Sesquiterpenes from the Roots of *Cichorium endivia*

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Twelve new sesquiterpene and sesquiterpene glycosides were obtained along with eleven known compounds from the roots of *Cichorium endivia* (Compositae). The compounds were identified as guaianolide, germacrenolide and elemanolide, based on spectroscopic methods and chemical evidence.

Key words *Cichorium endivia*; Compositae; sesquiterpene glycoside; cichorioside; β-D-fructofuranose

Cichorium endivia (Compositae) is indigenous to India and cultivated as a vegetable. Sesquiterpenes and their glycosides in this plant have already been reported.[1,2] Recently, sesquiterpenes in chicory roots exhibited several biological activities. Lactucin, lactucopicrin, and 11β,13-dihydrolactucin showed analgesic and sedative activities in mice,[3] and lactucin and lactucopicrin revealed antimalarial activity.[4] Moreover, 8-deoxylactucin demonstrated the inhibitory effect to DNA binding of nuclear factor (NF)κB and cyclooxygenase (COX)-2 protein expression.[2] Accordingly, we also started a detailed investigation of the constituents of the roots of *C. endivia*, seeking other sesquiterpenes and sesquiterpene glycosides, in the course of our research into terpenes and terpenoic glycosides of Compositous plants.

A methanol extract from the dried roots of *C. endivia* was suspended in water. The suspension was extracted with diethyl ether and partitioned into an ether-soluble fraction and a water-soluble fraction. The residue of each fraction was respectively chromatographed on a silica gel column and semi-preparative HPLC thereby affording compounds (**1**—**23**). The structural determination of known compounds was made based on comparisons of the NMR spectral data with data in the literature. Compounds **1**—**5**, **8**, **9**, **14**, **18**, **19** and **20** were known sesquiterpenes and sesquiterpene glycosides, and identified as 8-deoxylactucin (**1**),[5] lactucin (**2**),[5] lactucopicrin (**3**),[6] jacquinelin (**4**),[7] crepidiaside B (**5**),[8] 11β,13-dihydrolactucin (**8**),[9] cichorioside B (**9**),[1] 11β,13-dihydrolactucopicin (**14**),[10] sonchuside A (**18**),[11] cichorioside C (**19**)[1] and hypochoeroside A (**20**).[12]

Cichorioside D (**6**) was suggested to have the molecular formula $C_{27}H_{38}O_{13}$ based on high resolution (HR)-FAB-MS [*m*/*z*: 593.2203 $[M+Na]^+$]. In the ^{1}H- and ^{13}C-NMR spectra of **6**, two anomeric proton and carbon signals were observed at δ 4.89, 5.49 and δ 104.3, 102.6, in addition to signals due to the aglycone, and this aglycone was identified as **4**, according to the similarity of the ^{13}C-NMR spectral data. The acid hydrolysis of **6** and the *J* value and/or chemical shifts of each anomeric proton signal showed that the sugar moiety consisted of β-D-glucopyranose and α-L-rhamnopyranose.[13] Comparison of the ^{13}C-NMR spectral data of **6** with those of **5** indicated that β-D-glucopyranose was linked at the C-15 position of the aglycone, which was confirmed by irradiation at the anomeric proton of β-D-glucopyranose (δ 4.89) in a nuclear Overhauser effect (NOE) difference experiment. Moreover, NOEs were observed between the anomeric proton of α-L-rhamnopyranose (δ 5.49) and H-6 of β-D-glucopyranose (δ 4.59, 4.17). On the basis of the above results, compound **6** was determined to be jacquinelin 15-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside.

HR-FAB-MS showed the molecular formula of cichorioside E (**7**) to be $C_{27}H_{38}O_{14}$. The ^{1}H- and ^{13}C-NMR spectra indicated that **7** was also jacquinelin 15-*O*-diglycoside. From the results of acid hydrolysis and the NMR spectral data, the sugar sequence of **7** was found to consist of β-D-glucopyranose and β-D-fructofuranose.[14] In a ^{1}H-detected heteronuclear multiple-bond connectivity (HMBC) experiment on **7**, a long-range correlation was exhibited between the H-6 signal of β-D-glucopyranose (δ 4.27) and the C-2 signal of β-D-fructofuranose (δ 105.8). Thus, compound **7** was determined to be jacquinelin 15-*O*-β-D-fructofuranosyl-(2→6)-β-D-glucopyranoside.

HR-FAB-MS revealed the molecular formula of cichorioside F (**10**) to be $C_{21}H_{28}O_{10}$. Comparison of the ^{1}H- and ^{13}C-NMR spectral data of **10** with those of **7**, **8** and **9** and acid hydrolysis of **10** suggested that **10** was 11β,13-dihydrolactucin 15-*O*-β-D-fructofuranoside. The attached position of the β-D-fructofuranosyl group was identified by observation of a long-range correlation between the C-2 signal of β-D-fructofuranose (δ 106.1) and the H-15 signal of the aglycone (δ 5.45).

The molecular formulae of cichorioside G (**11**) and H (**12**) were suggested to be $C_{21}H_{28}O_{10}$, respectively, by HR-FAB-MS. Acid hydrolysis of **11** and **12** afforded D-glucose as each sugar moiety. Compound **11** was determined to be 11β,13-dihydrolactucin 8-*O*-β-D-glucopyranoside, on the basis of ^{1}H- and ^{13}C-NMR spectral data of **8** and deacylmatricarin 8-*O*-β-D-glucopyranoside.[15] The ^{13}C-NMR spectral data of compound **12** were similar to those of **11**, but the oxygenated methine signal was observed at δ 80.6. Because this methine carbon was correlated with H-8 (δ 2.40) and H-14 (δ 2.67) in the HMBC experiment, this signal was assignable to C-9 of the aglycone. Additionally, the anomeric proton signal of β-D-glucopyranoside (δ 4.86) showed a long-range correlation with this C-9 signal. In the NOE difference experiment, observation of an NOE between H-6 [δ 3.61 (1H, t, J=10.0 Hz)] and H-8β [δ 1.46 (1H, t, J=13.0 Hz)] suggested that H-8β and H-8α were pseudoaxial and pseudoequatorial, respectively. And the coupling constant of H-9 [δ 4.55 (1H, d, J=5.5 Hz)] revealed that the orientation of H-9 was pseudoequatorial, namely, β. Thus, the β-D-glucopyranosyl group was attached at the α-side of C-9, and cichorioside H (**12**) was determined to be 9α-hydroxyjacquinelin 9-*O*-β-D-glu-

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Table 1. ^{13}C-NMR Data of Compounds **6**, **7**, **10**—**13**, **16**, **17**, and **21**—**23**

