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Titanocene(III) chloride mediated radical-induced synthesis of 3,4-dihydroisocoumarins: synthesis of (±)-hydrangenol, (±)-phyllodulcin, (±)-macrophyllol and (±)-thunberginol G

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ABSTRACT

A radical-promoted synthesis of 3,4-dihydroisocoumarins has been achieved in moderate to good yields using titanocene(III) chloride (Cp_2TiCl) as the radical initiator. The total synthesis of four naturally occurring dihydrocoumarins hydrangenol, phyllodulcin, macrophyllol and thunberginol G has been accomplished using the radical technology. Cp_2TiCl was prepared in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and Zn-dust in THF under argon.

1. Introduction

The 3-aryl-3,4-dihydroisocoumarins constitute a class of naturally occurring compounds, which exhibit a broad range of significant biological activities such as antifungal, antiallergic, antileukaemic, antiulcer and antimalarial activities.[1] Although they are individually different by the number, and type of substituent on the aromatic ring, existence of 8-hydroxy group is very frequent at the core structure in many of them. Hydrangea Dulas Folium (*amacha* in Japanese), a natural medicine containing 3-aryl-3,4-dihydroisocoumarins was isolated from the fermented and dried leaves of *Hydrangea macrophylla* Seringe var. *thunbergii* Makino, a plant indigenous to Japan.[2] This is widely used in confectionary, drinks, oral refrigerant and a sweetening agent.[3] It is also used to make tea served during the Hanamatsuri (birth of Buddha) celebration. Hydrangenol (**1**) and phyllodulcin (**2**) are the chief constituents (Fig. 1) of this natural medicine along with other. Several biological activities have been shown by phyllodulcin, including antiallergic effects on the Schultz-Dale reaction,[4] inhibition of microsomal lipid peroxidation induced by NADPH and the Fenton-type reaction.[5] It has been shown by Matsuda that hydrangenol (**1**) suppresses T-lymphocyte proliferation induced by concanavalin A and compared the activity of hydrangenol (**1**) and thunberginol G (**4**) for T-lymphocyte suppression and concluded that 3′-OH group had no effect[6] in the same (Fig. 1). The discovery that phyllodulcin (**2**) is 600–800 times as sweet as sucrose and its medicinal importance has excited the chemist for structure–taste correlation in sweet dihydrochalcone and bitter flavone compounds.[7] Other dihydroisocoumarins do not show any sweetness property like phyllodulcin. A number of methods have been described for the synthesis of 3-aryl-3,4-dihydroisocoumarin derivatives, but most of these methods involve either *ortho*- or lateral-lithiation.[8] Other methods reported for the preparation of 3-aryl-3,4-dihydroisocoumarins involve cyclization of stilbene carboxylic acids,[9] cycloaddition reactions,[10] $AlCl_3$-mediated reaction,[11] polyketide-derived synthesis[12] and many others.[13] However, many of these methodologies suffer from harsh reaction conditions, multi-step procedures and inefficiency due to functional group intolerance.

The mildness and efficiency of radical-mediated reactions have significantly encouraged synthetic chemists in recent years to utilize radical technology in developing novel methodologies and their applications in natural product synthesis. In a continuation of our studies of the synthesis of natural products involving radical-induced reactions,[14] we have developed a mild and novel radical-mediated methodology to construct C-3 substituted 3,4-dihydroisocoumarins in a single operation with moderate to good yields using dicyclopentadienyl titanocene(III) chloride (Cp_2TiCl) as the radical initiator. Cp_2TiCl can easily be prepared from the

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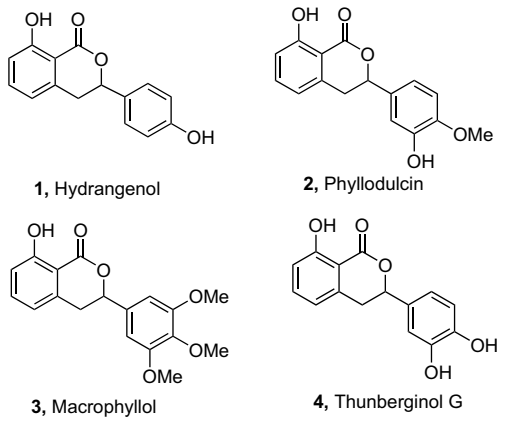


Figure 1.

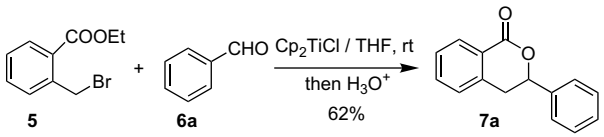
commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF.[15] The total synthesis of the four naturally occurring lactones hydrangenol (**1**), phyllodulcin (**2**), macrophyllol (**3**) and thunberginol G (**4**) has been successfully completed using the radical technology.

2. Results and discussion

In an initial experiment, a mixture of ethyl 2-bromomethylbenzoate (**5**) and benzaldehyde (**6a**) was treated with titanocene(III) chloride in THF at room temperature to afford 3-phenyl-3,4-dihydroisocoumarin **7** (Scheme 1) in 62% yield.[16] The reaction proceeds via a Barbier type addition[17] followed by in situ lactonization.

