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Efficient syntheses of (±)-hydrangenol, (±)-phyllodulcin and (±)-macrophyllol

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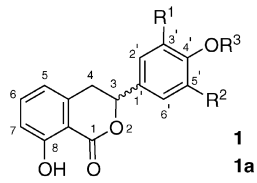
Abstract—In this paper we report on a efficient and flexible synthetic route towards the total syntheses of the dihydrocoumarine derivatives hydrangenol (**1**), phyllodulcin (**1a**) and macrophyllol (**6b**). The syntheses started with a readily available phosphonium salt **2** and suitable modified benzaldehydes **3/3a/3b** resulting in 46 to 61% overall yields in three to four-steps sequences. The racemic products could be separated by chiral HPLC. The evidence of the (*R*)-enantiomer for sweetness could be demonstrated for **1a**.

1. Introduction

The coumarines are a large group of naturally occurring heterocycles, ca over 1000 of them have been isolated from natural sources. Hydrangenol (**1**), a dihydroisocoumarine (Fig. 1), was isolated from *Hydrangea opuloides Steud*. var. otakusa.[1,2] Phyllodulcin (**1a**), which is a hydrangenol derivative and 1000 times sweeter than sugar, was isolated from *Hydrangea opuloides*, Steud. var. *thunbergii*, by Asahina and Asano.[1] Macrophyllol (**6b**), a dihydroisocoumarine (Scheme 1), was isolated from *Hydrangea macrophylla* subs. *Serrata* by Asakawa.[3]



	R^1	R^2	R^3
1	H	H	H
1a	H	OH	Me
6b	OMe	OMe	Me

Figure 1. Structures of hydrangenol (**1**), phyllodulcin (**1a**) and macrophyllol (**6b**).

Asahina and Asano[4,5] performed the first and five steps synthesis of hydrangenol (**1**) starting from 3-methoxyphthalic acid anhydride. However, the yield of the first step of the synthesis was only 1.5%. Naoi et al.[6] developed an alternative four steps synthesis of hydrangenol starting from 3-hydroxyhomophthalic acid and 4-benzyloxybenzaldehyde but with a moderate yield of 30% of the last step which deals with the decarboxylation of the benzylic carboxylic acid. Another synthetic route to hydrangenol was described by the reaction of *ortho*-lithiated 2-methylbenzamide with 4-methoxybenzaldehyde followed by saponification and cyclization (26% overall yield).[7,8] In a further synthetic route, hydrangenol was synthesized in five steps and 33% overall yield from 3-methoxyphenylacetic acid.[9] In this study, we report on an efficient synthetic route by which hydrangenol (**1**), phyllodulcin (**1a**) and macrophyllol (**6b**) can be obtained easily and in high yield.

2. Results and discussion

As the first step in the synthesis of hydrangenol (**1**) we performed the Wittig reaction between 4-benzyloxybenzaldehyde (**3**) and the phosphonium salt **2**[10] to give the stilbene **4** as *E*/*Z*-mixture (1:1) in 89% yield. Saponification of the ester **4** with ethanolic KOH afforded the stilbene-*o*-carboxylic acid **5** in a yield of 94%. The cyclization of **5** with trifluoroacetic acid gave the benzyl protected hydrangenol **6** in 87% yield. Debenzylation of **6** was afforded by hydrogenation (5 bar) in the presence of 5% Pd/C in ethyl acetate yielding (±)-hydrangenol (**1**) in a yield of 84%. Thus, **1** was synthesized in four steps with an overall yield of 61%.

