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Eudesmane derivatives from *Tessaria integrifolia*

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Abstract

Five eudesmane-type sesquiterpenoids were isolated from the methanol extract of the aerial part of *Tessaria integrifolia* Ruiz. et Pavon (Compositae). Their structures were elucidated on the basis of spectroscopic analysis as well as chemical evidence.

Keywords: *Tessaria integriforia*; Compositae; Sesquiterpene; Eudesmane; Glycoside; Integrifosides A–D; Integrifonol A; Anti-hyaluronidase activity

1. Introduction

Tessaria integrifolia Ruiz. et Pavon (Compositae) is used in the traditional medicine of Peru as an anti-asthmatic agent (Feo, 1992). Regarding the chemical constituents of this plant, the presence of squalene, β-amyrin acetate, bisthienyl derivatives, lignan, sesquiterpenes, flavones and caffeoyl quinic acid derivatives in the aerial part have been previously reported (Bohlmann, Zdero & Silva, 1977; Jakupovic, Misra, Thi, Bohlmann & Castro, 1985; Feo, D'agostino, Simone & Pizza, 1990; Guerreiro & Pestchanker, 1990; Peluso, Feo, Simone, Bresciano & Vuotto, 1995).

The present paper describes the isolation and structure elucidation of five new eudesmane derivatives, named integrifosides A–D, and integrifonol A from the methanol extract of the aerial part of this plant. Furthermore, integrifoside A and methyl 3,4-di-*O*-caffeoyl quinate, which were isolated from this extract (Ono, Masuoka, Odake, Ikegashira, Ito & Nohara, 1999), were investigated for their inhibitory effect on the activation of inactive hyaluronidase as induced by compound 48/80 (Kakegawa, Matsumoto & Satoh, 1985).

2. Results and discussion

The methanol extract of the aerial part of *T. integrifolia* Ruiz. et Pavon was successively subjected to Diaion HP-20, silica gel, Sephadex LH-20 and ODS column chromatographies (CC) as well as HPLC on ODS to afford five new eudesmane derivatives, integrifosides A (**1**), B (**2**), integrifonol A (**3**), and integrifosides C (**4**) and D (**5**).

Compound **1**, named integrifoside A, was concluded to have molecular formula of $C_{21}H_{36}O_8$ by the NMR spectra and by negative FABMS, which showed and an $[M - H]^-$ ion peak at m/z 415. The ^{1}H-NMR spectrum indicated signals due to three tertiary methyl groups (δ 1.87, 1.41, 1.39), two *exo*-methylene protons (δ 5.00, 5.09) and one anomeric proton (δ 4.89). The ^{13}C-NMR spectrum gave 21 carbon signals including two oxygenated methine carbons (δ 90.4, 68.0), one

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Table 1
^{1}H -NMR spectral data for compounds **1**, **1a**, **2**, **3**, **4** and **5** (500 MHz, in pyridine-d_5, TMS as internal standard)[a]