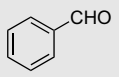
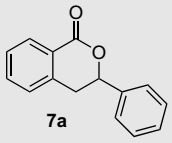
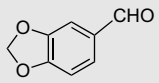
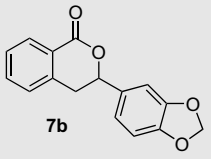
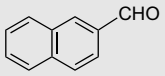
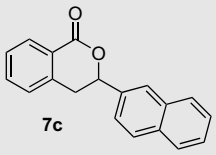
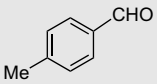
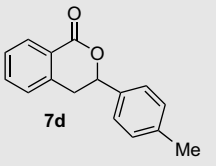
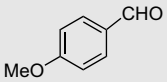
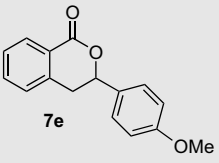
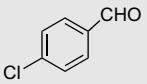
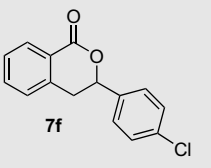
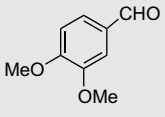
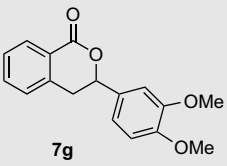
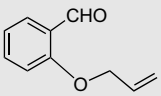
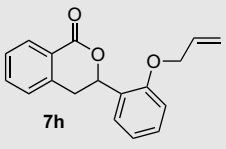
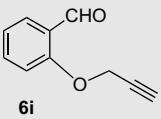
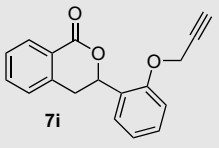
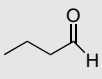
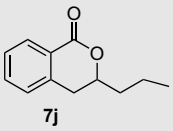
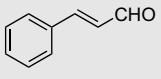
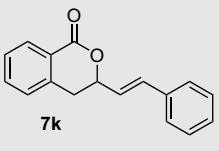
Encouraged by this result where various alkyl and aryl aldehydes **6a–l** were reacted with ethyl 2-bromomethylbenzoate in the presence of Cp_2TiCl and the results are summarized in Table 1. It is noteworthy that when tri-*n*-butyltin hydride was used as the radical mediator, only reduced **5** was obtained without a trace of dihydroisocoumarins. Reaction of ethyl 2-bromomethylbenzoate (**5**) with allyl and propargyl substituted salicylaldehydes **6h** and **6i** (entries 8 and 9, Table 1) furnished the expected dihydroisocoumarins **7h** and **7i**, respectively, without any intramolecular cyclizations, as observed previously in our laboratory.[14j] This is probably due to the fact that the formation of radicals from benzyl bromides by Cp_2TiCl is much faster than aldehydes. Cinnamyl aldehyde (**6k**) and furfural (**6l**) underwent radical-induced reaction with compound **5** to furnish **7k** and **7l**, respectively, in moderate yield (entries 11 and 12). 4-Nitrobenzaldehyde remained unchanged when it was treated with **5** under similar reaction conditions (entry 13). Ketones, such as cyclohexanone and acetophenone, reacted to generated self-coupling products in the presence of Cp_2TiCl without producing any of the desired dihydroisocoumarins.

After successful experiments with different types of aldehydes, our radical technology was applied to the synthesis of (±)-hydrangenol (**1**), a dihydroisocoumarin, isolated from *Hydrangea opuloides* Steud. var. *otakusa*.[8]



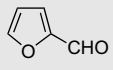
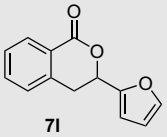
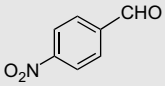
Scheme 1.

Table 1
Synthesis of 3,4-dihydrocoumarins

Entry	Aldehyde	Product[a]	Yield[b] (%)
1	 **6a**	 **7a**	62
2	 **6b**	 **7b**	59
3	 **6c**	 **7c**	51
4	 **6d**	 **7d**	60
5	 **6e**	 **7e**	56
6	 **6f**	 **7f**	48
7	 **6g**	 **7g**	53
8	 **6h**	 **7h**	54
9	 **6i**	 **7i**	56
10	 **6j**	 **7j**	53
11	 **6k**	 **7k**	51

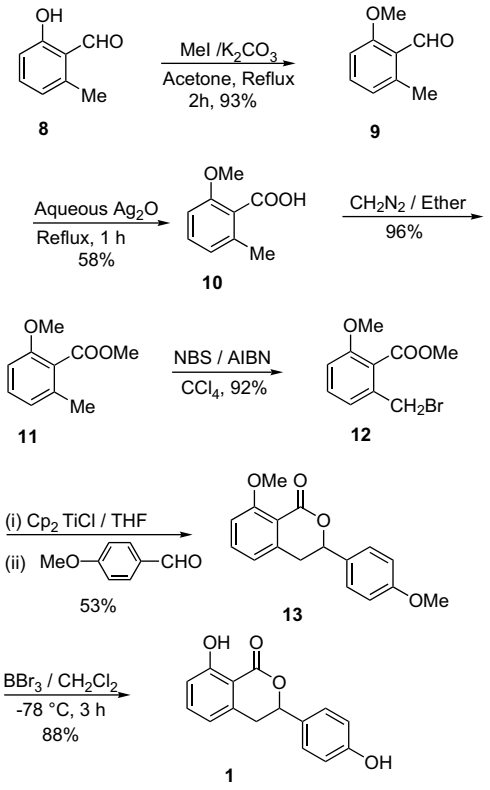
(*continued on next page*)

Table 1 (*continued*)

Entry	Aldehyde	Product[a]	Yield[b] (%)
12	 **6l**	 **7l**	47
13	 **6m**	No reaction	

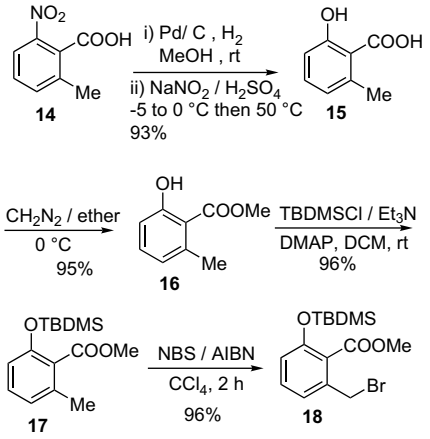
[a] Products were characterized by IR, NMR and HRMS studies.
[b] Yields refer to pure isolated products.

For this purpose, easily accessible[18] methyl 2-methyl-6-methoxybenzoate (**11**) was used as the starting material. Compound **11** was prepared from commercially available aldehyde **8** using the standard reaction sequences shown in Scheme 2. Phenol **8** on the treatment with MeI in the presence of K_2CO_3 gave ether **9**, which on oxidation followed by esterification afforded ester **11**. Compound **11**, on bromination with NBS in the presence of a catalytic amount of AIBN yielded **12** in 92% yield. The bromide **12** on treatment with Cp_2TiCl in THF under argon at room temperature in the presence of 4-methoxybenzaldehyde (**6e**) followed by decomposition afforded lactone **13** in 53% yield as a crystalline solid. Demethylation of **13** with boron tribromide in CH_2Cl_2 afforded hydrangenol (**1**)[2a,b] in 88% yield as colourless crystals.