Phyllodulcin (**1a**) and macrophyllol (**6b**) were synthesized by following a strategy of synthesis analogues to hydrangenol (**1**). Thus, phyllodulcin (**1a**) was synthesized starting from 3-benzyloxy-4-methoxybenzaldehyde (**3a**) in 58% overall yield. The same reaction sequence without final hydrogenation applied to 3,4,5-trimethoxybenzaldehyde

Keywords: coumarines; dihydrocoumarines; hydrangenol; phyllodulcin; macrophyllol.
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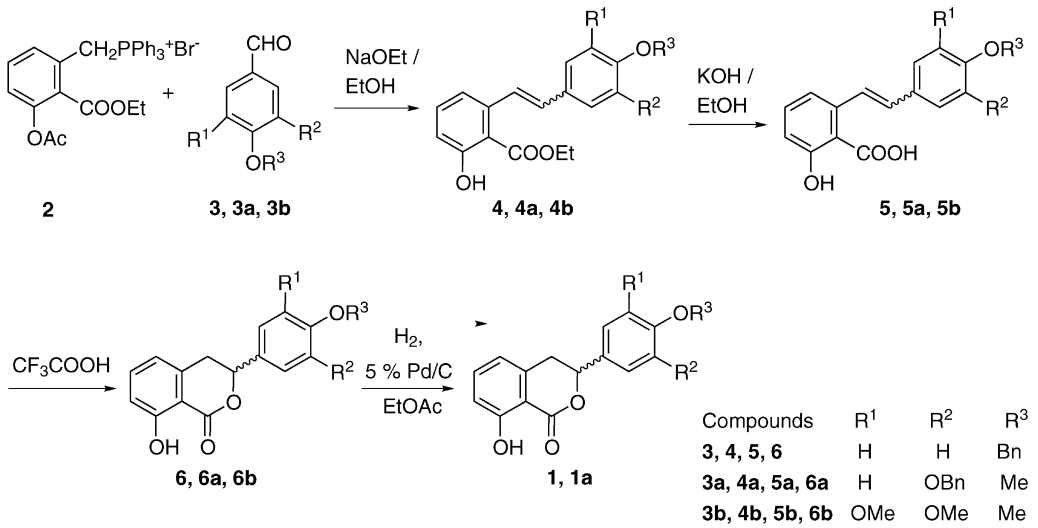

Scheme 1. Synthesis of hydrangenol (**1**), phyllodulcin (**1a**) and macrophyllol (**6b**).

(**3b**) resulted in macrophyllol (**6b**) in 46% overall yield. All of the racemic final compounds were separated by HPLC on a chiral phase. The (*R*)-phyllodulcin (**1a**) showed sweetness whereas, the (*S*)-enantiomer did not.

3. Experimental

3.1. General

The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AM 400 spectrometer. Mass spectra were obtained on Finnigan MAT 90 (CI, 120 eV) and MAT 311 (EI, 70 eV) spectrometers. Elemental analyzes were measured on a Leco CHNS-932 instrument. Melting points were obtained on a Büchi appartatus (Dr Tottoli) and are uncorrected. Column chromatography (CC) was performed using silica gel 60 (63–200 μm, ASTM) and TLC was performed on 0.2 mm silica gel (Merck 60 F_{254}).

The HPLC separation of the racemic samples of (**1**), (**1a**) and (**6b**) were performed on an chiral column (poly-*N*-methacrylo-L-leucin-D-menthylamide provided by Professor Dr H. Engelhardt, Instrumental and Environmental Analytical Chemistry, Saarland University) with *n*-heptane/tetrahydofurane (60:40) as eluent.

3.1.1. (*E*,*Z*)-2-(4′-Benzyloxyphenyl)-1-((3-hydroxy-2-ethoxycarbonyl)phenyl(ethene (4). To a solution of sodium ethoxide (10.2 g, 0.15 mol) in dry EtOH (300 mL) were added the phosphonium salt **2**[10] (56.4 g, 0.10 mol) and 4-benzyloxybenzaldehyde (**3**) (21.2 g, 0.10 mol). The resulting mixture was heated to reflux for 24 h. The solvent was removed, water was added (150 mL) and the organic layer was extracted with $CHCl_3$ (2×100 mL) and dried ($MgSO_4$). Evaporation of the solvent and CC of the residue eluting with $CHCl_3$ gave the stilbene **4** (33.5 g, 89%) as yellow needles. Mp 68–69°C (mixture of *E*/*Z*-stereoisomers, ratio 1:1). Anal. calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found C, 76.92; H, 5.90; ^{1}H NMR ($CDCl_3$) δ (ppm) 11.34 (s, 0.5H, OH-8), 11.24 (s, 0.5H, OH-8), 7.64–6.44 (m, 14H, Ar-H and CH═), 5.08 (s, 1H, OCH_2Ph), 4.98 (s, 1H, OCH_2Ph), 4.40 (m, 2H, COOCH_2CH$_3$), 1.38 (m, 3H, COOCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.29, 171.13, 162.64, 162.42, 157.77, 141.50, 141.34, 136.92, 134.41, 134.25, 131.96, 130.58, 130.38, 130.24, 130.06, 129.56, 128.60, 128.54, 128.00, 127.93, 127.76, 127.43, 122.28, 119.39, 116.68, 116.50, 115.16, 114.45, 111.04, 70.11, 69.93, 61.78, 14.31, 14.05; MS (CI) *m*/*z* (%) 375 (100, M^++1), 374 (76, M^+), 223 (14), 213 (33), 181 (40), 57 (94), 43 (22).

