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THREE DIHYDROISOCOUMARIN GLUCOSIDES FROM *HYDRANGEA MACROPHYLLA* SUBSP. *SERRATA**

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Key Word Index—*Hydrangea macrophylla* subsp. *serrata*; Saxifragaceae; macrophyllosides A, B and C; dihydroisocoumarin glucosides; bitter principles; plant growth inhibitory activity.

Abstract—Three new dihydroisocoumarin glucosides, macrophyllosides A, B and C were obtained from dry leaves of *Hydrangea macrophylla* subsp. *serrata*, together with the previously known hydrangenol 8-β-glucoside. Using NMR and CD techniques and some chemical transformation, the structures were elucidated as (3*S*)-3′,4′,5′-trimethoxyphenyl-8-β-D-glucopyranosyl dihydroisocoumarin, (3*R*)- and (3*S*)-3′,5′-dimethoxy-4′-hydroxyphenyl-8-β-D-glucopyranosyl dihydroisocoumarins. CD experiments indicated that hydrangenol 8-β-glucoside was the mixture of 3*S*- and 3*R*-stereoisomers.

INTRODUCTION

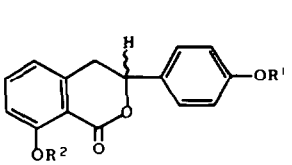
Hydrangea species (Saxifragaceae) are rich in dihydroisocoumarins. *H. macrophylla* var. *macrophylla* produces hydrangenol (**1**) [1] and hydrangenol 8-β-glucoside (**2**) [2]. (+)-Phyllodulcin (**3**) [3–6] possessing antimicrobial activity [7] and phyllodulcin 8-β-glucoside (**4**) [8] have been isolated from *H. macrophylla* var. *thunbergii*, together with stilbene derivatives (**26–29**). Compound **3** is 1000 times sweeter than sugar and used as a refrigerant [9]. *H. macrophylla* var. *thunbergii* is a variety of *H. macrophylla* subsp. *serrata* (= *H. macrophylla* var. *accuminata*) whose chemical constituents have not so far been studied. As part of our interest of physiologically active substances and chemosystematics of *Hydrangea* species, we have now investigated the chemical constituents of *H. macrophylla* subsp. *serrata*. In this paper we wish to report the isolation, structural elucidation and taste of three new dihydroisocoumarin glucosides and the plant growth inhibitory activity of stilbene derivatives derived from the new glucosides.

RESULTS AND DISCUSSION

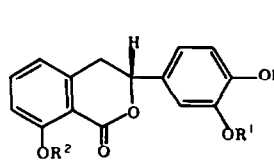
The dry leaves of *H. macrophylla* subsp. *serrata* were extracted with methanol and the crude extract partitioned between water and *n*-butanol. The butanol extract was chromatographed on silica gel to afford macrophylloside A (**5**; 0.79% for dry leaves), and a mixture of macrophyllosides B and C (**6** and **7**, 0.95%), along with the previously known hydrangenol 8-β-glucoside (**2**, 1.83%).

Macrophylloside A (5)

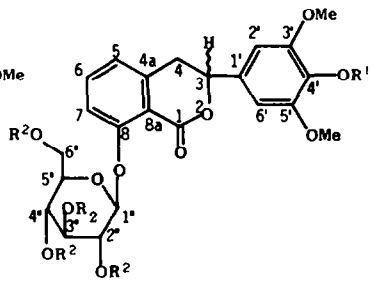
The spectral data of **5** showed the presence of a hydroxyl group (3440 cm^{-1}), a benzene ring (1605 and



1 $R^1=R^2=H$
2 $R^1=H$, $R^2=Glc$
9 $R^1=Ac$, $R^2=Glc\ Ac_4$, 3—H, 3R
10 $R^1=Ac$, $R^2=Glc\ Ac_4$, 3---H, 3S



3 $R^1=R^2=H$
4 $R^1=H$, $R^2=Glc$
16 $R^1=Me$, $R^2=H$
17 $R^1=R^2=Me$



5 $R^1=Me$, $R^2=H$, 3---H, 3S
6 $R^1=R^2=H$, 3—H, 3R
7 $R^1=R^2=H$, 3---H, 3S
8 $R^1=Me$, $R^2=Ac$, 3---H, 3S
18 $R^1=R^2=Ac$, 3—H, 3R
19 $R^1=R^2=Ac$, 3---H, 3S

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1510 cm^{-1}; 216, 237.5 and 300 nm) and a carbonyl group (1715 cm^{-1}). The ^1H NMR (Table 1) and ^{13}C NMR (Table 2) indicated the presence of three methoxyl groups, 5 protons on the benzene ring, two of which appeared as singlets, one methine group [δ_H 5.44 (*dd*, J = 10.5 and 3.4 Hz); δ_C 80.7 (*d*)] bearing an oxygen atom and one methylene proton [δ_H 3.19 (*dd*, J = 16.6 and 3.2 Hz), 3.28 (*dd*, J = 16.6 and 10.5 Hz); δ_C 36.9 (*t*)] which was coupled with the methine proton and ester carbonyl group [δ_C 164.9 (*s*)]. Acetylation of **5** gave a tetraacetate (**8**), whose high resolution mass spectrum (HRMS) exhibited a molecular ion at *m/z* 660.2067 in accord with the molecular formula $C_{23}H_{36}O_{15}$. The mass spectrum of **8** indicated the characteristic fragment ions of tetraacetyl glucoside at *m/z* 331, 169 and 109, respectively [10, 11]. As seen in Tables 1 and 2, the ^1H and ^{13}C NMR spectra of **8** were quite similar to those of the two pentaacetates (**9** and **10**) prepared from hydrangenol 8-β-glucoside (**2**) by acetylation, except for the signal pattern of the B-ring. The above spectra and chemical transformation indicated that **8** was 3-(3',4',5'-trimethoxyphenyl)-dihydroisocoumarin 8-pentaacetyl glucoside. This assignment was confirmed as follows. 3,4,5-Trimethoxybenzaldehyde (**11**) was reduced with sodium borohydride, followed by acetylation to give 3,4,5-trimethoxybenzyl acetate (**12**) whose NMR signal pattern was identical to that of the B-ring of **8**. Treatment of **5** with 1 N sulphuric acid gave macrophyllol (**13**), an dihydroisocoumarin possessing a hydrogen bonded carbonyl group (1660 cm^{-1}) and D-glucose which was identified as pentaacetyl-α-D-glucopyranoside ([α]$_D$ +100.5°) [12, 13] (Fig. 1). The NMR spectra of **13** resembled those of hydrangenol (**1**) and phyllodulcin (**3**), except for the signal pattern of the B-ring. Treatment of **13** with methanol–water in the presence of sodium bicarbonate to give a dihydrostilbene derivative (**14**), $C_{18}H_{20}O_7$ (HRMS: [M]$^+$ 348.1203; calc. 348.1209; 1660 cm^{-1}; δ_C 174.3 *s*) whose ^1H and ^{13}C NMR spectral data (Table 3) were very similar to those of combretastin (**15**) which shows antimitotic activity [14, 15]. The β-configuration of the glucose at C-8 of **5** was confirmed by the following NMR data: (i) the coupling constant of an anomeric proton (H-1″) of **5** and **8** was 7.6 Hz [16]; (ii) the signal pattern of the sugar moiety in the ^{13}C NMR spectrum of **8** was identical to that of the pentaacetates (**9** and **10**) prepared from hydrangenol 8-β-D-glucoside (**2**) whose absolute configuration at C-1″ has been established as β [2]; (iii) the coupling constant ($J_{C\text{-}H}$ = 165.7 Hz) of an anomeric carbon (C-1″) of **8** resembled that ($J_{C\text{-}H}$ = 166.0 Hz) of **9** and **10** [17]. The absolute configuration at C-3 of **5** was established by comparison of CD spectrum with that of (+)-phyllodulcin (**3**), whose absolute configuration at C-3 has been determined [18, 19] and its methylated derivative (**16**). Methylation of **3** with diazomethane gave two methylated products (**16**) and (**17**). Compound **13** gave a negative Cotton effect at 254 nm and a positive Cotton effect at 237 nm. On the other hand, compound **3** indicated negative and positive Cotton effects at 238 nm and 255 nm, respectively. The same spectrum as **3** was obtained in the case of **16**. Thus, the absolute configuration at C-3 of **5** was established as *S* and the total stereostructure of macrophylloside A was formulated as (3*S*)-3',4',5'-trimethoxyphenyl-8-β-D-glucopyranosyl dihydroisocoumarin (**5**).

