Structural Revisions of Blumenol C Glucoside and Byzantionoside B

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The absolute stereochemistry of blumenol C glucoside and byzantionoside B was revised here as (6*R*,9*S*)- and (6*R*,9*R*)-9-hydroxymegastigman-4-en-3-one 9-*O*-*β*-D-glucopyranosides, respectively, by modified Mosher's method. The empirical rules of ^{13}C-NMR chemical shift to determine the absolute stereochemistry of C-9 of 9-hydroxymegastigmane 9-*O*-*β*-D-glucopyranoside were also discussed.

Key words blumenol C glucoside; byzantionoside B; megastigmane glucoside

Blumenol C was first isolated from the leaves of *Podocarpus blumei* in 1972.[1)] The absolute stereochemistry of blumenol C was then determined as (6*R*,9*R*) by chemical conversion of related compound.[2)] Its glucoside, *i.e.* blumenol C glucoside (**1**), was then isolated from the aerial parts of *Epimedium grandiflorum* var. *thunbergianum* and the structure was determined by comparison of the spectral data of its aglycone, derived from enzymatic hydrolysis of **1**, with those of blumenol C.[3)] Recently, byzantionoside B (**2**) was isolated from the aerial parts of *Stachys byzantina* as the C-9 epimer of blumenol C glucoside.[4)] Modified Mosher's method is widely used recently for determination of the absolute stereochemistry of chiral secondary alcohol.[5)] In this study, the absolute configurations of these compounds (**1**, **2**) were reinvestigated by this reliable method.

Results and Discussion

Blumenol C glucoside (**1**) and byzantionoside B (**2**) were identified by comparison of the literature data at first (Tables 1, 2).[3,4)] The aglycones (**1a**, **2a**, respectively) were prepared by enzymatic hydrolysis of the glucosides. Their (*R*)- or (*S*)-MTPA esters were then prepared by the conventional procedure (**1b** and **1c** from **1a**, **2b** and **2c** from **2a**, see Experimental). The distribution patterns of $\Delta\delta_{S-R}$ values for **1b** and **1c**, and **2b** and **2c** clearly demonstrated that **1** and **2** possess 9*S* and 9*R* configurations, respectively (Figs. 1, 2). In addition, the application of the *β*-D-glucosylation-induced shift-trend rule[6)] also supported this result (Table 1). The absolute stereochemistry of C-6 was also confirmed by CD spectra. The CD data of **1** and **2** were essentially identical to that of sedumoside H of which the absolute stereochemistry was determined precisely by catalytic hydrogenation and application of CD octant rule, and also chemical conversion to related compound.[7,8)] Therefore, the actual structures of **1** and **2** must be (6*R*,9*S*)-9-hydroxymegastigman-4-en-3-one 9-*O*-*β*-D-glucopyranoside and (6*R*,9*R*)-9-hydroxymegastigman-4-en-3-one 9-*O*-*β*-D-glucopyranoside, respectively (Fig. 1).

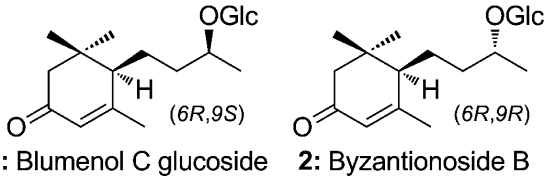

Fig. 1. Revised Structures of Blumenol C Glucoside (**1**) and Byzantionoside B (**2**)

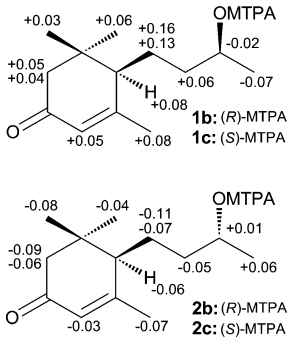

Fig. 2. Modified Mosher's Analysis for **1** and **2**

Thus, blumenol C glucoside (**1**) isn't the glucoside of blumenol C, but the glucoside of 9-*epi*-blumenol C in fact, and in other word, byzantionoside B is the really glucoside of blumenol C.