Carbon No.	**6**	**7**	**10**	**11**	**12**	**13**	**16**	**17**	**21**	**22**	**23**
Aglycone moiety											
1	131.8	131.8	132.6	133.3[a)]	132.6[a)]	133.7[a)]	48.3	49.8	127.6	128.8	148.2
2	195.1	195.1	194.9	195.0	196.3	195.9	27.6	25.3	35.7	33.1	111.6
3	134.5	134.5	133.6	133.2[a)]	132.8[a)]	133.6[a)]	33.6	34.8	77.5	83.6	144.6
4	169.8	169.7	171.6	175.4	176.8	172.7	149.6	149.0	143.9	134.0	110.9
5	49.9	49.8	49.6[a)]	49.1	48.9	54.9	49.2	57.0	125.3	133.4	52.6
6	83.9	83.9	81.1	81.5	83.6	70.3	106.9	110.5[a)]	78.2	65.0	78.3
7	55.6	55.6	61.8	60.8	46.3	58.9	160.8	158.4	60.6	55.6	59.3
8	25.9	25.9	69.2	78.3	29.4	76.2	120.8	122.3	81.0	79.5	68.6
9	37.5	37.5	49.4[a)]	47.1	80.6	41.7	152.0	144.3	51.9	47.5	50.3
10	152.7	152.8	146.8	147.4	150.4	145.5	73.9[a)]	88.3	134.5	132.8	43.0
11	41.3	41.4	41.9	41.6	41.1	39.9	121.9	119.5	40.4	41.0	41.9
12	177.4	177.4	177.6	177.9	177.6	178.5	170.9	170.3	179.9	179.2	179.5
13	12.3	12.3	16.0	16.1	12.3	9.7	60.2	60.7	18.5	11.8[a)]	15.0
14	21.4	21.4	21.4	21.4	19.8	21.1	73.7[a)]	65.2	17.6	16.8	20.5
15	68.9	69.0	62.7	62.6	62.4	70.2	110.8	110.8[a)]	12.3	11.9[a)]	13.2
Sugar moiety											
	Glc	Glc	Fru	Glc	Glc	Glc	Glc	Glc	Glc	Glc	Glc
-1	104.3	104.3	63.4	105.8	103.6	104.6	103.3	103.0	106.5	102.8	104.9
2	75.2	75.1	106.1	75.4	75.1	75.2	75.0	75.2	75.5	75.2	75.0
3	78.5	78.3	78.9	79.1	78.7	78.6	78.6[b)]	78.6[b)]	79.2	78.6[b)]	78.8
4	71.7	71.6	77.3	71.7	71.6	71.6	71.7	71.8	71.7	71.7	71.4
5	77.3	76.8	84.1	78.7	78.7	78.6	78.9[b)]	78.8[b)]	77.1	78.7[b)]	78.5
6	68.2	62.7	64.3	62.8	62.8	62.8	62.9	62.9	69.0	62.9	62.7
	Rha	Fru	—	—	—	—	—	—	Api	—	—
1	102.6	63.3	—	—	—	—	—	—	111.0	—	—
2	72.3	105.8	—	—	—	—	—	—	77.8	—	—
3	72.8	79.6	—	—	—	—	—	—	80.4	—	—
4	74.1	76.8	—	—	—	—	—	—	75.1	—	—
5	69.8	84.1	—	—	—	—	—	—	65.6	—	—
6	18.6	63.7	—	—	—	—	—	—	—	—	—

Measured in pyridine-d_5 solution at 35 °C. *a*), *b*) Signal assignments may be interchanged in each column. Glc: β-D-glucopyranose, Rha: α-L-rhamnopyranose, Fru: β-D-fructofuranose, Api: β-D-apiofuranose.

copyranoside.

HR-FAB-MS showed the molecular formula of cichorioside I (**13**) to be $C_{21}H_{28}O_{10}$. From measurements of two dimensional (2D)-NMR (^{1}H–^{1}H shift correlation spectroscopy (COSY), ^{1}H-detected heteronuclear multiple quantum coherency (HMQC) and HMBC), assignments of the proton and carbon signals were accomplished (see Table 1 and Experimental). Comparison of the ^{1}H-NMR spectroscopic data of **13** with those of **9** revealed the H-8 signal to be shifted downfield to δ 4.17. In the COSY spectrum, the H-6 (δ 3.62) signal revealed a correlation with the hydroxyl proton signal (δ 7.02). Thus, the carbonyl carbon at C-12 was esterified at the C-8 position. In the NOE difference experiment, NOEs were observed as follows: H-5α (δ 3.43) and H-7 (δ 2.70), H-9α (δ 2.72); H-6 and H-8, H-13 (δ 1.36). Hence, H-6, H-7 and H-8 retained β, α, and β-orientations, respectively, and the C-13 methyl group was placed on the β-side of C-11. Based on the above evidence, the structure of **13** was identified as shown in Chart 1.

The molecular formula of compound **15** appeared to be $C_{28}H_{31}NO_9$ by HR-FAB-MS [*m/z*: 526.2057 $[M+H]^+$, 548.1898 $[M+Na]^+$]. The ^{13}C-NMR spectral data of the aglycone moiety were similar to those of **14** except for the C-7, C-11 and C-13 signals, and five more carbon signals were observed at δ 177.2, 68.3, 55.8, 30.6 and 24.8. Based on the results of 2D-NMR (COSY, HMQC and HMBC) measurements, these signals were assigned to the prolyl group.[16] In the HMBC experiment, long-range correlations were exhibited between H-13 (δ 3.47, 3.32) and C-1″ (δ 68.3), C-4″ (δ 55.8); H-4″ (δ 2.81) and C-13 (δ 54.1); H-1″ (δ 3.80) and C-13. Thus, the prolyl group was linked at the C-13 position, and **15** was elucidated to be 11β,13-dihydro-13-prolyl-lactucopicrin.

HR-FAB-MS indicated the molecular formulae of both cichorioside J (**16**) and K (**17**) to be $C_{21}H_{26}O_{10}$. In the ^{13}C-NMR spectrum of the aglycone moiety of **16**, two methylene, two methine and one olefin carbon signal were observed at δ 33.6, 27.6, 49.2, 48.3 and 149.6 together with an exomethylene carbon signal at δ 110.8. The 2D-NMR experiment suggested that these carbons composed a cyclopentane ring system with an exomethylene. Comparison of the ^{13}C-NMR spectral data of **16** with those of parthoxetine[17] indicated the presence of α,β-unsaturated-γ-lactone in **16**. The ^{13}C-NMR spectrum of **16** showed two more olefin carbon signals (δ 152.0, 120.8), one acetal carbon signal (δ 106.9), one oxygenated quaternary carbon signal (δ 73.9) and two oxygenated methylene carbon signals (δ 73.7, 60.2). On the other hand, in the ^{1}H-NMR spectrum, two olefin proton signals [δ 6.82 (1H, br d, J=11.0 Hz) and 7.29 (1H, d J=11.0 Hz)] and two sets of oxygenated methylene proton signals [δ 4.10 (1H, d, J=8.5 Hz), 4.21 (1H, d, J=8.5 Hz) and δ 4.77 (1H, d, J=13.5 Hz), 4.94 (1H, d, J=13.5 Hz)] were present. Regarding the above signals, the $^1J_{CH}$s were confirmed as follows in the HMQC experiment; δ 152.0 and 6.82, δ 120.8 and 7.29, δ 73.7 and 4.10, 4.21, and δ 60.2 and 4.77, 4.99. These signals were assignable (see Table 1 and

