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IRIDOID GLUCOSIDES FROM *LINOCIERA SANGDA*

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Dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday

Abstract – A phytochemical investigation of the aerial parts of *Linociera sangda* led to the isolation of three new iridoid glucosides (**1–3**), together with nine known iridoid glucosides and a flavonoid glycoside, nicotiflorin. The structures of the new compounds were elucidated spectroscopically. Compounds **1–3** are members of a rare group of iridoids with a spiro lactone ring, and compound **3** is the first instance of an adduct of iridoid glucoside and flavonoid glycoside.

INTRODUCTION

Linociera is a genus of shrubs and trees of the family Oleaceae found in the tropics. *Linociera sangda* Gagnep. (syn. *Chionanthus microstigma* (Gagnep.) P.S.Green.) has been used as a nerve depressant remedy in Thailand. However, no phytochemical studies of *L. sangda* have been reported. In the course of our chemical studies on the glycosides of oleaceous plants,¹ we investigated the constituents of *L. sangda* and isolated three unknown iridoid glucosides (**1–3**), as well as ten known glycosides. This paper reports the structural determination of these novel complex compounds with a spiro lactone functionality.

RESULTS AND DISCUSSION

The *n*-BuOH soluble fraction of methanolic extracts of the aerial parts of *L. sangda* was separated by a combination of column chromatography, preparative thin-layer chromatography (TLC), and preparative high-performance liquid chromatography (HPLC) affording three new iridoid glucosides (**1–3**) together with nine known iridoid glucosides, asperuloside (**4**),² asperulosidic acid (**5**),³ daphylloside (**6**),² gaertneroside (**7**),^{4,6} 13*R*-*epi*-gaertneroside (**8**),⁷ 13-methoxygaertneroside (**9**),⁸

13-methoxy-*epi*-gaertneroside (**10**),⁸ epoxygaertneroside (**11**),⁴ and dehydrogaertneroside (**12**),⁴ and the flavonoid glycoside nicotiflorin (**13**)^{9,10} (Figure 1).