Aasen *et al.* reported the specific optical rotation value of blumenol C as $[\alpha]_D$ +54° (c=0.22, $CHCl_3$).[2)] Thus, blumenol C glucoside (**1**) was first misidentified as a glucoside of blumenol C, probably due to the moderate positive optical rotation value of aglycone [$[\alpha]_D^{22}$ +112.5° (c=0.52, $CHCl_3$)].[3)] However, the aglycones (**1a**, **2a**) prepared in this study from blumenol C glucoside (**1**) and byzantionoside B (**2**) showed $[\alpha]_D^{24}$ +80.5° (c=0.32, $CHCl_3$) and $[\alpha]_D^{23}$ +46.3° (c=0.08, $CHCl_3$), respectively, suggesting that it was difficult to distinguish these epimers only by optical rotation values at that time. Finally, it is noteworthy that there is a slight but clear difference between 9-*epi*-blumenol C (**1a**) and blumenol C (**2a**) for H_2-7 in ^{1}H-NMR spectra, *i.e.* 1.61 and 1.76 ppm for **1a**, and 1.45 and 1.93 ppm for **2a**. The comparison of chemical shifts of H_2-7 also provides the important criterion to distinguish each other (Table 2).

The above results arouse further interest that whether or not there was some trend in NMR spectra between (9*R*) and (9*S*)-*O*-*β*-D-glucopyranosides among related megastigmanes. It has been reported that the chemical shift at C-9 is indicative for 9*R* (*ca.* 77 ppm) and 9*S* (*ca.* 74 ppm) configuration for $\Delta^{7,8}$-type of 9-hydroxymegastigmane 9-*O*-*β*-D-glucopyranoside.[9,10)] This rule seems to be applicable for most compounds, however, in the case of staphylinoside I ($\delta_{C\text{-}9}$: 76.3 ppm, 9*S*) that possessed 6-OMe, this rule does not work well for the determination of C-9 configuration.[11)] Therefore, in this paper, this rule was also refined further by comparing with the literature data (Fig. 3). The stereochemistry of these compounds was determined by the reliable methods, *i.e.* modified Mosher's method, *β*-D-glucosylation-induced shift-trend rule, synthetic approach and chemical conversion.

The empirical rules observed here are as follows: The

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Table 1. ^{13}C-NMR Data for Blumenol C Glucoside (**1**) and Byzantionoside B (**2**) (150 MHZ)

C	**1** (C_5D_5N)	**1** (CD_3OD)	**1a** (CD_3OD)	**2** (C_5D_5N)	**2** (CD_3OD)	**2a** (CD_3OD)
1	36.4	37.4	37.4	36.3	37.4	37.4
2	47.8	48.2	48.3	47.8	48.2	48.2
3	198.4	202.4	202.2	198.4	202.5	202.3
4	125.4	125.6	125.6	125.4	125.5	125.5
5	165.2	169.8	169.7	165.2	170.1	169.7
6	51.3	52.7	52.6	51.2	52.5	52.5
7	25.7	26.7	27.5	26.0	26.9	27.3
8	36.7	37.5	39.9(−2.4)	37.1	37.9	39.9(−2.0)
9	76.0	77.7	68.9(+8.8)	74.2	75.7	68.6(+7.1)
10	22.0	22.0	23.5(−1.5)	19.9	19.9	23.6(−3.7)
11	28.7	29.1	29.1	28.8	29.1	29.1
12	27.1	27.5	27.4	27.1	27.6	27.5
13	24.3	25.0	24.9	24.3	25.0	24.8
1′	104.2	104.1		102.4	102.3	
2′	75.4	75.4		75.3	75.3	
3′	78.7	78.3		78.7	78.3	
4′	71.9	71.8		72.1	72.0	
5′	78.4	77.9		78.4	78.0	
6′	63.0	62.9		63.2	63.1	

Parenthesis is $\delta_{\text{glucoside-aglycone}}$.

Table 2. ^{1}H-NMR Data for Blumenol C Glucoside (**1**) and Byzantionoside B (**2**) (600 MHz)

