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Enantiodifferentiation in Taste Perception of the Phyllodulcins

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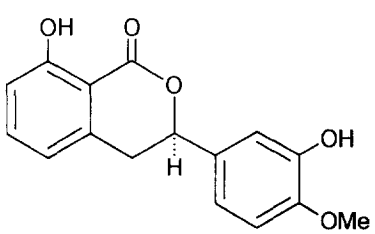
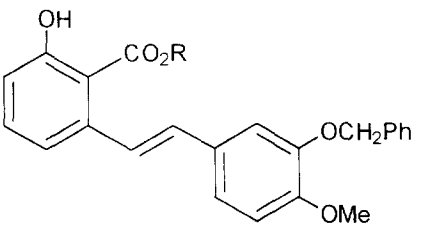
Abstract: Both enantiomers of phyllodulcin **1** have been prepared. Ester **2** was synthesized in a Wittig reaction from *O*-benzyl isovanillin. The corresponding stilbene carboxylic acid **3** could be cyclized with CF_3CO_2H to produce the 3'-benzyl ether **4** of (±)-phyllodulcin. Acylation with (1*R*,4*S*)-camphanoyl chloride gave first **5** and after hydrogenolysis of the benzyl ether group in **5** the diastereomeric esters **6**. The diastereomerically pure 8-(1*R*,4*S*)-camphanoate (+)-**6** of (*R*)-phyllodulcin could be isolated by repeated recrystallization. With (1*S*,4*R*)-camphanoyl chloride the enantiomeric 8-(1*S*,4*R*)-camphanoate (–)-**6** of (*S*)-phyllodulcin could be prepared via *ent*-**5** from a mixture of the diastereomeric esters *ent*-**6**. Ethanolysis of (+)-**6** gave (*R*)-phyllodulcin [(+)-**1**] with 99% ee. The enantiomeric (*S*)-(–)-**1** with 98% ee could be obtained from (–)-**6**. While (+)-**1**, the enantiomer occuring in fermented leaves of amacha, has an intense sweet taste, the enantiomer (–)-**1** is completely tasteless.

Amacha (*Hydrangea macrophylla* Seringe var. Thunbergii Makino) is a plant of the *Saxifragacea* family grown in Japan, whose fresh leaves become dark and sweet on fermentation and drying. They are used to make tea served on the Hanamatsuri (birth of Buddha) celebration. The sweet component of amacha, (+)-phyllodulcin (**1**), was isolated and its chemical structure determined by Asahina et al.[1,2]. Furthermore Arakawa[3] has shown the absolute configuration to be (*R*) by oxidative degradation to (*R*)-(+)-malic acid. (*R*)-(+)-Phyllodulcin (**1**) is 600 to 800 times sweeter than sucrose. In the leaves of amacha (+)-**1** is present as the non sweet β-D-glucoside[4,5]. The aglycone (+)-**1** is formed by fermentation. Several syntheses of (±)-phyllodulcin (**1**) have been described[6]. The (*R*)-(+)-enantiomer of **1** has only been prepared from plant material[1-5,7]. In the classical work of Asahina[1,2] it has been shown that (+)-**1** with mp 120 °C is converted into (±)-**1** with mp 131 °C by boiling in NaOH solution or in dilute ethanolic HCl. This may explain why mp and $[\alpha]_D$ of these specimens varies widely. Therefore we have prepared the pure enantiomers of **1** to determine their chiroptical properties and to test their effect upon the human sense of taste.