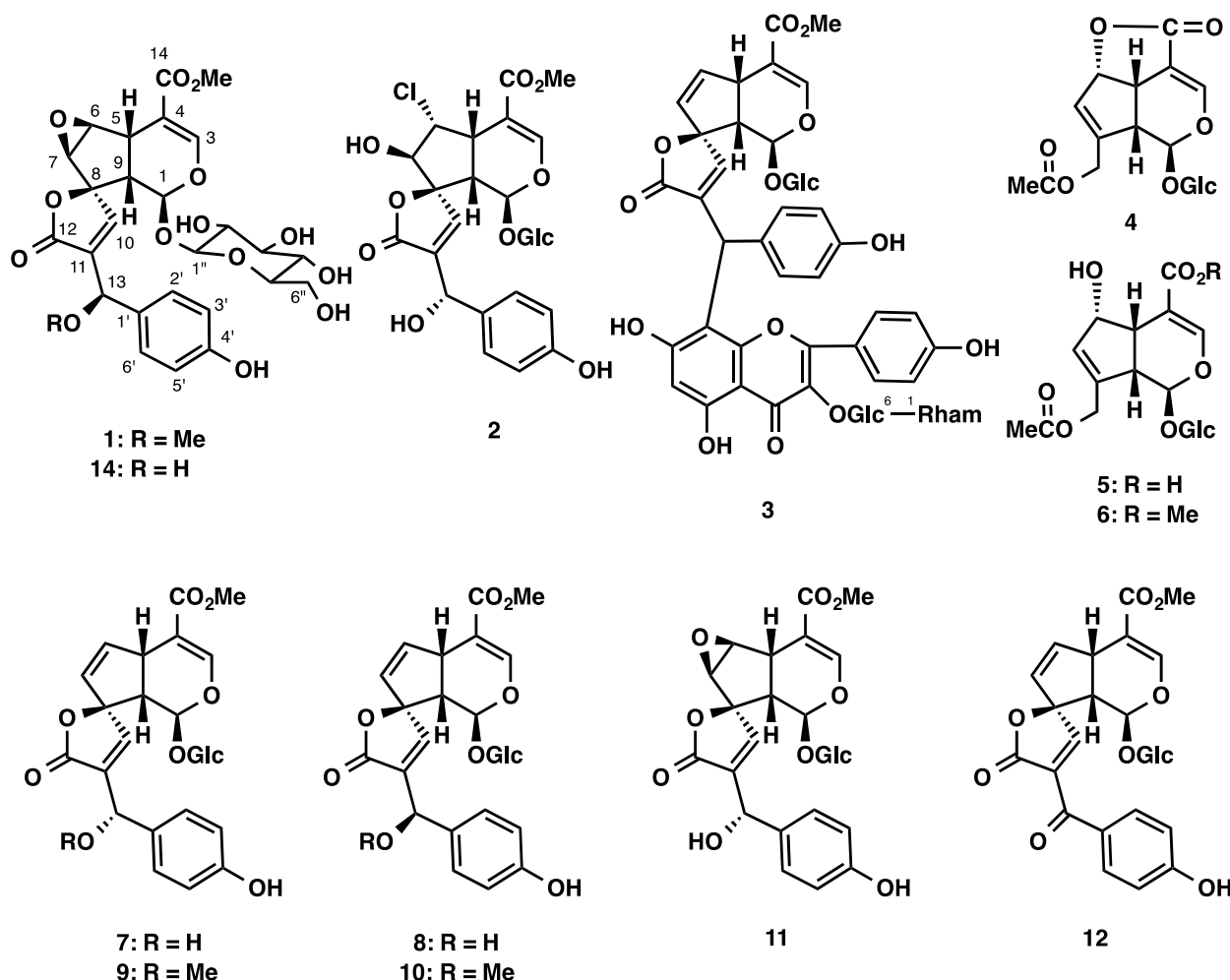


Figure 1. Structures of isolated iridoid glucosides **1**–**12** and 13*R*-*epi*-epoxygaertneroside (**14**)

Compound **1** was isolated as a colorless amorphous powder. The high-resolution secondary ion mass spectrum (HR-SIMS) of **1** exhibited a pseudomolecular ion $[M-H]^-$ at m/z 577.1558, indicating a molecular formula of C₂₇H₃₀O₁₄ for **1**. Its ¹H-NMR spectrum (Table 1) exhibited the typical signals of an iridoidic enol ether system conjugated with a carbomethoxy group (H-3, 14-OMe), an acetal proton (H-1), an anomeric proton (H-1''), and an olefinic proton (H-10) together with an oxymethine (H-13) and an aromatic AA'BB' spin system (H-2', H-3', H-5', and H-6') as in gaertneroside (**7**), a major glucoside of this plant material. Further signals were observed at δ_H 3.30 (m) and at δ_H 4.02 (br d, $J=2.0$ Hz) instead of characteristic signals due to the 6,7-double bond for **7**, indicating the presence of a 6,7-epoxide in **1**. A β -orientation of the epoxide ring was suggested by no coupling between H-5 and H-6, as discussed before for plumiepoixide.¹¹ These spectral features were closely similar to epoxygaertneroside (**11**) and 13*R*-*epi*-epoxygaertneroside (**14**), a constituent of *Pentas lanceolata*,⁷ except for the presence of an

additional methoxy signal at δ_{H} 3.29. In the ^{13}C -NMR spectrum of **1** (Table 1), the methoxy signal appeared at δ_{C} 57.1, and a downfield shift relative to **11** and **14** was seen for C-13 (**1**: δ_{C} 79.0, **11**: δ_{C} 70.0, **14**: δ_{C} 69.6), whereas upfield shifts were seen for C-11 (**1**: δ_{C} 138.6, **11**: δ_{C} 140.8, **14**: δ_{C} 140.5) and C-1' (**1**: δ_{C} 129.9, **11**: δ_{C} 133.0, **14**: δ_{C} 132.3). HMBC experiments with **1** showed a significant correlation from the methoxy group (δ_{H} 3.29) to C-13 (δ_{C} 79.0), which was assigned from the HMBC correlation with H-2' (6') (Figure 2). These findings implied that compound **1** possessed a methoxy group at C-13 in place of a hydroxy group in **11** or **14**.