3.1.2. (*E*,*Z*)-2-(4′-Benzyloxyphenyl)-1-((3-hydroxy-2-carboxy)phenyl(ethene (5). To a solution of the ethyl ester **4** (30.7 g, 82 mmol) in EtOH (300 mL) was added KOH (50.0 g, 0.89 mol). The mixture was heated to reflux for 24 h, concentrated and treated with water (250 mL). CH_2Cl_2 (200 mL) was added and the organic layer was dispatched. After acidification with concd HCl, the aqueous layer was extracted with CH_2Cl_2 (3×200 mL) and dried ($MgSO_4$). Removal of the solvent and recrystallization of the residue from $CHCl_3$/petroleum ether (9:1) gave the stilbene-*o*-carboxylic acid **5** (26.7 g, 94%) as yellow needles. Mp 130–135°C (7:3 mixture of *E*/*Z*-stereoisomers). Anal. calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found C, 76.17; H, 5.22; ^{1}H NMR (DMSO-d_6) δ (ppm) 7.47–6.50 (m, 14H, Ar-H and CH═), 5.12 (s, 1.45H, OCH_2Ph), 5.03 (s, 0.55H, OCH_2Ph); ^{13}C NMR (DMSO-d_6) δ (ppm) 170.65, 169.92, 158.18, 157.34, 155.83, 136.87, 136.33, 131.80, 130.62, 130.02, 129.92, 129.69, 128.92, 128.69, 128.31, 128.00, 127.71, 127.58, 124.06, 120.23, 119.89, 116.06, 115.10, 114.65, 114.30, 69.22, 69.07; MS (CI) *m*/*z* (%) 347 (12, M^++1), 257 (6), 214 (12), 213 (97), 195 (34), 165 (28), 153 (71), 123 (44), 107 (19), 91 (28).

3.1.3. 3-(4′-Benzyloxyphenyl)-8-hydroxy-3,4-dihydrobenzopyran-1-one (6). To a solution of the stilbene-*o*-carboxylic acid **5** (1.10 g, 3.18 mmol) in 1,2-dichloroethane (50 mL) were added trifluoroacetic acid (10 mL) in water (5 mL). The mixture was heated to reflux for 5 h. Evaporation of the solvent and CC of the residue eluting with EtOAc gave the dihydroisocoumarine **6** (0.96 g, 87%) as colourless needles. Mp 117–118°C. Anal. calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found C, 76.20; H, 5.27; ^{1}H

NMR ($CDCl_3$) δ (ppm) 11.01 (s, 1H, OH-8), 7.45–7.31 (m, 8H, Ar-H), 7.00 (d, J=8.4 Hz, 2H, H-3′ and H-5′), 6.91 (d, J=8.4 Hz, 1H, H-7), 6.72 (d, J=7.2 Hz, 1H, H-5), 5.51 (dd, X part of ABX system, J_{AX}=12.0 Hz, J_{BX}=3.2 Hz, 1H, H-3), 5.08 (s, 2H, OCH_2Ar), 3.31 (dd, A part of ABX system, J_{AB}=16.4 Hz, J_{AX}=12.0 Hz, 1H, H-4), 3.06 (dd, B part of ABX system, J_{AB}=16.8 Hz, J_{BX}=3.2 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ (ppm) 169.80, 169.29, 159.23, 139.41, 136.72, 136.27, 130.28, 128.61, 128.03, 127.70, 127.42, 117.71, 116.39, 115.09, 108.48, 80.67, 70.10, 34.96; MS (EI) *m/z* (%) 346 (5, M^+), 302 (7), 212 (4), 211 (5), 193 (2), 181 (3), 165 (7), 153 (4), 152 (4), 92 (8), 91 (100), 65 (15).

