Three New Guaianolides from Siyekucai (*Ixeris chinenseis*)

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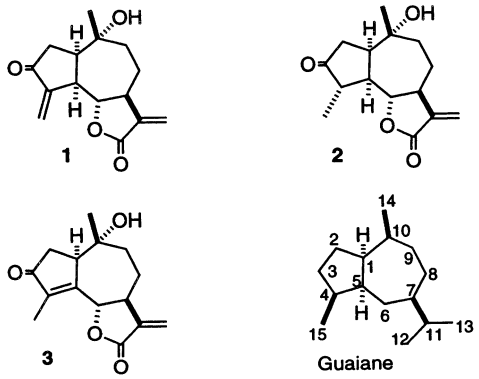
Three new guaianolides, 10α-hydroxy-3-oxoguaia-4(15),11(13)-dieno-12,6α-lactone (**1**), 10α-hydroxy-3-oxo-4*β*H-guaia-11(13)-eno-12,6α-lactone (**2**), and 10α-hydroxy-3-oxoguaia-4,11(13)-dieno-12,6α-lactone (**3**), named chinensiolides A, B, and C were isolated from the whole plant of Siyekucai (*Ixeris chinensis*). The structures were determined by HREIMS, UV, IR, and one- and two-dimensional NMR techniques (^{1}H and ^{13}C NMR, COSY, HMQC, HMBC, and NOE difference and NOESY experiments). Compounds **1** and **2** were indicated to be a mixture of flexible conformers by analyses of their 1D NOE and NOESY spectra as well as the temperature dependence of their ^{1}H and ^{13}C NMR spectra. Chinensiolide B (**2**) was transformed to chinensiolide C (**3**) in a three-step conversion.

The guaianolides represent one of the largest groups of sesquiterpene lactones covering over 500 known naturally occurring compounds.[1] Some of these compounds have been reported to possess antitumor,[2−4] root-growth stimulatory,[2,5] germination inhibitory,[6] antiulcer,[7] and immunocontrolling activities.[8−10]

Ixeris chinensis Nakai (Compositae),[11] known as Siyekucai, is a perennial plant that grows in various places in China. This plant is used in China as a folk medicine for the treatment of bronchitis, pneumonia, pharyngitis, dysentery, and poisonous indigestion on the basis of its antifebrile, antidotal, and analgesic effects.[12] Studies on other species of this genus revealed the presence of sesquiterpene lactones such as guaianolides, eudesmanolides, germacranolides, and their glycosides.[13−15] As a part of our studies on bitter substances, we have investigated *I. chinensis* and now report the isolation of three new guaianolides from this plant.

The *I. chinensis* plant material was collected in Qiqihar City, Heilongjiang Province, China, in summer. The methanolic extract of the fresh whole plant was defatted by extraction with hexane. The MeOH layer was concentrated, diluted with H_2O, and extracted with ethyl acetate. The ethyl acetate extracts were then subjected to separation with flash chromatography followed by HPLC on silica gel to give three new guaiane type α-methylene-*γ*-lactones (**1**, **2**, and **3**).

Chinensiolide A (**1**) had the composition $C_{15}H_{18}O_4$, which was determined by a combination of HREIMS and ^{1}H and ^{13}C NMR spectra. The IR spectrum of **1** indicated the existence of a hydroxyl group (3616 cm^{-1}), an α,*β*-unsaturated five-membered ring carbonyl (1730 and 1642 cm^{-1}), and an α,*β*-unsaturated *γ*-lactone (1770 and 1642 cm^{-1}). The ^{13}C NMR spectrum displayed 15 carbon resonances. Lactone and ketone carbonyls were located at *δ* 169.6 and 204.4, respectively. Signals for two carbons bearing oxygen were observed at *δ* 84.0 (d) and 74.1 (s). Exocyclic methylene resonances were observed at 120.6 (t) and 120.8 (t). Judging from the DEPT and HMQC spectra, the remaining



protonated carbon resonances were due to one methyl carbon, three methylene carbons, and three methine carbons. The ^{1}H NMR spectra showed one methyl, two exocyclic methylene, and one oxymethine proton. The connections of the protonated carbons (C-1 to C-2, C-1 to C-5, C-5 to C-6, C-6 to C-7, C-7 to C-8, and C-8 to C-9) were determined by the analysis of a ^{1}H−^{1}H COSY spectrum.