Scheme 2.

In a quest for a general method to synthesize all four natural products **1**–**4**, it was realized that the bromo-compound **18** could serve as a common precursor. Thus, compound **18** was prepared from the commercially available nitro-compound **14** in five steps, as shown in Scheme 3. Thus, compound **14** was transformed to phenol



Scheme 3.

15 via hydrogenation followed by diazotization. Compound **15** was then treated with diazomethane in ether to yield the corresponding methyl ester **16**. It is noteworthy that the phenolic hydroxyl group remains unaffected during the etherification with diazomethane, which is probably due to strong intramolecular hydrogen bonding. Phenol **16** was then protected with TBDMS-Cl to provide methyl ether **17**. Compound **17**, on photochemical bromination with NBS in the presence of a catalytic amount of AIBN yielded bromide **18**. This benzyl bromide was utilized as a common precursor for the synthesis of dihydrocoumarins (±)-hydrangenol (**1**), (±)-phyllodulcin (**2**), (±)-macrophyllol (**3**) and (±)-thunberginol G (**4**), as shown in Scheme 4. Thus, Cp_2TiCl-mediated reaction of compound **18** with aldehyde **20** followed by acidic workup furnished hydrangenol (**1**) in 51% yield. Similarly, reaction of **18** with aldehydes **21** and **22** gave phyllodulcin (**2**) and macrophyllol (**3**), respectively, in 57% and 55% yields. Radical-mediated reaction of **18** with aldehyde **23** furnished **19** (53%), which on treatment with BBr_3 in CH_2Cl_2 afforded thunberginol G (**4**) in 86% yield.

In summary, we have developed a mild and novel radical-induced method for the synthesis of C-3 substituted 3,4-dihydroisocoumarins using titanocene(III) chloride as the radical initiator. This radical technology has also been applied successfully to the total synthesis of the four naturally occurring dihydrocoumarins hydrangenol, phyllodulcin, macrophyllol and thunberginol G in racemic forms.

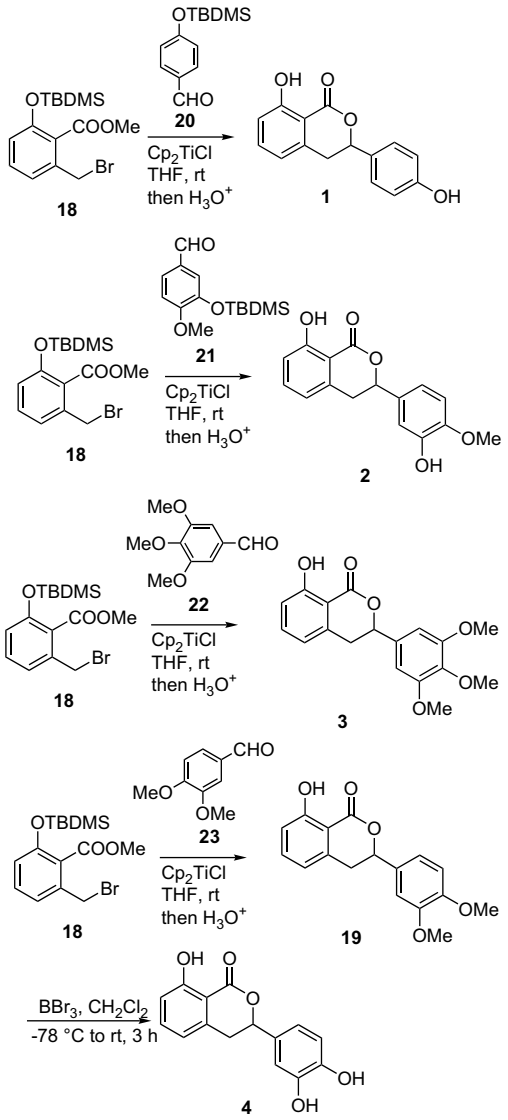
3. Experimental section

3.1. General

The compounds described are all racemates. Melting points were determined in open capillary tubes and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker DPX 300 spectrometer using tetramethyl silane as the internal standard. IR spectra were recorded on Shimadzu FT IR-8300. Column chromatography was performed on silica gel (60–120 mesh) and preparative TLC was performed using pre-coated silica 60 F_{254} plates (0.2 mm). High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument. Diethyl ether and tetrahydrofuran were freshly distilled from sodium. Methylene chloride was freshly distilled over calcium hydride. Light petroleum of boiling range 60–80 °C was used for chromatography.

3.2. Typical experimental procedure

A red solution of Cp_2TiCl_2 (747 mg, 3.0 mmol) in deoxygenated THF (40 mL) was stirred with activated zinc dust (393 mg, 6 mmol)



Scheme 4.

under argon until it turned green. This green solution was transferred to a dropping funnel by a cannula and was added dropwise for 9 h to a solution of the bromide **5** (1.5 mmol) and the aldehyde **6** (1.5 mmol) in THF (20 mL). The reaction mixture was then stirred for an additional 4 h. After completion of the reaction (monitored by TLC), it was decomposed slowly with 25% aqueous H_2SO_4. Most of the THF was removed under reduced pressure and the resulting residue was extracted with diethyl ether (3×25 mL). The organic layer was washed successively with water (2×10 mL), brine (2×10 mL) and finally dried (Na_2SO_4). Solvent was removed in vacuo to give the crude product, which was purified by column chromatography (ethyl acetate in light petroleum) to furnish **7**.

3.3. 3-Phenyl-3,4-dihydro-1*H*-isochromen-1-one (7a)

Colourless solid. Mp 87–89 °C; R_f=0.28 (10% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1722, 1271, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.14 (dd, J=3.2, 16.4 Hz, 1H), 3.35 (dd, J=11.9, 16.4 Hz, 1H), 5.57 (dd, J=3.2, 11.9 Hz, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.37–7.50 (m, 6H), 7.58 (dt, J=1.2, 7.5 Hz, 1H), 8.16 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.0, 80.4, 125.5, 126.5 (2C), 127.8, 128.3, 129.0, 129.1 (2C), 130.8, 134.3, 139.0, 139.4, 165.8; HRMS (ESI) calcd for $C_{15}H_{13}O_2$ 225.0915 $[M+H]^+$, found 225.0886.