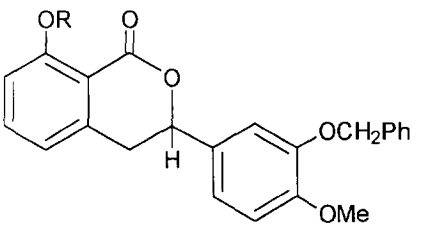


(*R*)-(+)-**1**

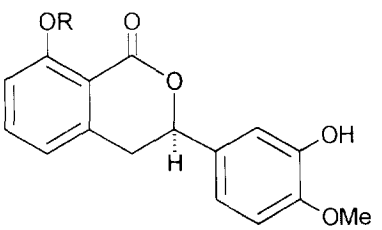
To achieve this goal suitable derivatives of (±)-phyllodulcin were synthesized. Wittig reaction of the known (3-acetoxy-2-ethoxycarbonylbenzyl)triphenylphosphonium bromide[8] and NaOEt with 3-benzyloxy-4-methoxybenzaldehyde gave the ethyl ester **2** in 79% yield. The corresponding acid **3** could be cyclized in CF_3CO_2H/CH_2Cl_2 to afford the 3'-benzyl ether (±)-**4** of phyllodulcin, in analogy to a procedure described[9] for the preparation of (±)-hydrangenol-4'-benzyl ether. The benzyl ether (±)-**4** was acylated with (1*R*,4*S*)-(+)-camphanoyl chloride[10] to give the diastereomeric esters **5**. All attempts to separate them by recrystallization or chromatography failed.

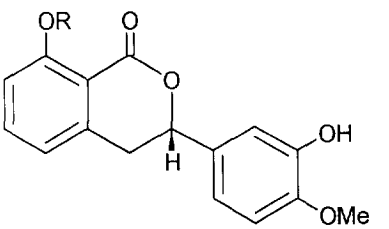


2 R = Et
3 R = H

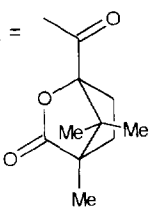


(±)-**4** R = H
(3*R*)- and (3*S*)-**5** R = (1*R*,4*S*)-camphanoyl
ent-**5** R = (1*S*,4*R*)-camphanoyl



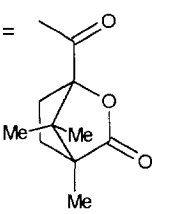


(+)-**6** R =



(1*R*,4*S*)

(−)-**6** R =

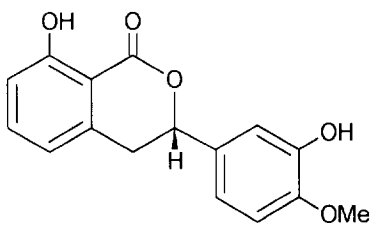


(1*S*,4*R*)

Hydrogenolysis of the benzyl ether group in **5** provided a mixture of the diastereomeric 8-camphanoyl derivatives **6** of phyllodulcin. Repeated crystallization from AcOEt gave the less soluble 8-(1*R*,4*S*)-camphanoyl derivative (+)-**6** of (*R*)-phyllodulcin with 99% diastereomeric purity according to its 500 MHz ^{1}H NMR spectrum. Treatment of (+)-**6** with NaOEt/EtOH for 3 min at 80 °C gave (1*R*,4*S*)-(+)-ethyl camphanoate and (*R*)-(+)-phyllodulcin (**1**) with $[\alpha]_D^{20} = +78.8$ (c = 1.01 in acetone). Acylation of this (*R*)-(+)-**1** with (+)-camphanoyl chloride[10] gave a 3',8-bis(camphanoyl) derivative with 99% diastereomeric purity

according to its 500 MHz ^{1}H NMR spectrum. Hence (*R*)-(+)-**1** with 99% ee was obtained in this resolution experiment. If the ethanolysis of (+)-**6** is conducted for more than 3 min the product (+)-**1** is partially racemized. The (*R*)-(+)-phyllodulcin isolated from amacha leaves by Asahina[2] had 87% ee, that isolated by Asakawa et al.[7] had 90% ee. Only Arakawas[3] highest specific rotation corresponds to an enantiomerically pure fraction, obtained by recrystallization of the natural product.

Acylation of (±)-**4** with (1*S*,4*R*)-(−)-camphanoyl chloride[11,12] to give *ent*-**5** and hydrogenolysis of the benzyl ether provided the diastereomeric esters *ent*-**6** of phyllodulcin. Repeated crystallization from AcOEt gave now the less soluble 8-(1*S*,4*R*)-camphanoyl derivative (−)-**6** of (*S*)-phyllodulcin with 98% diastereomeric purity according to its 500 MHz ^{1}H NMR spectrum. Short time ethanolysis, as in the experiment with the enantiomer above, gave (1*S*,4*R*)-(−)-ethyl camphanoate[13] and (*S*)-(−)-phyllodulcin [(−)-**1**] with 98% ee. (±)-Phyllodulcin could be obtained directly from the acid **3** by boiling in a conc. hydrochloric acid/methanol mixture[14] to effect cyclization and concomitant debenzylation.