H	1	1a	2	3	4	5
1α	1.14 *ddd* (2.5, 12.0, 12.0)	1.31 *ddd* (3.5, 13.0, 13.0)	1.24 *ddd* (3.0, 13.0, 13.0)	1.28 *ddd* (3.5, 13.0, 13.0)	1.12 *ddd* (3.5, 12.5, 12.5)	ca. 1.44
1β	ca. 1.40	ca. 1.51	1.35 *ddd* (3.0, 3.0, 13.0)	ca. 1.54	ca. 1.42	1.37 *ddd* (3.0, 4.0, 13.0)
2α	1.99 *m*	ca. 1.96[b]	ca. 2.00	1.96 *m*	2.00 *dddd* (3.5, 3.5, 5.0, 12.5)	1.99 *dddd* (4.0, 4.0, 4.0, 13.0)
2β	ca. 1.73	ca. 1.93[b]	1.72 *dddd* (3.0, 13.0, 13.0, 13.0)	1.90 *m*	1.76 *dddd* (3.5, 12.5, 12.5, 12.5)	1.80 *dddd* (3.0, 13.0, 13.0, 13.0)
3	3.77 *dd* (2.5, 12.0)	3.95 *dd* (5.0, 11.5)	3.79 *dd* (5.0, 13.0)	3.94 *dd* (5.0, 11.5)	3.78 *dd* (5.0, 12.5)	ca. 4.28
5	1.70 *d* (13.0)	1.79 *dd* (2.0, 12.5)	1.81 *dd* (2.0, 13.0)	1.73 *dd* (1.0, 13.0)	1.66 *dd* (1.0, 13.0)	2.32 *dd* (2.5, 12.5)
6α	2.44 *d* (13.0)	2.51 *dddd* (1.0, 1.0, 2.0, 12.5)	2.51 *ddd* (1.0, 2.0, 13.0)	2.79 *ddd* (1.0, 1.0, 13.0)	2.74 *br d* (13.0)	3.60 *ddd* (2.5, 5.5, 12.5)
6β	2.26 *ddd* (5.0, 13.0, 13.0)	2.36 *ddd* (5.5, 12.5, 12.5)	1.60 *ddd* (5.0, 13.0, 13.0)	2.29 *dd* (13.0, 13.0)	2.22 *dd* (13.0, 13.0)	1.78 *ddd* (12.5, 12.5, 12.5)
7	2.79 *br s*	2.84 *br s*	2.93 *br s*			3.04 *dd* (5.5, 12.5)
8	4.58 *br s*	4.62 *br s*	4.42 *ddd* (4.5, 4.5, 13.0)	4.53 *ddd* (1.0, 3.0, 3.0)	4.49 *br s*	
9a	1.62 *d* (12.0)	1.72 *dd* (3.0, 13.5)	1.69 *dd* (4.5, 13.0)	1.70 *dd* (3.0, 14.0)	1.62 *dd* (3.0, 14.0)	2.08 *d* (12.0)
9b	ca. 1.77	1.85 *ddd* (1.0, 3.0, 13.5)	ca. 2.00	2.01 *dd* (3.0, 14.0)	1.94 *dd* (3.0, 14.0)	2.30 *d* (12.0)
12	1.87 *s*	1.89 *s*	2.00 *s*	2.17 *s*	2.15 *s*	1.61 *s*
13a	5.00 *s*	5.01 *dd* (1.0, 1.0)	5.19 *dd* (1.0, 1.0)	5.11 *dd* (1.5, 1.5)	5.10 *dd* (1.5, 1.5)	1.67 *s*
13b	5.09 *s*	5.11 *s*	5.74 *s*	5.36 *s*	5.34 *s*	
14	1.41 *s*	1.54 *s*[b]	0.95 *s*	1.50 *s*	1.38 *s*[b]	0.93 *s*
15	1.39 *s*	1.53 *s*[b]	1.30 *s*	1.52 *s*	1.40 *s*[b]	1.42 *s*
1′	4.89 *d* (8.0)		4.92 *d* (8.0)		4.92 *d* (8.0)	5.39 *d* (8.0)
2′	4.01 *dd* (8.0, 8.5)		4.04 *dd* (8.0, 9.0)		4.04 *dd* (8.0, 9.0)	4.08 *dd* (8.0, 9.0)
3′	4.23 *dd* (8.5, 8.5)		4.25 *dd* (9.0, 9.0)		4.24 *dd* (9.0, 9.0)	4.27 *dd* (9.0, 9.0)
4′	4.18 *dd* (8.5, 8.5)		4.22 *dd* (9.0, 9.0)		4.21 *dd* (9.0, 9.0)	3.89 *dd* (9.0, 9.0)
5′	3.98 *m*		4.01 *m*		4.01 *m*	ca. 4.09
6′a	4.28 *dd* (5.5, 11.5)		4.32 *dd* (5.5, 11.5)		4.31 *dd* (5.0, 11.5)	ca. 4.11
6′b	4.51 *d* (11.5)		4.54 *dd* (2.5, 11.5)		4.55 *dd* (2.5, 11.5)	4.62 *br d* (10.5)

