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Divergent and concise total syntheses of dihydrochalcones and 5-deoxyflavones recently isolated from *Tacca* species and *Mimosa diplotricha*

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ABSTRACT

Dihydrochalcones and 5-deoxyflavones are types of compounds possessing various biologically interesting properties. Herein, we report the concise and divergent total syntheses of several naturally occurring dihydrochalcones and 5-deoxyflavones from readily available starting materials. The divergent strategy is based around manipulation of a common chalcone scaffold and features application of Algar–Flynn–Oyamada oxidation and benzoquinone C–H activation methodologies. These are the first reported total syntheses of these biologically interesting compounds and the concise and flexible route should be readily amenable to future analogue generation. Furthermore, this work provides an illustration of the utility of divergent synthesis for the expedient and step-economical preparation of natural product libraries.

1. Introduction

Flavonoids are a family of polyphenolic compounds. They are ubiquitous in plants,[1] and represent dietary constituents of potential importance to health.[2] Flavanoids are also emerging as a potentially important new class of pharmaceutical lead substrates.[1] Amongst the several classes of flavonoids, dihydrochalcones and 5-deoxyflavones have been reported to demonstrate a range of biologically interesting properties, including antiinflammatory,[3] antioxidant,[4,5] antidiabetic,[6] antileishmanial,[7] molluscidal[8] and anticancer[9] activities as well as chemopreventive effects.[10] Consequently, these compounds classes have attracted interest from both the synthetic and medicinal chemistry communities.[11] Recently, Peng et al. reported the isolation and characterization of five new dihydrochalcones, named taccabulins B–E (**1**–**4**) and evelynin B (**5**) from extracts of the plant species *Tacca chantrieri* and *Tacca integrifolia* (Fig. 1).[12] Some of these compounds were found to have interesting antiproliferative activities against various cancer cell lines, in addition to microtubule depolymerizing activities. In 2011, Lin et al. reported the

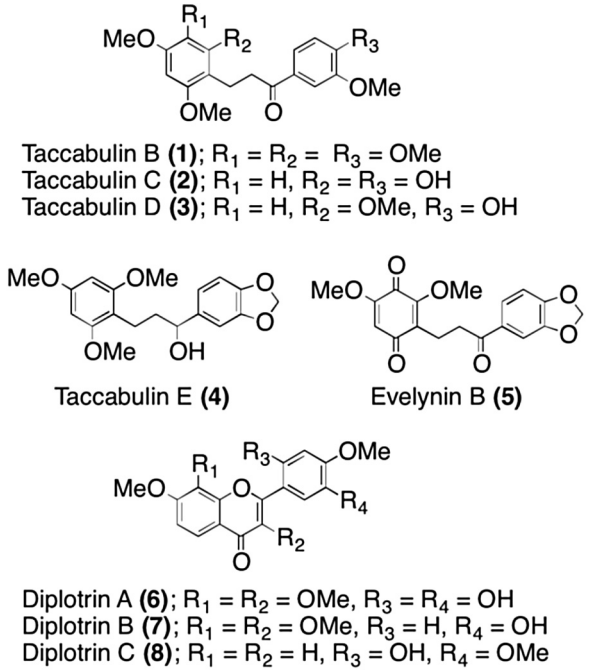

Fig. 1. Naturally occurring dihydrochalcones and 5-deoxyflavones isolated from *Tacca* species and *Mimosa diplotricha*.

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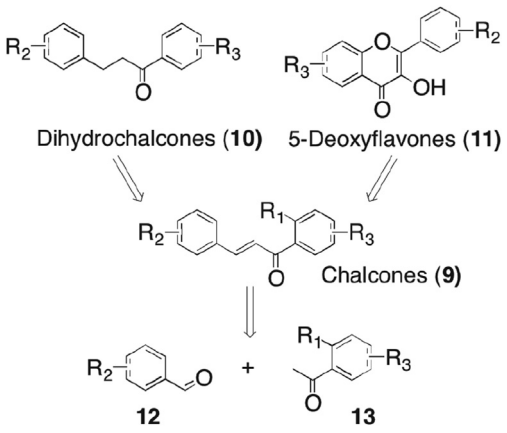
isolation of four previously unreported 5-deoxyflavanoes from *Mimosa diplotricha*, three of which were named diplotrins A–C (**6**–**8**).[13] The cytotoxic effects of these compounds were evaluated against several human cancer cell lines, with diplotrin B (**7**) found to have the most potent antiproliferative activity.