Table 1. ^1H - and ^{13}C -NMR spectral data of **1** and **2** in CD_3OD

		1				2			
C	δ_{H}			δ_{C}	δ_{H}			δ_{C}	
1	5.33	d	(1.0)	92.9	5.49	d	(10.0)	95.7	
3	7.56	d	(1.5)	153.8	7.61	d	(1.0)	154.7	
4				108.2				107.8	
5	3.46	br d	(8.5)	33.0	3.81	ddd	(10.0, 7.5, 1.0)	38.5	
6	3.30 ^a	m		59.2	4.46	ddd	(10.0, 6.0, 0.5)	66.5	
7	4.02	br d	(2.0)	57.8	4.60	d	(6.0)	83.4	
8				92.8				93.7	
9	2.77	dd	(8.5, 1.0)	43.7	2.45	br dd	(10.0, 7.5)	50.4	
10	7.04	d	(1.5)	148.2	7.78	d	(1.5)	149.9	
11				138.6				138.9	
12				171.5				172.2	
13	4.96	d	(1.5)	79.0	5.38	d	(1.0)	69.5	
14				168.0				168.7	
1'				129.9				133.4	
2', 6'	7.19	d	(8.5)	130.1	7.26	d	(8.5)	129.5	
3', 5'	6.77	d	(8.5)	116.4	6.79	d	(8.5)	116.4	
4'				159.0				158.4	
13-OMe	3.29	s		57.1					
14-OMe	3.77	s		52.0	3.74	s		52.1	
1''	4.53	d	(8.0)	99.7	4.75	d	(8.0)	101.5	
2''	3.12	dd	(9.0, 8.0)	74.5	3.21	dd	(9.0, 8.0)	74.7	
3''	3.30 ^a	m		77.9	3.39	t	(9.0)	77.8	
4''	3.26	m		71.4	3.29	dd	(10.0, 9.0)	71.5	
5''	3.30 ^a	m		78.4	3.34	m		78.7	
6''	3.64	dd	(12.0, 5.0)	62.6	3.63	dd	(12.0, 6.5)	63.0	
	3.85	dd	(12.0, 1.0)		3.93	dd	(12.0, 2.0)		

Values in parentheses are coupling constants in Hz. ^aOverlapped by solvent peak.

The absolute configuration of C-13 in **1** was deducible as *R*, as in 13*R*-*epi*-epoxygaertneroside (**14**), according to significant differences seen in the ^1H -NMR spectra of **1**, **11** and **14**.⁵ The chemical shifts of H-1, H-7, H-9, and H-10 of **1** (H-1: δ_{H} 5.33, H-7: δ_{H} 4.02, H-9: δ_{H} 2.77, H-10: δ_{H} 7.04) were closely

coincident with those reported for **14** (H-1: δ_{H} 5.33, H-7: δ_{H} 4.02, H-9: δ_{H} 2.77, H-10: δ_{H} 7.03),⁷ but differed from those of **11** (H-1: δ_{H} 5.05, H-7: δ_{H} 4.05, H-9: δ_{H} 2.73, H-10: δ_{H} 7.15). The differences could be ascribed to the anisotropic effect of the benzene ring.⁵ Furthermore, the same configuration in **1** as that in **8** and **10**, with their 13*R* configurations, was confirmed by their similar CD spectra without positive Cotton effects at wavelengths around 260 nm. The Cotton effect was observed in the CD spectra of glucosides with a 13*S* configuration, such as **7**, **9**, and **11**. Accordingly, compound **1** was elucidated as 13*R*-13-*O*-methyl-*epi*-epoxygaertneroside.