[a] Coupling constants (J) in Hz are given in parentheses.
[b] Assignments in each column may be interchangeable.

oxygenated quaternary carbon (δ 73.5), two sp^2 carbons (δ 146.6, 111.3) and one glucopyranosyl group (δ 104.9, 74.5, 78.1, 71.4, 78.1, 62.3) (Kasai, Suzuo, Asakawa & Tanaka, 1977; Kasai, Okihara, Asakawa, Mizutani & Tanaka, 1979). The ^{1}H- and ^{13}C-NMR spectroscopic signals were assigned with the aid of ^{1}H–^{1}H COSY, HMQC and HMBC techniques as shown in Tables 1 and 2, and the planar structure of **1**, which was a eudesmane-type sesquiterpene glucoside, could be characterized as illustrated in Fig. 1. The coupling constants of the signals due to the anomeric and methine protons indicated that the glucose (Glc) unit is β in a $^4C_1$ conformation when Glc is assumed to be in the D-form. The relative stereochemistry of the aglycone (Ag) moiety of **1** was determined by the NOE experiments and coupling constant values. Difference NOE spectra of **1** showed correlations between H-8 of Ag and H_3-12 of Ag and between H-3 of Ag and H-1 of Glc, but no NOE correlations were observed between H-3 of Ag and H_3-15 of Ag or between H-8 of Ag and H_3-14 of Ag. The coupling constants of H-3, H-5, H_2-6, H-7 and H-8 of Ag suggested the hydroxyl group at C-3 of Ag to be in an equatorial orientation and both the isopropenyl group at C-7 of Ag and the hydroxyl group at C-8 of Ag to be in the axial orientation. Enzymatic hydrolysis of **1** with β-glucosidase from almonds gave an aglycone (**1a**) and glucose, which was identified as the D-form by GC analysis according to Hara, Okabe & Mihashi (1987). In order to determine the absolute configuration of the aglycone, the ^{13}C-NMR data of **1** were compared with those of **1a**. The glycosylation shifts were observed at C-2, C-3 and C-4 of Ag with magnitudes −2.4, +10.5 and −1.8 ppm, respectively, indicating the absolute configuration at C-3 of Ag to be *S* according to Kasai et al. (1977) and Seo, Tomita, Tori & Yoshimura (1978). On the basis of the above evidence, the structure of integrifoside A was deduced to be **1**, as illustrated.

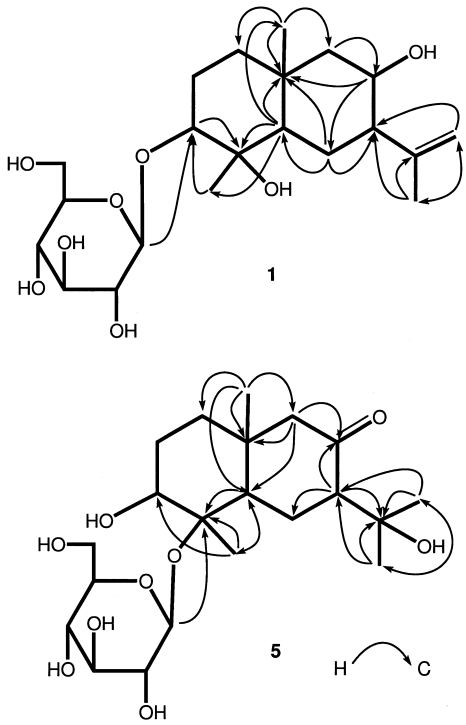


Fig. 1. ^{1}H–^{13}C long range correlations observed for **1** and **5** in the HMBC spectra.