C	**1** (C_5D_5N)	**1** (CD_3OD)	**1a** (CD_3OD)	**2** (C_5D_5N)	**2** (CD_3OD)	**2a** (CD_3OD)
2	2.08 (1H, d, 17)	1.98 (1H, d, 17)	2.00 (1H, d, 17)	2.07 (1H, d, 17)	1.97 (1H, d, 17)	1.99 (1H, m)
	2.49 (1H, d, 17)	2.48 (1H, d, 17)	2.44 (1H, d, 17)	2.45 (1H, d, 17)	2.46 (1H, d, 17)	2.44 (1H, d, 17)
4	5.89 (1H, s)	5.80 (1H, s)	5.81 (1H, s)	5.92 (1H, m)	5.80 (1H, s)	5.81 (1H, s)
6	1.78 (1H, m)	1.97 (1H, m)	1.99 (1H, m)	1.77 (1H, m)	1.99 (1H, m)	1.98 (1H, m)
7	1.75—1.89 (2H, m)	1.67 (1H, m)	1.61 (1H, m)	1.50 (1H, m)	1.50 (1H, m)	1.45 (1H, m)
		1.81 (1H, m)	1.76 (1H, m)	1.94 (1H, m)	1.98 (1H, m)	1.93 (1H, m)
8	1.66—1.77 (2H, m)	1.61 (1H, m)	1.51—1.56 (2H, m)	1.62 (1H, m)	1.61 (1H, m)	1.51—1.55 (2H, m)
		1.68 (1H, m)		1.76 (1H, m)	1.68 (1H, m)	
9	4.04 (1H, m)	3.82 (1H, m)	3.69 (1H, m)	4.06 (1H, m)	3.88 (1H, m)	3.69 (1H, m)
10	1.37 (3H, d, 6)	1.25 (3H, d, 6)	1.16 (3H, d, 6)	1.27 (3H, d, 6)	1.18 (3H, d, 6)	1.16 (3H, d, 6)
11	0.93 (3H, s)	1.02 (3H, s)	1.02 (3H, s)	0.92 (3H, s)	1.01 (3H, s)	1.02 (3H, s)
12	0.98 (3H, s)	1.09 (3H, s)	1.09 (3H, s)	0.94 (3H, s)	1.09 (3H, s)	1.09 (3H, s)
13	1.86 (3H, d, 1)	2.04 (3H, d, 1)	2.04 (3H, d, 1)	1.86 (3H, d, 1)	2.04 (3H, d, 1)	2.04 (3H, d, 1)
1′	4.90 (1H, d, 8)	4.32 (1H, d, 8)		4.89 (1H, d, 8)	4.33 (1H, d, 8)	
2′	3.97 (1H, m)	3.15 (1H, dd, 9, 8)		3.99 (1H, dd, 9, 8)	3.14 (1H, dd, 9, 8)	
3′	4.19 (1H, m)	3.34 (1H, dd, 9, 9)		4.25 (1H, dd, 9, 9)	3.35 (1H, dd, 9, 9)	
4′	4.19 (1H, m)	3.27 (1H, dd, 9, 9)		4.20 (1H, dd, 9, 9)	3.27 (1H, m)	
5′	3.94 (1H, m)	3.25 (1H, m)		3.95 (1H, m)	3.26 (1H, m)	
6′	4.36 (1H, dd, 12, 5)	3.66 (1H, dd, 12, 5)		4.35 (1H, dd, 12, 5)	3.65 (1H, dd, 12, 5)	
	4.53 (1H, dd, 12, 2)	3.85 (1H, dd, 12, 2)		4.54 (1H, dd, 12, 2)	3.85 (1H, dd, 12, 2)	

J in Hz. m: multiplet or overlapped. Chemical shift were determined by HH-COSY and HMQC.

chemical shift of C-8 is usually affected too large by the structure and substitution pattern around six-membered ring moiety. C-9 is also affected in a similar way but slightly. The ^{13}C chemical shifts of C-9, C-10 and Glc-1 are valuable to distinguish the stereochemistry of C-9 in methanol-d_4 (Figs. 3B, D). Especially, C-10 may be the most reliable to this purpose because it locates far from other substituent. The stereochemistry of C-6 may not affect the above empirical rule by judging from the data of C-6 epimeric counterparts (Figs. 3A, C).

Several compounds published by ourselves should be revised here as follows: salvionoside C[12] and leeaoside[13] must have 9*R* configuration, and euodionosides F and G[14] are of 9*S* configuration. Lauroside E[15] that was quoted as a known compound in our previous work[16,17] should be corrected to have 9*R* configuration.

Experimental

General Experimental Procedures The spectral data was taken by similar procedures described previously.[18] The absolute configuration of glucose was determined by HPLC analysis [JASCO OR-2090 plus: Optical rotation detector, SHODEX Asahipak NH2P-50: Φ=4.5 mm, L=25 cm, 75% CH_3CN aq., 1 ml/min].