Given the wide variety of biological activities typically associated with dihydrochalcones and 5-deoxyflavones, we were interested in a more extensive biological evaluation of compounds **1**–**8**. Furthermore, we have an on-going interest in exploring novel chemical space, including that around such biologically privileged structures.[14] Thus, we sought to develop a concise strategy that would provide efficient access to all of these natural compounds and which could potentially be adapted for later library production. Herein, we report the development of a divergent synthetic strategy for the expedient synthesis of dihydrochalcones **1**–**5** and 5-deoxyflavones **6**–**8**.[15] These are the first reported total syntheses of these biologically interesting compounds.

2. Results and discussion

Inspired by previous work by Zhang et al. on the synthesis of chalcones and 5-deoxyflavones, a divergent synthetic strategy towards compounds **1**–**8** based on the use of a chalcone scaffold (of the general form **9**) as the pivotal branching point was proposed (Scheme 1).[9] It was envisaged that hydrogenation of compounds **9** would yield dihydrochalcones **10**, whereas Algar–Flynn–Oyamada oxidation would furnish the 5-deoxyflavone framework **11**.[9] It was presumed that chalcones **9** could be easily accessed via a Claisen–Schmidt aldol condensation between benzaldehydes **12** and acetophenones **13**.[9]



Scheme 1. Retrosynthetic analysis of the dihydrochalcones **10** and 5-deoxyflavones **11**.

The total synthesis of taccabulins B–D (**1**–**3**) was achieved by the application of this divergent synthetic strategy (Scheme 2).

The benzaldehyde precursors **18** and **19** were prepared expediently from commercially available starting materials by methylation and Vilsmeir–Haack formylation.[16,17] Benzaldehyde **21** was obtained from **19** through use of a demethylation and MOM protection sequence.[18] In parallel, the common acetophenone building block **23** was prepared in good yield from the Eaton's reagent induced Fries rearrangement of 2-methoxyphenylacetate (**22**).[19] Benzaldehydes **18**, **21** and **19** were conveniently paired with **23** via a Claisen–Schmidt aldol condensation to yield **24**–**26**, respectively, in up to 71% yield.[9] Following methylation of **24** with dimethyl sulfate to give **27**, the key chalcone intermediates **25**–**27** were reduced with hydrogen and platinum(IV) oxide[20] to yield taccabulin B (**1**), taccabulin D (**3**) and **28**, which was subsequently converted to taccabulin C (**2**) by a HCl mediated MOM deprotection.

The total synthesis of taccabulin E (**4**) was accomplished in a similarly efficient manner (Scheme 3). Friedel–Crafts acylation and methylenation of catechol (**29**) allowed access to intermediate **31** in good yield.[21,22] Claisen–Schmidt aldol coupling with the previously prepared benzaldehyde **19** (Scheme 2) allowed access to chalcone **32** is satisfactory yield. Hydrogenation and sodium borohydride mediated ketone reduction lead smoothly to taccabulin E (**4**) in 83% yield over two steps.

The synthesis of evelynin B (**5**) relied upon Ilangovan's recently published quinone C–H activation methodology.[23] This radical-based strategy was utilized in place of the late-stage Claisen–Schmidt aldol coupling procedure (Scheme 4). The synthesis began with 3,4-dihydroxybenzoic acid (**34**) and which was swiftly converted into **36** following esterification and methylenation with diiodomethane.[24] The cyclopropanol precursor **37** was obtained in satisfactory yield upon treatment of **36** with EtMgBr and $MeTi(O^iPr)_3$.[25] Radical coupling of **37** and benzoquinone **39**, derived from the oxidation of **38** with [bis(trifluoroacetoxy)iodo]benzene,[26] proceeded to give evelynin B (**5**) in 27% yield.[23]