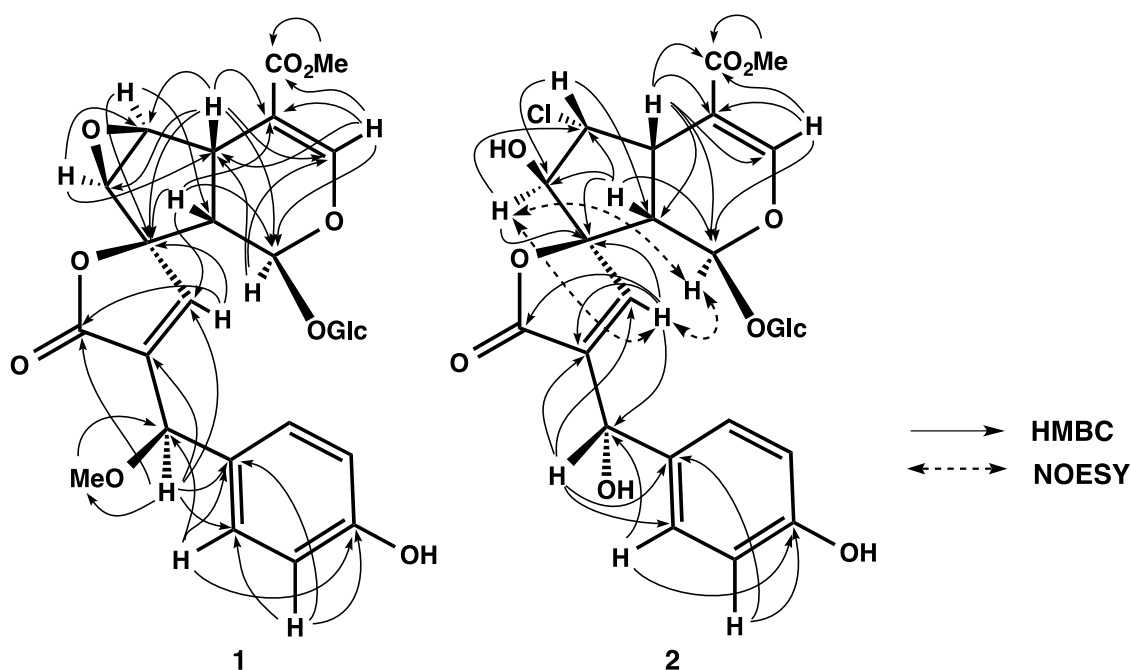


Figure 2. Key HMBC and NOESY correlations of compounds **1** and **2**

Compound **2**, $\text{C}_{26}\text{H}_{29}\text{ClO}_{14}$, was also isolated as an amorphous powder. A comparison of the UV, IR, and NMR spectroscopic features of **2** with those of **11** suggested a close relationship between their structures. The ^1H -NMR spectroscopic data of **2** resembled those of **11** except that **2** had signals for H-6 at δ_{H} 4.46 (ddd, $J=10.0, 6.0, 0.5$ Hz) and H-7 at δ_{H} 4.60 (d, $J=6.0$ Hz) instead of signals at δ_{H} 3.43 and 4.05 observed in **11**. These differences in the ^1H -NMR spectra of **2** and **11**, as well as their molecular formulas could be accounted for by the cleavage of an epoxy ring in **11** to form chlorohydrin between C-6 and C-7 in **2**. The ^{13}C -NMR chemical shifts of C-6 (δ_{C} 66.5) and C-7 (δ_{C} 83.4) suggested the substitution of a chlorine atom at C-6 and a hydroxy group at C-7. The stereochemistry of C-6 and C-7 was established using NOESY experiments and ^1H - ^1H coupling constants. Supposing that the configurations of C-1, C-5, and C-9 in the rigid skeleton of the iridoid molecule were the same as in compounds **4–12**, the NOESY correlations of H-1/H-7, H-7/H-10, and H-1/H-10 demonstrated the α -orientation of H-7 and

S-configuration of C-8 (Figure 2). From the coupling constants of $J_{5,6}$ (10.0 Hz) and $J_{6,7}$ (6.0 Hz), H-6 was concluded to be oriented β . Finally, the configuration of C-13 in **2** was determined to be *S* from a positive Cotton effect at 264 nm in the CD spectrum of **2**. Thus, the structure of **2** was elucidated as shown and designated as linocieroside.

Iridoid glucosides with a chlorohydrin moiety have been reported previously.^{12,13} As suggested for these compounds, compound **2** may also be biosynthesized from co-occurring **11** by attack of a chloride anion on the epoxy ring.

Table 2. ¹H- and ¹³C-NMR spectral data of **3** and ¹³C-NMR spectral data of **7** and **13** in CD₃OD