An HMBC experiment was used to assign the quaternary carbons and the attachment of lactone ring and the hydroxyl group. The correlation of the signal due to the quaternary carbon bearing a hydroxyl group at *δ* 74.1 (s) with those of H-1, H-2α,*β*, H-8α, H-9α,*β*, and H-14 placed the hydroxyl group at C-10. The correlation of the carbonyl carbon signal at *δ* 204.35 with those of H-1, H-2α,*β*, and H-15a,b placed the ketone carbonyl group at C-3. The HMBC correlation of a nonprotonated olefinic carbon at *δ* 145.2 with H-1, H-5, H-6, and H-15a indicated the location of an exo-methylene at C-4. The HMBC correlation of five carbon atoms of the *γ*-lactone moiety [C-12 (carbonyl carbon at *δ* 169.6) with H-13a,b (exocyclic methylene protons); C-13 with H-7; C-11 with H-7, H-13a; C-7 with H-8α,*β*, H-9α,*β*, H-13a,b; and C-6 with H-1, H-5] as well as the ^{1}H−^{1}H COSY correlation of H-6 with H-5 and H-7 allowed unambiguous connection of the α-methylene-*γ*-lactone to the C-6 and C-7 positions. These spectroscopic analyses indicated that compound **1** possessed the guaianolide structure 10-hydroxy-3-oxoguaia-4(15),11(13)-dieno-12,6-lactone. The coupling constant between H-1 and H-5 (J = 8.0 Hz) indicated the A,B *cis* ring fusion and the coupling constant of H-6 ($J_{5,6}$ = 9.8 Hz and $J_{6,7}$ = 9.8 Hz) indicated

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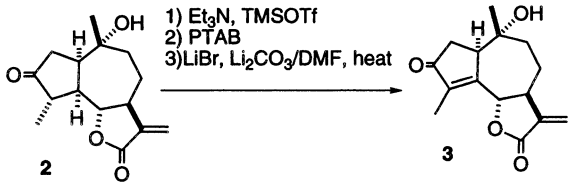
a *trans* relationship of H-5 and H-6 and the existence of a *trans*-fused γ-lactone. The stereochemistry at C-10 Me (H-14), H-6, H-1, H-5, and H-7 was determined by 1D NOE and NOESY experiments. The stereostructure indicated in structure **1** was fully supported by the results of NOE experiments.

Chinensiolide B (**2**) had the composition $C_{15}H_{20}O_4$, which was determined by a combination of HREIMS and ^1H and ^{13}C NMR spectra. The IR spectrum of **2** indicated the existence of a hydroxyl group (3612 cm^{-1}), a five-membered ring carbonyl (1744 cm^{-1}), and an α,β-unsaturated γ-lactone (1770 and 1646 cm^{-1}). The ^{13}C NMR spectrum displayed 15 carbon resonances. Lactone and ketone carbonyl signals were located at δ 169.9 and 219.3, respectively. Two signals of carbons bearing oxygen were observed at δ 85.8 (d) and 73.1 (s). An exocyclic methylene resonance was observed at 119.4 (t). Judging from the DEPT and HMQC spectra, it was clear that the remaining protonated carbon resonances were due to two methyl carbons, three methylene carbons, and four methine carbons. The ^1H NMR showed a singlet methyl, a doublet methyl, an exocyclic methylene, and an oxymethine proton. In addition to spectral data mentioned above, the $^1H-^1H$ correlations of H-4 and H-5 and H-4 and H-15 in the $^1H-^1H$ COSY spectrum suggested that **2** was the 4,15-dihydro derivative of **1**. The relationships of the protonated carbons were determined by analysis of the $^1H-^1H$ COSY spectrum and the assignments of quaternary and carbonyl carbons, and the attachment of a lactone ring and a hydroxyl group was determined by analysis of the HMBC spectrum by the analogous discussion for **1**. Thus, compound **2** possessed the guaianolide structure 10-hydroxy-3-oxoguaia-11(13)-eno-12,6-lactone. The coupling constant between H-1 and H-5 (J = 8.0 Hz) indicated A,B *cis* ring fusion, and the coupling constant of H-6 ($J_{5,6}$ = 10.0 Hz and $J_{6,7}$ = 10.0 Hz) indicated the existence of *trans*-fused γ-lactone. The stereochemistry of C-4 Me and C-10 Me were determined to be the α- and β-configuration, respectively, by the NOESY experiment. Thus, a strong NOESY correlation was observed between H-4 and H-6 and between H-6 and H-14.