3.4. 3-(1,3-Benzodioxol-5-yl)-3,4-dihydro-1*H*-isochromen-1-one (7b)

White solid. Mp 138–140 °C. R_f=0.25 (10% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1705, 1448, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (dd, J=3.0, 16.4 Hz, 1H), 3.28 (dd, J=12.0, 16.4 Hz, 1H), 5.42 (dd, J=3.0, 12.0 Hz, 1H), 5.95 (s, 2H), 6.79 (d, J=8.0 Hz, 1H), 6.89 (dd, J=1.0, 8.0 Hz, 1H), 6.95 (d, J=1.0 Hz, 1H), 7.25 (d, J=7.4 Hz, 1H), 7.39 (dd, J=7.5, 7.6 Hz, 1H), 7.54 (dd, J=7.4, 7.5 Hz, 1H), 8.10 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.5, 78.8, 100.2, 105.7, 107.2, 118.9, 124.0, 126.3, 126.8, 129.3, 131.3, 132.8, 137.8, 146.8, 146.9, 164.2; HRMS (ESI) calcd for $C_{16}H_{13}O_4$ 269.0808 $[M+H]^+$, found 269.0849.

3.5. 3-(Naphthalen-2-yl)-3,4-dihydro-1*H*-isochromen-1-one (7c)

White solid. Mp 135–136 °C. R_f=0.31 (10% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1718, 1286, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.23 (dd, J=2.5, 16.3 Hz, 1H), 3.43 (dd, J=11.9, 16.3 Hz, 1H), 5.73 (dd, J=2.5, 11.9 Hz, 1H), 7.30 (d, J=7.4 Hz, 1H), 7.45 (dd, J=7.4,7.7 Hz, 1H), 7.50–7.61 (m, 4H), 7.86–7.96 (m, 4H), 8.18 (d, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.5, 79.9, 123.5, 125.0, 125.1, 126.3, 126.4, 127.2, 127.6, 127.8, 128.0, 128.4, 130.3, 133.0, 133.1, 133.8, 135.8, 138.8, 165.2; HRMS (ESI) calcd for $C_{19}H_{15}O_2$ 275.1067 $[M+H]^+$, found 275.1026.

3.6. 3-(4-Methylphenyl)-3,4-dihydro-1*H*-isochromen-1-one (7d)

Colourless solid. Mp 92–94 °C. R_f=0.34 (10% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1724, 1263, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.11 (dd, J=3.1, 16.4 Hz, 1H), 3.34 (dd, J=11.9, 16.4 Hz, 1H), 5.53 (dd, J=3.1, 11.9 Hz, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.28 (d, J=7.6 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.43 (dd, J=7.5, 7.6 Hz, 1H), 7.57 (t, J=7.5 Hz, 1H), 8.15 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.9, 55.7, 80.2, 114.2 (2C), 125.6, 127.8, 128.1 (2C), 128.2, 130.8, 131.1, 134.3, 139.5, 160.3, 165.9; HRMS (ESI) calcd for $C_{16}H_{14}O_2Na$ 261.0891 $[M+Na]^+$, found 261.0892.

3.7. 3-(4-Methoxyphenyl)-3,4-dihydro-1*H*-isochromen-1-one (7e)

White solid. Mp 106–108 °C. R_f=0.25 (10% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1716, 1515, 1255, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.08 (dd, J=3.0, 16.4 Hz, 1H), 3.34 (dd, J=12.0, 16.4 Hz, 1H), 3.81 (s, 3H), 5.49 (dd, J=3.0, 12.0 Hz, 1H), 6.92 (d, J=8.7 Hz, 2H), 7.27 (d, J=7.5 Hz, 1H), 7.36–7.44 (m, 3H), 7.55 (t, J=7.5 Hz, 1H), 8.13 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.4, 55.3, 79.8, 114.0 (2C), 125.1, 127.3, 127.6 (2C), 127.8, 130.4, 130.6, 133.8, 139.0, 159.8, 165.4; HRMS (ESI) calcd for $C_{16}H_{15}O_3$ 255.1016 $[M+H]^+$, found 255.1004.

3.8. 3-(4-Chlorophenyl)-3,4-dihydro-1*H*-isochromen-1-one (7f)

Colourless solid. Mp 81–83 °C. R_f=0.37 (10% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1714, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (dd, J=3.3, 16.4 Hz, 1H), 3.23 (dd, J=11.8, 16.4 Hz, 1H), 5.46 (dd, J=3.3, 11.8 Hz, 1H), 7.20 (d, J=7.6 Hz, 1H), 7.29–7.39 (m, 5H), 7.50 (dd, J=7.5, 7.6 Hz, 1H), 8.07 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.7, 79.3, 125.9, 127.5, 127.6, 128.2, 128.9, 129.0, 130.6, 131.3, 134.2, 137.2, 138.7, 165.2; HRMS (ESI) calcd for $C_{15}H_{12}O_2Cl$ 259.0520 $[M+H]^+$, found 259.0557.

3.9. 3-(3,4-Dimethoxyphenyl)-3,4-dihydro-1*H*-isochromen-1-one (7g)

Colourless needles. Mp 102–104 °C. R_f=0.28 (20% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1714, 1278, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.11(dd, J=3.0, 16.4 Hz, 1H), 3.37 (dd, J=12.0, 16.4 Hz, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 5.51 (dd, J=3.0, 12.0 Hz, 1H), 6.88 (d, J=8.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 7.03 (s, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H), 7.57 (dd, J=7.5, 7.6 Hz, 1H), 8.15 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.4, 55.9 (2C), 79.9, 109.4, 110.9, 118.6, 125.0, 127.3, 127.8, 130.3, 131.0, 133.8, 139.0, 149.1, 149.2, 165.4; HRMS (ESI) calcd for $C_{17}H_{17}O_4$ 285.1121 $[M+H]^+$, found 285.1115.