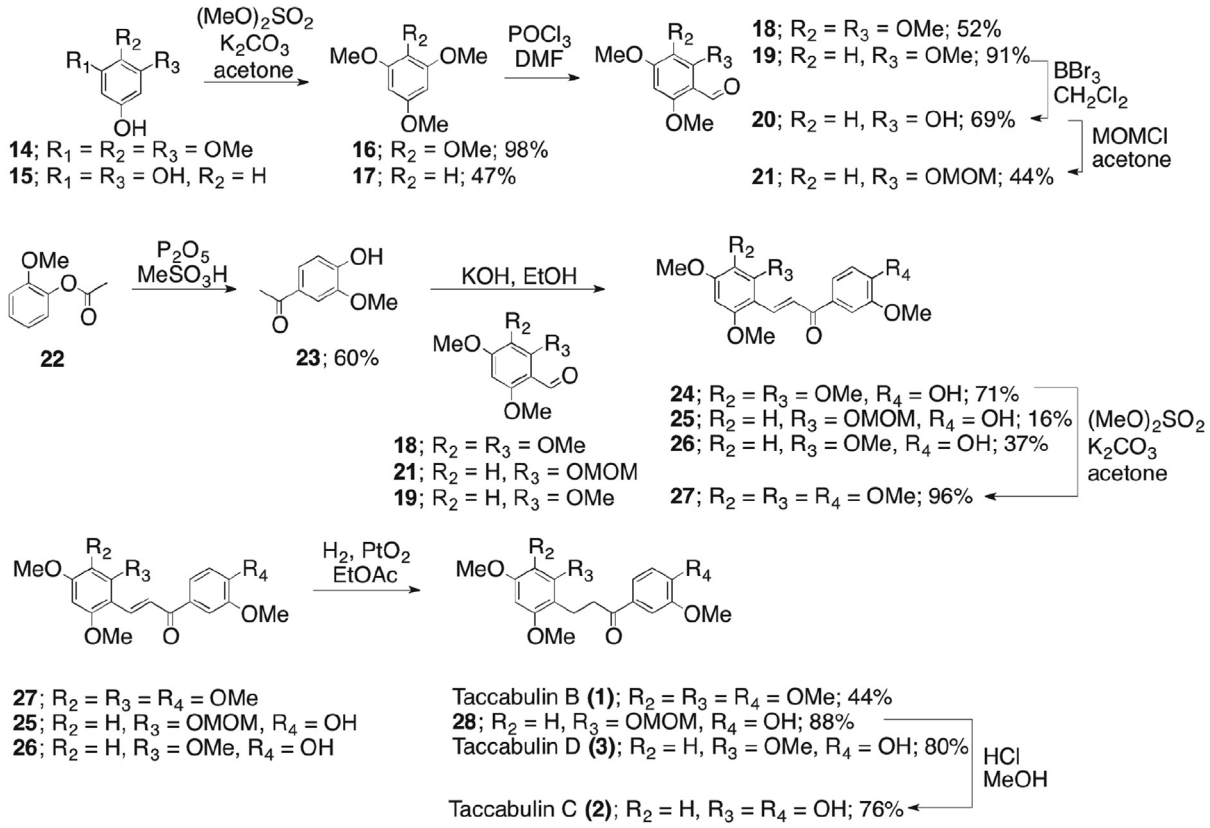
With the five newly synthesized dihydrochalcones (**1**–**5**) in hand, attention was turned towards the preparation of the 5-deoxyflavones (**6**–**8**). A similar divergent synthetic strategy was to be employed with the key difference being the late-stage Algar–Flynn–Oyamada oxidation, which would afford the core flavone framework (Scheme 5).

The presence of hydroxyl functionality in the target diplotrins necessitated the use of a protecting group strategy. Benzyl ethers were chosen to protect the hydroxyl groups because their removal is straightforward typically yielding analytically pure products without the need for column chromatography. The synthesis commenced with the acylation and selective methylation of pyrogallin (**40**) and resorcinol (**41**) to yield **44** and **45**, respectively (Scheme 5).[27–30] Alongside, two of the three required aldehyde building blocks for the Claisen–Schmidt aldol condensation needed synthesis. Benzaldehyde **48** was obtained from the formylation of **46** with trimethyl orthoformate and $AlCl_3$.[29] Benzaldehyde **47** underwent selective demethylation with BBr_3 in good yield to afford **50**.[31] With the necessary aldehydes in hand, the free hydroxyl functionality in **48**, isovanillin (**49**) and **50** were protected as benzyl ethers by reaction with benzyl bromide in the presence of K_2CO_3.[32–34] Union of fragments **51** and **52** with **44** and **53** with **45** by aldol coupling afforded the Algar–Flynn–Oyamada cyclization precursors **54**, **55** and **56** in generally acceptable yields.