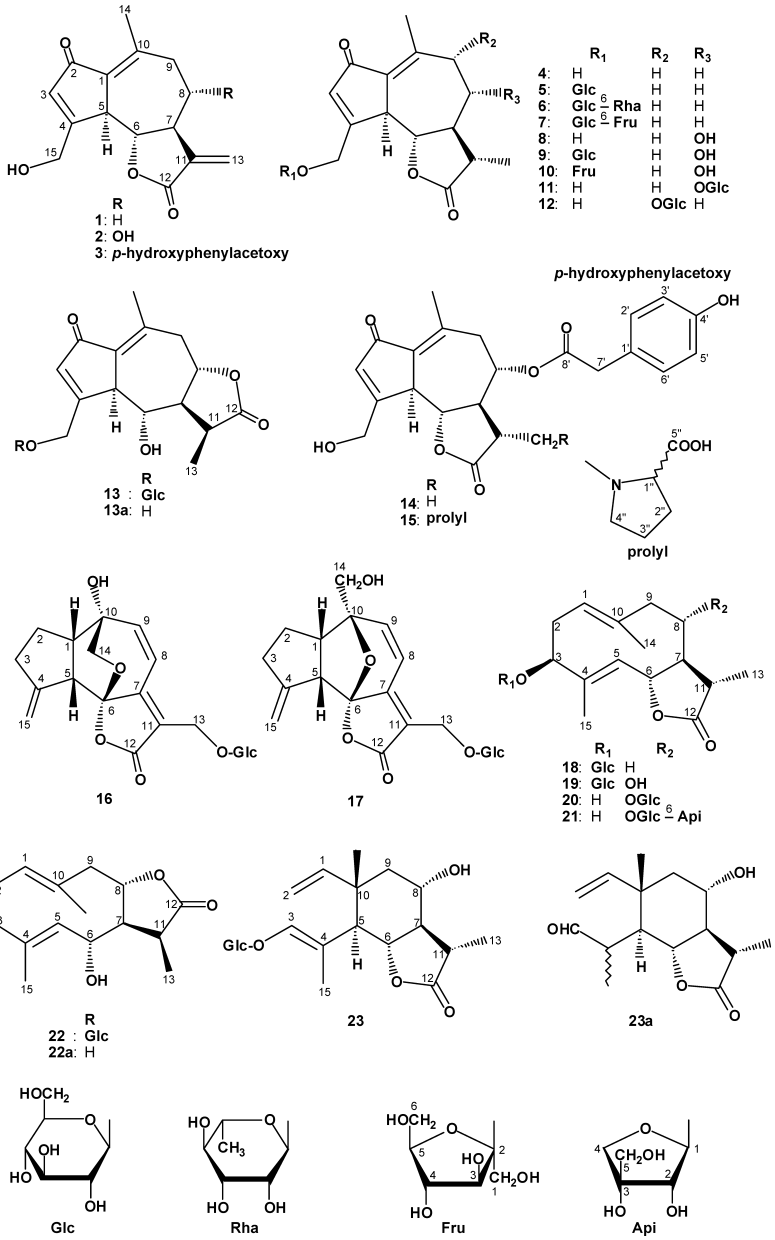

Chart 1. Structures of Compounds **1**—**23**, **13a**, **22a**, and **23a**

Experimental) based on the appearance of long-range correlations in the HMBC experiment. The $^{3}J_{HCOC}$ between H-14 (δ 4.21, 4.10) and C-6 (δ 106.9) suggested an ether linkage. Moreover, in the NOE difference experiment, NOEs were observed between H-1 (δ 3.01) and H-14 (δ 4.21); H-14 (δ 4.21) and H-5 (δ 3.78); H-14 (δ 4.10) and H-9 (δ 6.82); H-8 (δ 7.29) and H-13 (δ 4.77, 4.94); and H-13 and the anomeric proton of β-D-glucopyranose (δ 4.87). Thus, C-14 was present on the β-side of C-10, H-1 and H-5 retained β-orientations, and the sugar was linked at the C-13 position. On the basis of these results, the relative structure of **16** was determined as shown in Chart 1. The NMR spectral data of **17** were similar to those of **16**. On comparison of the ^{13}C-NMR spectral data of **17** with those of **16**, one acetal carbon signal and one oxygenated quaternary carbon signal were also found at δ 110.5 and 88.3, and a hydroxymethyl carbon signal was present at δ 65.2, instead of the oxygenated methylene carbon signal. These carbon signals were assigned to C-6, C-10 and C-14, respectively, based on the result of the HMBC experiment. In consideration of the molecular formula and existence of the acetal carbon at C-6 and oxygenated quaternary carbon at C-10, **17** possessed an ether linkage between the C-6 and C-10 positions. Moreover, the presence of NOEs between H-9 (δ 6.82) and H-14 (δ 4.05, 4.11), H-14 and H-1 (δ 3.30), H-1 and H-5 (δ 3.88), and H-9 and H-2 (δ 1.59) suggested that C-14 was present on the α-side of C-10, and H-1 and H-5 also retained β-orientations. Hence, the relative structure of **17** was identified as shown in Chart 1.

HR-FAB-MS showed the molecular formula of cichoriioside L (**21**) to be $C_{26}H_{40}O_{13}$. The ^{13}C-NMR spectrum of **21** was similar to that of **20**, but signals due to one more sugar unit were observed, which was identified as apiose by acid hydrolysis. Acid hydrolysis of **21** also afforded **20** together with apiose, and comparison of the ^{13}C-NMR spectral data of the sugar moiety in **21** with those of icariside D_1[18] and F_2[19]

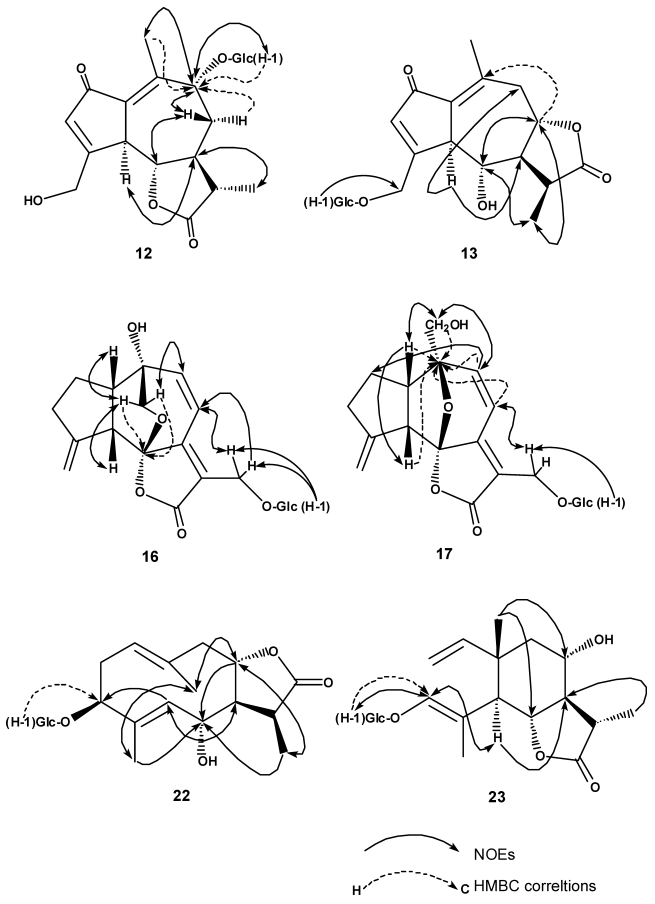

Chart 2. Important NOEs and HMBC Correlations in Compounds **12**, **13**, **16**, **17**, **22**, and **23**

suggested β-D-apiofuranose was linked at the C-6 position of β-D-glucopyranose of **20**. This sugar sequence was supported by results of the NOE difference experiment. Namely, irradiation of the anomeric protons of β-D-glucopyranose (δ 5.01) and β-D-apiofuranose (δ 5.67) showed NOEs to H-8 of the aglycone (δ 4.22) and H-6 of β-D-glucopyranose (δ 4.07), respectively. Thus, the structure of **21** was identified as shown in Chart 1.

The molecular formula of cichorioside M (**22**) was suggested to be $C_{21}H_{32}O_9$, the same as **19**, on the basis of HR-FAB-MS. In the ^{13}C- and ^{1}H-NMR spectrum of **22**, the C-6, H-6 and C-8, H-8 signals were observed at δ 65.0, 4.71 and δ 79.5, 4.63, respectively. A comparison of the NMR spectroscopic data of **22** with those of **19** revealed a γ-lactone ring to be present at the C-7 and C-8 positions of the aglycone. The stereochemistry of **22** was established by the NOE difference experiment and enzymatic hydrolysis, which afforded **22a** from **22**. The orientation of the hydroxyl group at C-3 of **22a** was concluded to be β from the coupling constant of H-3 [δ 4.49 (1H, br dd, J=10.0, 6.0 Hz)] compared with those of 3β-hydroxygermacranolides (dd, J=10, 5.5—7 Hz)[20—23] and 3α-hydroxygermacranolide (t, J=3 Hz).[20] Consequently, in compound **22**, the β-D-glucopyranosyl group was attached at the β-side of C-3, in consideration of the result of the HMBC experiment. The presence of NOEs between H-5 [δ 5.10 (1H, br d, J=10.0 Hz)] and H-3α, H-7 [δ 2.53 (1H, td, J=10.0, 7.5 Hz)] was taken to indicate an α-orientation for H-7. The multiplicity of the H-6 signal [δ 4.71 (1H, td, J=10.0, 3.0 Hz)] showed a β-orientation for H-6. Moreover, NOEs were revealed between H-8 and H-6, H-13 (δ 1.67), H-14 (δ 1.45); H-14 and H-15 (δ 1.86); and H-15 and H-6, suggesting a β-orientation for H-8, the existence of a C-13 methyl group on the β-side of C-11, and the C-14 and C-15 methyl groups being oriented above the plane of the medium ring. Hence, the structure of **22** was identified as shown in Chart 1.