3.10. 3-[2-(Prop-2-en-1-yloxy)phenyl]-3,4-dihydro-1*H*-isochromen-1-one (7h)

Colourless oil. R_f=0.34 (10% ethyl acetate in light petroleum); IR (neat): ν_{max} 1724, 1492, 1272, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.13–3.16 (m, 2H), 4.52 (ddd, J=1.5, 3.2, 6.5 Hz, 2H), 5.18 (dd, J=1.5, 10.5 Hz, 1H), 5.29 (dd, J=1.5, 17.3 Hz, 1H), 5.87–6.02 (m, 2H), 6.84 (d, J=8.3 Hz, 1H), 6.97 (dd, J=7.0, 7.6 Hz, 1H), 7.19–7.26 (m, 2H), 7.36 (t, J=7.5 Hz, 1H), 7.49 (dt, J=1.4, 7.6 Hz, 1H), 7.55 (dd, J=1.4, 7.6 Hz, 1H), 8.09 (dd, J=0.7, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.8, 69.3, 75.6, 112.1, 117.8, 121.5, 125.6, 127.2, 127.7, 127.8, 128.1, 129.7, 130.8, 133.4, 134.2, 140.0, 155.2, 166.2; HRMS (ESI) calcd for $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1172, found 281.1160.

3.11. 3-[2-(Prop-2-yn-1-yloxy)phenyl]-3,4-dihydro-1*H*-isochromen-1-one (7i)

Colourless oil. R_f=0.20 (10% ethyl acetate in light petroleum); IR (neat): ν_{max} 2117, 1720, 1276, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (t, J=2.3 Hz, 1H), 3.19–3.22 (m, 2H), 4.74 (d, J=2.3 Hz, 2H), 5.95 (m, 1H), 7.04 (d, J=8.5 Hz, 1H), 7.09 (t, J=7.6 Hz, 1H), 7.26–7.45 (m, 3H), 7.56 (dt, J=1.2, 7.4 Hz, 1H), 7.64 (dd, J=1.2, 7.6 Hz, 1H), 8.16 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.6, 56.2, 75.0, 76.0, 78.4, 112.2, 122.0, 125.3, 127.1, 127.5, 127.8, 128.0, 129.4, 130.4, 133.9, 139.6, 153.9, 165.8; HRMS (ESI) calcd for $C_{18}H_{15}O_3$ $[M+H]^+$ 279.1016, found 279.1008.

3.12. 3-Propyl-3,4-dihydro-1*H*-isochromen-1-one (7j)

Colourless oil. R_f=0.56 (10% ethyl acetate in light petroleum); IR (neat): ν_{max} 1716, 1261, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J=7.1 Hz, 3H), 1.47–1.89 (m, 4H), 2.81–2.97 (m, 2H), 4.44–4.53 (m, 1H), 7.18 (d, J=7.5 Hz, 1H), 7.33 (dd, J=7.4, 7.5 Hz, 1H), 7.48 (dd, J=7.4, 7.5 Hz, 1H), 8.04 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.3, 33.3, 37.1, 78.6, 125.8, 127.5, 127.7, 130.4, 133.7, 139.3, 165.8; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067, found 191.1073.

3.13. 3,4-Dihydro-3-styrylisochromen-1-one (7k)

Colourless oil. R_f=0.27 (10% ethyl acetate in light petroleum); IR (neat): ν_{max} 1722, 1606, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.08–3.24 (m, 2H), 5.18–5.25 (m, 1H), 6.34 (dd, J=6.3, 16.0 Hz, 1H), 6.79 (d, J=16.0 Hz, 1H), 7.27–7.44 (m, 7H), 7.56 (t, J=7.4 Hz, 1H), 8.13 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.2, 79.1, 125.6, 126.3, 127.1 (2C), 127.8, 128.2, 128.7, 129.1 (2C), 130.8, 133.7, 134.2, 136.2, 139.0, 165.5; HRMS (ESI) calcd for $C_{17}H_{14}O_2Na$ 273.0891 $[M+Na]^+$, found 273.0891.

3.14. 3-(Furan-2-yl)-3,4-dihydroisochromen-1-one (7l)

Colourless oil. R_f=0.28 (10% ethyl acetate in light petroleum); IR (neat): ν_{max} 1732, 1606, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.21 (dd, J=3.4, 16.5 Hz, 1H), 3.55 (dd, J=10.9, 16.5 Hz, 1H), 5.59 (dd, J=3.4, 10.9 Hz, 1H), 6.37 (d, J=1.6 Hz, 1H), 6.41 (d, J=3.1 Hz, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.39–7.43 (m, 2H), 7.56 (d, J=7.5 Hz, 1H), 8.11 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.6, 73.1, 109.1, 110.6, 125.0, 127.6, 128.0, 130.5, 134.1, 138.6, 143.2, 150.8, 164.8; HRMS (ESI) calcd for $C_{13}H_{10}O_3Na$ 237.0528 $[M+Na]^+$, found 237.0525.

3.15. 2-Methoxy-6-methyl-benzaldehyde (9)

To a solution of 2-hydroxy-6-methyl-benzaldehyde (340 mg, 2.5 mmol) in dry acetone (15 mL), potassium carbonate (414 mg, 3 mmol) and methyl iodide (529 mg, 3.75 mmol) were added and refluxed for 2 h. After cooling, the mixture was concentrated under reduced pressure and then water (20 mL) was added to it. The reaction mass was extracted with diethyl ether (3×15 mL). The combined organic layer was washed with water (10 mL), brine (10 mL) and finally dried (Na_2SO_4). The organic layer was concentrated under reduced pressure and the residue obtained was purified by column chromatography over silica gel (5% ethyl acetate in light petroleum) to give the corresponding methyl ether **9** (93%) as a colourless solid. Mp 38–40 °C. R_f=0.50 (7% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1683, 1596, 1473, 1271, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.82 (s, 3H), 6.73 (d, J=7.8 Hz, 1H), 6.77 (d, J=7.8 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 10.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 55.6, 109.0, 123.2, 124.0, 134.4, 141.8, 163.1, 192.1; HRMS (ESI) calcd for $C_9H_{11}O_2$ 151.0754 $[M+H]^+$ found 151.0756.