Macrophyllosides B (**6**) *and C* (**7**)

Compounds **6** and **7** were obtained as a mixtures. As the isolation of the two compounds was difficult by prep. TLC and HPLC, the mixture was acetylated and the resulting acetates chromatographed on silica gel to afford the two pentaacetates (**18** and **19**) in the ratio *ca* 1:1, whose HRMS showed the same molcular ions at *m/z* 688.1986, indicating the molecular formula, $C_{33}H_{36}O_{16}$. All the spectral data of **18** resembled those of **19**, except for the sign of specific optical rotation. As indicated in Tables 1 and 2, the NMR spectral data of **18** and **19** were almost identical to those of **8**–**10**, except for the absence of one methoxyl group in B-ring, replacing three methoxyl groups as in **8**–**10**. The signal pattern of the two protons on the B-ring of **18** and **19** was very close to those of 4-acetoxy-3,5-dimethoxybenzyl acetate (**21**), prepared from **20** in three steps (Fig. 2). The above spectral and chemical data suggested that **6** and **7** might be 3-(3',5'-demethoxy-4'-hydroxy-phenyl)-8-β-glucopyranosyl- or 3-(3',5'-dimethoxy-4'-β-glucopyranosylphenyl)-8-hydroxydihydroisocoumarin, having a different absolute configuration at C-3. The mixture of **6** and **7** underwent smooth hydrolysis with 1 N sulphuric acid to yield D-glucose,

Table 1. ^1H NMR chemical shifts and coupling constants (Hz, in parentheses) for

Proton	1	3	5	8	9	10	12
3	5.58 *dd* (12.2, 3.4)	5.43 *dd* (12.2, 3.2)	5.44 *dd* (10.5, 3.4)	5.40 *dd* (10.5, 3.4)	5.37 *dd* (12.5, 3.4)	5.47 *dd* (10.7, 3.2)	
4	3.12 *dd* (16.5, 3.4)	3.04 *dd* (16.6, 3.2)	3.19 *dd* (16.6, 3.4)	3.12 *dd* (16.6, 3.4)	3.04 *dd* (15.9, 3.4)	3.04 *dd* (16.4, 3.2)	
	3.35 *dd* (16.6, 12.2)	3.24 *dd* (16.6, 12.2)	3.28 *dd* (16.6, 10.5)	3.27 *dd* (16.6, 10.5)	3.24 *dd* (15.9, 12.5)	3.26 *dd* (16.4, 10.7)	
5	6.84 *d* (7.8)	6.71 *d* (7.3)	7.01 *d* (7.1)	7.02 *d* (7.6)	7.01 *d* (7.6)	7.01 *d* (7.6)	
6	7.47 *dd* (7.8, 7.8)	7.41 *dd* (7.3, 7.3)	7.53 *dd* (7.1, 7.1)	7.48 *dd* (7.6, 7.6)	7.47 *dd* (7.6, 7.6)	7.47 *dd* (7.6, 7.6)	
7	6.88 *d* (7.8)	6.89 *d* (7.3)	7.27 *d* (7.1)	7.23 (7.6)	7.21 *d* (7.6)	7.23 *d* (7.6)	
2'	7.36 *d* (8.3)	6.99 *d* (2.0)	6.75 *s*	6.65 *s*	7.48 *d* (8.5)	7.45 *d* (8.8)	6.59 *s*
3'	6.90 *d* (8.3)				7.13 *d* (8.5)	7.12 *d* (8.8)	
5'	6.90 *d* (8.3)	6.83 *d* (8.3)			7.13 *d* (8.5)	7.12 *d* (8.8)	
6'	7.36 *d* (8.3)	6.91 (8.3, 2.0)	6.75 *s*	6.65 *s*	7.48 *d* (8.5)	7.45 *d* (8.8)	6.59 *s*
1″			4.94 *d* (7.6)	5.10 *d* (7.6)	5.21 *d* (7.8)	5.09 *d* (7.6)	
4'-OMe		3.86*s*	3.74 *s*	3.85 *s*			3.84 *s*
3'-OMe 5'-OMe			3.82 *s*	3.87 *s*			3.87 *s*

*Compounds **3**, **8**–**19**, **21** and **22** were measured in $CDCl_3$ solution, TMS as internal standard. Compounds **1** and **5** were measured

identified as its pentaacetate, and an aglycone (**22**), followed by methylation with diazomethane to afford macrophyllol (**13**) ($[\alpha]_D \pm 0°$). Compound **22** was further treated with methanol–water in alkali solution to give a stilbene derivative (**23**). Reduction of **22** with sodium borohydride–palladium chloride gave a dihydrostilbene derivative (**24**), which was also derived from **23** by hydrogenation.