Cichorioside N (**23**) possessed the molecular formula, $C_{21}H_{32}O_9$, according to HR-FAB-MS. The ^{13}C-NMR spectrum of **23** showed four olefin carbon signals (δ 110.9, 111.6, 144.6, 148.2), three methyl carbon signals (δ 13.2, 15.0, 20.5), and one hydroxymethine carbon signal (δ 68.6) together with the signals due to the γ-lactone and β-D-glucopyranosyl groups. In the ^{1}H-NMR spectrum, characteristic signals due to a vinyl group and one olefin proton were observed at δ 4.92 (1H, dd, J=17.5, 1.0 Hz), 4.98 (1H, dd, J=11.0, 1.0 Hz), 5.87 (1H, dd, J=17.5, 11.0 Hz) and 6.63 (1H, d, J=1.0 Hz), respectively, along with the methyl proton signals [δ 1.07 (3H, s), 1.63 (3H, d, J=7.0 Hz) and 1.86 (3H, d, J=1.0 Hz)]. Thus, this compound was suggested to be an elemanone-type of sesquiterpene glucoside.[24] The proton and carbon signals of **23** were assignable (see Table 1 and Experimental) based on the 2D-NMR measurements. The HMBC experiment indicated a long-range correlation between the anomeric proton signal of β-D-glucopyranose (δ 5.13) and the C-3 signal (δ 144.6). Furthermore, an aldehyde proton signal was observed at δ 9.92 in the ^{1}H-NMR spectrum of **23a** obtained by enzymatic hydrolysis of **23**. These results indicated that **23** was an enol glucoside at C-3. The J value of H-5 signals showed that H-5 oriented to α. The observed NOE between H-3 (δ 6.63) and H-5α (δ 2.31) indicated an E-configuration of the double bond between the C-3 and C-4 positions. Additionally, NOEs between H-14 (δ 1.07) and H-6 (δ 4.42), H-8 (δ 4.19); H-5α and H-7 (δ 1.95); H-7 and H-13 (δ 1.63) suggested that H-6, H-7, and H-8 had β-, α-, and β-orientations, respectively, and the C-13 methyl group was present on the α-side of C-11. Thus, these results led us to conclude the structure of **23** shown in Chart 1.

In this investigation, twelve new sesquiterpene and sesquiterpene glycosides were obtained along with eleven known compounds. From the previous literatures,[1—4] the major and bioactive sesquiterpene constituents in the roots of this plant were considered to be guaianolides such as lactucin, 8-deoxylactucine and lactucopicrin. However, because many kinds and a large amount of guaiane-type sesquiterpene glycosides were contained in the roots, we are interested in the biological activities of these glycosides as well as guaianolides. And this is the first report on the occurrence of an elemanone-type sesquiterpene glycoside in *Cichorium* spp.

Experimental

General Procedure Optical rotation measurements were obtained using a JASCO DIP-1000 digital polarimeter. FAB-MS spectra were collected on a JEOL JMS-700 spectrometer in *m*-nitrobenzyl alcohol or glycerol, whereas both ^{1}H- and ^{13}C-NMR spectra were recorded in pyridine-d_5 solution at 35 °C on a JEOL JNM A-400 (400, 100.40 MHz, respectively) spectrometer. Chemical shifts are given in the δ (ppm) with tetramethylsilane (TMS) as an internal standard. UV spectra were measured with a JASCO V-630 spectrophotometer. A Hitachi G-3000 gas chromatograph was utilized for GC and JASCO 800 and 900 system instruments were employed for

HPLC analyses.

Plant Material The roots of *C. endivia* (No. 3254M) were provided by Saladcosmo Co., Ltd. These dried materials were stored in a herbarium of the University of Shizuoka.

Extraction and Isolation The dried roots of *C. endivia* (3.1 kg) were extracted three times with MeOH under reflux. The extract was concentrated under reduced pressure and the residue was suspended in H_2O. This suspension was extracted with Et_2O. The Et_2O extract was evaporated to dryness, and the residue (58.5 g) was then chromatographed on a silica gel column with a $CHCl_3$–MeOH (98 : 2—9 : 1) system to get four fractions (A (26.4 g), B (4.2 g), C (0.79 g) and D (2.1 g)). Using semi-preparative HPLC (Inertsil ODS-3 30 mm i.d.×50 cm and YMC-ODS 20 mm i.d.×25 cm: 20—25% CH_3CN in water and 25—50% MeOH in water), fraction B (1.4 g) afforded compounds **1** (6 mg), **2** (20 mg), **3** (42 mg), **4** (22 mg), **8** (55 mg) and **14** (14 mg).

The H_2O layer of the MeOH extract was passed through a porous polymer gel (Mitsubishi Diaion HP-20) column with absorbed material being eluted with MeOH–H_2O (1 : 1), MeOH–H_2O (7 : 3) and MeOH, respectively. The MeOH–H_2O (1 : 1) fraction from the Diaion HP-20 column was dried *in vacuo*, and the residue (19.7 g) was subjected to silica gel column chromatography with a $CHCl_3$–MeOH–H_2O (90 : 10 : 1—90 : 16 : 1) system to obtain three partitions (A (1.80 g), B (1.6 g) and C (4.3 g)). Using semi-preparative HPLC (Inertsil ODS-3 30 mm i.d.×50 cm, Capcellpak ODS-UG80 30 mm i.d.×25 cm, YMC-ODS 20 mm i.d.×25 cm and Develosil C8 20 mm i.d.×25 cm: 7.5—20% CH_3CN in water and 25—40% MeOH in water), fractions B (0.5 g) and C (3.9 g) yielded compounds **1** (20 mg), **2** (6 mg), **5** (937 mg), **6** (8 mg), **7** (13 mg), **8** (60 mg), **9** (2.28 g), **10** (8 mg), **11** (25 mg), **12** (4 mg), **13** (41 mg), **15** (21 mg), **16** (3 mg), **17** (4 mg), **18** (72 mg), **19** (128 mg), **20** (64 mg), **21** (3 mg), **22** (9 mg) and **23** (25 mg).

Cichorioside D (**6**): Amorphous powder. $[\alpha]_D^{23}$ −42° (c=0.78, MeOH). UV λ_{max}^{MeOH} nm (log ε): 256 (4.19). FAB-MS m/z: 593 $[M+Na]^+$. HR-FAB-MS m/z: 593.2203 (Calcd for $C_{27}H_{38}O_{13}Na$: 593.2210). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.95 (1H, q, 1.5, H-3), 5.49 (1H, d, 1.5, H_{rha}-1), 5.24 (1H, dd, 17.5, 1.5, H-15), 4.95 (1H, br d, 17.5, H-15), 4.89 (1H, d, 8.0, H_{glc}-1), 4.59 (1H, dd, 11.5, 2.0, H_{glc}-6), 4.57 (overlapping, H_{rha}-2), 4.48 (1H, dd, 9.5, 3.0, H_{rha}-3), 4.32 (1H, dq, 9.5, 6.0, H_{rha}-5), 4.19 (1H, t, 9.5, H_{rha}-4), 4.18 (1H, t, 8.0, H_{glc}-3), 4.17 (1H, dd, 11.5, 6.0, H_{glc}-6), 4.05 (1H, t, 8.0, H_{glc}-2), 4.03 (1H, t, 8.0, H_{glc}-4), 3.98 (1H, m, H_{glc}-5), 3.59 (1H, br d, 10.0, H-5), 3.43 (1H, t, 10.0, H-6), 2.44 (3H, br s, H-14), 2.26 (overlapping, H-8), 2.24 (1H, dq, 12.0, 7.0, H-11), 2.06 (1H, ddd, 14.0, 6.5, 1.0, H-9), 1.82 (1H, ddd, 12.0, 10.0, 3.0, H-7), 1.69 (1H, m, H-9), 1.61 (3H, d, 6.0, H_{rha}-6), 1.11 (3H, d, 7.0, H-13), 1.10 (overlapping, H-8).