(*S*)-(−)-**1**

With the synthetic (*R*)-(+)-**1** and the enantiomeric (*S*)-(−)-**1** available, we were able to study the differences of taste perception with these compounds. While (*R*)-(+)-phyllodulcin, the enantiomer occuring in fermented leaves of amacha, has an intensive sweet taste, the other enantiomer (*S*)-(−)-**1** is completely tasteless. Racemic (±)-**1** has also a sweet taste, as observed already by Asahina et al.[1]. Such taste perception differences of enantiomers are quite common in the case of many amino acids[15], but are by no means universal. For example, it has been reported[16] that in the case of the monosaccharides e.g. glucose, both enantiomers have virtually the same sweetness. The fact that the (*S*)-(−)-**1** enantiomer of phyllodulcin is tasteless, will make it necessary to modify the proposed[16,17] receptor model for sweetness. Only molecules with the chirality sense of (*R*)-(−)-**1** should be able to interact with the binding site of the receptor.

EXPERIMENTAL SECTION

^{1}H (500.13 and 270.17 MHz) and ^{13}C (125.77 and 67.94 MHz) NMR spectra were recorded on a Bruker AM-500-FT and a Jeol JNM-EX 270 instrument (δ in ppm referenced to residual solvent signal, with chemical shifts referred to TMS; multiplicities as determined from DEPT spectra). Optical rotations were measured on a Perkin Elmer 241 polarimeter. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT IR

spectrometer. Melting points were determined on a Büchi 510 melting point apparatus. Column chromatography: Kieselgel 60 (from Merck). Kieselgel 60 F_{254} glass plates (from Merck) were used for TLC, compounds were visualized by conc. H_2SO_4/5 min 160 °C. All solvents were distilled before use. Ether and THF were filtered through ICN Alumina B. Elemental analyses were performed by the microanalytical laboratory of Ilse Beetz, D 96317 Kronach.

(E)-Ethyl 6-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]-2-hydroxybenzoate (**2**): A mixture of (3-acetyloxy-2-ethoxycarbonylbenzyl)-triphenylphosphonium bromide[8] (9.682 g, 17.18 mmol) in 1 M NaOEt in EtOH (52 ml, 52 mmol) was stirred for 20 min at room temp. Then 3-benzyloxy-4-methoxy-benzaldehyde[18] (4.22 g, 17.4 mmol) was added and the resulting mixture was heated under reflux for 6 h. The mixture was concentrated in vacuo, the residue was extracted twice with 200 ml of toluene. The extracts were washed with 70 ml of 1 M H_2SO_4 and 50 ml of water, dried (Na_2SO_4) and the solvent was evaporated. The residue (12.41 g) was chromatographed on 1 kg of silica gel with cyclohexane/AcOEt (5:1) to afford 5.497 g (79%) of **2** as yellow crystals, mp 110-112 °C (ref.[14] 105-107 °C), R_f = 0.19. 320 mg of **2** was recrystallized from 10 ml of EtOH to give 269 mg of **2** mp 111-113 °C. – IR (CCl_4): $\tilde{\nu}$ = 3200 cm^{-1} (br, OH), 3066, 2984 (CH), 2836 (OCH_3), 1664 (C=O), 1599, 1574, 1513 (C=C), 1266, 1212 (C-O). – ^{1}H NMR ($CDCl_3$): δ = 1.36 (t, J = 7.1 Hz, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 4.39 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.19 (s, 2 H, $PhCH_2O$), 6.70 (d, J = 16.0 Hz, 1 H, 1''-H), 6.89-6.93 (2 H, 3-H, 5-H), 7.03-7.08 (3 H, 2'-H, 5'-H, 6'-H), 7.31-7.49 (6 H, 4-H, Ph), 7.53 (d, J = 16.0 Hz, 1 H, 2''-H), 11.24 (s, 1 H, OH). – ^{13}C NMR ($CDCl_3$): δ = 14.3 (q, CH_3), 56.0 (q, OCH_3), 61.7 (t, OCH_2CH_3), 71.2 (t, $PhCH_2O$), 110.9 (s, C-1), 111.9, 112.0, 116.7, 119.4, 120.4, 127.2, 127.85, 127.87, 128.6, 130.4, 137.0 (10 d, 1 s, C-3, C-5, C-1'', C-2'', C-2', C-5', C-6', Ph), 130.5 (s, C-1'), 134.2 (d, C-4), 141.4 (s, C-6), 148.4, 149.8 (2 s, C-3', C-4'), 162.4 (s, C-2), 171.2 (s, C=O).