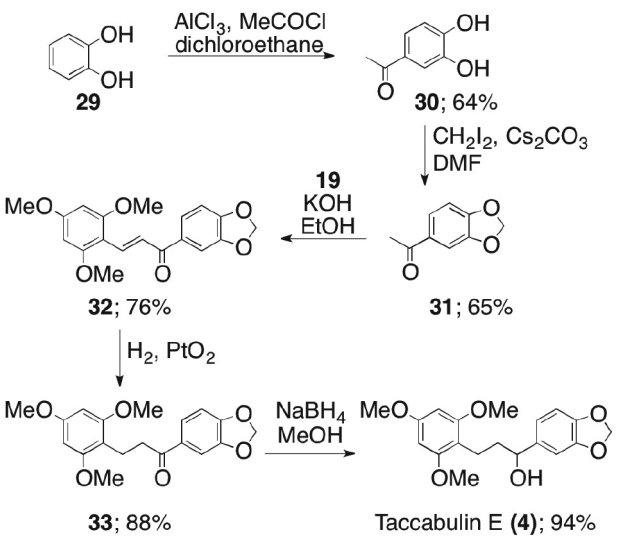
Diplotrins A (**6**) and B (**7**) were rapidly obtained from **54** and **55**, respectively, by Algar–Flynn–Oyamada oxidation,[9] methylation and benzyl deprotection[9] (Scheme 6). Simultaneously, **56** was cyclized into the flavone scaffold by treatment with iodine in DMSO and deprotected to afford diplotrin C (B).[35]

3. Conclusions

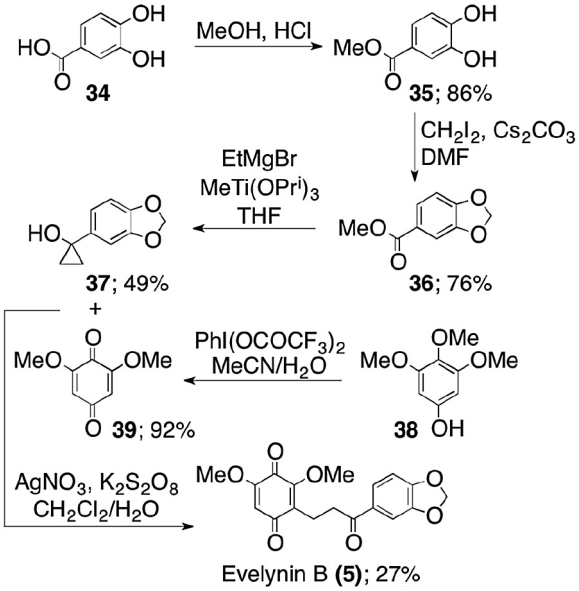
In summary, the first total synthesis of taccabulins B–E (**1**–**4**), evelynin B (**5**) and diplotrins A–C (**6**–**8**) was accomplished from commercially available starting materials. A concise divergent strategy was employed whereby a common chalcone scaffold was prepared by a Claisen–Schmidt aldol condensation and transformed into either the dihydrochalcones or the 5-deoxyflavones by hydrogenation or Algar–Flynn–Oyamada oxidation, respectively. Evelynin B (**5**) was also synthesized in an expedient manner from commercially available starting materials. The Evelynin B (**5**) framework was constructed through use of Ilangovan's benzoquinone C–H activation methodology.[23] All the final natural products were generated on milligram (typically multimilligram) scale, which should provide sufficient material for screening in a large number of biological assays. The results from these studies should yield further valuable information on the biological capabilities of



Scheme 2. Synthesis of taccabulin B (**1**), C (**2**) and D (**3**).



Scheme 3. Synthesis of taccabulin E (**4**).



