Å^{-3}$.

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[1]) CCDC-971184 contains the supplementary crystallographic data for this work. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

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