The location of a glucose at C-8 in **6** and **7** was confirmed by the following spectral evidence. The IR spectrum of the mixture of **6** and **7** showed an intense absorption band at 1705 cm^{-1}, attributable to a non-hydrogen bonded carbonyl group [20]. In the ^{13}C NMR spectra of **18** and **19**, the glycosylation shift was observed in C-7 and C-8a [21]. The β-configuration of the glucose at C-8 of **6** and **7** was established by the coupling constant of the anomeric protons at H-1″ (J = 7.8 Hz) in both **18** and **19** [16] and of the anomeric carbons at C-1″ (J = 166.3 Hz) in **18** and (J = 166.0 Hz) in **19**, whose values were in accord with those of **9** and **10**. Confirmation of the absolute configuration at C-3 of **18** and **19** was provided by the CD curve (see Experimental). Compound **19** showed the same Cotton effect as that of **8** whose absolute configuration at C-3 has been determined as *S*. On the other hand, **18** displayed the expected opposite Cotton curve to **8**, indicating that the absolute configuration at C-3 of **18** was *R*. Compound **19** was further converted into **13** in three steps as shown in Fig. 1. On the basis of the above spectral and chemical evidence, the stereostructures of macrophyllosides B and C are presented as the formulae **6** and **7**, respectively. Furthermore, the absolute configuration at C-3 of the two acetates (**9** and **10**) of hydrangenol 8-β-D-glucoside (**2**) was also established by the CD spectra (see Experimental) to be 3*R* and 3*S*, respectively showing that **2** was present as an inseparable mixture of the two stereoisomers (**3R** and **3S**) in *Hydrangea* species.

As phyllodulcin (**3**) is an intense sweetening agent, the dihydroisocoumarins obtained in this experiment were tested for this property. Compounds **1**, **8**, **13**, **18**, **19** and **22** did not show any taste, however, **5** and the mixtures of **6** and **7** displayed a surprisingly intense bitter taste inducing vomiting. The stilbene derivatives (**23** and **24**) inhibited germination (100%) and elongation of second coleoptile (70–68%) of rice in husk at the concentration of 500 ppm. This activity is almost the same as that of lunularic acid (**25**) which is the dormant substance isolated from some liverworts [22].

Table 4 shows the distribution of dihydroisocoumarins and stilbene derivaties found in three *Hydrangea* species. *H. macrophylla* subsp. *serrata* is morphologically quite similar to *H. macrophylla* var. *thunbergii*, however, the former species lacks **3** and **4**, and stilbenes (**26–29**). Although the three species produce 4′-hydroxyphenyl dihydroisocoumarin in common, their chemical profiles are quite different.

EXPERIMENTAL

All mps were uncorr. The solvent used for spectral determination were: TMS–$CDCl_3$ [^1H NMR (400 MHz) and ^{13}C NMR (100 MHz)]; EtOH (UV); $CHCl_3$ (IR and $[\alpha]_D$) and dioxane (CD) unless otherwise stated.

Plant materials. *Hydrangea macrophylla* subsp. *serrata* (Thumb.) Makino (= *H. macrophylla* var. *acuminata f.* Thunb. (Sieb.) Hatusima) was collected in Kenzan mountain, Tokushima prefecture in July 1984 and identified by Dr G. Murata, Department of Botany, Kyoto University. A voucher specimen has been deposited in the Herbarium of the Institute of Pharmacognosy, Tokushima Bunri University. Dried leaves of *Hydrangea macrophylla* var. *thunbergii* Makino was purchased in the market in July 1985.

Extraction and isolation. Fresh leaves of *H. macrophylla* subsp. *serrata* was dried overnight and the air-dried material (554 g) extracted with × 2 hot MeOH (7 l). The extract, evapd to dryness at 30–40° gave a residue (89.1 g) which the partitioned between *n*-BuOH and H_2O. The conc. *n*-BuOH extract gave a residue (48.50 g) which was chromatographed on silica gel (1.5 kg) column and eluted with $CHCl_3$ with increasing amounts of MeOH (0–12%). The fraction (11–13) eluted by 12% MeOH–$CHCl_3$ contained white crystals which were recryst. from MeOH-Et_2O to afford pure macrophylloside A (**5**) (4.350 g, 0.79% for dry leaves). mp 110–112°; $[\alpha]_D$ −134.4° (MeOH; *c*1.22); UV λ_{max} nm (log ε): 216.0 (4.51), 237.5 (4.15) and 300 (3.65); ^1H NMR and ^{13}C NMR: see Tables 1 and 2. (Found: C, 58.55; H, 5.60. $C_{24}H_{28}O_{11}$ requires: C, 58.53; H, 5.73).

The fraction (14–19) gave a white powdery material (5.25 g, 0.95%) whose ^1H NMR spectrum indicated the presence of two

compounds **1**, **3**, **5**, **8–10**, **12**, **13**, **16**, **18**, **19**, **21** and **22***

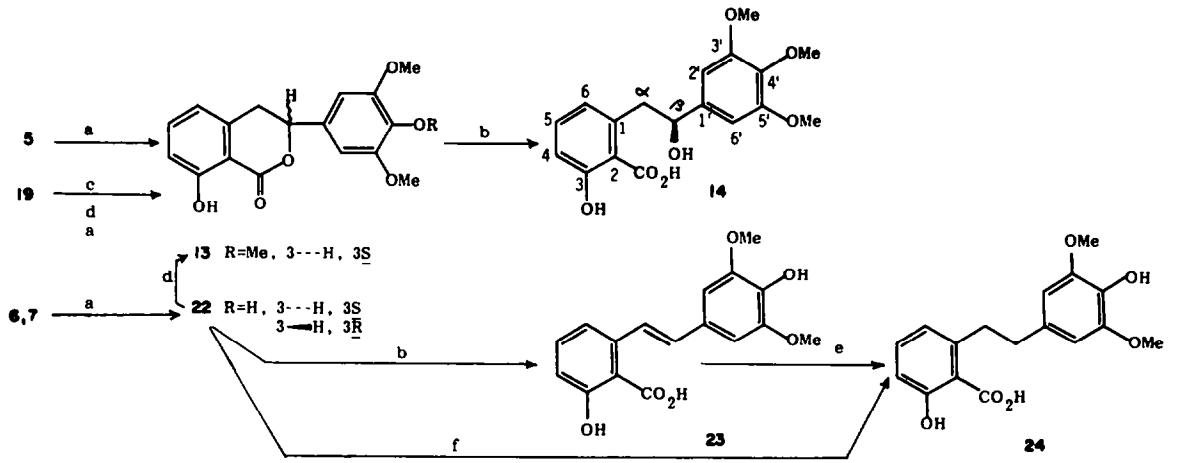
13	16	18	19	21	22
5.52 *dd* (12.5, 2.9	5.52 *dd* (12.1, 3.3)	5.33 *dd* (9.8, 3.4)	5.34 *dd* (12.5, 3.4)		5.50 *dd* (12.5, 3.2)
3.10 *dd* (16.5, 2.9)	3.10 *dd* (16.5, 3.3)	3.05 *dd* (16.6, 3.4)	3.05 *dd* (16.6, 3.4)		3.10 *dd* (16.6, 3.2)
3.22 *dd* (16.5, 12.5)	3.33 *dd* (16.5, 12.1)	3.20 *dd* (16.6, 9.8)	3.20 *dd* (16.6, 12.5)		3.31 *dd* (16.6, 12.5)
6.75 *d* (7.7)	6.73 *d* (7.3)	7.01 *d* (7.1)	7.02 *d* (7.6)		6.74 *d* (7.3)
7.46 *dd* (7.7, 7.7)	7.44 *dd* (7.3, 7.3)	7.48 *dd* (7.1, 7.1)	7.48 *dd* (7.6, 7.6)		7.45 *dd* (7.3, 7.3)
6.93 *d* (7.7)	6.91 *d* (7.3)	7.21 *d* (7.1)	7.21 *d* (7.6)		6.92 *d* (7.3)
6.68 *s*	7.00 *d* (1.8)	6.71 *s*	6.71 *s*	6.60 *s*	6.68 *s*
	6.88 *d* (8.1)				
6.68 *s*	6.97 *dd* (8.1, 1.8)	6.71 *s*	6.71 *s*	6.60 *s*	6.68 *s*
		5.21 *d* (7.8)	5.22 *d* (7.8)		
3.87 *s*	3.92 *s*				
3.89 *s*	3.90 *s*	3.85 *s*	3.85 *s*	3.81 *s*	3.91 *s*

