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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 spirolactone 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 spirolactone 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).

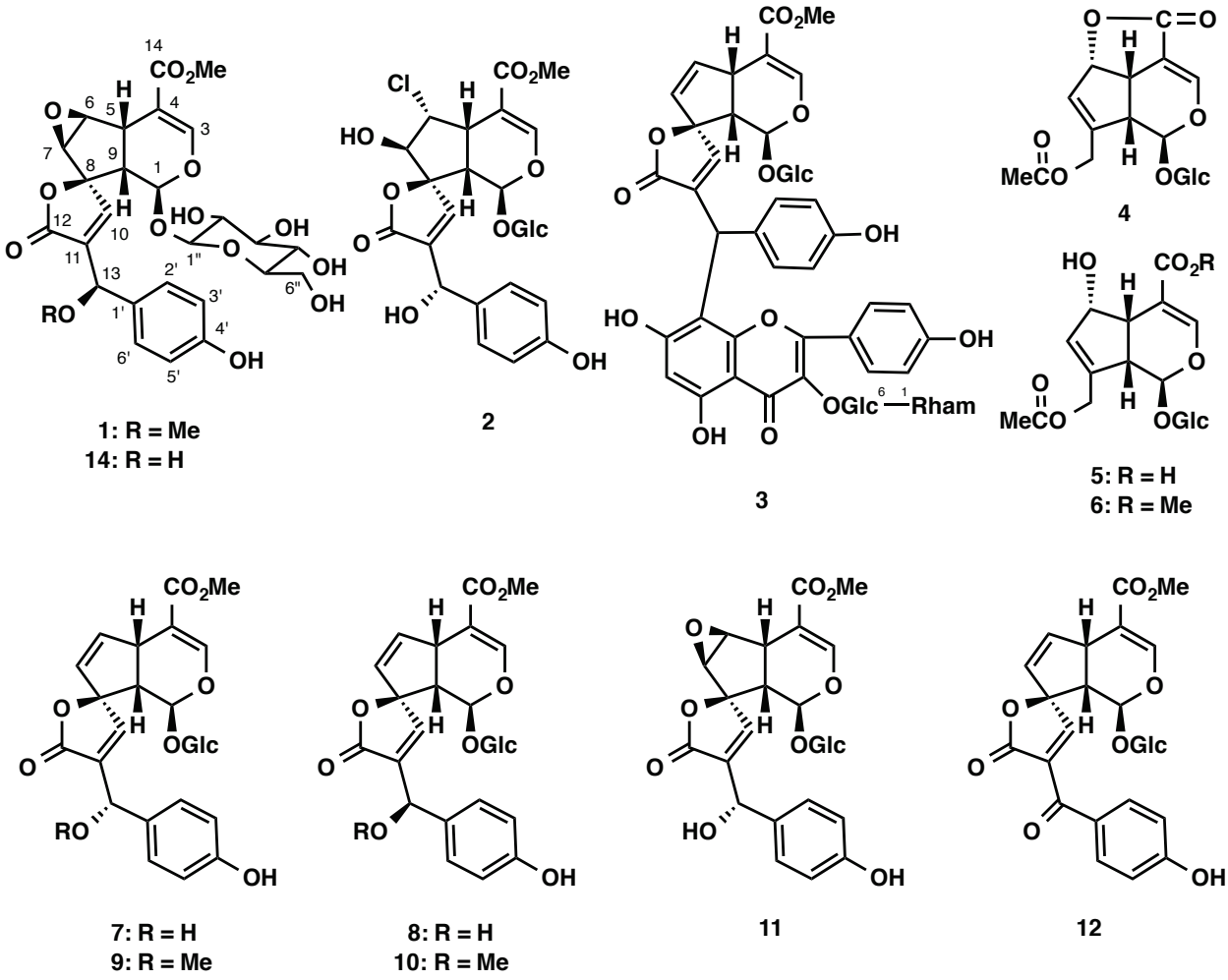


**Figure 1.** Structures of isolated iridoid glucosides **1**−**12** and 13*R*-*epi*-epoxygaertneroside (**14**)

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 $C_{27}H_{30}O_{14}$ for **1**. Its $^1$H-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 $\delta_H$ 3.30 (m) and at $\delta_H$ 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 plumiepoxide.[11] These spectral features were closely similar to epoxygaertneroside (**11**) and 13*R*-*epi*-epoxygaertneroside (**14**), a constituent of *Pentas lanceolate*,[7] except for the presence of an