Blumenol C Glucoside (**1**): Amorphous powder; $[\alpha]_D^{23}$ +49.0° (c=2.15, MeOH); IR ν_{max} (film) cm^{-1}: 3399, 2963, 1650, 1377, 1258, 1161, 1076, 1035; UV λ_{max} (MeOH) nm (log ε): 238 (4.06) (c=2.30×10^{-5} M, MeOH); ^{13}C- and ^{1}H-NMR (C_5D_5N and CD_3OD): Tables 1 and 2; CD $\Delta\varepsilon$ (nm): +0.63 (331), +4.25 (234) (c=2.30×10^{-5} M, MeOH); HR-ESI-TOF-MS (positive-ion mode) m/z: 395.2043 $[M+Na]^+$ (Calcd for $C_{19}H_{32}O_7Na$: 395.2040).

Byzantionoside B (**2**): Amorphous powder; $[\alpha]_D^{24}$ +27.0° (c=0.21, MeOH); IR ν_{max} (film) cm^{-1}: 3399, 2964, 1645, 1377, 1255, 1160, 1076, 1036; UV λ_{max} (MeOH) nm (log ε): 239 (4.24) (c=2.82×10^{-5} M, MeOH);

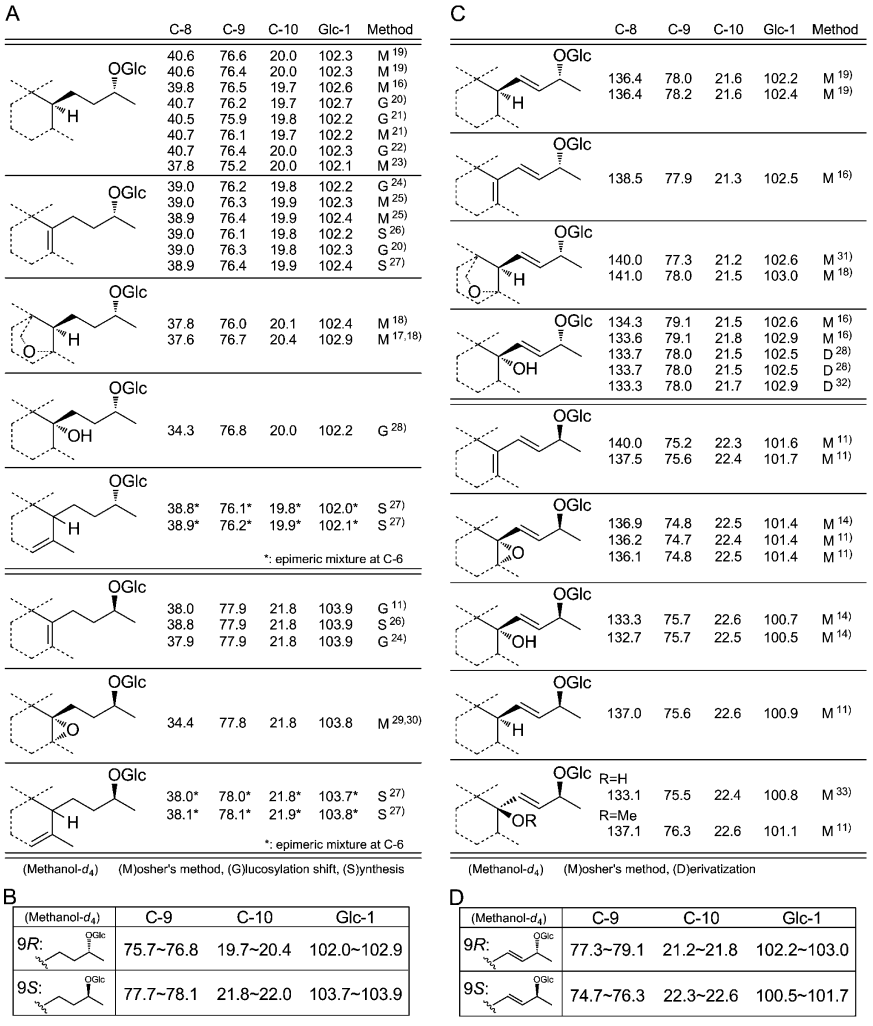

Fig. 3. ^{13}C Chemical Shifts Nature for Related Compounds

(A, C) Structures and chemical shifts, (B) chemical shift feature for 9-hydroxymegastigmane 9-*O*-*β*-D-glucopyranosides possessing saturated C-7 to 10, (D) chemical shift feature for $\Delta^{7,8}$-type of 9-hydroxymegastigmane 9-*O*-*β*-D-glucopyranosides.