in CD_3COCD_3 and CD_3OD, respectively.

Table 2. ^{13}C NMR chemical shifts of compounds

C	1	3	5	8	9	10
1	169.6 *s*	169.8 *s*	164.9 *s*	160.9 *s*	160.9 *s*	160.4 *s*
3	81.0 *d*	80.7 *d*	80.7 *d*	79.0 *d*	78.6 *d*	78.3 *d*
4	34.8 *t*	34.9 *t*	36.9 *t*	36.6 *t*	36.7 *t*	36.4 *t*
4a	140.0 *s*	139.5 *s*	142.9 *s*	141.2 *s*	141.4 *s*	141.1 *s*
5	118.0 *d*	118.2 *d*	117.0 *d*	118.6 *d*	117.6 *d*	118.4 *d*
6	136.0 *d*	136.3 *d*	136.3 *d*	134.3 *d*	134.2 *d*	134.4 *d*
7	115.6 *d*	116.3 *d*	122.5 *d*	122.5 *d*	122.3 *d*	122.7 *d*
8	161.8 *s*	162.1 *s*	160.2 *s*	158.0 *s*	157.8 *s*	158.0 *s*
8a	108.5 *s*	108.4 *s*	115.5 *s*	116.3 *s*	116.2 *s*	116.1 *s*
1′	129.1 *s*	131.0 *s*	135.9 *s*	134.0 *s*	141.4 *s*	135.9 *s*
2′	127.9 *d*	110.7 *d*	104.7 *d*	103.7 *d*	121.8 *d*	121.8 *d*
3′	115.3 *d*	145.8 *s*	154.6 *s*	153.5 *s*	127.4 *d*	127.3 *d*
4′	157.6 *s*	147.1 *s*	139.0 *s*	138.5 *s*	150.8 *s*	150.7 *s*
5′	115.3 *d*	112.7 *d*	154.6 *s*	153.5 *s*	127.4 *d*	127.3 *d*
6′	127.9 *d*	118.2 *d*	104.7 *d*	103.7 *d*	121.8 *d*	121.8 *d*
1″			103.0 *d*	100.0 *d*	99.8 *d*	100.0 *d*
2″			74.5 *d*	71.0 *d*	70.4 *d*	70.7 *d*
3″			78.4 *d*	72.3 *d*	72.1 *d*	72.2 *d*
4″			71.1 *d*	68.5 *d*	68.5 *d*	68.3 *d*
5″			77.7 *d*	72.6 *d*	72.6 *d*	72.5 *d*
6″			62.5 *t*	62.1 *t*	62.0 *t*	62.0 *t*
OMe		65.0 *q*	56.7 *q*	56.4 *q*		
			61.0 *q*	60.8 *q*		

*Compounds **3**, **8**–**18**, **21** and **22** were measured in $CDCl_3$ solution, TMS as internal standard.
[a,b] These assignments are interchangeable.



a) 1N-H_2SO_4 b) $NaHCO_3$/MeOH-H_2O c) $Ba(OH)_2$ d) CH_2N_2 e) H_2/10% Pd-C f) $NaBH_4$-$PdCl_2$

Fig. 1.

glucosides, macrophyllosides B (**6**) and C (**7**) which were inseparable on TLC an HPLC. The mixture of **6** and **7**: $[\alpha]_D$ −35.5° (MeOH; *c*1.30); UV λ_{max} nm (log ε): 216.5 (4.51), 242 (4.15) and 302 (3.62); (Found: C, 55.42; H, 5.65. $C_{23}H_{26}O_{11} \cdot H_2O$ requires: C, 55.64; H, 5.68). The mixture (**6** and **7**) was acetylated and the resulting acetates purified by silica gel CC to afford pure acetates (**18** and **19**) (see below).

From the fraction (20–22), hydrangenol-8-β-D-glycoside (**2**) (10.150 g, 1.83%) was obtained as crystals mp 190–194°; $[\alpha]_D$ −50.1° (EtOH; *c*0.20); UV λ_{max} nm (log ε): 218.5 (4.24), 228 (4.24), 285 (3.55) and 301 (3.62); (Found: C, 60.02; H, 5.38, $C_{21}H_{22}O_9$ requires: C, 60. 28; 5.30).