additional methoxy signal at $\delta_H$ 3.29. In the $^{13}$C-NMR spectrum of **1** (Table 1), the methoxy signal appeared at $\delta_C$ 57.1, and a downfield shift relative to **11** and **14** was seen for C-13 (**1**: $\delta_C$ 79.0, **11**: $\delta_C$ 70.0, **14**: $\delta_C$ 69.6), whereas upfield shifts were seen for C-11 (**1**: $\delta_C$ 138.6, **11**: $\delta_C$ 140.8, **14**: $\delta_C$ 140.5) and C-1' (**1**: $\delta_C$ 129.9, **11**: $\delta_C$ 133.0, **14**: $\delta_C$ 132.3). HMBC experiments with **1** showed a significant correlation from the methoxy group ($\delta_H$ 3.29) to C-13 ($\delta_C$ 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.** $^1$H- and $^{13}$C-NMR spectral data of **1** and **2** in $CD_3OD$

| | **1** | | | | **2** | | | |
|---|---|---|---|---|---|---|---|---|
| C | $\delta_H$ | | | $\delta_C$ | $\delta_H$ | | | $\delta_C$ |
| 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. [a]Overlapped 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 $^1$H-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: $\delta_H$ 5.33, H-7: $\delta_H$ 4.02, H-9: $\delta_H$ 2.77, H-10: $\delta_H$ 7.04) were closely

coincident with those reported for **14** (H-1: $\delta_H$ 5.33, H-7: $\delta_H$ 4.02, H-9: $\delta_H$ 2.77, H-10: $\delta_H$ 7.03),[7] but differed from those of **11** (H-1: $\delta_H$ 5.05, H-7: $\delta_H$ 4.05, H-9: $\delta_H$ 2.73, H-10: $\delta_H$ 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.