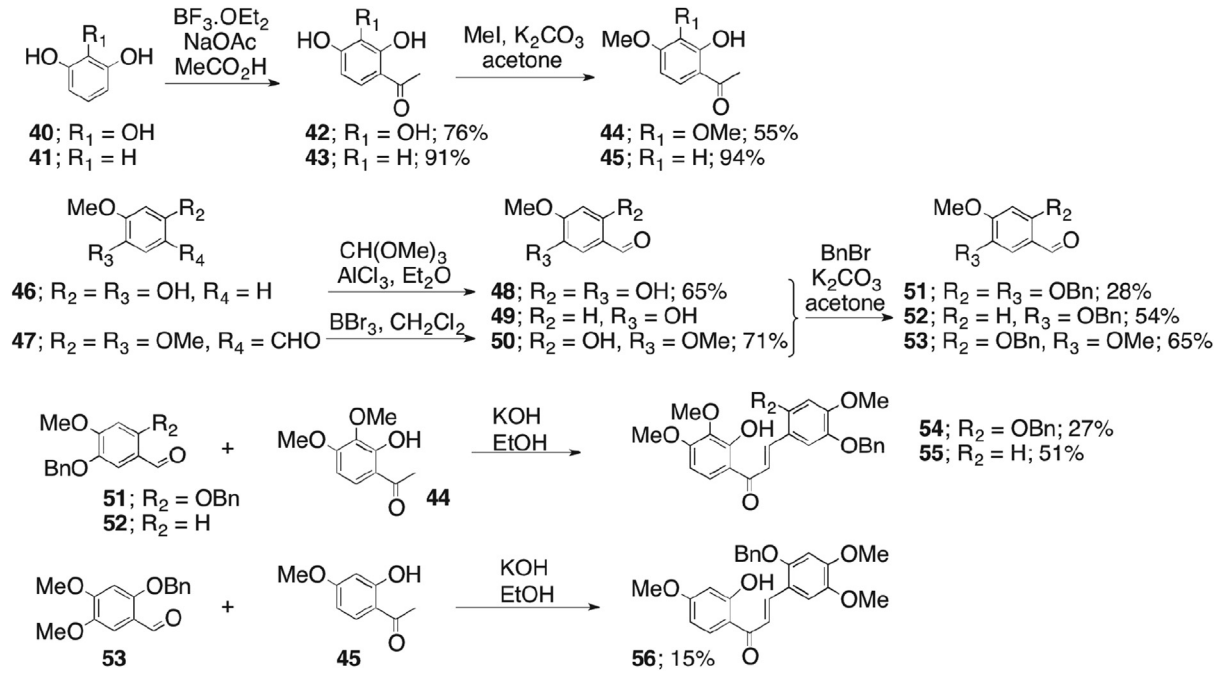
Scheme 4. Synthesis of evelynin B (**5**).

these natural products. The work reported herein provides an illustration of the utility of divergent synthesis for the expedient and step-economical preparation of natural product libraries. The concise and flexible nature of our divergent route should make it readily amenable to analogue preparation. The synthesis of structurally related unnatural chalcones and 5-deoxyflavones is currently underway. The results from these investigations, along with the outcomes of biological screening efforts, will be reported in due course.

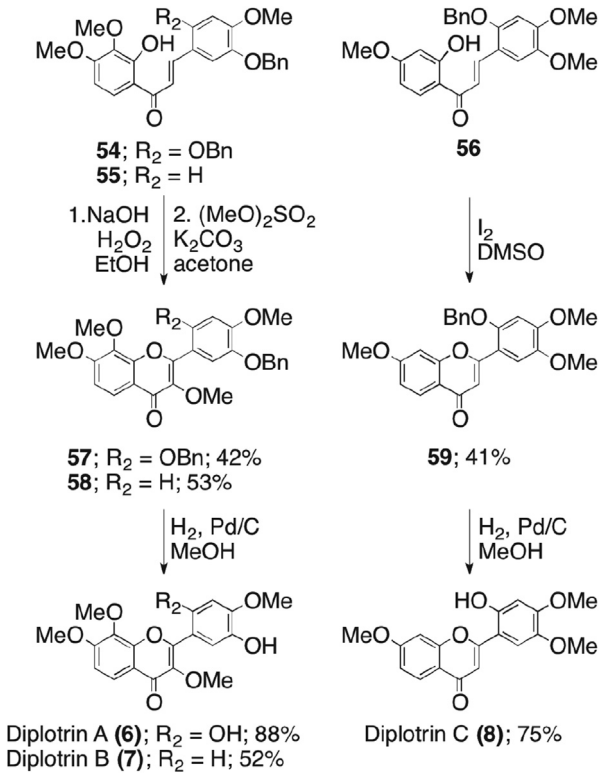
4. Experimental section

4.1. General information

All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise stated. All the experiments were carried out under a nitrogen



Scheme 5. Synthesis of the 5-deoxyflavone cyclization precursors.



Scheme 6. Synthesis of diplotrin A (**6**), B (**7**) and C (**8**).

atmosphere unless otherwise stated. Melting points were measured using a Büchi B545 melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on precoated Merck silica gel GF_{254} plates. IR spectra were recorded on a Perkin–Elmer Spectrum One (FT-IR) spectrophotometer. Flash column chromatography was performed on silica gel (230–400 mesh). ^1H NMR and ^{13}C NMR were recorded on a Bruker Avance 500 MHz instrument in $CDCl_3$, $(CD_3)_2CO$ and DMSO-d_6. HRMS was recorded on a Micromass Q-TOF mass spectrometer or a Waters LCT Premier Time of Flight mass spectrometer.