Acetylation of **5**. Compound **5** (203 mg) was acetylated with Ac_2O–pyridine (4 ml each). After the usual work-up, the reaction product was cryst. from EtOH to give macrophylloside A tetraacetate (**8**) (224 mg) as colourless needles. Mp 237–240° (decomp.); $[\alpha]_D$ −137.5° (dioxane; *c*0.16); UV λ_{max} nm (log ε): 212.5 (4.05), 240 (3.60) and 305 (3.19); ^{1}H NMR and ^{13}C NMR (see Tables 1 and 2); CD curve $[\theta]_{276}$ −15260, $[\theta]_{246}$ −16310 and $[\theta]_{205}$ −38430; HRMS: $[M]^+$ found 660.2067; calc. for

1, 3, 5, 8–10, 12, 13, 16, 18, 19, 21 and 22*

12	13	16	18	19	21	22
	169.7 *d*	169.7 *s*	160.9 *s*			168.9 *s*
	81.0 *d*	80.7 *d*	79.0 *d*	79.3 *d*		80.2 *d*
	35.3 *t*	34.9 *t*	37.0 *t*	36.5 *t*		35.2 *t*
	138.4 *s*	139.3 *s*	136.8 *s*	137.9 *s*		138.6 *s*
	118.0 *d*	117.8 *d*	117.5 *d*	117.5 *d*		117.3 *d*
	136.4 *d*	136.2 *d*	134.3 *d*	134.9 *d*		135.6 *d*
	116.4 *d*	116.1 *d*	122.3 *d*	122.9 *d*		115.6 *d*
	162.3 *s*	162.1 *s*	157.8 *s*	158.6 *s*		161.4 *s*
	108.4 *s*	108.2 *s*	116.1 *s*	116.2 *s*		107.8 *s*
131.5 *s*	133.6 *s*	130.3 *s*	136.8 *s*	134.9 *s*	134.4 *s*	134.5 *s*
105.7 *d*	103.4 *d*	109.3 *d*[a]	102.8 *d*	103.7 *d*	105.1 *d*	102.6 *d*
153. 4 *s*	153.5 *s*	149.0 *s*[b]	152.3 *s*	153.0 *s*	152.2 *s*	146. 4 *s*
138. 1 *s*	139.3 *s*	149.4 *s*[b]	128.7 *s*	129.3 *s*	128.6 *s*	128.3 *s*
153.4 *s*	153.5 *s*	110.9 *d*[a]	152.3 *s*	153.0 *s*	152.2 *s*	146.4 *s*
105.7 *d*	103.4 *d*	118.7 *d*	102.8 *d*	103.7 *d*	105.1 *d*	102.6 *d*
			99.7 *d*	100.0 *d*		
			70.4 *d*	71.8 *d*		
			72.2 *d*	72.6 *d*		
			68.5 *d*	68.9 *d*		
			72.6 *d*	73.4 *d*		
			62.0 *t*	62.5 *t*		
56.2 *q*	56.2 *q*	55.8 *q*	56.3 *q*	56.3 *q*	56.1 *q*	56.1 *q*
60.8 *q*	60.9 *q*					

Compounds **1**, **5** and **19** were measured in CD_3COCD_3, CD_3OD and C_5D_5N solution, respectively.

Table 3. ^1H and ^{13}C NMR chemical shifts (Hz, in parantheses) for compounds **14** and **15***

	14	15 [14]
Proton		
2		6.74–6.93
4	6.77 *d* (7.7)	
5	7.21 *dd* (7.7, 7.7)	6.74–6.93
6	6.62 *d* (7.7)	6.74–6.93
2′	6.61 *s*	6.64 *s*
6′	6.61 *s*	6.64 *s*
α	3.31 *m*	2.91 *m*
β	4.84 *dd* (9.2, 5.2)	4.83 *dd* (9, 5)
4′OMe	3.73 *s*	3.90 *s*
3′,5′OMe	3.79 *s*	
Carbon		
1	138.0 *s*	131.3 *s*[a]
2	104.2 *s*	110.8 *d*[b]
3	162.3 *s*	145.5 *s*[c]
4	116.5 *d*	145.8 *s*[c]
5	133.9 *d*	115.6 *d*[b]
6	124.8 *d*	121.0 *d*[b]
1′	142.2 *s*[a]	137.4 *s*[a]
2′	104.2 *d*	103.0 *d*
3′	154.2 *s*	153.3 *s*
4′	142.4 *s*[a]	139.7 *s*[a]
5′	154.2 *s*	153.3 *s*
6′	104. 2 *d*	103.0 *d*
α	46.6 *t*	45.6 *t*
β	76.2 *d*	75.5 *d*

*Compounds **14** and **15** were measured in CD_3OD and $CDCl_3$ solution, respectively.

[a,b,c] These assignments are interchangeable.

$C_{32}H_{36}O_{15}$: 660.2055; EIMS *m/z* (rel. int.): 660 $[M]^+$ (3.2), 331 (37), 211 (6), 169 (100), 109 (37) and 43 (10); (Found: C, 57.76; 5.40. $C_{32}H_{36}O_{15}$ requires C, 58.18; H, 5.49).

Acetylation of **2**. Compound **2** (1.150 g) was acetylated using the procedure described above* to give acetates (1.520 g), followed by CC on silica gel (200 g) eluted by $CHCl_3$ with increasing amounts of EtOAc to give the pentaacetates (**9**, 520 mg and **10**, 556 mg) of hydrangenol 8-β-D-glucoside (**2**), respectively. Compound **9**: mp 240–242° (from EtOAc–Et_2O); $[\alpha]_D$ +37.4° (*c*0.43); UV λ_{max} nm (log ε): 210.5 (4.27), 236 (3.72) and 296.5 (3.47); ^1H and ^{13}C NMR (see Tables 1 and 2); CD curve $[\theta]_{288}$ +2850, $[\theta]_{278}$ +2550, $[\theta]_{250}$ +5560 and $[\theta]_{206}$ +7650; (found: C, 59.10; H, 5.09. $C_{21}H_{32}O_{14}$ requires: C, 59.23; H, 5.13). **10**: mp 242–244.5° (from EtOAc–Et_2O); $[\alpha]_D$ −120.5° (*c*0.42); UV λ_{max} nm (log ε): 213.5 (4.45), 235 (4.00), 298 (3.59); CD curve $[\theta]_{276}$ −9290, $[\theta]_{257}$ −7860 and $[\theta]_{204}$ −26430; (Found: C, 59.52; H, 5.02. $C_{31}H_{32}O_{14}$ requires: 59.23; H, 5.13).

Preparation of **12**. To 3,4,5-trimethoxybenzaldehyde (**11**) (70 mg) in MeOH (60 ml) was added $NaBH_4$ (36 mg) and stirred for 1 hr at room temp. Work-up as usual gave a colourless oil (68 mg) which was acetylated with Ac_2O–pyridine (2 ml each) to give 3,4,5-trimethoxybenzyl acetate (**12**) (71 mg) as colourless oil. IR ν_{max} cm^{-1}: 1735, 1595, 1460, 1312, 1215 and 1125; EIMS *m/z* (rel. int.): 240 $[M]^+$ (99), 198 (51) and 181 (100).