3.1.4. 3-(4′-Hydroxyphenyl)-8-hydroxy-3,4-dihydrobenzopyran-1-one (hydrangenol) (1). To a solution of the benzyl protected dihydroisocoumarine **6** (2.10 g, 6.06 mmol) in EtOAc (100 mL) were added 5% Pd/C (0.50 g). The mixture was hydrogenated (5 bar, Parr apparatus). The catalyst was filtered off and the solvent was removed. Recrystallization from ethanol afforded hydrangenol (**1**) (1.30 g, 84%) as colourless needles. Mp 170–174°C (lit.:[3] 180–181°C). Anal. calcd for $C_{15}H_{12}O_4$C, 70.31; H, 4.72. Found C, 70.24; H, 4.69; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.95 (s, 1H, OH-8), 9.64 (s, 1H, OH-4′), 7.50 (dd, J=8.0 Hz, 1H, H-6), 7.31 (d, J=8.4 Hz, 2H, H-2′ and H-6′), 6.88 (dd, J=8.4 Hz, 1H, H-7), 6.85 (d, J=7.6 Hz, 1H, H-5), 6.82 (d, J=8.4 Hz, 2H, H-3′ and H-5′), 5.62 (dd, X part of ABX system, J_{AX}=12.0 Hz, J_{BX}=2.8 Hz, 1H, H-3), 3.36 (dd, A part of ABX system, J_{AB}=16.4 Hz, J_{AX}= 12.4 Hz, 1H, H-4), 3.10 (dd, B part of ABX system, J_{AB}=16.4 Hz, J_{BX}=2.8 Hz, 1H, H-4); ^{13}C NMR (DMSO-d_6) δ (ppm) 169.32, 160.97, 157.79, 140.46, 136.21, 128.41, 128.16, 118.30, 115.39, 115.19, 108.39, 80.44, 33.49; MS (EI) *m/z* (%) 256 (45, M^+), 238 (39), 212 (49), 210 (46), 182 (27), 181 (31), 165 (37), 105 (25), 85 (55), 83 (93), 57 (47), 55 (46), 43 (100), 39 (83).

3.1.5. (*E*,*Z*)-2-(3′-Benzyloxy-4′-methoxyphenyl)-1-((3-hydroxy-2-ethoxycarbonyl)phenyl) ethene (4a). To a solution of sodium ethoxide (10.2 g, 0.15 mol) in dry EtOH (300 mL) was added the phosphonium salt **2**[10] (56.4 g, 0.10 mol) and 3-benzyloxy-4-methoxybenzaldehyde (**3a**) (24.2 g, 0.10 mol) The mixture was heated to reflux for 24 h, concentrated and treated with water (150 mL). The organic layer was extracted with $CHCl_3$ (2×100 mL) and dried ($MgSO_4$). Evaporation of the solvent and CC of the residue eluting with $CHCl_3$ gave the stilbene **4a** (37.0 g, 92%) as yellow needles. Mp 91–93°C (6:4 mixture of *E*/*Z*-stereoisomers). Anal. calcd for $C_{25}H_{24}O_4$: C, 74.24; H, 5.98. Found C, 74.20; H, 5.98; ^{1}H NMR ($CDCl_3$) δ (ppm) 11.38 (s, 0.4H, OH-8), 11.24 (s, 0.6H, OH-8), 7.55–6.35 (m, 13H, Ar-H and CH=), 5.18 (s, 1.2H, OCH_2Ar), 4.77 (s, 0.8H, OCH_2Ar), 4.35 (m, 2H, $COOCH_2CH_3$), 3.90 (s, 1.8H, OCH_3), 3.83 (s, 1.2H, OCH_3), 1.31 (m, 3H, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.24, 171.04, 162.74, 162.44, 157.01, 149.94, 148.56, 147.50, 141.43, 137.16, 134.40, 134.26, 132.08, 131.92, 130.90, 130.70, 130.48, 130.06, 129.49, 128.60, 128.43, 127.93, 127.64, 127.56, 127.28, 126.79, 122.71, 122.35, 120.52, 119.48, 116.75, 116.53, 114.68, 112.31, 112.12, 111.68, 111.40, 111.08, 71.34, 70.66, 61.76, 56.14, 55.96, 14.36, 14.01; MS (EI) *m/z* (%) 404 (0.6, M^+), 277 (1), 223 (1), 212 (1), 180 (5), 160 (4), 149 (5), 134 (25), 91 (18), 85 (47), 83 (71), 47 (23), 45 (60), 43 (100).