Table 2
^{13}C-NMR spectral data for compounds **1**, **1a**, **2**, **3**, **4** and **5** (in pyridine-d_5, TMS as internal standard)[a]

C	1	1a	2	3	4	5
1	40.4	41.0	39.8	40.5	40.2	38.5
2	26.3	28.7	27.0	28.7	26.7	27.5
3	90.4	79.9	90.5	79.8	90.6	73.2
4	73.5	75.3	73.6	75.2	73.7	83.6
5	46.9	47.9	47.0[b]	50.3	49.6	48.6
6	19.0	19.4	24.3	27.6	27.5	24.4
7	48.4	48.9	46.8[b]	76.3	76.2	60.5
8	68.0	68.3	69.0	70.9	70.8	211.5
9	47.3	47.9	49.4	47.9	47.6	60.4
10	34.7	35.7	35.5	35.2	34.5	40.5
11	146.6	147.0	145.1	148.4	148.3	70.9
12	23.3	23.5	25.5	20.0[b]	20.0[b]	25.3
13	111.3	111.5	114.4	113.0	113.1	29.3
14	21.4	22.0	19.7	22.2[b]	21.8[b]	19.9
15	18.8	17.6	18.8	17.8	19.2	16.3
1′	104.9		105.3		105.3	95.7
2′	74.5		74.8		74.8	76.0
3′	78.1		78.5		78.5	78.7
4′	71.4		71.7		71.7	72.1
5′	78.1		78.5		78.5	79.2
6′	62.3		62.6		62.6	63.2

[a] **1**, **2**, **3**, **4**, **5** at 100 MHz and **1a** at 125 MHz.
[b] Assignments in each column may be interchangeable.

Compound **2**, named integrifoside B, showed the same $[M - H]^-$ ion peak at *m/z* 415 as did **1** in the negative FABMS, and the ^{1}H- and ^{13}C-NMR spectra of **2** were similar to those of **1**, except for the splitting pattern of the signal due to H-8 of Ag, the shift to higher-field of the signals due to H-6β of Ag and H_3-14 of Ag, and the shift to lower-field of the signal due to H-13b of Ag, which was deshielded by the hydroxyl group at C-8 of Ag. In addition, NOEs were observed between H-3 of Ag and H-1 of Glc, between H-3 of Ag and H-5 of Ag, between H-6α of Ag and H_3-12 of Ag, as well as between H-8 of Ag and H_3-14 of Ag in the difference NOE spectra of **2**. Thus, **2** was concluded to be the epimer of **1** at C-8 of Ag.

Compound **3**, named integrifonol A, exhibited no parent ion peak but an $[M - H_2O]$ ion peak at *m/z*

252 in the EIMS. The ^{1}H-NMR spectrum was similar to that of **1a**, apart from the chemical shift of the signal due to H-6α, H-9b, H-13b and H_3-12 and the loss of that due to H-7. From these data, **3** was considered to be a derivative of **1a**, in which one additional hydroxyl group was attached to C-7. This assumption was confirmed by the ^{13}C-NMR and difference NOE spectra of **3**. In comparing the chemical shifts of the ^{13}C-NMR spectroscopic signals between **1a** and **3**, the signals due to C-6 and C-7 were shifted downfield by 8.2 and 27.4 ppm, respectively; the chemical shifts of the other signals were similar to those of **1a**. In the difference NOE experiment, irradiation of the H-3 signal caused an NOE enhancement of the signal due to H-5, and irradiation of the H_3-12 signal enhanced the H-5 and H-8 resonances. Further, irradiation of the signals due to H_3-14 and H_3-15 afforded NOE enhancements of H-6β and H-2β, respectively. The structure of integrifonol A was therefore determined to be **3**.

Compound **4**, named integrifoside C, showed an $[M - H]^-$ ion peak at *m/z* 431 in the negative FABMS, which was 16 mass units larger than those observed for **1** and **2**. The ^{1}H- and ^{13}C-NMR spectra were similar to those of **3**, with the additional signals due to β-glucopyranosyl group, suggesting **4** to be a glucoside of **3**. In the NOE difference spectra, irradiation of H-3 of Ag gave an NOE to H-1 of Glc. Moreover, the ^{13}C-NMR spectrum of **4** exhibited, as compared to that of **3**, glycosylation shifts of −2.0 ppm at C-2, +10.8 ppm at C-3 and −1.5 ppm at C-4. Thus, the β-glucopyranosyl group is attached to the hydroxyl group at C-3 of the Ag to yield a structure for **4** as shown.