Cichorioside E (**7**): Amorphous powder. $[\alpha]_D^{23}$ −56.9° (c=1.09, MeOH). UV λ_{max}^{MeOH} nm (log ε): 256 (4.11). FAB-MS m/z: 609 $[M+Na]^+$. HR-FAB-MS m/z: 609.2161 (Calcd for $C_{27}H_{38}O_{14}Na$: 609.2159). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.91 (1H, br s, H-3), 5.18 (1H, dd, 17.5, 1.5, H-15), 5.14 (1H, d, 8.0, H_{fru}-3), 4.99 (overlapping, H_{fru}-4), 4.97 (1H, br d, 17.5, H-15), 4.82 (1H, d, 8.0, H_{glc}-1), 4.50 (1H, ddd, 8.0, 5.0, 3.0, H_{fru}-5), 4.48 (1H, dd, 11.0, 4.5, H_{glc}-6), 4.31 (overlapping, H_{fru}-6), 4.27 (1H, dd, 11.0, 2.5, H_{glc}-6), 4.24 (1H, d, 11.5, H_{fru}-1), 4.22 (1H, d, 11.5, H_{fru}-1), 4.21 (1H, t, 8.0, H_{glc}-4), 4.14 (1H, t, 8.0, H_{glc}-3), 3.99 (1H, t, 8.0, H_{glc}-2), 3.85 (1H, m, H_{glc}-5), 3.56 (1H, br d, 10.0, H-5), 3.43 (1H, t, 10.0, H-6), 2.45 (3H, br s, H-14), 2.26 (overlapping, H-8), 2.24 (1H, dq, 12.0. 7.0, H-11), 2.07 (1H, br dd, 14.0, 6.0, H-9), 1.82 (1H, ddd, 12.0, 10.0, 3.0, H-7), 1.71 (1H, m, H-9), 1.13 (3H, d, 7.0, H-13), 1.11 (1H, br q, 12.0, H-8).

Cichorioside F (**10**): Amorphous powder. $[\alpha]_D^{23}$ −33° (c=0.76, MeOH). UV λ_{max}^{MeOH} nm (log ε): 256 (4.14). FAB-MS m/z: 463 $[M+Na]^+$. HR-FAB-MS m/z: 463.1573 (Calcd for $C_{21}H_{28}O_{10}Na$: 463.1580). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.93 (1H, q, 1.0, H-3), 6.83 (1H, br d, 5.5, C-8-OH), 5.45 (1H, dd, 18.0, 2.0, H-15), 5.28 (1H, d, 8.0, H_{fru}-3), 5.09 (1H, dd, 18.0, 1.0, H-15), 4.98 (1H, t, 8.0, H_{fru}-4), 4.62 (1H, ddd, 8.0, 6.0, 3.0, H_{fru}-5), 4.40 (1H, br d, 12.0, H_{fru}-6), 4.33 (1H, dd, 12.0, 6.0, H_{fru}-6), 4.31 (1H, br d, 11.5, H_{fru}-1), 4.26 (1H, br d, 11.5, H_{fru}-1), 3.80 (1H, br td, 10.0, 4.0, H-8), 3.49 (1H, t, 10.0, H-6), 3.45 (1H, br d, 10.0, H-5), 2.81 (1H, dd, 13.5, 10.0, H-9α), 2.72 (1H, dq, 12.0, 7.0, H-11), 2.53 (1H, dd, 13.5, 2.0, H-9β), 2.46 (3H, br s, H-14), 2.17 (1H, dt, 12.0, 10.0, H-7), 1.66 (3H, d, 7.0, H-13).

Cichorioside G (**11**): Amorphous powder. $[\alpha]_D^{25}$ −30° (c=0.85, pyridine). UV λ_{max}^{MeOH} nm (log ε): 257 (4.08). FAB-MS m/z: 441 $[M+H]^+$, 463 $[M+Na]^+$. HR-FAB-MS m/z: 463.1602 (Calcd for $C_{27}H_{28}O_{10}Na$: 463.1580). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.97 (1H, br s, H-3), 5.30 (1H, br d, 18.5, H-15), 5.01 (1H, d, 8.0, H_{glc}-1), 4.73 (1H, br d, 18.5, H-15), 4.54 (1H, dd, 12.0, 2.5, H_{glc}-6), 4.36 (1H, dd, 12.0, 5.5, H_{glc}-6), 4.21 (overlapping, H_{glc}-3, H_{glc}-4), 4.02 (1H, t, 8.0, H_{glc}-2), 3.97 (1H, m, H_{glc}-5), 3.92 (1H, br t, 10.0, H-8), 3.65 (overlapping, H-5, H-6), 3.24 (1H, dd, 13.5, 2.0, H-9β), 2.92 (1H, dq, 12.0, 7.0, H-11), 2.76 (1H, dd, 13.5, 10.0, H-9α), 2.66 (3H, br s, H-14), 2.46 (1H, m, H-7), 1.86 (3H, d, 7.0, H-13).

Cichorioside H (**12**): Amorphous powder. $[\alpha]_D^{24}$ +62° (c=0.39, MeOH). UV λ_{max}^{MeOH} nm (log ε): 256 (4.20). FAB-MS m/z: 441 $[M+H]^+$, 463 $[M+Na]^+$. HR-FAB-MS m/z: 463.1594 (Calcd for $C_{21}H_{28}O_{10}Na$: 463.1580). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.94 (1H, q, 1.5, H-3), 5.20 (1H, br d, 19.0, H-15), 4.86 (1H, d, 8.0, H_{glc}-1), 4.55 (1H, d, 5.5, H-9β), 4.49 (1H, dd, 12.0, 2.0, H_{glc}-6), 4.48 (1H, br d, 18.5, H-15), 4.34 (1H, dd, 12.0, 5.0, H_{glc}-6), 4.22 (1H, t, 8.0, H_{glc}-4), 4.20 (overlapping, H_{glc}-3), 4.18 (1H, br d, 10.0, H-5), 4.01 (1H, t, 8.0, H_{glc}-2), 3.93 (1H, m, H_{glc}-5), 3.61 (1H, t, 10.0, H-6), 3.17 (1H, ddd, 13.0, 10.0, 3.0, H-7), 2.67 (3H, br s, H-14), 2.40 (1H, ddd, 13.0, 5.5, 3.0, H-8α), 2.37 (1H, dq, 13.0, 7.0, H-11), 1.46 (1H, t, 13.0, H-8β), 1.26 (3H, d, 7.0, H-13).