3.1.6. (*E*,*Z*)-2-(3′-Benzyloxy-4′-methoxyphenyl)-1-((3-hydroxy-2-carboxy)phenyl) ethene (5a). To a solution of the ethyl ester **4a** (18.7 g, 46.2 mmol) in EtOH (200 mL) was added KOH (27.5 g, 0.49 mol). The mixture was heated to reflux for 24 h, concentrated and treated with water (250 mL). CH_2Cl_2 (100 mL) was added and the organic layer was dispatched. After acidification with concd HCl, the aqueous layer was extracted with CH_2Cl_2 (3×200 mL) and dried ($MgSO_4$). Removing of the solvent and recrystallization of the residue from 1,2-dichloroethane gave stilbene carboxylic acid **5a** (15.8 g, 91%) as yellow needles. Mp 131–134°C. Anal. calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found C, 73.42; H, 5.38; ^{1}H NMR (DMSO-d_6) δ (ppm) 7.47–6.83 (m, 13H, Ar-H and CH=), 5.10 (s, 2H, OCH_2Ar), 3.82 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6) δ (ppm) 170.08, 156.04, 149.29, 147.91, 136.95, 136.54, 130.78, 130.35, 130.29, 128.30, 127.70, 124.52, 119.68, 119.43, 116.31, 114.76, 113.79, 110.07, 69.96, 55.51; MS (EI) *m/z* (%) 377 (5, M^+), 332 (4), 242 (4), 92 (9), 91 (100), 85 (8), 83 (13), 65 (8), 60 (5), 55 (4), 51 (4), 47 (9), 45 (14), 44 (11), 43 (23).

3.1.7. 3-(3′-Benzyloxy-4′-methoxyphenyl)-8-hydroxy-3,4-dihydrobenzopyran-1-one (6a). To a solution of the stilbene-*o*-carboxylic acid **5a** (8.40 g, 22.3 mmol) in 1,2-dichloroethane (100 mL) was added trifluoroacetic acid (15.0 mL) in water (7 mL). The mixture was heated to reflux for 3 h, evaporation of the solvent and CC of the residue eluting with EtOAC gave the dihydroisocoumarine **6a** (7.14 g, 85%) as colourless needles. Mp 141–143°C. Anal. calcd for $C_{23}H_{20}O_5$: C, 73.50; H, 5.36. Found C, 73.60; H, 5.37; ^{1}H NMR ($CDCl_3$) δ (ppm) 10.99 (s, 1H, OH-8), 7.44–7.2 (m, 6H, Ar-H), 7.00 (dd, J=8.4 Hz, 2H, Ar-H), 6.88 (d, J=8.0 Hz, 2H, Ar-H), 6.68 (d, J=7.4 Hz, 1H, Ar-H), 5.44 (dd, X part of ABX system, J_{AX}=12.0 Hz, J_{BX}=3.2 Hz, 1H, H-3), 5.13 (s, 2H, OCH_2Ar), 3.87 (s, 3H, OCH_3), 3.25 (dd, A part of ABX system, J_{AB}=16.2 Hz; J_{AX}=12.3 Hz, 1H, H-4), 3.03 (dd, B part of ABX system, J_{AB}=16.2 Hz, J_{BX}=3.2 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ (ppm) 169.77, 162.25, 150.33, 148.40, 139.36, 136.85, 136.28, 130.34, 128.53, 127.92, 127.43, 119.51, 117.92, 116.33, 112.53, 111.82, 108.42, 80.69, 71.28, 56.06, 34.91; MS (EI) *m/z* (%) 376 (0.3, M^+), 242 (0.6), 92 (1), 91 (16), 58 (33), 43 (100), 42 (16).