Compound **5**, named integrifoside D, showed an $[M - H]^-$ ion peak at *m/z* 431, and the ^{1}H-NMR spectrum of **5** gave analogous signals to those of **1**, **2** and **4**, except for the appearance of a signal due to an additional tertiary methyl group, the loss of signals due to two *exo*-methylene protons, and downfield shift of the anomeric proton signal (δ 5.39). The ^{13}C-NMR spectrum displayed signals due to two oxygenated quaternary carbons (δ 83.6, 70.9), an oxygenated methine carbon (δ 73.2), a carbonyl carbon (δ 211.5) and a β-glucopyranosyl group (δ 95.7, 76.0, 78.7, 72.1, 79.2, 63.2), which was attached to the tertiary hydroxyl group as determined from the chemical shift of the anomeric carbon signal (Kasai et al., 1977, 1979). ^{1}H- and ^{13}C-NMR signals were assigned as shown in Tables 1 and 2 using similar NMR spectroscopic techniques as for **1**, and the planar structure of **5** was defined as illustrated in Fig. 1. The stereostructure of **5** was characterized on the basis of difference NOE spectra, in which the correlations were as shown in Fig. 2. The structure of integrifoside D was therefore determined to be **5**.

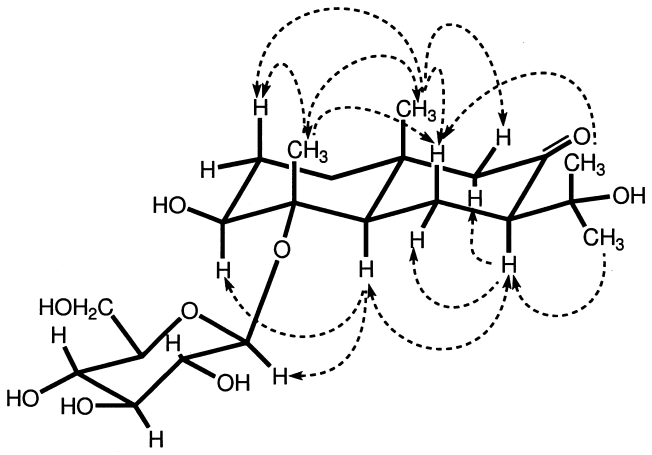
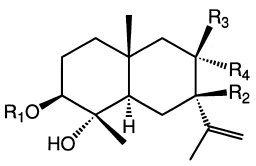


Fig. 2. NOEs observed for **5** in the NOE difference spectra.

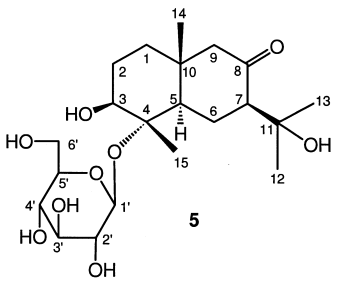
Though the absolute configurations of **2**–**5** have not been confirmed, they are presumably the same as that of **1** based on biogenetic considerations.

Hyaluronidase is involved in histamine release from mast cells. Therefore, inhibition of this enzyme is an anti-allergy index for the Type-1 allergic response, which produces such symptoms as pollenosis and asthma (Sakamoto, Nagai & Koda, 1980; Kakegawa et al., 1985). Compounds **1** and methyl 3,4-di-*O*-caffeoyl quinate (**6**), which were isolated from this plant (Ono et al., 1999) were assayed for their inhibitory effect on the activation of inactive hyaluronidase as induced by compound 48/80 (Kakegawa et al., 1985). The inhibition ratios of **1** and **6** were 3% and 31%, respectively, at a final concentration of 0.2 mM. The ratio of **6** was about one third that (76%) of a standard anti-allergic agent, disodium chromoglycate (DSCG).

Therefore, caffeoyl quinic acid derivatives reported as the chemical constituents of *T. integrifolia* Ruiz. et Pavon (Guerreiro & Pestchanker, 1990; Feo, D'agostino, Simone & Pizza, 1990; Ono et al., 1999) are considered to be the active principles responsible for the anti-inflammatory action of this plant.