^{13}C- and ^{1}H-NMR (C_5D_5N and CD_3OD): Tables 1 and 2; CD $\Delta\varepsilon$ (nm): +0.68 (332), +2.53 (235) (c=2.82×10^{-5} M, MeOH); HR-ESI-TOF-MS (positive-ion mode) *m/z*: 395.2038 $[M+Na]^+$ (Calcd for $C_{19}H_{32}O_7Na$: 395.2040).

Enzymatic Hydrolysis Blumenol C glucoside (**1**) and byzantionoside B (**2**) were hydrolyzed with *β*-glucosidase. The aglycone and glucose was separated by TLC ($CHCl_3$: MeOH : H_2O, 15 : 6 : 1, *Rf* values, **1**: 0.63, aglycone (**1a**): 0.81, **2**: 0.67, aglycone (**2a**): 0.87, and glucose: 0.15). The absolute configuration of glucose was determined to be D-series by HPLC analysis. (6*R*,9*S*)-9-hydroxymegastigman-4-en-3-one, 9-*epi*-blumenol C (**1a**): gummy syrup; $[\alpha]_D^{24}$ +80.5° (c=0.32, $CHCl_3$); IR ν_{max} (film) cm^{-1}: 3416, 2964, 1658, 1374, 1255, 1126; UV λ_{max} (MeOH) nm (log ε): 239 (4.14); ^{13}C- and ^{1}H-NMR (CD_3OD): Tables 1 and 2; CD $\Delta\varepsilon$ (nm): +1.65 (333), +2.54 (242) (c=2.14×10^{-5} M, MeOH); HR-ESI-TOF-MS (positive-ion mode) *m/z*: 233.1510 $[M+Na]^+$ (Calcd for $C_{13}H_{22}O_2Na$: 233.1512). (6*R*,9*R*)-9-hydroxymegastigman-4-en-3-one, blumenol C (**2a**): gummy syrup; $[\alpha]_D^{23}$ +46.3° (c=0.08, $CHCl_3$); IR ν_{max} (film) cm^{-1}: 3423, 2963, 1658, 1372, 1292, 1256, 1126; UV λ_{max} (MeOH) nm (log ε): 239 (3.83) (c=3.16×10^{-5} M, MeOH); ^{13}C- and ^{1}H-NMR (CD_3OD): Tables 1 and 2; CD $\Delta\varepsilon$ (nm): +0.61 (327), +2.75 (231) (c=2.14×10^{-5} M, MeOH); HR-ESI-TOF-MS (positive-ion mode) *m/z*: 233.1509 $[M+Na]^+$ (Calcd for $C_{13}H_{22}O_2Na$: 233.1512).