3.16. 2-Methoxy-6-methyl-benzoic acid (10)

Fresh silver oxide was prepared by treating aqueous solution of silver nitrate (680 mg, 4 mmol) in 1 M aqueous sodium hydroxide solution (8 mL) and the suspension was stirred at room temperature for 30 min. A solution of 2-methoxy-6-methyl-benzaldehyde **9** (300 mg, 2 mmol) in a 1 M aqueous sodium hydroxide solution (15 mL) was added to the suspension of silver oxide, and the mixture was refluxed gently for 1 h. After cooling, the mixture was filtered off and the aqueous alkaline solution was acidified with 20% hydrochloric acid and extracted with diethyl ether (3×15 mL). The combined organic layer was washed successively with water (10 mL), brine (10 mL) and finally dried (Na_2SO_4). The organic layer was concentrated under reduced pressure and the residue obtained was purified by column chromatography over silica gel (25% ethyl acetate in light petroleum) to yield the corresponding carboxylic acid **10** (58%) as a colourless solid. Mp 138–140 °C. R_f=0.31 (25% ethyl acetate in light petroleum); IR (KBr): 3012, 2559, 1697, 1587, 1473, 1296, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.88 (s, 3H), 6.81 (d, J=8.1 Hz, 1H), 6.55 (d, J=8.1 Hz, 1H), 7.29 (t, J=8.1 Hz, 1H), 10.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 56.5, 109.2, 122.3, 123.5, 131.5, 138.4, 157.3, 173.4. HRMS (ESI) calcd for $C_9H_{10}O_3$ 189.0528 $[M+Na]^+$, found 189.0527.

3.17. Methyl 2-methoxy-6-methylbenzoate (11)

To a solution of 2-methoxy-6-methyl-benzoic acid **10** (415 mg, 2.5 mmol) in ether (10 mL) at 0 °C, diazomethane (5 mmol) in ether (10 mL) was added dropwise and stirred for 2 h. After removing the excess diazomethane it was diluted with ether (20 mL). The ether layer was washed successively with water (10 mL), brine (10 mL) and finally dried (Na_2SO_4). The organic layer was concentrated under reduced pressure and the residue obtained was purified by column chromatography over silica gel (5% ethyl acetate in light

petroleum) to obtain the ester **11** as a colourless oil (96%). R_f=0.45 (5% ethyl acetate in light petroleum); IR (neat): ν_{max} 1733, 1585, 1473, 1267, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 6.73 (d, J=8.1 Hz, 1H), 6.77 (d, J=8.1 Hz, 1H), 7.21 (t, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 52.1, 55.8, 108.4, 122.3, 123.7, 130.3, 136.4, 156.4, 168.8; HRMS (ESI) calcd for $C_{10}H_{12}O_3$ 203.0684 $[M+Na]^+$, found 203.0667.

3.18. Methyl 2-(bromomethyl)-6-methoxybenzoate (12)

N-Bromosuccinamide (356 mg, 2 mmol) was added to a solution of **11** (360 mg, 2.0 mmol) in carbon tetrachloride (5 mL) and was heated to reflux in the presence of visible light. Then, a catalytic amount of AIBN was added and the reflux was continued for 2 h. After cooling to room temperature the precipitated solid was filtered off and the filtrate was concentrated under reduced pressure and the residue was extracted with diethyl ether (3×15 mL). The organic layer was washed successively with water (2×10 mL), brine (2×10 mL) and finally dried (Na_2SO_4). After removal of the solvent in vacuo the residue obtained was purified by column chromatography over silica gel (5% ethyl acetate in light petroleum) to furnish the benzyl bromide **12** (476 mg, 92%) as a colourless oil. R_f=0.42 (5% ethyl acetate in light petroleum); IR (neat): ν_{max} 1730, 1585, 1471, 1271, 1114, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.93 (s, 3H), 4.48 (s, 2H), 6.86 (d, J=8.4 Hz, 1H), 6.98 (d, J=7.7 Hz, 1H), 7.30 (dd, J=7.7, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0, 52.5, 56.1, 111.6, 122.3, 123.2, 131.1, 136.5, 156.9, 167.5; HRMS (ESI) calcd for $C_{10}H_{11}BrO_3Na$ 280.9790 $[M+Na]^+$, found 280.9786.

3.19. Preparation of 8-methoxy-3-(4-methoxyphenyl)-3,4-dihydro-1*H*-isochromen-1-one (13)

A red solution of Cp_2TiCl_2 (747 mg, 3.0 mmol) in deoxygenated THF (40 mL) was stirred with activated zinc dust (393 mg, 6 mmol) under argon until it turned green. This green solution was transferred to a dropping funnel by a cannula and was added dropwise for 9 h to a solution of the bromide **12** (390 mg, 1.5 mmol) and 4-methoxybenzaldehyde (205 mg, 1.5 mmol) in dry deoxygenated THF (20 mL) under argon. The reaction mixture was stirred for an additional 8 h and was decomposed slowly with 25% aqueous H_2SO_4. Most of THF was removed under reduced pressure and resulting residue was extracted with diethyl ether (3×25 mL). The organic layer was washed successively with water (2×10 mL), brine (2×10 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude material obtained was purified by column chromatography over silica gel (25% ethyl acetate in light petroleum) to furnish **13** (227 mg, 53%) as colourless needles. Mp 152–154 °C. R_f=0.29 (25% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1728, 1595, 1475, 1240, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.98 (dd, J=2.6, 16.2 Hz, 1H), 3.23 (dd, J=11.9, 16.2 Hz, 1H), 3.78 (s, 3H), 3.92 (s, 3H), 5.32 (dd, J=2.6, 11.9 Hz, 1H), 6.81 (d, J=7.5 Hz, 1H), 6.83–6.93 (m, 3H), 7.35 (d, 8.6 Hz, 2H), 7.45 (dd, J=7.7, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.6, 55.3, 56.2, 78.9, 111.1, 113.9 (2C), 119.3, 120.2, 127.7 (2C), 130.6, 134.7, 141.8, 159.8, 161.2, 162.5; HRMS (ESI) calcd for $C_{17}H_{16}O_4Na$ 307.0946 $[M+Na]^+$, found 307.0944.