(E)-6-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]-2-hydroxybenzoic Acid (**3**): A solution of **2** (2.266 g, 5.60 mmol) and 2 M KOH (30 ml, 60 mmol) in 30 ml of EtOH was heated under reflux for 4 h. The solution was concentrated in vacuo and partitioned between 50 ml of water and 20 ml of diethyl ether. The aqueous layer was acidified with 15 ml of 5 M H_2SO_4 and extracted twice with 150 ml of diethyl ether. The extracts were washed with 50 ml of 0.1 M H_2SO_4, dried (Na_2SO_4) and the solvent was evaporated to give 2.074 g (98%) of **3** as yellow crystals, mp 137-140 °C (ref.[14] 133-135 °C), R_f = 0.25 (cyclohexane/AcOEt/AcOH, 66:33:1). 41 mg of **3** was recrystallized from 2 ml of AcOEt to give 34 mg of **3**, mp 138.5-140.5 °C. – IR ($CHCl_3$): $\tilde{\nu}$ = 3493, 3200 cm^{-1} (br, OH), 3038, 2935 (CH), 2840 (OCH_3), 1665 (C=O), 1599, 1513 (C=C), 1264 (C-O). – ^{1}H NMR ($CDCl_3$): δ = 3.92 (s, 3 H, OCH_3), 5.20 (s, 2 H, $PhCH_2O$), 6.77 (d, J = 15.8 Hz, 1 H, 1''-H), 6.89-6.96 (2 H, 3-H, 5-H), 7.08-7.11 (3 H, 2'-H, 5'-H, 6'-H), 7.27-7.48 (6 H, 4-H, Ph), 7.59 (d, J = 15.8 Hz, 1 H, 2''-H), 11.03 (br, OH). – ^{13}C NMR ($CDCl_3$): δ = 56.1 (q, OCH_3), 71.2 (t, $PhCH_2O$), 109.3 (s, C-1), 111.9, 112.4, 116.9, 119.8, 120.6, 127.3, 127.5, 127.9, 128.6, 131.5, 137.1 (10 d, 1 s, C-3, C-5, C-1'', C-2'', C-2', C-5', C-6', Ph), 130.4 (s, C-1'), 135.5 (d, C-4), 142.5 (s, C-6), 148.3, 149.9 (2 s, C-3', C-4'), 163.3 (s, C-2), 174.9 (s, C=O).

(±)-3-(3-Benzyloxy-4-methoxyphenyl)-3,4-dihydro-8-hydroxy-1H-2-benzopyran-1-one [(±)-**4**]: A mixture of **3** (1.022 g, 2.72 mmol), trifluoroacetic acid (2.0 ml, 3.0 g, 26 mmol) and water (1 ml, 1 g, 0.06 mmol) in 50 ml of dichloromethane was heated under reflux for 12 h. EtOH (50 ml) was added and the solvent was