4.2. General procedures

4.2.1. General procedure A: synthesis of chalcones (GP-A). To a stirred solution of KOH (12.0 equiv) in absolute EtOH (50 mL) cooled to 0 °C in an ice-bath was added dropwise a solution of the corresponding acetophenone (1.0 equiv) and aldehyde (1.0 equiv) in EtOH (20 mL). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 72 h under nitrogen. The resulting mixture was then poured into ice-water (100 mL) and acidified to pH 3–4 with 3 M HCl. The aqueous solution was extracted with $CHCl_3$ (3×100 mL) and the combined organic layer was washed with satd $NaHCO_3$ (2×100 mL), brine (2×100 mL), dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography over silica and recrystallized from absolute EtOH to afford the corresponding chalcones.

4.2.2. General procedure B: synthesis of dihydrochalcones (GP-B). To a stirred solution of the corresponding chalcone in MeOH (10 mL) was added platinum(IV) oxide (2 mol %) and the reaction mixture was stirred vigorously at room temperature under a hydrogen atmosphere until TLC analysis indicated complete consumption of starting material. The resulting mixture was filtered through a pad of Celite and washed with additional MeOH (2×10 mL). The combined organic filtrate was concentrated in vacuo and the crude residue was purified by flash column chromatography over silica to afford the corresponding dihydrochalcones.

4.2.3. General procedure C: synthesis of flavonols (GP-C). To a stirred solution of the corresponding chalcone (0.3 mmol) in MeOH (5 mL) were added 16% NaOH (aq) (0.6 mL) and 15% H_2O_2 (0.3 mL). The reaction mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. The resulting mixture was then poured into

ice-water (50 mL) and acidified to pH 3–4 with 3 M HCl. The aqueous solution was extracted with $CHCl_3$ (3×50 mL) and the combined organic layer was washed with satd $NaHCO_3$ (2×50 mL), brine (2×50 mL), dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography over silica to afford the corresponding flavonols.

4.2.4. General procedure D: synthesis of hydroxyflavones (GP-D). To a stirred solution of the corresponding flavone (1.0 equiv) in MeOH (10 mL) was added 10% palladium/carbon (Pd/C) and the reaction mixture was stirred vigorously at room temperature under a hydrogen atmosphere until TLC analysis indicated complete consumption of starting material. The resulting mixture was filtered through a pad of Celite and washed with additional MeOH (2×10 mL). The combined organic filtrate was concentrated in vacuo and the crude residue was purified by flash column chromatography over silica to afford the corresponding hydroxyflavones.

4.3. Experimental details and characterization data

*4.3.1. Synthesis of 1-(3,4-dimethoxyphenyl)-3-(2,3,4,6-tetramethoxyphenyl)propan-1-one—taccabulin B (**1**).* A mixture of chalcone **27** (115 mg, 0.296 mmol) and platinum(IV) oxide (2.60 mg, 0.0114 mmol) in MeOH (5 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, PE/EtOAc; 1:1) to afford **1** (50.7 mg, 44%) as a white powdery solid. Mp 88–90 °C. TLC R_f=0.39 (PE/EtOAc; 1:1). IR ν_{max} (neat)/cm^{-1}: 2953m (C–H str), 2838w (C–H str), 1738m (C=O str), 1657m, 1596s (C=C str), 1583s (C=C str), 1514s (C=C str), 1496m, 1452s, 1437m, 1407s, 1329m, 1300m, 1278m, 1261s, 1227s, 1214s, 1142m, 1128m, 1102s, 1065w, 1043m, 1021s. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.99 (2H, t, J 9.5 Hz, $-CH_2CH_2CO-$), 3.11 (2H, t, J 6.0 Hz, $-CH_2CH_2CO-$), 3.79 (3H, s, $-OCH_3$), 3.83 (3H, s, $-OCH_3$), 3.88 (3H, s, $-OCH_3$), 3.89 (3H, s, $-OCH_3$), 3.94 (3H, s, $-OCH_3$), 3.95 (3H, s, $-OCH_3$), 6.30 (1H, s, ArH), 6.88 (1H, d, J 8.5 Hz, ArH), 7.57 (1H, d, J 2.0 Hz, ArH), 7.64 (1H, dd, J 8.5, 2.0 Hz, ArH). ^{13}C NMR (500 MHz, $CDCl_3$): δ 19.2, 38.7, 55.8, 56.0, 56.0, 56.2, 60.9, 61.2, 92.5, 109.9, 110.3, 115.3, 122.8, 130.2, 136.4, 148.9, 151.9, 152.5, 153.0, 153.8, 199.1. HRMS (ESI^+) m/z=391.1735 $[M+H]^+$ found, $C_{21}H_{27}O_7^+$ required 391.1751.