Chinensiolide C (**3**) had the composition $C_{15}H_{18}O_4$, which was determined by a combination of HREIMS and ^1H and ^{13}C NMR spectra. The IR spectrum of **3** showed the existence of a hydroxyl group (3616 cm^{-1}), an α,β-unsaturated five-membered ring carbonyl (1710 and 1608 cm^{-1}), and an α,β-unsaturated γ-lactone (1776 and 1646 cm^{-1}). The ^{13}C NMR spectrum displayed 15 carbon resonances. Lactone and ketone carbonyls were located at δ 168.9 and 207.5, respectively. Resonances for carbons bearing oxygen were observed at δ 81.9 (d) and 74.4 (s). An exocyclic methylene resonance was observed at 120.7 (t). Judging from the DEPT and HMQC spectra, it was clear that the remaining protonated carbon resonances were due to two methyl, three methylene, and two methine carbons. The ^1H NMR showed two methyls, an exocyclic methylene, and an oxymethine proton. One of the methyl groups (δ 1.94, s) was shown to connect to the double bond (C_4) by the $^1H-^1H$ correlations H-1 and H-15 and H-6 and H-15 in the H−H COSY spectrum. These spectral data suggested that **3** was the endo-isomer of **1**. Connectivity of the protonated carbons was determined by analysis of the $^1H-^1H$ COSY spectrum and the assignment of quaternary and carbonyl carbons, and the attachment of the lactone ring and the hydroxyl group was determined by HMBC analysis. Thus, compound **3** has the guaianolide structure 10-hydroxy-3-oxoguaia-4,11(13)-dieno-12,6-lactone. The coupling constant of H-6 ($J_{6,7}$ = 10.7 Hz) indicated the existence of a *trans*-fused γ-lactone. The stereochemistry of the C-10 Me (H-14) and H-6 was determined to be the β-configuration, and the stereochemistry of H-1 and H-7 was determined to be the α-configuration by 1D NOE and NOESY experiments, as well as the coupling pattern of H-6 mentioned above.

The C-9 and C-14 signals of **1** and **2** were very weak and broad at 20 °C in $CDCl_3$ and pyridine-d_5 at 125 MHz; however **3** showed strong, sharp C-14 and C-9 signals. Although at 100 and 50 MHz the C-14 and C-9 signals of **1** and **2** were stronger and sharper than those at 125 MH, they still were not as sharp as expected. We then examined the temperature dependence of the ^{13}C NMR spectra of **1** and **2** in pyridine-d_5 at 125 and 100 MHz. The temperature was changed from −40 °C to 80 °C. The C-14 and C-9 signals of **2** became sharp at temperatures higher than 60 °C at 125 MHz. Unfortunately, **1** decomposed during the experiments at elevated temperatures, but the spectroscopic behavior of **2** in ^{13}C NMR was similar to **1**. The ^{13}C NMR signals of **2** became broad at −40 °C at 100 MHz, but the expected separation of the signals due to different conformations was not observed. The ^{13}C NMR behavior of **1**, **2**, and **3** may be explained by the conformational changes of their seven-membered B ring. The temperature dependence of **1** and **2** showed that the conformational change of **1** and **2** was slow at room temperature and rapid at temperatures higher than 60 °C in the time scale of ^{13}C NMR. NOE experiments also suggested different conformations of the seven-membered B ring of **1** and **2** at room temperature. On the contrary, NOE experiments of **3** showed only NOE correlations based on a single conformation. Details of the various NMR experiments are summurized in the Supporting Information.

Treatment of **2** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of Et_3N using CH_2Cl_2 as a solvent, followed by bromination of the resulting silyl enol ether with phenyltrimethylammonium perbromide (PTAB), gave the α-bromoketone in a one-pot operation. Dehydrobromination of this crude bromide with LiBr and Li_2CO_3 in DMF at 120 °C gave **3**. The ^1H NMR spectrum of **3** prepared from **2** was identical with that of natural chinensiolide C (**3**).



Experimental Section

General Experimental Procedures. Melting points are uncorrected. Optical rotation, $[\alpha]_D$, values were measured using a Horiba Sepa-200 polarimeter. UV spectra were measured in MeOH using a Nihonbunko V-550 UV/vis spectrophotometer. ^1H and ^{13}C NMR spectra were measured with a Varian Unity-plus instrument. ^1H NMR assignments were determined by H−H COSY experiments. ^{13}C NMR assignments were determined using DEPT, HMBC, and HMQC experiments. HREIMS were recorded on a JEOL-HX 110 instrument. CH_2Cl_2, Et_3N, and DMF were distilled from CaH_2. Reactions were run under an atmosphere of Ar. Silica gel 70−200 mesh was employed for column chromatography and silica gel 230−400 mesh for flash column chromatography.

Plant Material. Whole plants of Siyekucai (*Ixeris chinensis* Nakai) were collected in Qiqihar City, Heilongjiang Province, China, on July 30, 1998. The plant was identified by Dr.