evaporated. The residue (1.034 g) was recrystallized from 10 ml of EtOH to afford 0.925 g (91%) of (±)-**4** as pale yellow crystals, mp 146-148 °C (ref.[19] 145-146 °C), R_f = 0.43 (cyclohexane/AcOEt, 2:1). – IR ($CHCl_3$): $\tilde{\nu}$ = 3200 cm^{-1} (br, OH), 3034, 2937 (CH), 2840 (OCH_3), 1680 (C=O), 1619, 1586, 1519 (C=C), 1464 (CH), 1263, 1228 (C-O). – ^{1}H NMR ($CDCl_3$): δ = 3.05 (dd, *J* = 16.5, *J* = 3.3 Hz, 1 H, 4-H_{cis}), 3.26 (dd, *J* = 16.5, *J* = 11.9 Hz, 1 H, 4-H_{trans}), 3.90 (s, 3 H, OCH_3), 5.16 (s, 2 H, PhCH_2O), 5.49 (dd, *J* = 11.9, *J* = 3.3 Hz, 1 H, 3-H), 6.71 (d, *J* = 7.6 Hz, 1 H, 5-H), 6.89-7.02 (4 H, 7-H, 2'-H, 5'-H, 6'-H), 7.33-7.46 (6 H, 6-H, Ph), 10.99 (s, 1 H, OH). – ^{13}C NMR ($CDCl_3$): δ = 34.9 (t, C-4), 56.0 (q, OCH_3), 71.1 (t, $PhCH_2O$), 80.7 (d, C-3), 108.3 (s, C-8a), 111.6, 112.2, 119.4 (3 d, C-2', C-5', C-6'), 116.3 (d, C-7), 117.9 (d, C-5), 127.4, 127.9, 128.5, 136.7 (Ph), 130.2 (s, C-1'), 136.3 (d, C-6), 139.3 (s, C-4a), 148.3, 150.2 (2 s, C-3', C-4'), 162.2 (s, C-8), 169.8 (s, C-1).

(3R and 3S)-3-(3-Benzyloxy-4-methoxyphenyl)-8-[(1R,4S)-camphanoyloxy]-3,4-dihydro-1H-2-benzopyran-1-one (**5**): A solution of (±)-**4** (3.317 g, 8.81 mmol) in pyridine (10 ml, 9.8 g, 124 mmol) and 20 ml of dichloromethane was added to a stirred solution of (1*R*,4*S*)-(+)-camphanoyl chloride[10] (2.901 g, 13.39 mmol) in pyridine (10.0 ml, 9.8 g, 124 mmol) at room temp. After 1.5 h at room temp. the resulting slurry was added dropwise into 200 ml of 1 M H_2SO_4 and extracted twice with 200 ml of AcOEt. The extracts were washed with 100 ml of 1 M K_2CO_3 and 100 ml of water, dried (Na_2SO_4) and the solvent was evaporated to afford 4.874 g (99%) of **5** as ivory coloured crystals, mp 79-90 °C, R_f = 0.52 (cyclohexane/AcOEt, 1:1). – IR (CCl_4): $\tilde{\nu}$ = 2971 cm^{-1} (CH), 2845 (OCH_3), 1798, 1760, 1738 (C=O), 1612, 1519 (C=C), 1470 (CH), 1251 (C-O). – ^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 9 H, 3 CH_3), 1.17, 1.19, 1.20 (3 s, 9 H, 3 CH_3), 1.68-1.78 (2 H), 1.92-2.03 (2 H), 2.29-2.39 (2 H), 2.59-2.72 (2 H), (5''-H_{endo}, 5''-H_{exo}, 6''-H_{endo}, 6''-H_{exo}), 3.02-3.10 (2 H, 4-H_{cis}), 3.19-3.29 (2 H, 4-H_{trans}), 3.87 (s, 6 H, 2 OCH_3), 5.13 (s, 4 H, 2 PhCH_2O), 5.36-5.44 (2 H, 3-H), 6.86-7.45 (20 H, 5-H, 7-H, 2'-H, 5'-H, 6'-H, Ph), 7.57 (t, *J* = 7.9 Hz, 2 H, 6-H). - ^{13}C NMR ($CDCl_3$): δ = 9.6, 9.6 (2 q, 7''-Me_{anti}), 16.54, 16.56, 16.6, 16.6 (4 q, 4''-Me, 7''-Me_{syn}), 28.8, 28.8 (2 t, C-5''), 31.1, 31.1 (2 t, C-6''), 35.8, 35.9 (2 t, C-4), 54.42, 54.44, 54.96, 54.98 (4 s, C-4'', C-7''), 55.9, 55.9 (2 q, 2 OCH_3), 71.0, 71.0 (2 t, 2 $PhCH_2O$), 79.3, 79.3 (2 d, C-3), 91.1, 91.1 (2 s, C-1''), 111.5, 111.5, 112.0, 112.1, 119.2, 119.3, (6 d, C-2', C-5', C-6'), 117.8, 117.9 (2 s, C-8a), 122.7, 122.8, 125.8, 125.8 (4 d, C-5, C-7), 127.3, 127.4, 127.8, 127.8, 128.5, 128.5, 136.7, 136.7 (6 d, 2 s, 2 Ph), 130.27, 130.31 (2 s, C-1'), 134.55, 134.59 (2 d, C-6), 141.2, 141.3 (2 s, C-4a), 148.17, 148.18, 150.0, 150.0 (4 s, C-3', C-4'), 150.7, 150.8 (2 s, C-8), 161.48, 161.50, 165.8, 165.9 (4 s, C-1, 1''-CO_2), 178.01, 178.02 (2 s, C-3'') Anal. calcd. for $C_{33}H_{32}O_8$ (556.62): C, 71.21; H, 5.79. Found: C, 70.32; H, 5.56. All attempts to separate the diastereomeric esters **5** by recrystallization or chromatography failed.