	R_1	R_2	R_3	R_4
1 :	Glc	H	OH	H
2 :	Glc	H	H	OH
3 :	H	OH	OH	H
4 :	Glc	OH	OH	H



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3. Experimental

3.1. General

^{1}H-NMR, HMQC and HMBC: 500 MHz; ^{13}C-NMR: 125 and 100 MHz; NOE (400 MHz); (TMS as internal standard). CC: Diaion HP-20 (Mitsubishi Chemical), Sephadex LH-20 (Pharmacia Fine Chemicals) and silica gel 60 (230–400 mesh, Merck). HPLC: YMC pack ODS-AQ (250 mm × 20 mm i.d., YMC Co.). GC: silicone OV-1 (30 m × 0.32 mm i.d., Ohio Valley Specialty Chem.).

3.2. Plant material

Tessaria integrifolia Ruiz. et Pavon was purchased in October 1993 from Fundation pala la Investigacion Tecnologica del Recurso Agrobiologico Andio, a research institute of Andes agricultural bioresources in Peru, and identified by Sokurates Shiota, Executive Director, Fundation pala la Investigacion Tecnologica del Recurso Agrobiologico Andio. A voucher specimen is deposited at the Laboratory of Chemistry, Research Institute of General Education, Kyushu Tokai University.

3.3. Extraction and isolation

The aerial part of *T. integrifolia* Ruiz. et Pavon (2.00 kg) was extracted with MeOH. The MeOH extract (175.5 g) was chromatographed over Diaion HP-20 (60% MeOH, 80% MeOH, MeOH, acetone) to give fr. 1 (98.2 g), fr. 2 (26.6 g), fr. 3 (30.7 g) and fr. 4 (18.0 g). Fr. 1 was partitioned between BuOH and H_2O. The BuOH layer (53.9 g) was successively subjected to Diaion HP-20 (H_2O, 10% MeOH, 40% MeOH, MeOH), silica gel ($CHCl_3$–MeOH–H_2O, 14:2:0.1, 10:2:0.1, 8:2:0.2, 7:3:0.5, 6:4:1), Sephadex LH-20 (60% MeOH) and HPLC (MeOH–H_2O) to yield **1** (124 mg), **2** (27 mg), **3** (4 mg), **4** (12 mg) and **5** (6 mg).

Integrifoside A (**1**). Powder, $[\alpha]_D^{19}$ −12.7° (MeOH; *c* 5.9); FABMS (negative) *m/z* 415 $[M - H]^-$; ^{1}H- and ^{13}C-NMR spectral data: see Tables 1 and 2.

Integrifoside B (**2**). Powder, $[\alpha]_D^{19}$ −16.0° (MeOH; *c* 1.9); FABMS (negative) *m/z* 415 $[M - H]^-$; ^{1}H- and ^{13}C-NMR spectral data: see Tables 1 and 2.

Integrifonol A (**3**). Powder, $[\alpha]_D^{19}$ +43.0° (MeOH; *c* 0.5); EIMS *m/z* 252 $[M - H_2O]^+$; ^{1}H- and ^{13}C-NMR spectral data: see Tables 1 and 2.

Integrifoside C (**4**). Powder, $[\alpha]_D^{19}$ 0° (MeOH; *c* 1.0); FABMS (negative) *m/z* 431 $[M - H]^-$; ^{1}H- and ^{13}C-NMR spectral data: see Tables 1 and 2.

Integrifoside A (**5**). Powder, $[\alpha]_D^{19}$ +39.4° (MeOH; *c* 0.8); FABMS (negative) *m/z* 431 $[M - H]^-$; ^{1}H- and ^{13}C-NMR spectral data: see Tables 1 and 2.