Takahide Kurosawa, Department of Biology, Faculty of Science, Tohoku University, Sendai, Japan. A voucher specimen (1998-7-30) was deposited at the laboratory of Natural Products, Department of Pharmacy Engineering, Qiqihar University.

Extraction and Isolation. Fresh whole plant (1524 g) was crushed and extracted with MeOH (2.5 L) for 3 days. The MeOH extract was concentrated to 1.5 L and extracted with hexane (2 × 300 mL). The hexane extracts were dried (Na_2SO_4) and concentrated to give an oily residue (10.0 g). Water (1 L) was added to the MeOH layer, and this was extracted with EtOAc (3 × 800 mL). The EtOAc extracts were dried (Na_2SO_4) and concentrated to give oily material (4.0 g), which was separated into nine fractions with flash chromatography [4.6 cm i.d. column packed with silica gel (200 g), EtOAc−hexane (1:1, 1500 mL, fractions 1−4), EtOAc (2000 mL, fractions 5−7), MeOH (1000 mL, fractions 8, 9)]. Fraction 6 (362 mg) was further separated by HPLC [INERTSIL PREP-SIL (GL-Science), 25 × 1 cm i.d. stainless column, EtOAc, 5 mL/min] into four fractions. The third peak (t_R 9.04 min) gave a compound (5.0 mg), which was recrystallized from MeOH two times to give chinensiolide A (**1**) (3.1 mg, 0.0002%). The fourth peak (t_R 9.92 min) gave a crude solid compound (13.2 mg). Further purification by HPLC using the same conditions gave crystalline material, which was recrystallized from MeOH to give chinensiolide B (**2**) (11.4 mg, 0.0007%). Fraction 7 (300 mg) was further separated by HPLC [INERTSIL PREP-SIL (GL-Science), 25 × 1 cm i.d. stainless column, EtOAc−MeOH (95:5), 5 mL/min] into four fractions. The second peak (t_R 6.94 min) gave crystalline chinensiolide C (**3**) (15.9 mg, 0.0010%).

Chemical Transformation of 2 to 3. A solution of **2** (4.80 mg, 0.0184 mmol) in CH_2Cl_2 (150 μL) containing Et_3N (15.1 mL, 0.109 mmol) was treated at 0 °C with TMSOTf (10.6 μL, 0.054 mmol) for 50 min. A solution of PTAB (10.3 mg, 7.2 mmol) in CH_2Cl_2 (50 μL) was added to the mixture, which was stirred for 5 min at 0 °C and worked up to give a crude, oily product (12.0 mg), which was purified by flash chromatography [0.4 cm column, silica gel 0.5 g, EtOAc−hexane (4:6)] to give the bromide (1.5 mg). The solution of the bromide in DMF (150 μL) was treated with LiBr (1.3 mg, 0.015 mmol) and Li_2CO_3 (1.3 mg, 0.018 mmol) at 120 °C for 20 min. The mixture was worked up and purified by flash column chromatography [0.4 cm column, silica gel 0.5 g, EtOAc−hexane (4:6)] and HPLC [silica gel, 20 × 0.46 i.d.; EtOAc−hexane (4:6), 2.0 mL/min] to give **3** (0.3 mg, 9%).

Chinensiolide A (1): colorless plates; 110.5−112 °C; $[\alpha]^{20}_D$ +13.3° (*c* 0.015, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 236 (4.21) nm; IR ($CHCl_3$) ν_{max} 3616, 2944, 1770, 1730, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.27 (1H, d, J = 3.8 Hz, H-13a), 6.19 (1H, br d, J = 2.7 Hz, H-15a), 5.73 (1H, br d, J = 2.5 Hz, H-15b), 5.55 (1H, d, J = 3.1 Hz, H-13b), 4.13 (1H, dd, J = 9.8, 9.8 Hz, H-6), 3.33 (1H, dddd, J = 9.8, 8.0, 2.7, 2.5 Hz, H-5), 3.13 (1H, ddddd, J = 10.5, 9.8, 4.5, 3.8, 3.1 Hz, H-7), 2.76 (1H, dd, J = 18.2, 6.0, H-2β), 2.60 (1H, ddd, J = 8.5, 8.0, 6.0 Hz, H-1), 2.48 (1H, dd, J = 18.2, 8.5 Hz, H-2α), 2.27 (1H, dddd, J = 14.5, 6.0, 6.0, 4.5 Hz, H-8α), 1.99 (1H, ddd, J = 14.5, 6.0, 6.0 Hz, H-9β) 1.79 (1H, ddd, J = 14.5, 9.0, 6.0 Hz, H-9α), 1.50 (1H, dddd, J = 14.5, 10.0, 9.0, 6.0 Hz, H-8β), 1.11 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.4 (s, C-3), 169.6 (s, C-12), 145.2 (s, C-4), 139.4 (s, C-11), 120.8 (t, C-15), 120.6 (t, C-13), 84.0 (d, C-6), 74.1 (s, C-10), 47.8 (d, C-5), 46.0 (d, C-1), 44.0 (d, C-7), 40.3 (t, C-2), 40.0 (t, C-9), 26.8 (q, C-14), 25.3 (t, C-8); HREIMS *m*/*z* 262.1197 (calcd for $C_{15}H_{18}O_4$ 262.1205).