(3R and 3S)-3-(3-Benzyloxy-4-methoxyphenyl)-8-[(1S,4R)-camphanoyloxy]-3,4-dihydro-1H-2-benzopyran-1-one (ent-**5**): Analogously prepared as described above for **5** from (1*S*,4*R*)-(–)-camphanoyl chloride[11,12] (1.960 g, 9.05 mmol) in pyridine (5.0 ml, 4.9 g, 62 mmol) and (±)-**4** (2.113 g, 5.61 mmol) in pyridine (10 ml, 9.8 g, 124 mmol) and 20 ml of dichloromethane to afford 3.121 g (100%) ent-**5** as ivory coloured crystals, mp 79-89 °C, R_f = 0.52 (cyclohexane/AcOEt, 1:1).

(3R)-(+)-8-[(1R,4S)-Camphanoyloxy]-3,4-dihydro-3-(3-hydroxy-4-methoxyphenyl)-1H-2-benzopyran-1-one [(+)-**6**]: A solution of the diastereomeric esters **5** (4.701 g, 8.44 mmol) in 150 ml of AcOEt was stirred with

950 mg of 5% Pd-C under H_2 (1 bar) for 6 h at room temp. The mixture was filtered through Celite, the residue was washed with 150 ml of AcOEt and the filtrate was concentrated. The residue (3.932 g, mp 83-99 °C) was recrystallized from 8 ml of AcOEt (1.912 g, mp 181-193 °C), 5 ml of AcOEt (1.478 g, mp 191-194 °C), 5 ml of AcOEt (1.358 g, mp 189-192 °C) and 5 ml of AcOEt to give 1.281 g (33%) of (+)-**6** as colourless crystals, mp 187-190 °C, $[\alpha]_D^{20}$ = +83.0 (c = 0.98, acetone). - IR ($CHCl_3$): $\tilde{\nu}$ = 3544 cm^{-1} (OH), 3034, 2972, 2938 (CH), 2846 (OCH_3), 1783, 1729 (C=O), 1612, 1515, (C=C), 1470 (CH), 1270, 1236 (C-O). – ^{1}H NMR ($CDCl_3$): δ = 1.16 (2 s, 6 H, 2 CH_3), 1.21 (s, 3 H, CH_3), 1.75 (m, 1 H), 1.95 (m, 1 H), 2.36 (m, 1 H), 2.66 (m, 1 H), (5''-H_{endo}, 5''-H_{exo}, 6''-H_{endo}, 6''-H_{exo}), 3.12 (dd, *J* = 16.5 , *J* = 3.3 Hz, 1 H, 4-H_{cis}), 3.32 (dd, *J* = 16.5 , *J* = 11.7 Hz, 1 H, 4-H_{trans}), 3.90 (s, 3 H, OCH_3), 5.45 (dd, *J* = 11.7 , *J* = 3.3 Hz, 1 H, 3-H), 5.67 (s, 1 H, OH), 6.86 (d, *J* = 8.3 Hz, 1 H, 5'-H), 6.95 (dd, *J* = 8.3, *J* = 2.0 Hz, 1 H, 6'-H), 6.99 (d, *J* = 2.0 Hz, 1 H, 2'-H), 7.09 (d, *J* = 8.3 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 1 H), (3-H, 5-H), 7.59 (dd, *J* = 8.3, *J* = 7.6 Hz, 1 H, 6-H). The signal at δ = 5.42 for 3-H of the diastereomeric ester has disappeared. – ^{13}C NMR ($CDCl_3$): δ = 9.7 (q, 7''-Me_{anti}), 16.58, 16.64 (2 q, 7''-Me_{syn}, 4''-Me), 28.8 (t, C-5''), 31.1 (t, C-6''), 35.8 (t, C-4), 54.4, 55.0 (2 s, C-4'', C-7''), 55.9 (q, OCH_3), 79.3 (d, C-3), 91.1 (s, C-1''), 110.5 (d, C-2'), 112.5 (d, C-5'), 117.95 (s, C-8a), 118.04 (d, C-6'), 122.7, 125.9 (2 d, C-5, C-7), 131.0 (s, C-1'), 134.6 (d, C-6), 141.3 (s, C-4a), 145.7, 146.8 (2 s, C-3', C-4'), 150.7 (s, C-8), 161.5, 165.8 (2 s, C-1, 1''-CO_2), 178.1 (s, C-3''). – Anal. calcd. for $C_{26}H_{26}O_8$ (466.49): C, 66.94; H, 5.62. Found: C, 66.89, H, 5.56.