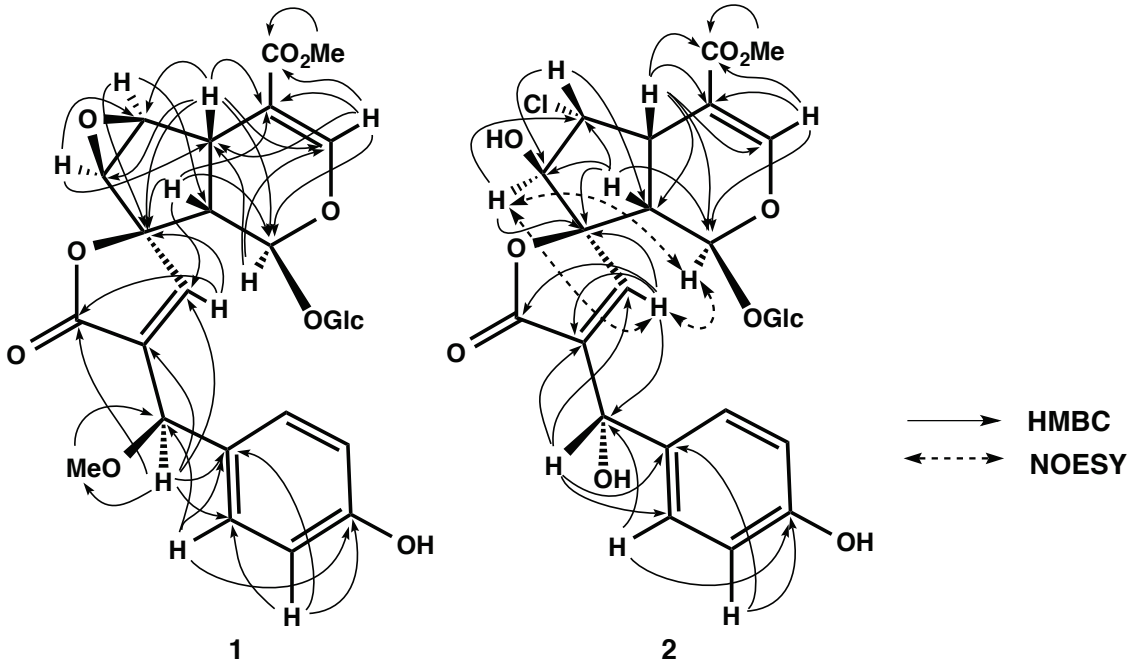


**Figure 2.** Key HMBC and NOESY correlations of compounds **1** and **2**

Compound **2**, $C_{26}H_{29}ClO_{14}$, 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 $^1$H-NMR spectroscopic data of **2** resembled those of **11** except that **2** had signals for H-6 at $\delta_H$ 4.46 (ddd, *J*=10.0, 6.0, 0.5 Hz) and H-7 at $\delta_H$ 4.60 (d, *J*=6.0 Hz) instead of signals at $\delta_H$ 3.43 and 4.05 observed in **11**. These differences in the $^1$H-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 ($\delta_C$ 66.5) and C-7 ($\delta_C$ 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 $^1$H-$^1$H 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 $\alpha$-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.** $^{1}$H- and $^{13}$C-NMR spectral data of **3** and $^{13}$C-NMR spectral data of **7** and **13** in $CD_3OD$

| Gaertneroside unit of **3** | | | | | **7** | Nicotiflorin unit of **3** | | | | | **13** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C | $\delta_H$ | | | $\delta_C$ | $\delta_C$ | C | $\delta_H$ | | | $\delta_C$ | $\delta_C$ |
| 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 $[M-H]^-$ at *m/z* 1123.1941, consistent with a molecular formula of $C_{53}H_{56}O_{27}$. The $^{1}$H-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 $\delta_H$ 6.76–7.62, an aromatic singlet at $\delta_H$ 6.30, a methyl group at $\delta_H$ 1.14 (d, *J*=6.0 Hz), and two anomeric protons at $\delta_H$ 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 $^1$H-$^1$H 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 spirolactone ring linked with a flavonoid glycoside.