3.20. Synthesis of hydrangenol (1)

A solution of BBr_3 (1 M, 2 mL) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of dimethyl ether **13** (142 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was then allowed to warm to room temperature and was stirred for an additional 3 h. It was decomposed with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic layer was washed successively with water (2×10 mL), brine (2×10 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude material obtained was purified by column chromatography over silica gel (30% ethyl acetate in light petroleum) to furnish hydrangenol (**1**) (113 mg, 88%) as a white solid; mp179–181 °C (lit.[2c] 180–181 °C). R_f=0.15 (20% ethyl acetate in light petroleum); IR (KBr): ν_{max} 3354, 1658, 1460, 1230, 1028 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.10 (dd, J=2.5, 16.4 Hz, 1H), 3.37 (dd, J=12.0, 16.4 Hz, 1H), 5.63 (dd, J=2.5, 12.0 Hz, 1H), 6.79 (d, J=8.2 Hz, 2H), 6.83–6.89 (m, 2H), 7.31 (d, J=8.2 Hz, 2H), 7.50 (t, J=7.9 Hz, 1H), 9.62 (s, 1H, phenolic OH), 10.92 (s, 1H, phenolic OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.4, 81.4, 109.3, 116.1 (2C), 116.3, 119.1 (2C), 129.2, 129.3, 137.2, 141.5, 158.7, 161.8, 170.2; HRMS (ESI) calcd for $C_{15}H_{12}O_4Na$ 279.0633 $[M+Na]^+$, found 279.0649.

3.21. 2-Hydroxy-6-methyl-benzoic acid (15)

To a stirred solution of 2-methyl-6-nitro-benzoic acid **14** (1.0 g, 5.52 mmol) in dry methanol (10 mL), 10% Pd on activated charcoal (20 mg) was added and then hydrogen gas was purged to it. The reaction mixture was allowed to stir for overnight. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The solid mass obtained was dissolved into 9% aqueous H_2SO_4 solution (10 mL). The resulting solution was cooled to −5 °C and a cold saturated solution of $NaNO_2$ (419 mg, 6.07 mmol) was added slowly to it with hand shaking. Then, it was left for 20 min at room temperature and was heated until the temperature reached to 50 °C. Heating was continued until evolution of N_2 ceases. The reaction mass was extracted with diethyl ether (3×50 ml). The combined organic extract was washed successively with water (2×15 mL), brine (20 mL) and finally dried (Na_2SO_4). After removal of the solvent the crude product obtained was purified by column chromatography over silica gel (15% ethyl acetate in light petroleum) to furnish **15** (780 mg, 93%) as colourless needles. Mp 154–156 °C. R_f=0.22 (20% ethyl acetate in light petroleum); IR (KBr): ν_{max} 3075, 1647, 1444, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H), 6.77 (d, J=7.4 Hz, 1H), 6.87 (d, J=8.3 Hz, 1H), 7.34 (dd, J=8.3, 7.4 Hz, 1H), 11.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 111.1, 116.0, 123.4, 135.6, 143.1, 163.9, 176.1. Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.13; H, 5.28.

3.22. Methyl 2-hydroxy-6-methylbenzoate (16)

To a solution of **15** (760 mg, 5.0 mmol) in diethyl ether (10 ml) at 0 °C, diazomethane (15 mmol) in ether (10 mL) was added dropwise and stirred for 2 h. After removing the excess diazomethane the ether layer was washed with water (10 mL), brine (10 mL) and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure the residue obtained was purified by column chromatography over silica gel (10% ethyl acetate in light petroleum) to give the corresponding ester **16** (788 mg, 95%) as a colourless oil. R_f=0.32 (15% ethyl acetate in light petroleum); IR (KBr): ν_{max} 3039, 1664, 1442, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.93 (s, 3H), 6.69 (d, J=7.4 Hz, 1H), 6.83 (d, J=8.3 Hz, 1H), 7.25 (dd, J=7.4, 8.3 Hz, 1H), 11.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0, 52.1, 112.3, 115.6, 122.9, 134.2, 141.3, 162.9, 172.2. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.01; H, 6.12.

3.23. Methyl 2-(*tert*-butyldimethylsilyloxy)-6-methylbenzoate (17)

A solution of **16** (830 mg, 5.0 mmol) in dichloromethane (20 mL) was stirred with triethylamine (1.02 g, 10 mmol), DMAP (62.5 mg, 0.5 mmol) and TBDMS-Cl (904 mg, 6.0 mmol) for 10 h at room temperature. Then, the reaction mixture was diluted with diethyl ether (20 mL). The ether layer was washed successively with water

(15 mL), brine (15 mL) and finally dried (Na_2SO_4). After evaporation of the solvent the residual mass was chromatographed over silica gel (5% ethyl acetate in light petroleum) to afford **17** (1.35 g, 96%) as a colourless oil. R_f=0.62 (5% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1735, 1467, 1290, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.22 (s, 6H), 0.97 (s, 9H), 2.28 (s, 3H), 3.87 (s, 3H), 6.67 (d, J=8.2 Hz, 1H), 6.78 (d, J=7.5 Hz, 1H), 7.13 (dd, J=7.5, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.3 (2C), 18.1, 19.4, 25.6 (3C), 52.0, 116.4, 122.7, 126.6, 130.0, 136.7, 152.5, 169.0; HRMS (ESI) calcd for $C_{15}H_{25}O_3Si$ 281.1567 $[M+H]^+$, found 281.1552.

3.24. Methyl 2-(*tert*-butyldimethylsilyloxy)-6-(bromomethyl)-benzoate (18)

N-Bromosuccinamide (356 mg, 2 mmol) was added to a solution of **17** (560 mg, 2 mmol) in CCl_4 (10 ml) and heated to reflux under visible light. A catalytic amount of AIBN (4 mg) was added and the reflux continued for 2 h. After cooling, the solids were filtered off and the filtrate concentrated under reduced pressure. It was diluted with diethyl ether (20 mL) and washed with water (10 mL), brine (10 mL) and finally dried (Na_2SO_4). After removal of the solvent in vacuo the residue obtained was purified by column chromatography over silica gel (5% ethyl acetate in light petroleum) to obtain the benzyl bromide **18** (688 mg, 96%) as a colourless oil. R_f=0.60 (5% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1728, 1465, 1296, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.22 (s, 6H), 0.97 (s, 9H), 3.90 (s, 3H), 4.49 (s, 2H), 6.79 (d, J=7.9 Hz, 1H), 6.98 (d, J=7.6 Hz, 1H), 7.22 (dd, J=7.6, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.3 (2C), 18.1, 25.6 (3C), 30.3, 52.3, 119.6, 122.7, 126.0, 130.8, 136.9, 153.2, 167.8; HRMS (ESI) calcd for $C_{15}H_{23}O_3BrSiNa$ 381.0497 $[M+Na]^+$, found 381.0529.