(3S)-(–)-8-[(1S,4R)-Camphanoyloxy]-3,4-dihydro-3-(3-hydroxy-4-methoxyphenyl)-1H-2-benzopyran-1-on [(–)-**6**]: Analogously prepared as described above for (+)-**6** from the diastereomeric esters ent-**5** (3.547 g, 6.38 mmol), 130 ml of AcOEt and 5% Pd-C (822 mg). The residue (2.981 g, mp 83-98 °C) was recrystallized from 7 ml of AcOEt (1.628 g, mp 170-188 °C), 3 ml of AcOEt (1.249 g, mp 192.0-197.1 °C), 4 ml of AcOEt (1.092 g, mp 193-197 °C) and 5 ml of AcOEt to give 1.018 g (34%) (–)-**6** as colourless crystals, mp 187-190 °C, $[\alpha]_D^{20}$ = –82.2 (c = 0.47, acetone). The signal at δ = 5.42 in the 500 MHz ^{1}H NMR($CDCl_3$) spectrum for 3-H of the diastereomeric ester has disappeared.

(3R)-(+)-3,4-Dihydro-8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-1H-2-benzopyran-1-one [*(+)-Phyllodulcin*, (+)-**1**]: A solution of (+)-**6** (0.960 g, 2.06 mmol) in 100 ml (10 mmol) of 0.1 M NaOEt in EtOH was boiled under reflux for 3 min, then immediately poured into 50 ml of ice cooled 1 M H_2SO_4. The resulting slurry was extracted twice with 200 ml of dichloromethane. The extracts were washed twice with 50 ml of water, dried (Na_2SO_4) and the solvent was evaporated. The residue (1.094 g) was chromatographed on 200 g of silica gel with cyclohexane/AcOEt (2:1) to give 0.581 g (99%) of (–)-**1** as colourless crystals, R_f = 0.27, mp 122.5-123.5 °C (ref.[3] 120-121 °C), $[\alpha]_D^{20}$ = –78.1 (c = 0.99, acetone) (ref.[3] +80.8, c = 1.14, acetone). 0.580 g of (+)-**1** were recrystallized from 4.0 ml of EtOH to give 0.515 g of (+)-**1**, mp 123.9-124.5 °C, $[\alpha]_D^{20}$ = +78.8 (c = 1.01, acetone). – IR ($CHCl_3$): $\tilde{\nu}$ = 3530 cm^{-1} (OH), 3100 (br, OH), 2840 (OCH_3), 1672 (C=O), 1615, 1580, 1505 (C=C), 1455 (CH), 1280 (C-O). – ^{1}H NMR ($CDCl_3$): δ = 3.07 (dd, *J* = 16.5, *J* = 3.3 Hz, 1 H, 4-H_{cis}), 3.28 (dd, *J* = 16.5, *J* = 11.9 Hz, 1 H, 4-H_{trans}), 3.90 (s, 3 H, OCH_3), 5.47 (dd, *J* = 11.9, *J* = 3.3 Hz, 1 H, 3-H), 5.78 (s, 1 H, OH), 6.73 (d, *J* = 7.6 Hz, 1 H, 5-H), 6.86 (d, *J* = 8.3 Hz, 1 H, 5'-H), 6.91 (d, *J* = 8.6 Hz, 1 H, 7-H), 6.94 (dd, *J* = 8.3, *J* = 2.0 Hz, 1 H, 6'-H), 7.01 (d, *J* = 2.0 Hz, 1 H, 2'-H) 7.43 (dd, *J* = 8.6, *J* = 7.6 Hz, 1 H, 6-H), 11.01 (s, 1 H, OH). – ^{13}C NMR ($CDCl_3$): δ = 34.9 (t, C-4), 56.0 (q, OCH_3), 80.6 (d, C-3), 108.4 (s, C-8a), 110.5 (d, C-2'), 112.6 (d, C-5'), 116.3 (d, C-7), 117.9 (d, C-5), 118.2 (d, C-6'), 131.0 (s, C-1'), 136.3