Preparation of (*R*)- and (*S*)-MTPA Esters MTPA esters were prepared from **1a** and **2a** by the procedure described previously.[18] (6*R*,9*S*)-9-hydroxymegastigman-4-en-3-one (*R*)-MTPA ester (**1b**): Amorphous powder; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ_H: 7.54—7.51 (2H, m, aromatic protons), 7.41—7.37 (3H, m, aromatic protons), 5.78 (1H, s, H-4), 5.12 (1H, m, H-9), 3.57 (3H, br s, OMe), 2.24 (1H, d, J=17 Hz, H-2a), 2.00 (1H, d, J=17 Hz, H-2b), 1.85 (3H, d, J=1 Hz, H_3-13), 1.77 (1H, br t, J=5 Hz, H-6), 1.73—1.62 (2H, m, H_2-8), 1.58 (1H, m, H-7a), 1.34 (1H, m, H-7b), 1.36 (3H, d, J=6 Hz, H_3-10), 0.98 (3H, s, H_3-11), 0.95 (3H, s, H_3-12); HR-ESI-TOF-MS (positive-ion mode) *m/z*: 449.1907 $[M+Na]^+$ (Calcd for $C_{23}H_{29}O_4F_3Na$: 449.1910). (6*R*,9*S*)-9-hydroxymegastigman-4-en-3-one (*S*)-MTPA ester (**1c**): Amorphous powder; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ_H: 7.53—7.51 (2H, m, aromatic protons), 7.42—7.38 (3H, m, aromatic protons), 5.83 (1H, s, H-4), 5.10 (1H, m, H-9), 3.51 (3H, br s, OMe), 2.29 (1H, d, J=17 Hz, H-2a), 2.04 (1H, d, J=17 Hz, H-2b), 1.93 (3H, d, J=1 Hz, H_3-13), 1.85 (1H, br t, J=5 Hz, H-6), 1.78—1.68 (2H, m, H_2-8), 1.71 (1H, m, H-7a), 1.50 (1H, m, H-7b), 1.29 (3H, d, J=6 Hz, H_3-10), 1.01 (6H, s, H_3-11, H_3-12); HR-ESI-TOF-MS (positive-ion mode) *m/z*: 449.1914 $[M+Na]^+$ (Calcd for $C_{23}H_{29}O_4F_3Na$: 449.1910). (6*R*,9*R*)-9-hydroxymegastigman-4-en-3-one (*R*)-MTPA ester (**2b**): Amorphous powder; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ_H: 7.54—7.51 (2H, m, aromatic protons), 7.43—7.38 (3H, m, aromatic protons), 5.83 (1H, s, H-4), 5.09 (1H, m, H-9), 3.51 (3H, br s, OMe), 2.27 (1H, d, J=17 Hz, H-2a), 2.02 (1H, d, J=17 Hz, H-2b), 1.94 (3H, d, J=1 Hz, H_3-13), 1.77 (2H, m, H_2-8), 1.77—1.68 (1H, m, H-6), 1.68 (1H, m, H-7a), 1.41 (1H, m, H-7b), 1.30 (3H, d, J=6 Hz, H_3-10), 1.01 (3H, s, H_3-12), 1.00 (3H, s, H_3-11); HR-ESI-TOF-MS (positive-ion mode) *m/z*: 449.1904 $[M+Na]^+$ (Calcd for $C_{23}H_{29}O_4F_3Na$: 449.1910). (6*R*,9*R*)-9-hydroxymegastigman-4-en-3-one (*S*)-MTPA ester (**2c**): Amorphous powder; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ_H: 7.56—7.51 (2H, m, aromatic protons), 7.43—7.38 (3H, m, aromatic protons), 5.80 (1H, s, H-4), 5.10 (1H, m, H-9), 3.58 (3H, br s, OMe), 2.18 (1H, d, J=17 Hz, H-2a), 1.96 (1H, d, J=17 Hz, H-2b), 1.87 (3H, d, J=1 Hz, H_3-13), 1.72 (2H, m, H_2-8), 1.72—1.61 (1H, m, H-6), 1.61 (1H, m, H-7a), 1.30 (1H, m, H-7b), 1.36 (3H, d, J=6 Hz, H_3-10), 0.92 (3H, s, H_3-11), 0.97 (3H, s, H_3-12); HR-ESI-TOF-MS (positive-ion mode) *m/z*: 449.1905 $[M+Na]^+$ (Calcd for $C_{23}H_{29}O_4F_3Na$: 449.1910).