Gaertneroside unit of 3					7		Nicotiflorin unit of 3				13	
C	δ_{H}			δ_{C}	δ_{C}	C	δ_{H}			δ_{C}	δ_{C}	
1	5.34	d	(3.0)	93.6	94.5	2				159.8	159.5	
3	7.23	br s		151.7	152.5	3				135.7	135.6	
4				111.6	110.9	4				179.5	179.5	
5	3.76	m		39.4	40.4	5				161.8	163.1	
6	6.21	dd	(5.5, 2.5)	139.9	141.6	6	6.30	s		100.1	100.0	
7	5.05	m		130.1	130.0	7				164.4	166.1	
8				97.7	98.1	8				107.0	95.0	
9	2.95	dd	(8.0, 3.0)	50.3	50.8	9				156.1	158.6	
10	6.62	d	(1.5)	151.2	150.1	10				106.0	105.7	
11				137.4	137.9	1'				122.7	122.8	
12				174.1	172.4	2', 6'	7.62	d	(8.5)	132.6	132.4	
13	5.65	br s		38.0	69.9	3', 5'	6.76	d	(8.5)	116.1	116.2	
14				168.3	168.5	4'				161.4	161.5	
1'				132.0	133.3	1''	5.02	d	(7.5)	105.0	104.6	
2', 6'	7.13	d	(8.5)	130.5	129.7	2''	3.36 ^a	m		75.8	75.8	
3', 5'	6.81	d	(8.5)	116.5	116.3	3''	3.36 ^a	m		77.2 ^b	77.3	
4'				157.3	158.6	4''	3.25 ^a	m		71.6	71.5	
OMe	3.71	s		52.0	52.0	5''	3.36 ^a	m		78.1 ^c	78.2	
1''	4.55	d	(8.0)	99.5	100.5	6''	3.25	m		68.8	68.6	
2''	3.13	d	(9.0)	74.5	74.5		3.75	br d	(9.5)			
3''	3.25 ^a	m		77.9 ^b	77.9	1'''	4.45	d	(1.0)	102.4	102.5	
4''	3.25 ^a	m		71.6	70.9	2'''	3.61	dd	(3.0, 1.0)	72.1	72.1	
5''	3.25 ^a	m		78.5 ^c	78.4	3'''	3.53	dd	(9.5, 3.0)	72.4	72.3	
6''	3.59	dd	(12.0, 6.5)	62.9	62.2	4'''	3.36	m		74.0	73.9	
	3.90	dd	(12.0, 2.0)	93.6	94.5	5'''	3.43	m		69.7	69.8	
						6'''	1.14	d	(6.0)	18.0	18.0	

Values in parentheses are coupling constants in Hz. ^{a-c} Assignments may be interchanged.

Compound **3** was isolated as a yellow amorphous powder. The HR-SIMS of **3** exhibited a pseudomolecular ion $[\text{M}-\text{H}]^-$ at m/z 1123.1941, consistent with a molecular formula of C₅₃H₅₆O₂₇. The ¹H-NMR spectrum of **3** (Table 2) showed the signals assignable to a gaertneroside (**7**) unit, but it also

exhibited additional signals for a *para*-substituted aromatic ring with an AA'BB' spin system at δ_{H} 6.76–7.62, an aromatic singlet at δ_{H} 6.30, a methyl group at δ_{H} 1.14 (d, $J=6.0$ Hz), and two anomeric protons at δ_{H} 5.02 (d, $J=7.5$ Hz) and 4.45 (d, $J=1.0$ Hz). These signals corresponded with nicotiflorin (kaempferol 3-*O*-rutinoside) (**13**), a constituent of this plant species, except for the absence of one aromatic proton. These observations suggested that compound **3** was composed of a gaertneroside unit and a nicotiflorin unit. The linkage of the two units was determined by comparison of the ^{13}C -NMR chemical shifts of **3** with those of **7** and **13**. The signal for C-13 of the gaertneroside (**7**) moiety in **3** resonated at higher frequency than that of **7**, indicating this carbon was not oxygenated. On the other hand, C-5, C-7, and C-9 of the nicotiflorin unit in **3** were upfield-shifted, and C-8 recognized as a quaternary carbon was downfield-shifted. These results implied that C-13 of gaertneroside moiety was connected to C-8 of nicotiflorin moiety through a C-C bond. The position of the linkage was further supported by the HMBC correlations of H-13 of the gaertneroside unit with C-7, C-8, and C-9 of the nicotiflorin unit (Figure 3). The proposed structure was fully confirmed using the ^1H - ^1H COSY, HMQC and HMBC correlations. The configuration of C-13 in the gaertneroside unit of **3** could not be determined by spectroscopic means used for **1** and **2**. The stereochemistry of **3**, except for the configuration of the chiral center, was considered to be the same as in **7** and **13** based on biosynthetic considerations and the similarity of their ^{13}C -NMR spectra. Thus, the structure of **3** was determined as illustrated and designated as linociesangdoside. This is the first instance of a unique iridoid glucoside with a spiro lactone ring linked with a flavonoid glycoside.