Cichorioside I (**13**): Amorphous powder. $[\alpha]_D^{25}$ −73.4° (c=1.14, MeOH). UV λ_{max}^{MeOH} nm (log ε): 258 (4.20). FAB-MS m/z: 463 $[M+Na]^+$. HR-FAB-MS m/z: 463.1594 (Calcd for $C_{21}H_{28}O_{10}Na$: 463.1580). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 7.04 (1H, br s, H-3), 7.02 (overlapping, C-6-OH), 5.53 (1H, dd, 17.5, 2.0, H-15), 5.15 (1H, br d, 17.5, H-15), 4.94 (1H, d, 8.0, H_{glc}-1), 4.47 (1H, br d, 12.0, H_{glc}-6), 4.31 (1H, dd, 12.0, 4.0, H_{glc}-6), 4.19 (overlapping, H_{glc}-3, H_{glc}-4), 4.17 (1H, td, 10.5, 2.0, H-8), 4.09 (1H, t, 8.0, H_{glc}-2), 3.83 (1H, m, H_{glc}-5), 3.62 (1H, td, 10.5, 7.0, H-6), 3.43 (1H, br d, 10.5, H-5), 3.17 (1H, quint, 7.5, H-11), 2.72 (1H, dd, 13.0, 10.5, H-9α), 2.70 (1H, td, 10.5, 7.5, H-7), 2.61 (1H, dd, 13.0, 2.0, H-9β), 2.49 (3H, br s, H-14), 1.36 (3H, d, 7.5, H-13).

11β,13-Dihydro-13-prolyl-lactucopicrin (**15**): Amorphous powder. $[\alpha]_D^{24}$ −47.7° (c=1.10, pyridine). UV λ_{max}^{MeOH} nm (log ε): 234 (sh), 255 (4.20). FAB-MS m/z: 526 $[M+H]^+$, 548 $[M+Na]^+$. HR-FAB-MS m/z: 526.2057, 548.1898 (Calcd for $C_{28}H_{32}NO_9$: 526.2077, $C_{28}H_{31}NO_9Na$: 548.1897). ^{13}C-NMR (pyridine-d_5 at 35 °C) δ: 194.8 (C-2), 177.2 (C-5″), 176.5 (C-12), 175.5 (C-4), 171.7 (C-8′), 158.3 (C-4′), 145.6 (C-10), 133.5 (C-1), 133.2 (C-3), 131.2×2 (C-2′, C-6′), 124.9 (C-1′), 116.5×2 (C-3′, C-5′), 81.3 (C-6), 71.7 (C-8), 68.3 (C-1″), 62.5 (C-15), 55.8 (C-4″), 54.1 (C-13), 52.3 (C-7), 49.5 (C-5), 47.2 (C-11), 44.9 (C-9), 40.7 (C-7′), 30.6 (C-2″), 24.8 (C-3″), 21.2 (C-14). ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 7.45 (2H, br d, 8.5, H-2′, H-6′), 7.18 (2H, br d, 8.5, H-3′, H-5′), 6.96 (1H, br s, H-3), 5.27 (1H, dd, 18.5, 2.0, H-15), 5.09 (1H, td, 11.0, 1.5, H-8), 4.61 (1H, dd, 18.5, 2.0, H-15), 3.92 (2H, s, H-7′), 3.80 (1H, dd, 9.0, 5.0, H-1″), 3.79 (overlapping, H-5, H-6), 3.51 (1H, m, H-7), 3.47 (1H, dd, 14.0, 2.5, H-13), 3.43 (1H, m, H-4″), 3.32 (1H, dd, 14.0, 5.0, H-13), 2.97 (1H, dd, 13.5, 11.0, H-9α), 2.87 (1H, ddd, 12.0, 5.0, 2.5, H-11), 2.81 (1H, q, 9.0, H-4″), 2.46 (3H, br s, H-14), 2.43 (1H, dd, 13.5, 2.0, H-9β), 2.14 (1H, m, H-2″), 2.10 (1H, m, H-2″), 1.85 (1H, m, H-3″), 1.69 (1H, m, H-3″).

Cichorioside J (**16**): Amorphous powder. $[\alpha]_D^{23}$ −11° (c=0.32, MeOH). UV λ_{max}^{MeOH} nm (log ε): 277 (4.00). FAB-MS m/z: 461 $[M+Na]^+$. HR-FAB-MS m/z: 461.1428 (Calcd for $C_{21}H_{26}O_{10}Na$: 461.1424). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 7.29 (1H, d, 11.0, H-8), 6.82 (1H, d, 11.0, H-9), 5.18 (1H, br s, H-15), 5.02 (1H, br s, H-15), 4.94 (1H, d, 13.5, H-13), 4.87 (1H, d, 8.0, H_{glc}-1), 4.77 (1H, d, 13.5, H-13), 4.56 (1H, br d, 12.0, H_{glc}-6), 4.34 (1H, dd, 12.0, 5.0, H_{glc}-6), 4.21 (1H, d, 8.5, H-14), 4.18 (overlapping, H_{glc}-3, H_{glc}-4), 4.10 (1H, d, 8.5, H-14), 4.01 (1H, t, 8.0, H_{glc}-2), 3.92 (1H, m, H_{glc}-5), 3.78 (1H dq, 11.0, 1.5, H-5), 3.01 (1H, td, 11.0, 3.0, H-1), 2.35 (1H, m, H-3), 2.21 (1H, m, H-3), 2.02 (1H, m, H-2), 1.85 (1H, m, H-2).

Cichorioside K (**17**): Amorphous powder. $[\alpha]_D^{23}$ +110° (c=0.45, MeOH). UV λ_{max}^{MeOH} nm (log ε): 263 (3.91). FAB-MS m/z: 461 $[M+Na]^+$. HR-FAB-MS m/z: 461.1429 (Calcd for $C_{21}H_{26}O_{10}Na$: 461.1424). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 7.41 (1H, d, 9.5, H-8), 6.82 (1H, d, 9.5, H-9), 4.94 (1H, br s, H-15), 4.92 (1H, d, 14.0, H-13), 4.91 (1H, br s, H-15), 4.89 (1H, d, 8.0, H_{glc}-1), 4.77 (1H, d, 14.0, H-13), 4.56 (1H, br d, 12.0, H_{glc}-6), 4.34 (1H, dd, 12.0, 6.0, H_{glc}-6), 4.18 (overlapping, H_{glc}-3, H_{glc}-4), 4.11 (1H, br d, 12.0, H-14), 4.05 (1H, br d, 12.0, H-14), 4.02 (1H, t, 8.0, H_{glc}-2), 3.91 (1H, m, H_{glc}-5), 3.88 (1H, dq, 11.0, 1.5, H-5), 3.30 (1H, ddd, 11.0, 9.5, 2.0, H-1), 2.56 (1H, m, H-3), 2.12 (1H, dd, 17.0, 9.0, H-3), 1.62 (2H, m, H-2).

Cichorioside L (**21**): Amorphous powder. $[\alpha]_D^{23}$ +12° (c=0.27, MeOH). FAB-MS m/z: 583 $[M+Na]^+$. HR-FAB-MS m/z: 583.2380 (Calcd for $C_{26}H_{40}O_{13}Na$: 583.2367). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 5.67 (1H, d, 2.0, H_{api}-1), 5.01 (1H, d, 8.0, H_{glc}-1), 5.01 (1H, br t, 9.5, H-6), 4.96 (1H, br d, 12.0, H-1), 4.90 (1H, br d, 9.5, H-5), 4.73 (1H, d, 9.0, H_{glc}-6), 4.69 (1H, d, 2.0, H_{api}-2), 4.55 (1H, d, 9.5, H_{api}-4), 4.52 (overlapping, H-3), 4.33 (1H, d, 9.5, H_{api}-4), 4.22 (1H, br t, 11.0, H-8), 4.15 (overlapping, H_{api}-5×2, H_{glc}-3), 4.07 (1H, d, 9.0, H_{glc}-6), 4.07 (1H, m, H_{glc}-5),

3.99 (1H, br t, 8.0, H_{glc}-2), 3.94 (1H, br t, 9.0, H_{glc}-4), 3.54 (1H, dq, 11.0, 7.0, H-11), 3.42 (1H, br d, 11.0, H-9), 2.49 (overlapping, H-2×2, H-9), 2.32 (1H, br dt, 11.0, 9.5, H-7), 1.91 (3H, br s, H-15), 1.83 (3H, br s, H-14), 1.82 (overlapping, H-13).