3.1.8. 3-(3′-Hydroxy-4′-methoxyphenyl)-8-hydroxy-3,4-dihydrobenzopyran-1-one (phyllodulcin) (1a). To a solution of the dihydroisocoumarine **6a** (4.40 g, 11.7 mmol) in EtOAc (200 mL) was added 5% Pd/C (0.50 g). The mixture was hydrogenated (5 bar, Parr apparatus). The catalyst was filtered off and the EtOAc solution was concentrated. The residue was recrystallized from EtOH and afforded phyllodulcin (**1a**) (2.70 g, 81%) as colourless needles. Mp 128–129°C (lit.:[7] 128–130°C, lit.:[3] 118–120°C). Anal. calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found C, 67.05; H, 4.95; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.93 (s, 1H, OH-8), 9.14 (s, 1H, OH-5′), 7.50 (dd, 1H, J=8.0, 7.6 Hz, H-6), 6.96–6.83 (m, 5H, Ar-H), 5.62 (dd, 1H, X part of ABX system, J_{AX}=11.6 Hz, J_{BX}=3.2 Hz, H-3), 3.77 (s, 3H, OCH_3), 3.32 (dd, 1H, A part of ABX

system, J_{AB}=16.4 Hz; J_{AX}=12.0 Hz, H-4), 3.14 (dd, 1H, B part of ABX system, J_{AB}=16.4 Hz, J_{BX}=3.2 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ (ppm) 169.20, 160.92, 147.92, 146.47, 140.35, 136.25, 130.72, 118.34, 117.52, 115.39, 113.92, 111.96, 108.42, 80.16, 55.61, 33.55; MS (EI) *m/z* (%) 286 (11, M^+), 268 (3), 242 (2), 225 (3), 181 (2), 134 (3), 105 (2), 97 (4), 95 (3), 91 (2), 85 (6), 83 (7), 77 (3), 71 (9), 69 (11), 57 (18), 55 (14), 45 (100), 46 (34), 43 (54).

3.1.9. (*E*,*Z*)-2-(3′,4′,5′-Trimethoxyphenyl)-1-((3-hydroxy-2-ethoxycarbonyl)phenyl) ethene (4b). To a solution of sodium ethoxide (10.2 g, 0.15 mol) in dry EtOH (350 mL) were added the phosphonium salt **2**[10] (56.4 g, 0.10 mol) and 3,4,5-trimethoxybenzaldehyde (**3b**) (19.6 g, 0.10 mol). The mixture was heated to reflux for 24 h, concentrated and treated with water (150 mL). The organic layer was extracted with $CHCl_3$ (2×100 mL) and dried ($MgSO_4$). Evaporation of the solvent and CC of the residue eluting with $CHCl_3$ gave the stilbene **4b** (32.9 g, 92%) as orange oil (1:1 mixture of *E*/*Z*-stereoisomers). Anal. calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.19. Found C, 66.97; H, 6.17; ^{1}H NMR ($CDCl_3$) δ (ppm) 11.33 (s, 0.5H, OH-8), 11.28 (s, 0.5H, OH-8), 7.69–6.26 (m, 7H, Ar-H and CH=), 4.40 (m, 2H, COOCH_2CH$_3$), 3.89 (s, 3H, OCH_3), 3.79 (s, 2H, OCH_3), 3.59 (s, 4H, OCH_3), 1.41 (m, 3H, COOCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.18, 170.99, 162.66, 162.51, 157.00, 153.68, 153.48, 152.72, 141.17, 141.08, 138.26, 137.29, 134.44, 134.31, 133.18, 131.97, 131.76, 131.19, 130.73, 129.19, 127.94, 122.23, 119.54, 117.00, 116.64, 111.51, 111.01, 106.82, 106.42, 103.83, 61.88, 61.80, 60.94, 60.80, 56.28, 56.12, 55.78, 14.39, 14.04; MS (CI) *m/z* (%) 358 (1, M^+), 197 (16), 196 (100), 181 (28), 134 (7), 125 (10).