*4.3.2. Synthesis of 1-(4-hydroxy-3-methoxyphenyl)-3-(2-hydroxy-4,6-dimethoxyphenyl)propan-1-one—taccabulin C (**2**).* To a stirred solution of chalcone **28** (69.0 mg, 0.183 mmol) in MeOH (5 mL) was added 3 M HCl (1 mL) dropwise over 10 min and the resulting mixture was heated at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. The crude residue was resuspended in EtOAc (30 mL), washed with H_2O (3×20 mL), brine (2×20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc; 1:1) to afford **2** (46.5 mg, 76%) as a pale white powdery solid. Mp 160–162 °C. TLC R_f=0.39 (PE/EtOAc; 1:1). IR ν_{max} (neat)/cm^{-1}: 3108w(br) (O–H str), 2999w (C–H str), 2935w (C–H str), 2839w (C–H str), 1737m (C=O str), 1651m, 1618m, 1580s (C=C str), 1522m (C=C str), 1501w (C=C str), 1453m, 1374m, 1297m, 1281s, 1218s, 1198s, 1188s, 1166s, 1144s, 1116w, 1096s, 1057m, 1026m. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.74 (2H, t, J 9.2 Hz, $-CH_2CH_2CO-$), 2.92 (2H, t, J 6.8 Hz, $-CH_2CH_2CO-$), 3.68 (3H, s, $-OCH_3$), 3.70 (3H, s, $-OCH_3$), 3.82 (3H, s, $-OCH_3$), 6.04 (1H, d, J 2.4 Hz, ArH), 6.06 (1H, d, J 2.4 Hz, ArH), 6.85 (1H, d, J 8.4 Hz, ArH), 7.46 (1H, d, J 2.0 Hz, ArH), 7.51 (1H, dd, J 8.4, 2.0 Hz, ArH), 9.37 (1H, s, OH), 9.94 (1H, s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): δ 18.6, 37.9, 54.9, 55.4, 55.5, 89.7, 93.6, 107.4, 111.2, 114.9, 122.8, 128.4, 147.4, 151.5, 156.2, 158.7, 158.8, 198.4. HRMS (ESI^-) m/z=331.1196 $[M-H]^+$ found, $C_{18}H_{19}O_6^+$ required 331.1187.

*4.3.3. Synthesis of 1-(4-hydroxy-3-methoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propan-1-one—taccabulin D (**3**).* A mixture of chalcone **26** (300 mg, 0.871 mmol) and platinum(IV) oxide (11.5 mg, 0.0506 mmol) in MeOH (10 mL) was reacted according to GP-B. The crude solid was purified by flash column chromatography (SiO_2, PE/EtOAc; 1:1) to afford **3** (241 mg, 80%) as a white powdery solid. Mp 126–128 °C. TLC R_f=0.41 (PE/EtOAc; 1:1). IR ν_{max} (neat)/cm^{-1}: 3470m(br) (O–H str), 2942m (C–H str), 2841w (C–H str), 1740 m (C=O str), 1669s, 1593s (C=C str), 1515s (C=C str), 1500m (C=C str), 1459s, 1420s, 1375w, 1295s, 1269s, 1241m, 1218s, 1200s, 1189s, 1145s, 1130m, 1109s, 1055m, 1038m, 1027m. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.76 (2H, t, J 9.0 Hz, $-CH_2CH_2CO-$), 2.91 (2H, t, J 7.0 Hz, $-CH_2CH_2CO-$), 3.74 (6H, s, $-OCH_3$), 3.76 (3H, s, $-OCH_3$), 3.81 (3H, s, $-OCH_3$), 6.21 (2H, s, ArH), 6.85 (1H, d, J 8.5 Hz, ArH), 7.42 (1H, d, J 2.0 Hz, ArH), 7.49 (1H, dd, J 8.5, 2.0 Hz, ArH), 9.93 (1H, br s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): δ 18.4, 37.8, 55.2, 55.5, 55.6, 90.8, 108.6, 111.1, 114.9, 122.8, 128.4, 147.5, 151.5, 158.3, 159.3, 198.1. HRMS (ESI^+) m/z=369.1305 $[M+Na]^+$ found, $C_{19}H_{22}O_6Na^+$ required 369.1309.