Acid hydrolysis of **5**. 1 N H_2SO_4 (40 ml) was added to **5** (1.500 g) and stirred for 1 hr at 80–90°. The resulting mixture was extracted with EtOAc and the conc. extract purified by CC on silica gel using C_6H_6–EtOAc gradient to give macrophyllol (**13**) (465 mg). Mp 151–153.5° (from EtOAc–Et_2O); $[\alpha]_D$ −58.0° (MeCOMe; *c* 0.81); UV λ_{max} nm (log ε): 216 (4.61), 237.5 (4.10) and 318 (4.73); IR ν_{max}^{KBr} cm^{-1}: 3400, 1660, 1618, 1590, 1460, 1225, 1115 and 1000; ^1H and ^{13}C NMR (see Tables 1 and 2); CD curve (MeOH) $[\theta]_{313}$ −1140, $[\theta]_{254}$ −8290 and $[\theta]_{237}$ +4860; HRMS: found: 330.1096; calc. for $C_{18}H_{18}O_6$: 330.1103; EIMS *m/z* (rel. int.): 330 $[M]^+$ (100), 312 (30), 237 (23) and 134 (21);

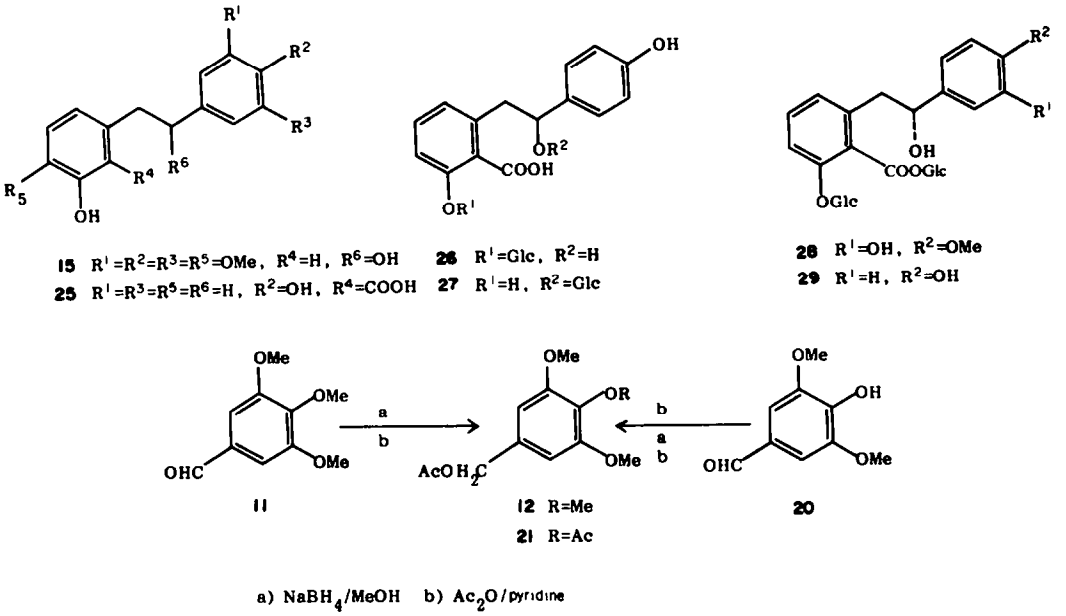


Fig. 2.

Table 4. Distribution of dihydroisocoumarins and stilbene derivatives in three *Hydrangea* species

Compounds	Species		
	H. macrophylla var. *macrophylla* [1, 2]	H. macrophylla subsp. *serrata*	*H. macrophylla* var. *thunbergii* [3–6, 8]
Hydrangenol (**1**)	+		+
Hydrangenol 8-*β*-glucoside (**2**)	+	+	+
Phyllodulcin (**3**)			+
Phyllodulcin 8-*β*-glucoside (**4**)			+
Macrophylloside A (**5**)		+	
Macrophylloside B (**6**)		+	
Macrophylloside C (**7**)		+	
Hydrangea glucoside A (**26**)			+
Hydrangea glucoside B (**27**)			+
Stilbene glucoside I (**28**)			+
Stilbene glucoside II (**29**)			+

(found: C, 65.89; H, 5.49. $C_{18}H_{18}O_6$ requires: C, 65.44; H, 5.49).

The water layer was concd *in vacuo* at 40–50° to afford the residue (350 mg) which was acetylated with Ac_2O–pyridine (5 ml each) for 2 hr at 0–5° and then 16 hr at room temp. Work-up as usual gave pentaacetyl-α-D-glucopyranoside (125 mg). Mp 112–113° (lit. [12, 13]; $[\alpha]_D$ +110.5° (1.5) (lit. [12, 13] +102°).

Alkaline hydrolysis of **13**. To compound **13** (120 mg) in MeOH (8 ml)–H_2O (4 ml) was added $NaHCO_3$ (207 mg) and refluxed for 4 hr at 70–80°. The resulting mixture was acidified with 1 N H_2SO_4 and extracted with EtOAc and the combined extracts dried, filtered and evapd. The residue (118 mg) was recryst. from $CHCl_3$–Et_2O to give a dihydrostilbene derivative (**14**) (109 mg) as colourless needles. Mp 157–159.5°; $[\alpha]_D$ +17.6° (*c* 0.57); UV λ_{max} nm (log ε): 219.5 (4.36); 230 (4.10), 282.5 (3.20) and 313 (3.58); ^1H and ^{13}C NMR (see Tables 1 and 2); HRMS: $[M]^+$ (found 348.1203; calc. for $C_{18}H_{20}O_7$ 348.1209), $[M-H_2O]^+$ (found 330.1094; calc. for $C_{18}H_{18}O_6$ 330.1103).

Isolation of hydrangenol (**1**) *and* (+)-*phyllodulcin* (**3**) *from H. macrophylla* var. *thunbergii*. Dry leaves of *H. macrophylla* var. *thunbergii* (2.0 kg) was extracted × 3 with MeOH (5 l). The same treatment of the methanol extract as described in the extraction of *H. macrophylla* subsp. *serrata* gave the residue (121 g) which was chromatographed on silica gel (1 kg) column eluted by *n*-hexane, with increasing amounts of EtOAc (0–100%). The fraction (30.5 g) eluted with 30% EtOAc–*n*-hexane contained sweet material which was further chromatographed on silica gel (500 g) using a CH_2Cl_2–EtOAc gradient to give (+)-phyllodulcin (**3**) (9.85 g, 0.49% for dry leaves) and hydrangenol (**1**) (3.95 g, 0.20%)