(d, C-6), 139.3 (s, C-4a), 145.7, 146.9 (2 s, C-4', C-3'), 162.1 (s, C-8), 169.8 (s, C-1). The less polar fractions contained (+)-ethyl (1*R*,4*S*)-camphanoate, mp 57-59 °C (ref.[13] 59-60 °C).

(+)-**1** was treated with two equivalents of (1*R*,4*S*)-(+)-camphanoyl chloride to furnish the 3',8-bis(camphanoyl) derivative with a signal at δ = 5.48 (dd, *J* = 11.5, *J* = 3.0 Hz, 1 H) in the 500 MHz ^{1}H NMR($CDCl_3$) spectrum produced by the 3-H. The signal of the diastereomeric biscamphanoate at δ = 5.46 was barely visible and had less than 1% intensity.

(3S)-(−)-3,4-Dihydro-8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-1H-2-benzopyran-1-one [*(−)-Phyllodulcin*, (−)-**1**]: Analogously prepared as described above for (+)-**1** from (−)-**6** (0.881 g, 1.89 mmol) and 110 ml (11 mmol) of 0.1 M NaOEt in EtOH to give 0.538 g (99%) of (−)-**1** as colourless crystals, R_f = 0.27 (cyclohexane/AcOEt, 2:1), mp 122.2-123.5 °C, $[\alpha]_D^{20}$ = −76.5 (c = 0.99, acetone). 0.530 g were recrystallized from 4.0 ml of EtOH to give 0.432 g of (−)-**1**, mp 123.7-124.5 °C, $[\alpha]_D^{20}$ = −77.6 (c = 1.02, acetone). The less polar fractions contained (−)-ethyl (1*S*,4*R*)-camphanoate, mp 57-59 °C (ref.[13] 59-60 °C).

(−)-**1** was treated with two equivalents of (1*S*,4*R*)-(−)-camphanoyl chloride to furnish the 3',8-bis(camphanoyl) derivative with a signal at δ = 5.48 in the 500 MHz ^{1}H NMR($CDCl_3$) spectrum produced by the 3-H. The signal of the diastereomeric biscamphanoate at δ = 5.46 had approximately 1% intensity.

(±)-3,4-Dihydro-8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-1H-2-benzopyran-1-one [*(±)-Phyllodulcin*, (±)-**1**]: A mixture of **2** (189 mg, 0.50 mmol), 8 ml of conc. HCl and 8 ml of MeOH was heated under reflux for 4 h and then poured into 20 ml of ice cold water. The resulting mixture was extracted twice with 50 ml of AcOEt. The extracts were washed twice with 20 ml of water, dried (Na_2SO_4) and evaporated. The residue was recrystallized from 1 ml of EtOH to afford 103 mg (72%) of (±)-**1** as colourless crystals, mp 131-132 °C (ref.[14] 130-132 °C).

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