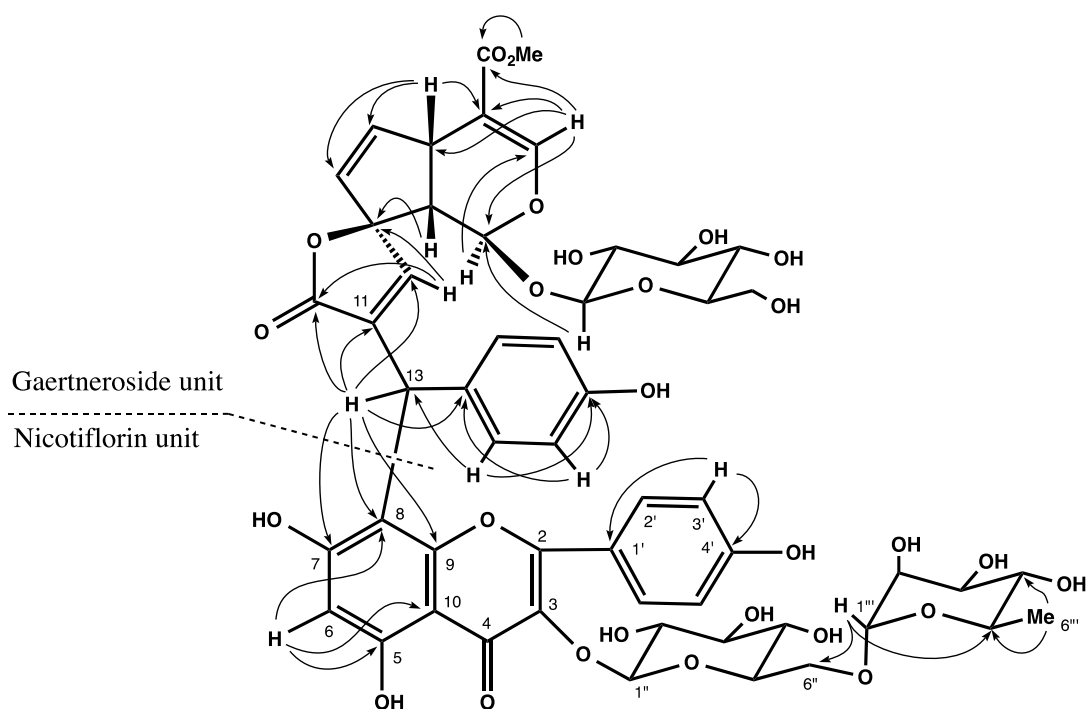


Figure 3. Key HMBC correlations of compound **3**

Iridoids **1–8** are structurally related to the iridoids, a relatively rare group of iridoids containing a spiro lactone ring. This type of glucosides has previously been found in the Rubiaceae^{4-8,14-16} and Apocynaceae^{17,18} but never been isolated from Oleaceae.

EXPERIMENTAL

General procedures. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer and IR spectra on a Shimadzu FTIR-8200 infrared spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter and CD spectra on a Shimadzu-AVIV 62 A DS circular dichroism spectrometer. HR-SIMS were obtained using a Hitachi M-4100 mass spectrometer with glycerol as the matrix. NMR experiments were performed using a Varian VXR-500 spectrometer with tetramethylsilane as an internal standard. Thin-layer chromatography was performed on precoated Kieselgel 60F₂₅₄ plates (Merck), and spots were visualized using UV light.

Plant material. *Linociera sangda* were collected at Kapok W.F., Chumphon, Thailand in April 1988 and identified by Dr. T. Smitinand (The Forest Herbarium, Royal Forest Department, Bangkok, Thailand).