as white crystals, respectively. **3**: mp 118–120° (from Et_2O); $[\alpha]_D$ +71.0 (Me_2CO; *c* 1.31); UV λ_{max} nm (log ε): 214 (4.51), 230 (4.07), 289 (3.64) and 318 (3.70); ^1H and ^{13}C NMR (see Tables 1 and 2); CD curve (MeOH) $[\theta]_{313}$ +1710, $[\theta]_{238}$ −8000 and $[\theta]_{255}$ +9430; HRMS: $[M]^+$ (found 286.0830; calc. for $C_{16}H_{14}O_5$ 286.0842); EIMS *m/z* (rel. int.): 286 $[M]^+$ (100), 269 (62), 253 (13), 240 (39), 225 (68), 197 (50) and 134 (83). **1**: mp 180–181° (from $CHCl_3$–Et_2O); $[\alpha]_D$ −1.9° (dioxane; *c*0.9); UV λ_{max} nm (log ε): 213.5 (4.46), 227 (4.24), 245 (3.95) and 316 (3.77); ^1H and ^{13}C NMR (see Tables 1 and 2); EIMS *m/z* (rel. int.): 256 $[M]^+$ (100), 238 (73), 210 (59) and 134 (23); (found: C, 70.20; H, 4.59, $C_{15}H_{12}O_4$ requires: 70.30; H, 4.72).

Methylation of **3**. To compound **3** (1.35 g) in MeOH (20 ml) was added CH_2N_2—Et_2O (10 ml) and allowed to stand for 2 hr at 0–5°. The resulting mixture (1.40 g), after removal of the solvent, was chromatographed on silica gel (80 mg) using a $CHCl_3$–EtOAC gradient to give a dimethoxy (**16**) (129 mg, 9%) and a trimethoxy derivatives (**17**) (1.19 g, 76%), respectively. **16**: mp 102–103° (from *n*-hexane–Et_2O); $[\alpha]_D$ +63.9° (Me_2CO; *c*0.78); UV λ_{max} nm (log ε): 213.5 (4.53), 230 (4.16), 282 (3.61) and 316.5 (3.72); ^1H and ^{13}C NMR (see Tables 1 and 2); CD (MeOH) curve $[\theta]_{304}$ +1170, $[\theta]_{254}$ +5840 and $[\theta]_{236}$ −2210; HRMS: $[M]^+$ (found: 300.1007; calc. for $C_{17}H_{16}O_5$ 300.0998); (found: C, 68.24; H, 5.39, $C_{17}H_{16}O_5$ requires: C, 67.99; H, 5.37).

17: Mp 116–117° (from *n*-hexane–Et_2O); $[\alpha]_D$ +15.6° (*c*1.37); UV λ_{max} nm (log ε): 217 (4.40), 235.5 (4.17), 287 (3.67) and 308 (3.75); ^1H NMR: δ3.02 (1H, *dd*, *J* = 16.1, 2.7 Hz, H-4), 3.27 (1H, *dd*, *J* = 16.1, 12.0 Hz, H-4), 3.88, 3.90, 3.95 (each 3H, 3 × OMe), 5.34 (1H, *dd*, *J* = 12.0, 2.7 Hz, H-3), 6.84 (1H, *d*, *J* = 7.6 Hz, H-5), 6.85 (1H, *d*, *J* = 8.1 Hz, H-5'), 6.94 (1H, *d*, *J* = 7.6 Hz, H-7), 6.96 (1H, *dd*, *J* = 8.1, 2.0 Hz, H-6'), 7.20 (1H, *d*, *J* = 2.0, H-2'), 7.47 (1H, *dd*, *J* = 7.6, 7.6 Hz, 6-H); HRMS: $[M]^+$ (found: 314.1183; calc. for $C_{18}H_{18}O_5$ 314.1155); EIMS *m/z* (rel. int.): 314 $[M]^+$ (76), 239 (10), 181 (31), 148 (100), 90 (59).

Acetylation of the mixtures **6** *and* **7**. The mixture (1.15 g) of compounds **6** and **7** was acetylated with Ac_2O–pyridine (each 10 ml) to give acetates which were chromatographed on silica gel eluted by $CHCl_3$, with increasing amounts of EtOAc. From the fraction (6–20) and (22–47), macrophylloside B pentaacetate (**18**) (669 mg) and macrophylloside C pentaacetate (**19**) (574 mg) were obtained as colourless crystals, respectively. **18**: mp 237–238° (from Et_2O–EtOAc); $[\alpha]_D$ +46.8° (*c*0.62); UV λ_{max} nm (log ε): 216.5 (4.38); 230 (4.10), 281 (3.45) and 299 (3.64); ^1H and ^{13}C NMR (see Tables 1 and 2); CD curve, $[\theta]_{290}$ +5000, $[\theta]_{247}$ +1344 and $[\theta]_{206}$ +28750; HRMS: $[M]^+$ (found: 688.2010; calc. for $C_{33}H_{36}O_{16}$: 688.2004); EIMS *m/z* (rel. int.): 688 (0.5), 331 (58), 211 (5), 169 (100), 109 (37), 43 (24). (found: C, 56.89; H, 5.15. $C_{33}H_{36}O_{16}$ requires: C, 57.56; H, 5.25). **19**: mp 237–238° (from Et_2O–EtOAc); $[\alpha]_D$ −131.0° (*c*0.45); UV λ_{max} nm (log ε): 216.5 (4.37), 230 (4.09), 282.5 (3.44) and 298 (3.57); ^1H and ^{13}C NMR (see Tables 1 and 2); CD curve, $[\theta]_{275}$ −12080, $[\theta]_{243}$ −15840 and $[\theta]_{206}$ −85000; HRMS: $[M]^+$ (found: 688.1986; calc. for $C_{33}H_{36}O_{16}$: 688.2004); EIMS *m/z* (rel. int.): 688 $[M]^+$ (0.5), 331 (58), 211 (6), 169 (100), 109 (49), 43 (26); (found: C, 57.42; H, 5.24; $C_{33}H_{36}O_{16}$ requires: C, 57.56; H, 5.27).

Preparation of **21**. Syringaldehyde (**20**) (105 mg) was acetylated with Ac_2O–pyridine (2 ml each) to give a monoacetate (125 mg), mp 107–108°. To the MeOH soln (12 ml) of the acetate was added $NaBH_4$ (61 mg) at 0° and stirred for 30 min. The resulting mixture was poured into 1 N HCl and extracted with EtOAc. Work-up as usual gave the residue (119 mg) which further acetylated to give 3,5-dimethoxy-4-acetoxybenzyl acetate (**21**) (95 mg) as a colourless oil. ^1H and ^{13}C NMR (see Tables 1 and 2); EIMS *m/z* (rel. int.): 268 $[M]^+$ (1), 226 (100), 184 (40), 167 (50).