Cichorioside M (**22**): Amorphous powder. $[\alpha]_D^{25}$ +2.9° (c=0.90, MeOH). FAB-MS m/z: 451 $[M+Na]^+$. HR-FAB-MS m/z: 451.1942 (Calcd for $C_{21}H_{32}O_9Na$: 451.1944). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.64 (1H, d, 3.0, C-6-OH), 5.10 (1H, br d, 10.0, H-5), 4.80 (overlapping, H-1), 4.71 (1H, td, 10.0, 3.0, H-6), 4.70 (1H, d, 8.0, H_{glc}-1), 4.68 (overlapping, H-3), 4.63 (1H, td, 10.0, 2.0, H-8), 4.54 (1H, br d, 11.5, H_{glc}-6), 4.38 (1H, dd, 11.5, 4.5, H_{glc}-6), 4.22 (1H, t, 8.0, H_{glc}-4), 4.11 (1H, t, 8.0, H_{glc}-3), 4.05 (1H, t, 8.0, H_{glc}-2), 3.76 (1H, m, H_{glc}-5), 3.26 (1H, quint, 7.5, H-11), 2.87 (1H, br d, 12.5, H-9), 2.53 (1H, td, 10.0, 7.5, H-7), 2.49 (overlapping, H-2), 2.44 (1H, td, 12.0, 11.0, H-2), 2.36 (1H, dd, 12.5, 10.0, H-9), 1.86 (3H, d, 1.5, H-15), 1.67 (3H, d, 7.5, H-13), 1.45 (3H, br s, H-14).

Cichorioside N (**23**): Amorphous powder. $[\alpha]_D^{23}$ +38.0° (c=1.13, MeOH). FAB-MS m/z: 429 $[M+H]^+$, 451 $[M+Na]^+$. HR-FAB-MS m/z: 429.2129, 451.1944 (Calcd for $C_{21}H_{33}O_9$: 429.2125, $C_{21}H_{32}O_9Na$: 451.1944). ^{13}C-NMR: shown in Table 1. ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.63 (1H, d, 1.0, H-3), 5.87 (1H, dd, 17.5, 11.0, H-1), 5.13 (1H, d, 8.0, H_{glc}-1), 4.98 (1H, dd, 11.0, 1.0, H-2), 4.92 (1H, dd, 17.5, 1.0, H-2), 4.47 (1H, dd, 12.0, 2.0, H_{glc}-6), 4.42 (1H, t, 11.0, H-6), 4.33 (1H, dd, 12.0, 4.0, H_{glc}-6), 4.25 (overlapping, H_{glc}-3, H_{glc}-4), 4.19 (overlapping, H-8), 4.13 (1H, t, 8.0, H_{glc}-2), 3.93 (1H, m, H_{glc}-5), 2.83 (1H, dq, 11.0, 7.0, H-11), 2.31 (1H, d, 11.0, H-5), 1.99 (1H, dd, 12.0, 4.0, H-9), 1.95 (1H, q, 11.0, H-7), 1.86 (1H, t, 12.0, H-9), 1.86 (3H, d, 1.0, H-15), 1.63 (3H, d, 7.0, H-13), 1.07 (3H, s, H-14).

Acid Hydrolysis of Compounds 6, 7, 10—12, 16 and 17 Compounds **6**, **7**, **10**, **11**, **16** and **17** (*ca.* 0.5 mg) were dissolved in dioxane and 2 M HCl (50 μl each), and heated at 100 °C for 1 h. Compound **12** was dissolved in 1 M H_2SO_4, and heated for 30 min. After hydrolysis, the reaction mixture was neutralized with an Amberlite IRA-60E column, and the eluate was concentrated. The residue was partitioned between EtOAc and H_2O. The H_2O layer was concentrated to dryness and the residue was stirred with D-cysteine methyl ester hydrochloride, hexamethyldisilazane and trimethylsilylchloride in pyridine using the same procedures as in previous reports.[25,26] After the reactions, the supernatant was subjected to GL analysis. GC conditions: column, GL capillary column TC-1 (GL Science, Inc.) 0.25 mm×30 m; carrier gas, N_2; column temperature, 230 °C; t_R 21.0 min (D-glucose), 20.2 min (L-glucose), 13.9 min (D-rhamnose), 14.2 min (L-rhamnose), 16.7 min (D-fructose), 17.2 min (L-fructose). The t_Rs for L-glucose, D-rhamnose and L-fructose were obtained from their enantiomers (D-glucose+L-cysteine, L-rhamnose+L-cysteine and D-fructose+L-cysteine). D-Glucose was detected in **6**, **7**, **11**, **12**, **16** and **17**. L-Rhamnose was found in **6**, and D-fructose was identified in **7** and **10**.

Acid Hydrolysis of Compound 21 Compound **21** (*ca.* 0.5 mg) was dissolved in dioxane and 2 M HCl (50 μl each), and heated at 100 °C for 5 min. After hydrolysis, the reaction mixture was neutralized with an Amberlite IRA-60E column, and the eluate was concentrated. By HPLC analysis, compound **20** (hypochoeroside A) was detected in the above residue. HPLC conditions: column, YMC-ODS-AM 4.6 mm×25 cm; flow rate, 1.0 ml/min; solvent, 10% CH_3CN in water; t_R 17.8 min (**20**). The remaining residue was reduced with $NaBH_4$ (*ca.* 1 mg) for 1 h at room temperature. The procedures to obtain alditol acetate were described in a previous paper.[27] Apiitol acetate was detected in **21** by GC analysis. GC conditions: column, Supelco SP-2380^{TM} capillary column 0.25 mm×30 m; carrier gas, N_2; column temperature, 250 °C; t_R 7.8 min (apiitol acetate).

Enzymatic Hydrolysis of Compounds 13, 22 and 23 Compounds **13** (7 mg), **22** (6 mg) and **23** (9 mg) were dissolved in EtOH (0.25 ml) and H_2O (1.25 ml), respectively, then cellulase (Sigma Chem. Co.) (*ca.* 30 mg) was added to each solution. The mixtures of **13** and **23** were stirred at 40 °C for 4 h, and the mixture of **22** was stirred for 1 d. After hydrolysis, the reaction mixtures were diluted with H_2O and extracted with EtOAc. Compounds **13a** (2 mg), **22a** (2 mg) and **23a** (2 mg) were purified from the residue of each EtOAc layer using HPLC (column, YMC-ODS 10 mm×25 cm; flow rate, 3.0 ml/min; solvent, **13a**, 15% CH_3CN in water, **22a**, 17.5% CH_3CN in water, **23a**, 27.5% CH_3CN in water).

Cichoriolide I (**13a**): Amorphous powder. $[\alpha]_D^{25}$ −22° (c=0.22, MeOH). UV λ_{max}^{MeOH} nm (log ε): 257 (4.13). FAB-MS m/z: 301 $[M+Na]^+$. HR-FAB-MS m/z: 301.1077 (Calcd for $C_{15}H_{18}O_5Na$: 301.1052). ^{13}C-NMR (pyridine-d_5 at 35 °C) δ: 196.0 (C-2), 178.5 (C-12), 177.8 (C-4), 145.3 (C-10), 134.0 (C-1), 132.8 (C-3), 76.3 (C-8), 70.3 (C-6), 63.3 (C-15), 58.9 (C-7), 55.1 (C-5), 41.7 (C-9), 39.9 (C-11), 21.1 (C-14), 9.7 (C-13). ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 7.17 (1H, d, 7.0, C-6-OH), 7.03 (1H, br t, 4.0, C-15-OH), 6.98 (1H, br s, H-3), 5.48 (1H, br dd, 18.0, 4.0, H-15), 4.88 (1H, br d, 18.0, H-15), 4.19 (1H, td, 10.5, 2.0, H-8), 3.65 (1H, td, 10.5, 7.0, H-6), 3.58 (1H, br d, 10.5, H-5), 3.17 (1H, quint, 7.5, H-11), 2.76 (1H, dd, 13.5, 10.5, H-9), 2.72 (1H, td, 10.5, 7.5, H-7), 2.62 (1H, dd, 13.5, 2.0, H-9), 2.52 (3H, s, H-14), 1.36 (3H, d, 7.5, H-13).