3.1.10. (*E*,*Z*)-2-(3′,4′,5′-Trimethoxyphenyl)-1-((3-hydroxy-2-carboxy)phenyl) ethene (5b). To a solution of the ethyl ester **4b** (28.0 g, 78.1 mmol) in EtOH (200 mL) was added KOH (50.0 g, 0.89 mol). The mixture was heated to reflux for 24 h, concentrated and treated with water (250 mL). CH_2Cl_2 was added and the organic layer was dispatched. After acidification with concd HCl, the aqueous layer was extracted with CH_2Cl_2 (3×200 mL) and concentrated. Recrystallization of the residue in EtOH gave the stilbene carboxylic acid **5b** (24.9 g, 96%) as yellow needles. Mp 177–180°C. Anal. calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found C, 65.38; H, 5.52; ^{1}H NMR (DMSO-d_6) δ (ppm) 7.30–6.83 (m, 7H, Ar-H and CH=), 3.82 (s, 6H, OCH_3), 3.69 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6) δ (ppm) 169.97, 156.04, 153.06, 137.69, 136.33, 132.63, 130.80, 130.58, 125.93, 119.79, 116.50, 115.01, 103.98, 60.05, 55.84; MS (EI) *m/z* (%) 330 (2, M^+), 196 (15), 181 (17), 135 (29), 134 (100), 106 (46), 105 (36), 95 (14), 79 (23), 78 (61), 77 (35), 66 (14), 65 (23), 51 (36), 38 (67).

3.1.11. 3-(3′,4′5′-Trimethoxyphenyl)-8-hydroxy-3,4-dihydrobenzopyran-1-on (6b) (macrophyllol). To a solution of the stilbene-*o*-carboxylic acid **5b** (9.95 g, 30.1 mmol) in 1,2-dichloroethane (75 mL) was added trifluoroacetic acid (20.0 mL) in water (10 mL). The mixture was heated to reflux for 28 h. The solvent was removed under reduced pressure and the residue was diluted with EtOAc. The organic layer was washed with NaOH solution (0.5 M) and concentrated. Recrystallization of the residue in EtOAc gave macrophyllol (**6b**) (5.50 g, 55%) as colourless needles. Mp 165–166°C (lit.:[3] 151–153.5°C). Anal. calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found C, 65.37; H, 5.46; ^{1}H NMR ($CDCl_3$) δ (ppm) 10.98 (s, 1H, OH-8), 7.45 (dd, *J*=8.4 Hz, 1H, H-6), 6.92 (d, *J*=8.4 Hz, 1H, H-7), 6.74 (d, *J*=7.6 Hz, 1H, H-5), 6.68 (s, 2H, H-2′ and H-6′), 5.51 (dd, X part of ABX system, J_{AX}=12.4 Hz, J_{BX}=2.8 Hz, 1H, H-3), 3.88 (2s, 9H, OCH_3), 3.31 (dd, A part of ABX system, J_{AB}=16.4 Hz, J_{AX}=12.4 Hz, 1H, H-4), 3.12 (dd, B part of ABX system, J_{AB}=16.4 Hz, J_{BX}=2.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ (ppm) 169.68, 162.34, 153.56, 139.24, 138.53, 136.42, 133.55, 117.94, 116.47, 108.39, 103.48, 80.95, 60.86, 56.29, 35.35; MS (EI) *m/z* (%) 330 (2.5, M^+), 196 (9), 181 (13), 134 (100), 106 (50), 105 (38), 95 (14), 79 (20), 78 (64), 77 (31), 63 (26), 50 (47).

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