3.25. Phyllodulcin (2)

A solution of **18** (537 mg, 1.5 mmol) and 3-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde **21** (400 mg, 1.5 mmol) in THF (15 mL) was reacted in the presence of Cp_2TiCl in THF followed by acidic work-up as described for the preparation of **13** to give phyllodulcin (**2**) as a colourless needles (245 mg, 57%). Mp 127–129 °C (lit. 128–130 °C). R_f=0.16 (20% ethyl acetate in light petroleum); IR (KBr): ν_{max} 3352, 1670, 1618, 1230 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.16 (dd, J=3.2, 16.5 Hz, 1H), 3.37 (dd, J=11.6, 16.5 Hz, 1H), 3.78 (s, 3H), 5.66 (dd, J=3.2, 11.6 Hz, 1H), 6.87–6.97 (m, 5H), 7.53 (dd, J=7.9, 8.0 Hz, 1H), 9.12 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.5, 55.6, 80.1, 108.4, 111.9, 113.9, 115.4, 117.5, 118.4, 130.7, 136.3, 140.4, 146.4, 147.9, 160.9, 169.2; HRMS (ESI) calcd for $C_{16}H_{14}O_5Na$: 309.0739 $[M+Na]^+$, found 309.0730.

3.26. Macrophyllol (3)

A solution of **18** (537 mg, 1.5 mmol) and 3,4,5-trimethoxybenzaldehyde **22** (294 mg, 1.5 mmol) in THF (15 mL) was reacted in the presence of Cp_2TiCl in THF followed by acidic work-up as described for the preparation of **13** to give macrophyllol (**3**) as a colourless needles (272 mg, 55%). Mp 149–151 °C (lit.[2c] 151–153 °C). R_f=0.22 (25% ethyl acetate in light petroleum); IR (KBr): ν_{max} 3408, 1664, 1620, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.12 (dd, J=2.8, 16.5 Hz, 1H), 3.32 (dd, J=12.1, 16.5 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 6H), 5.52 (dd, J=2.8, 12.1 Hz, 1H), 6.67 (s, 2H), 6.75 (d, J=7.3 Hz, 1H), 6.93 (d, J=8.4 Hz, 1H), 7.45 (dd, J=7.8, 8.0 Hz, 1H), 10.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.5, 56.4 (2C), 61.0, 81.1, 103.4 (2C), 108.5, 116.6, 118.1, 120.3, 133.7, 136.6, 139.3, 153.6 (2C), 162.5, 169.8; HRMS (ESI) calcd for $C_{18}H_{18}O_6Na$ 353.1001 $[M+Na]^+$, found 353.1014.

3.27. Synthesis of hydrangenol (1) from 18

A solution of **18** (537 mg, 1.5 mmol) and 4-(*tert*-butyldimethylsilyloxy)-benzaldehyde **20** (354 mg, 1.5 mmol) in THF (15 mL) was reacted in the presence of Cp_2TiCl in THF followed by acidic work-up as described for the preparation of **13** to give hydrangenol (**1**) as colourless needles (196 mg, 51%).

3.28. Thunberginol G dimethyl ether (19)

A solution of **18** (537 mg, 1.5 mmol) and 3,4-dimethoxybenzaldehyde **23** (250 mg, 1.5 mmol) in THF (15 mL) was reacted in the presence of Cp_2TiCl in THF followed by acidic work-up as described for the preparation of **13** to give compound **19** as a colourless needles (238 mg, 53%). Mp 105–107 °C. R_f=0.27 (25% ethyl acetate in light petroleum); IR (KBr): ν_{max} 1670, 1616, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.99 (dd, J=3.1, 16.5 Hz, 1H), 3.22 (dd, J=12.2, 16.5 Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 5.41 (dd, J=3.1, 12.2 Hz, 1H), 6.63 (d, J=7.3 Hz, 1H), 6.76–6.89 (m, 4H), 6.84–6.89 (m, 2H), 7.33 (dd, J=7.9, 8.0 Hz, 1H), 10.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.1, 56.0 (2C), 80.9, 108.4, 109.4, 111.0, 116.3, 118.0, 118.8, 130.4, 136.4, 139.4, 149.2, 149.5, 162.2, 169.9; HRMS (ESI) calcd for $C_{17}H_{17}O_5$ 301.1071 $[M+H]^+$, found 301.1077.

3.29. Thunberginol G (4)

Compound **19** (150 mg, 0.5 mmol) was treated with BBr_3 (1 M, 2 mL) in CH_2Cl_2 (2 mL) following the same procedure described for **1** to give thunberginol (**4**) (117 mg, 86%) as a white solid. Mp 176–178 °C. R_f=0.21 (30% ethyl acetate in light petroleum); IR (KBr): ν_{max} 3303, 1658, 1614, 1203 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.12 (dd, J=2.9, 16.5 Hz, 1H), 3.33 (dd, J=11.8, 16.5 Hz, 1H), 5.59 (dd, J=2.9, 11.8 Hz, 1H), 6.77–6.91 (m, 5H), 7.51 (dd, J=7.8, 7.9 Hz, 1H), 9.07 (s, 1H), 9.10 (s, 1H), 10.95 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.1, 80.0, 108.0, 113.7, 114.9 (2C), 117.3, 117.9, 128.5, 135.8, 140.1, 144.7, 145.3, 160.4, 168.9; HRMS (ESI) calcd for $C_{15}H_{12}O_5Na$: 295.0583 $[M+Na]^+$, found 295.0584.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.075.

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