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References

1) Weiss G., Koreeda M., Nakanishi K., *Chem. Commun.*, **1973**, 565—566 (1973).
2) Aasen A. J., Hlubucek J. R., Enzell C. R., *Acta Chem. Scand., Ser. B*, **28**, 285—288 (1974).
3) Miyase T., Ueno A., Takizawa N., Kobayashi H., Oguchi H., *Chem. Pharm. Bull.*, **36**, 2475—2484 (1988).
4) Takeda Y., Zhang H., Masuda T., Honda G., Otsuka H., Sezik E., Yesilada E., Sun H., *Phytochemistry*, **44**, 1335—1337 (1997).
5) Kusumi T., Ooi T., Ohkubo Y., Yabuuchi T., *Bull. Chem. Soc. Jpn.*, **79**, 965—980 (2006).
6) Kasai R., Suzuno M., Asakawa J., Tanaka O., *Tetrahedron Lett.*, **18**, 175—178 (1977).
7) Ninomiya K., Morikawa T., Zhang Y., Nakamura S., Matsuda H., Muraoka O., Yoshikawa M., *Chem. Pharm. Bull.*, **55**, 1185—1191 (2007).
8) Yoshikawa M., Morikawa T., Zhang Y., Nakamura S., Muraoka O., Matsuda H., *J. Nat. Prod.*, **70**, 575—583 (2007).
9) Çaliş İ., Kuruüzüm-Uz. A., Lorenzetto P. A., Rüedi P., *Phytochemistry*, **59**, 451—457 (2002).
10) Pabst A., Barron D., Semon E., Schreier P., *Phytochemistry*, **31**, 451—457 (1992).
11) Yu Q., Matsunami K., Otsuka H., Takeda Y., *Chem. Pharm. Bull.*, **53**, 800—807 (2005).
12) Takeda Y., Zhang H., Matsumoto T., Otsuka H., Oosio Y., Honda G., Tabata M., Fujita T., Sun H., Sezik E., Yesilada E., *Phytochemistry*, **44**, 117—120 (1997).
13) Kaewkrud W., Otsuka H., Ruchirawat S., Kanchanapoom T., *J. Nat. Med.*, **61**, 449—451 (2007).
14) Yamamoto M., Akita T., Koyama Y., Sueyoshi E., Matsunami K., Otsuka H., Shinzato T., Takashima A., Aramoto M., Takeda Y., *Phytochemistry*, **69**, 1586—1596 (2008).
15) Marino S., Borbone N., Zollo F., Ianaro A., Meglio P., Iorizzi M., *J. Agric. Food Chem.*, **52**, 7525—7531 (2004).
16) Sueyoshi E., Liu H., Matsunami K., Otsuka H., Shinzato T., Aramoto M., Takeda Y., *Phytochemistry*, **67**, 2483—2493 (2006).
17) Matsunami K., Takamori I., Shinzato T., Aramoto M., Kondo K., Otsuka H., Takeda Y., *Chem. Pharm. Bull.*, **54**, 1403—1407 (2006).
18) Matsunami K., Otsuka H., Kondo K., Shinzato K., Kawahata M., Yamaguchi K., Takeda Y., *Phytochemistry*, **70**, 1277—1285 (2009).
19) Morikawa T., Zhang Y., Nakamura S., Matsuda H., Muraoka O., Yoshikawa M., *Chem. Pharm. Bull.*, **55**, 435—441 (2007).
20) Otsuka H., Tamaki A., *Chem. Pharm Bull.*, **50**, 390—394 (2002).
21) Otsuka H., Zhong X.-N., Hirata E., Shinzato T., Takeda Y., *Chem. Pharm. Bull.*, **49**, 1093—1097 (2001).
22) Otsuka H., Yao M., Kamada K., Takeda Y., *Chem. Pharm. Bull.*, **43**, 754—759 (1995).
23) Nakamura S., Zhang Y., Pongpiriyadacha Y., Wang T., Matsuda H., Yoshikawa M., *Heterocycles*, **75**, 131—143 (2008).
24) Otsuka H., *Phytochemistry*, **37**, 461—465 (1994).
25) Zhang Y., Nakamura S., Pongpiriyadacha Y., Matsuda H., Yoshikawa M., *Chem. Pharm. Bull.*, **56**, 547—553 (2008).
26) Yamano Y., Shimizu Y., Ito M., *Chem. Pharm. Bull.*, **51**, 878—882 (2003).
27) Ma S.-J., Watanabe N., Yagi A., Sakata K., *Phytochemistry*, **56**, 819—825 (2001).
28) Otsuka H., Kamada K., Ogimi C., Hirata E., Takushi A., Takeda Y., *Phytochemistry*, **35**, 1331—1334 (1994).
29) Otsuka H., Shitamoto J., He D.-H., Matsunami K., Shinzato T., Aramoto M., Takeda Y., Kanchanapoom T., *Chem. Pharm. Bull.*, **55**, 1600—1605 (2007).
30) Kanchanapoom T., Kasai R., Chumsri P., Hiraga Y., Yamasaki K., *Phytochemistry*, **58**, 333—336 (2001).
31) Morikawa H., Kasai R., Otsuka H., Hirata E., Shinzato T., Aramoto M., Takeda Y., *Chem. Pharm. Bull.*, **52**, 1086—1090 (2004).
32) Nagatani Y., Warashina T., Noro T., *Chem. Pharm. Bull.*, **49**, 1388—1394 (2001).
33) Otsuka H., Hirata E., Shinzato T., Takeda Y., *Phytochemistry*, **62**, 763—768 (2003).