Chinensiolide B (2): colorless plates: 195−199.5 °C; $[\alpha]^{20}_D$ +2.6° (*c* 0.469, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 216 (3.77) nm; IR ($CHCl_3$) ν_{max} 3612, 2972, 2940, 1770, 1744, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.27 (1H, d, J = 3.5 Hz, H-13a), 6.20 (1H, s, OH), 5.44 (1H, d, J = 3.5 Hz, H-13b), 4.14 (1H, dd, J = 10.0, 10.0 Hz, H-6), 3.08 (1H, br t, J = 10.5 Hz, H-7), 3.02 (1H, br dd, J = 19.0, 6.5 Hz, H-2β), 2.51 (1H, br dq, J = 8.0, 7.3 Hz, H-4), 2.49 (1H, dd, J = 19.0, 9.5 Hz, H-2α), 2.35 (1H, ddd, J = 10.0, 8.0, 8.0 Hz, H-5), 2.27 (1H, ddd, J = 9.5, 8.0, 6.5 Hz, H-1), 2.15 (1H, dddd, J = 14.0, 6.0, 5.0, 4.5 Hz, H-8α), 2.08 (1H, ddd, J = 14.0, 6.0, 5.0 Hz, H-9β), 1.36 (1H, dddd, J = 14.5, 11.0, 9.0, 5.0 Hz, H-8β), 1.36 (1H, ddd, J = 14.0, 9.0, 6.0 Hz, H-9α), 1.26 (3H, s, H-14), 1.24 (3H, d, J = 7.3 Hz, H-15); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 219.3 (s, C-3), 169.9 (s, C-12), 141.3 (s, C-11), 119.4 (t, C-13), 85.8 (d, C-6), 73.1 (s, C-10), 50.5 (d, C-5), 48.3 (d, C-4), 46.5 (d, C-1), 44.5 (d, C-7), 40.6 (t, C-9), 40.3 (t, C-2), 27.1 (q, C-14), 25.9 (t, C-8), 15.9 (q, C-15); HREIMS *m*/*z* 264.1355 (calcd for $C_{15}H_{20}O_4$ 264.1362).

Chinensiolide C (3): colorless microcrystals (15.9 mg); 185.5−186.5 °C; $[\alpha]^{20}_D$ +73.2° (*c* 1.070, MeOH); UV (MeOH) λ_{max} (log ϵ) 231 (4.35) nm; IR ($CHCl_3$) ν_{max} 3616, 2940, 1776, 1710, 1646, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.32 (1H, d, J = 2.4 Hz, H-13a), 5.61 (1H, d, J = 2.4 Hz, H-13b), 4.82 (1H, d, J = 10.7 Hz, H-6), 3.27 (1H, br s, H-1), 3.06 (1H, br t, J = 10.7 Hz, H-7), 2.59 (1H, m, H-2), 2.30 (1H, br d, J = 13.9 Hz, H-8α), 2.13 (1H, br d, J = 13.9 Hz, H-9β), 1.94 (3H, br s, H-15), 1.88 (1H, ddd, J = 13.9, 13.9, 3.1 Hz, H-9α), 1.50 (1H, ddd, J = 13.9, 13.9, 3.1 Hz, H-8β), 0.98 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.5 (s, C-3), 168.9 (s, C-12), 160.8 (s, C-5), 143.0 (s, C-4), 137.7 (s, C-11), 120.7 (t, C-13), 81.9 (d, C-6), 74.4 (s, C-10), 50.5 (d, C-1), 44.9 (t, C-9), 44.5 (d, C-7), 37.2 (t, C-2), 25.0 (t, C-8), 21.3 (q, C-14), 9.5 (q, C-15); HREIMS *m*/*z* 262.1221 (calcd for $C_{15}H_{18}O_4$ 262.1205).

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Supporting Information Available: Details of the NMR experiments performed on compounds **1**, **2**, and **3** are summerized in Tables 1−3. Included are six pages of actual spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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