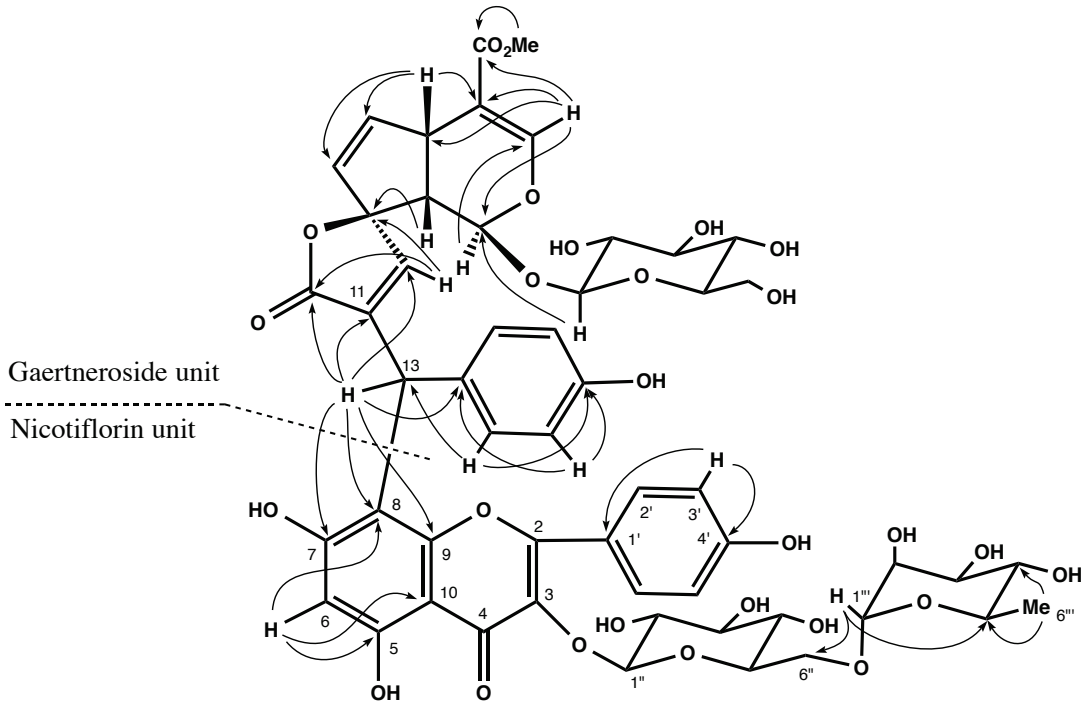


**Figure 3.** Key HMBC correlations of compound **3**

Iridoids **1**–**8** are structurally related to the iridoids, a relatively rare group of iridoids containing a spirolactone 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 $60F_{254}$ 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 $H_2O$ and extracted successively with $CHCl_3$ and *n*-BuOH. The *n*-BuOH extract (7.9 g) was subjected to column chromatography on a Wako-gel LP-$40C_{18}$ (Wako Pure Chemical Industries Ltd, Osaka, Japan) column. Elution with MeOH-$H_2O$ mixtures of the indicated MeOH content gave 5 fractions (I–V). Fraction I (10% MeOH eluent, 637 mg) was further purified using preparative HPLC (μBondasphere 5μ C18-100Å, $H_2O$-MeOH, 7:3) and preparative TLC ($CHCl_3$-MeOH-AcOH, 8:2:1 or acetone-$CHCl_3$-$H_2O$, 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 ($H_2O$-MeOH, 3:2, 63:37, 1:1, 11:9, 13:7 or $H_2O$-MeCN, 4:1, 7:3, 1:1) and preparative TLC ($CHCl_3$-MeOH, 7:3, $CHCl_3$-MeOH-AcOH, 8:2:0.05 or acetone-$CHCl_3$-$H_2O$, 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).

**13*R*-13-*O*-Methyl-*epi*-epoxygaertneroside (1):** Colorless amorphous powder, $[\alpha]_D^{29}$ −138 (*c* 0.19, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$): 223 (4.30), 287sh (3.22) nm; CD (MeOH) $\lambda_{max}$ ($\Delta\varepsilon$): 226 (−14.1) nm; IR (KBr) $\nu_{max}$: 3407, 1769, 1717, 1638, 1296, 1078 $cm^{-1}$; $^1H$- and $^{13}C$-NMR: see Table 1; HR-SIMS *m/z* 577.1551 $[M-H]^-$ (calcd for $C_{27}H_{29}O_{14}$, 577.1558).

**Linocieroside (2):** Colorless amorphous powder, $[\alpha]_D^{27}$ −29 (*c* 0.28, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$): 224 (4.32), 287sh (3.11) nm; CD (MeOH) $\lambda_{max}$ ($\Delta\varepsilon$): 223 (−13.2), 233 (−12.6), 264 (+1.1) nm; IR (KBr) $\nu_{max}$: 3375, 1753, 1701, 1637, 1516, 1443, 1313, 1076 $cm^{-1}$; $^1H$- and $^{13}C$-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) $\lambda_{max}$ (log $\varepsilon$): 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) $\nu_{max}$: 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) $\lambda_{max}$ ($\Delta\varepsilon$): 223 (−12.9), 264 (+3.1) nm.

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

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

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

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

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

## ACKNOWLEDGEMENTS

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