3.4. Enzymatic hydrolysis of 1

Compound **1** (9 mg) was dissolved in HOAc–NaOAc buffer solution (pH 6.2, 1 ml), and β-glucosidase (from almonds, Lot 102H4008, Sigma, 7.0 mg) was added. The mixture was left to stand at 37°C for 5 days. After removal of the solvent under reduced pressure, the residue was extracted with MeOH, and the MeOH extract was chromatographed on silica gel ($CHCl_3$–MeOH–H_2O, 10:2:0.1, 8:2:0.2, 7:3:0.5, 6:4:1) to give **1a** (3.5 mg) and a monosaccharide (2 mg). **1a**: Powder, ^{1}H-NMR spectral data (in pyridine-d_5): Table 1; ^{1}H-NMR spectral data (in $CDCl_3$, 500 MHz) δ: 4.94 (*ddd*-like, J = 1.5, 1.5, 1.5 Hz, Ha-13), 4.73 (*s*, H-13b), 4.25 (*ddd*, J = 3.0, 3.0, 3.0 Hz, H-8), 3.43 (*dd*, J = 4.5, 12.0 Hz, H-3), 2.43 (*br s*, H-7), 1.78 (*s*, H_3-12), 1.13 (*s*, H_3-14 or H_3-15), 1.11 (*s*, H_3-14 or H_3-15). ^{13}C-NMR spectral data: Table 2. The monosaccharide was converted into a trimethylsilyl ether of the methyl thiazolidine 4(*R*)-carboxylate derivatives and subjected to GC analysis (detector: FID, column temperature: 230°C, injector temperature: 270°C, detector temperature: 270°C, carrier gas: He) (Hara et al., 1987). The retention time of this product was identical with that of an authentic sample of D-glucose derivative.

3.5. Assay of anti-hyaluronidase activity of 1 and 6

Test samples were dissolved in DMSO and each solution was diluted with 0.1 M HOAc–NaOAc buffer solution (pH 4.0) 10 times. Hyaluronidase (from Bovine Testes Lot 94H8000, 880 units/mg solid, Sigma), hyaluronic acid potassium salt (from Human Umbilical Cord Lot M7A8466, Nacalai Tesque) and compound 48/80 (Sigma) were dissolved with the same buffer, respectively. Hyaluronidase activity was determined by the method of Kakegawa et al. (1985). The control sample was prepared from the mixture containing all ingredients except the test compound. DSCG (Sigma) was used as standard sample.

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References

Bohlmann, F., Zdero, C., & Silva, M. (1977). *Phytochemistry*, *16*, 1302.

Feo, V. D., D'agostino, M., Simone, F. D., & Pizza, C. (1990). *Fitoterapia*, *61*, 474.
Feo, V. D. (1992). *Fitoterapia*, *63*, 417.
Guerreiro, E., & Pestchanker, M. J. (1990). *Phytochemistry*, *29*, 877.
Hara, S., Okabe, H., & Mihashi, K. (1987). *Chem. Pharm. Bull*, *35*, 501.
Jakupovic, J., Misra, L. N., Thi, T. V. C., Bohlmann, F., & Castro, V. (1985). *Phytochemistry*, *24*, 3053.
Kakegawa, H., Matsumoto, H., & Satoh, T. (1985). *Chem. Pharm. Bull*, *33*, 642.
Kasai, R., Suzuo, M., Asakawa, J., & Tanaka, O. (1977). *Tetrahedron Letters*, *2*, 175.
Kasai, R., Okihara, M., Asakawa, J., Mizutani, K., & Tanaka, O. (1979). *Tetrahedron*, *35*, 1427.
Peluso, G., Feo, V. D., Simone, F. D., Bresciano, E., & Vuotto, M. L. (1995). *J. Nat. Prod*, *58*, 639.
Ono, M., Masuoka, C., Odake, Y., Ikegashira, S., Ito, Y., & Nohara, T. (1999). Food Sci. Technol. Res., submitted.
Sakamoto, K., Nagai, H., & Koda, A. (1980). *Immunopharmacology*, *2*, 139.
Seo, S., Tomita, Y., Tori, K., & Yoshimura, Y. (1978). *J. Am. Chem. Soc*, *100*, 3331.