Cichoriolide M (**22a**): Amorphous powder. $[\alpha]_D^{26}$ +103° (c=0.23, MeOH). FAB-MS m/z: 267 $[M+H]^+$, 289 $[M+Na]^+$. HR-FAB-MS m/z: 289.1411 (Calcd for $C_{15}H_{22}O_4Na$: 289.1416). ^{13}C-NMR (pyridine-d_5 at 35 °C) δ: 179.2 (C-12), 136.4 (C-4), 132.4 (C-10), 130.7 (C-5), 129.6 (C-1), 79.6 (C-8), 78.1 (C-3), 65.0 (C-6), 55.8 (C-7), 47.5 (C-9), 41.0 (C-11), 36.1 (C-2), 16.9 (C-14), 11.8, 11.6 (C-13, C-15). ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 6.62 (1H, br s, C-3-OH), 6.38 (1H, br d, 3.0, C-6-OH), 5.05 (overlapping, H-5), 5.04 (overlapping, H-1), 4.72 (1H, td, 10.0, 3.0, H-6), 4.69 (1H, td, 10.5, 2.0, H-8), 4.49 (1H, br dd, 10.0, 6.0, H-3), 3.27 (1H, quint, 7.5, H-11), 2.93 (1H, br d, 12.5, H-9), 2.60 (overlapping, H-2), 2.58 (1H, td, 10.5, 7.5, H-7), 2.51 (1H, td, 12.0, 10.0, H-2), 2.43 (1H, dd, 12.5, 10.5, H-9), 1.85 (3H, d, 1.5, H-15), 1.69 (3H, d, 7.5, H-13), 1.52 (3H, br s, H-14).

Cichoriolide N (**23a**): Amorphous powder. $[\alpha]_D^{26}$ +37° (c=0.23, MeOH). FAB-MS m/z: 289 $[M+Na]^+$. HR-FAB-MS m/z: 289.1416 (Calcd for $C_{15}H_{22}O_4Na$: 289.1416). ^{13}C-NMR (pyridine-d_5 at 35 °C) δ: 204.5 (C-3), 178.9 (C-12), 147.6 (C-1), 113.3 (C-2), 78.6 (C-6), 68.3 (C-8), 59.5 (C-7), 51.8 (C-5), 50.8 (C-9), 45.3 (C-4), 43.0 (C-10), 41.2 (C-11), 19.0 (C-14), 16.7 (C-15), 14.9 (C-13). ^{1}H-NMR (pyridine-d_5 at 35 °C) δ: 9.92 (1H, d, 2.5, H-3), 6.52 (1H, d, 5.5, C-8-OH), 5.76 (1H, dd, 17.0, 11.0, H-1), 5.07 (1H, dd, 11.0, 1.0, H-2), 5.05 (1H, dd, 17.0, 1.0, H-2), 4.51 (1H, t, 11.5, H-6), 4.15 (1H, m, H-8), 2.76 (1H, dq, 12.0, 7.0, H-11), 2.58 (1H, qt, 7.5, 2.5, H-4), 1.94 (overlapping, H-9), 1.92 (overlapping, H-5, H-7), 1.79 (1H, dd, 13.0, 11.0, H-9), 1.60 (3H, d, 7.0, H-13), 1.24 (3H, d, 7.5, H-15), 1.15 (3H, s, H-14).

The residue of each H_2O layer was reacted with D-cysteine methyl ester hydrochloride, hexamethyldisilazane and trimethylsilylchloride in pyridine using the above procedures. D-Glucose was detected in all compounds.

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References

1) Seto M., Miyase T., Umehara K., Ueno A., Hirano Y., Otani N., *Chem. Pharm. Bull.*, **36**, 2423—2429 (1988).
2) Kisiel W., Michalska K., *Fitoterapia*, **77**, 354—357 (2006).
3) Wesolowska A., Nikiforuk A., Michalska K., Kisiel W., Chojnacka-Wojicik E., *J. Ethnopharmacol.*, **107**, 254—258 (2006).
4) Bischoff T. A., Kelly C. J., Karchesy Y., Laurantos M., Nguyen-Dinh P., Arefi A. G., *J. Ethnopharmacol.*, **95**, 455—547 (2004).
5) Pyrec J. S., *Rocz. Chem.*, **51**, 2165—2170 (1977).
6) Nishimura K., Miyase T., Ueno A., Noro T., Kuroyanagi M., Fukushima S., *Chem. Pharm. Bull.*, **34**, 2518—2521 (1986).
7) Barrera J. B., Breton-Funes J. L., Gonzales A. G., *J. Chem. Soc.*, **1966**, 1298—1301 (1966).
8) Adegawa S., Miyase T., Ueno A., Noro T., Kuroyanagi M., Fukushima S., *Chem. Pharm. Bull.*, **33**, 4906—4911 (1985).
9) Sarg T. M., Omar A. A., Khafagy S. M., Grenz M., Bohlmann F., *Phytochemistry*, **21**, 1163 (1982).
10) Beek T. A., Maas P., King B. M., Leclercq E., Voragen A. G. J., Groot A., *J. Agric. Food Chem.*, **38**, 1035—1038 (1990).
11) Miyase T., Fukushima S., *Chem. Pharm. Bull.*, **35**, 2869—2874 (1987).
12) Ohmura K., Miyase T., Ueno A., *Phytochemistry*, **28**, 1919—1924 (1989).
13) Kasai R., Okihara M., Asakawa J., Mizutani K., Tanaka O., *Tetrahedron*, **35**, 1427—1432 (1979).
14) Kitajima J., Kamoshita A., Ishikawa T., Takano A., Fukuda T., Isoda S., Ida Y., *Chem. Pharm. Bull.*, **51**, 673—678 (2003).
15) Michalska K., Kaisel W., *Planta Med.*, **69**, 181—183 (2003).
16) Li Y., Jia Z.-J., *Phytochemistry*, **28**, 3395—3397 (1989).
17) Ortega A., Maldonado E., *Phytochemistry*, **25**, 699—701 (1986).
18) Miyase T., Ueno A., Takizawa N., Kobayashi H., Oguchi H., *Chem. Pharm. Bull.*, **35**, 3713—3719 (1987).
19) Miyase T., Ueno A., Takizawa N., Kobayashi H., Oguchi H., *Chem. Pharm. Bull.*, **36**, 2475—2484 (1988).
20) Irwin M. A., Geissman T. A., *Phytochemistry*, **12**, 875—878 (1973).
21) Bohlmann F., Zdero C., Robinson H., King R. M., *Phytochemistry*, **20**, 2029—2030 (1981).
22) Bohlmann F., Zdero C., *Phytochemistry*, **18**, 336—337 (1979).

23) Bohlmann F., Mahanta P. K., Suwita A., Suwita A., Natu A. A., Zdero C., Dorner W., Ehlers D., Grenz M., *Phytochemistry*, **16**, 1973—1981 (1977).
24) Gonzale A. G., Barrera J. B., Garcia T. Z., Rosas F. E., *Phytochemistry*, **23**, 2071—2072 (1984).
25) Hara S., Okabe H., Mihashi K., *Chem. Pharm. Bull.*, **35**, 501—506 (1987).
26) Zhang D., Miyase T., Kuroyanagi M., Umehara K., Ueno A., *Chem. Pharm. Bull.*, **44**, 173—179 (1996).
27) Nagatani T., Warashina T., Noro T., *Chem. Pharm. Bull.*, **49**, 1388—1394 (2001).