Isolation of compounds. Dried aerial parts of *L. sangda* (2.14 kg) were extracted with MeOH under reflux. After concentration, the extract (43.2 g) was suspended in H₂O and extracted successively with CHCl₃ and *n*-BuOH. The *n*-BuOH extract (7.9 g) was subjected to column chromatography on a Wako-gel LP-40C₁₈ (Wako Pure Chemical Industries Ltd, Osaka, Japan) column. Elution with MeOH-H₂O mixtures of the indicated MeOH content gave 5 fractions (I–V). Fraction I (10% MeOH eluent, 637 mg) was further purified using preparative HPLC (μ Bondasphere 5 μ C18-100Å, H₂O-MeOH, 7:3) and preparative TLC (CHCl₃-MeOH-AcOH, 8:2:1 or acetone-CHCl₃-H₂O, 8:2:1) to give **4** (6 mg), **5** (4 mg), and **11** (6 mg). The following fractions of the initial column chromatography were also purified by preparative HPLC (H₂O-MeOH, 3:2, 63:37, 1:1, 11:9, 13:7 or H₂O-MeCN, 4:1, 7:3, 1:1) and preparative TLC (CHCl₃-MeOH, 7:3, CHCl₃-MeOH-AcOH, 8:2:0.05 or acetone-CHCl₃-H₂O, 8:2:1). Fraction II (20% MeOH eluent, 1562 mg) yielded **6** (3 mg), **7** (1.14 g), and **2** (4 mg); Fraction III (20–30% MeOH eluent, 473 mg): **8** (28 mg), and **1** (2 mg); Fraction IV (30% MeOH eluent, 237 mg): **10** (38 mg), and **12** (2 mg); Fraction V (30–40% MeOH eluent, 144 mg): **13** (5 mg), **9** (2 mg), and **3** (18 mg).

13R-13-O-Methyl-epi-epoxygaertneroside (1): Colorless amorphous powder, $[\alpha]_D^{29} -138$ (*c* 0.19, MeOH); UV (MeOH) λ_{\max} (log ϵ): 223 (4.30), 287sh (3.22) nm; CD (MeOH) λ_{\max} ($\Delta \epsilon$): 226 (–14.1) nm; IR (KBr) ν_{\max} : 3407, 1769, 1717, 1638, 1296, 1078 cm^{–1}; ¹H- and ¹³C-NMR: see Table 1; HR-SIMS *m/z* 577.1551 [M–H][–] (calcd for C₂₇H₂₉O₁₄, 577.1558).

Linocieroside (2): Colorless amorphous powder, $[\alpha]_D^{27} -29$ (*c* 0.28, MeOH); UV (MeOH) λ_{\max} (log ϵ): 224 (4.32), 287sh (3.11) nm; CD (MeOH) λ_{\max} ($\Delta \epsilon$): 223 (–13.2), 233 (–12.6), 264 (+1.1) nm; IR (KBr) ν_{\max} : 3375, 1753, 1701, 1637, 1516, 1443, 1313, 1076 cm^{–1}; ¹H- and ¹³C-NMR: see Table 1; HR-SIMS

m/z 599.1162 $[M-H]^-$ (calcd for $C_{26}H_{28}ClO_{14}$, 599.1168).

Linociesangdoside (3): Yellow amorphous powder, $[\alpha]_D^{24} -30$ (c 0.76, MeOH); UV (MeOH) λ_{max} ($\log \epsilon$): 223 (4.57), 234sh (4.46), 245sh (4.33), 250 (4.31), 257 (4.32), 263 (4.33), 275sh (4.20), 352 (4.00) nm; IR (KBr) ν_{max} : 3409, 1747, 1697, 1647, 1512, 1074 cm^{-1} ; 1H - and ^{13}C -NMR: see Table 2; HR-SIMS m/z 1123.1941 $[M-H]^-$ (calcd for $C_{53}H_{55}O_{27}$, 1123.1932).

Gaertneroside (7): $[\alpha]_D^{27} +49$ (c 1.04, MeOH); CD (MeOH) λ_{max} ($\Delta \epsilon$): 223 (-12.9), 264 (+3.1) nm.

13R-Epi-gaertneroside (8): $[\alpha]_D^{27} -152$ (c 0.85, MeOH); CD (MeOH) λ_{max} ($\Delta \epsilon$): 227 (-24.2) nm.

13-Methoxygaertneroside (9): $[\alpha]_D^{29} +52$ (c 0.82, MeOH); CD (MeOH) λ_{max} ($\Delta \epsilon$): 224 (-7.4), 260 (+2.5) nm.

13-Methoxy-epi-gaertneroside (10): $[\alpha]_D^{29} -150$ (c 0.23, MeOH); CD (MeOH) λ_{max} ($\Delta \epsilon$): 228 (-25.8) nm.

Epoxygaertneroside (11): $[\alpha]_D^{28} -3.5$ (c 0.45, MeOH); CD (MeOH) λ_{max} ($\Delta \epsilon$): 218 (-7.7), 233 (-2.9), 254 (+2.7) nm.

Dehydrogaertneroside (12): $[\alpha]_D^{29} -28$ (c 0.23, MeOH); CD (MeOH) λ_{max} ($\Delta \epsilon$): 233 (-9.0) nm.

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