Acid hydrolysis of the mixtures of **6** *and* **7**. The mixtures (2.60 g) of compounds **6** and **7** were treated as above for the preparation of **13** to give the residue (1.65 g), followed by recryst. from Et_2O–EtOAc to afford 4'-demethylmacrophyllol (**22**) (1.37 g) as colourless needles. mp 154–155.5°; $[\alpha]_D$ ±0° (*c* 0.72); UV λ_{max} nm (log ε): 217.5 (4.48), 243.5 (4.17) and 317 (3.77); ^1H and ^{13}C NMR (see Tables 1 and 2); HRMS: $[M]^+$ (found; 316.0939; calc. for $C_{17}H_{16}O_6$ 316.0947); EIMS *m/z* (rel. int.): 316 (100), 298 (10), 279 (11), 134 (18); (found: C, 64.89; H, 5.11. $C_{17}H_{26}O_6$ requires C, 64.55; H, 5.10).

The water layer was treated as described in the hydrolysis of **5** to give pentaacetyl-α-D-glucopyranoside (257 mg). mp 112–113° (lit. [12, 13] 112–113°); $[\alpha]_D$ +107.5° (*c* 1.8) (lit. (12, 13] +102°).

Methylation of **22**. Compound **22** (226 mg) was treated as for prep. of **16** and **17** to yield a methylated product which was further purified by prep. TLC ($CHCl_3$–EtOAc 4:1) to give macrophyllol (**13**) (54 mg) 151–154°; $[\alpha]_D$ ±0° (Me_2CO, *c*0.72) and the starting material (**22**) (126 mg), respectively. The former compound was identical to 3*S*-macrophyllol (**13**) in all respect, except for the value of the specific optical rotation.

Alkaline hydrolysis of **22**. $NaHCO_3$ (200 mg) was added to compound **22** (305 mg) in MeOH (10 ml) and H_2O (2 ml) and then refluxed for 1 hr at 70–80°. The resulting mixture was acidified with 1 N H_2SO_4 and extracted with EtOAc. The usual work-up afforded a stilbene, which was recryst. from $CHCl_3$ to furnish **23** (254 mg) as yellow needles. Mp 115–116°; UV λ_{max} nm (log ε): 214 (4.46), 342 (4.18) and 346.5 (4.19); ^1H NMR (CD_3OD): δ3.90 (3H, *s*, OMe), 6.80 (2H, *s*, H-2' and 6'), 6.82 (1H, *d*, *J* = 7.6 Hz, H-4), 6.86 (1H, *d*, *J* = 16.1 Hz, H-β), 7.32 (1H, *d*, *J* = 7.6 Hz, H-6), 7.33 (1H, *dd*, *J* = 7.6, 7.6 Hz, H-5) and 7.59 (1H, *d*, *J* = 16.1 Hz, H-α); ^{13}C NMR (CD_3OD + $CDCl_3$): 56.7 (*q*, 2 × OMe), 105.4 (*d*, C-2' and C-6'), 122.4 (*s*, C-2), 116.8 (*d*, C-4), 119.4 (*d*, C-β), 127.8 (*d*, C-6), 129.5 (*s*, C-4'), 132.2 (*d*, C-5), 134.9 (C-α), 137.3 (*s*, C-1'), 142.4 (*s*, C-1), 148.9 (*s*, C-3' and C-5'), 163.2 (*s*, C-3) and 173.4 (*s*, COOH): HRMS: $[M]^+$ (found: 316.0927; calc. for $C_{17}H_{16}O_6$ 316.0947).

Reduction of **22**. To compound (**22**) (251 mg) in MeOH (20 ml) was added $PdCl_2$ (140 mg). $NaBH_4$ (300 mg) was added to the above soln little by little for 10 min with stirring and stirred further for 30 min. The resulting mixture was filtered and the filtrate concd *in vacuo* to give a residue which was extracted with EtOAc and the combined extracts dried and evapd. The residue was chromatographed on silica gel using $CHCl_3$–MeOH gradient to yield a bibenzyl derivative (**24**) (199 mg) as white needles. mp 149–151.5 (from Et_2O–EtOAc); UV λ_{max} nm (log ε): 219 (4.38), 230 (4.10), 284.5 (3.39) and 312 (3.59); ^1H NMR (CD_3OD): δ2.78 (2H, *t*, *J* = 8.3 Hz, H-β), 3.18 (2H, *t*, *J* = 8.3 Hz, H-α), 3.78 (6H, *s*, 2 × OMe), 6.43 (2H, *s*, H-2' and H-6'), 6.65 (1H, *d*, *J* = 7.6 Hz, H-6), 6.75 (1H, *d*, *J* = 7.6 Hz, H-4) and 7.21 (1H, *dd*, *J* = 7.6, 7.6 Hz, H-5); ^{13}C NMR (CD_3OD + $CDCl_3$): 39.4, 39.5 (*t*, C-α and C-β), 56.6 (*q*, 2 × OMe), 106.6 (*d*, C-2' and C-6'), 115.5 (*s*, C-2), 115.9 (*d*, C-4), 123.2 (*d*, C-6), 133.8 (*d*, C-5), 134.2, 134.4 (*s*, C-1' and C-4'); 146.0 (*s*, C-1), 148.8 (*s*, C-3' and C-5'), 167.2 (*s*, C-3) and 175.4 (*s*, COOH); HRMS: $[M]^+$ (found; 318.1096; calc. for $C_{17}H_{18}O_6$ 318.1104); EIMS *m/z* (rel. int.): 318 $[M]^+$ (26), 167 (100), 151 (2).

Hydrogenation of **23**. Compound **23** (20 mg) in EtOAc (10 ml) was hydrogenated in the presence of 10% Pd-C (100 mg) for 5 hr. The usual work-up gave a bibenzyl derivative (**24**) (15 mg), whose physical and spectral data were identical to those of the bibenzyl (**24**) prepared from **22**.

Conversion of **19** *to* **13**. To **19** (175 mg) in MeOH (40 ml) was added $Ba(OH)_2$ (2 ml) and stirred for 4 hr at room temp. The reaction mixture was neutralized with Amberlite IR 120 (H^+), filtered and the conc. filtrate (126 mg) dissolved in MeOH (10 ml) was treated with CH_2N_2–Et_2O (5 ml) for 2 hr at 0–5°. 1 N H_2SO_4 was added and the mixture stirred for 2 hr at 80–90°. Extraction with EtOAc gave a residue which was purified by prep. TLC ($CHCl_3$–EtOAc 4:1) to give macrophyllol (**13**) (26 mg). $[\alpha]_D$

$-54.8°$ (Me_2CO; *c* 0.80); HRMS: $[M]^+$ (found: 330.1096; calc. for $C_{18}H_{18}O_6$ 330.1103), whose physical and spectral data were identical to those of (−)-macrophyllol (**13**) prepared from **5**.

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