*4.3.4. Synthesis of 1-(4,5-dimethylenedioxyphenyl)-3-(2,4,6-trimethoxyphenyl)propan-1-ol—taccabulin E (**4**).* To a stirred solution of chalcone **33** (200 mg, 0.581 mmol) in dry MeOH (10 mL) while cooling to 0 °C in an ice-bath was added $NaBH_4$ (58.0 mg, 1.54 mmol) portionwise over 15 min under nitrogen. The reaction mixture was first stirred at 0 °C for 1 h and then at room temperature for 8 h. Water (20 mL) was added to the resulting suspension and the mixture was partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3×20 mL). The combined organic extracts were washed with H_2O (2×50 mL), brine (2×50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, PE/EtOAc; 1:1) to afford **4** (190 mg, 94%) as a white powdery solid. Mp 108–110 °C. TLC R_f=0.32 (PE/EtOAc; 2:1). IR ν_{max} (neat)/cm^{-1}: 3439w(br) (O–H str), 2971w (C–H str), 2841w (C–H str), 1739m (C=O str), 1596s (C=C str), 1499s (C=C str), 1488s, 1457s, 1438s, 1415m, 1375w, 1321w, 1230s, 1208s, 1148s, 1128s, 1111s, 1055w, 1034s, 1011m. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.85–1.90 (2H, m, $-CH_2CH_2CH-$), 2.75 (2H, t, J 7.0 Hz, $-CH_2CH_2CH-$), 3.06 (1H, br s, OH), 3.83 (9H, s, $-OCH_3$), 4.40–4.43 (1H, m, $-CH_2CH_2CH-$), 5.93 (2H, s, $-OCH_2O-$), 6.17 (2H, s, ArH), 6.74–6.79 (2H, d, J 8.0 Hz, ArH), 6.78 (1H, dd, J 8.0, 1.5 Hz, ArH), 6.83 (1H, d, J 1.5 Hz, ArH). ^{13}C NMR (500 MHz, $CDCl_3$): δ 18.7, 38.7, 55.3, 55.7, 72.6, 90.6, 100.8, 106.5, 107.8, 109.8, 119.1, 138.8, 146.4, 147.5, 158.7, 159.4. HRMS (ESI^-) m/z=345.1320 $[M-H]^+$ found, $C_{19}H_{21}O_6^+$ required 345.1333.

*4.3.5. Synthesis of 1-(4,5-dimethylenedioxyphenyl)-2(-3,5-dimethoxycyclohexa-2,5-diene-1,4-dione) propan-1-one—evelynin B (**5**).* To a mixture of methylene cyclopropanol **37** (172 mg, 0.964 mmol), 2,6-dimethoxy-*p*-benzoquinone **39** (149 mg, 0.886 mmol) and silver nitrate (30.6 mg, 0.180 mmol) in CH_2Cl_2/H_2O (10 mL; 1:1 mixture) was added potassium persulfate ($K_2S_2O_8$) (715 mg, 2.65 mmol) at room temperature with stirring under nitrogen. The resulting biphasic reaction mixture was stirred for a further 3 h at room temperature until TLC analysis indicated completion of the reaction. The organic layer was separated, washed with H_2O (2×50 mL), brine (2×50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, PE/EtOAc; 1:1) to afford **5** (82.6 mg, 27%) as a bright yellow powdery solid. Mp 78–80 °C. TLC R_f=0.44 (PE/

EtOAc; 1:1). IR ν_{max} (neat)/cm^{-1}: 3077w (C–H str), 2942w (C–H str), 1674s (C=O str), 1643s (C=O str), 1627m, 1598s (C=C str), 1502m (C=C str), 1489m, 1443s, 1362m, 1295w, 1272w, 1240s, 1181m, 1111m, 1086s, 1036s, 1017m. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.63 (2H, t, J 8.4 Hz, –CH_2CH$_2$CO–), 3.00 (2H, t, J 7.2 Hz, –CH$_2$CH_2CO–), 3.77 (3H, s, –OCH$_3$), 3.87 (3H, s, –OCH$_3$), 6.04 (1H, s, ArH), 6.13 (2H, s, –OCH_2O–), 7.03 (1H, d, J 8.4 Hz, ArH), 7.41 (1H, d, J 1.6 Hz, ArH), 7.58 (1H, dd, J 8.4, 2.0 Hz, ArH). ^{13}C NMR (500 MHz, DMSO-d_6): δ 18.4, 36.9, 56.6, 60.7, 102.0, 106.8, 107.3, 108.1, 124.4, 130.9, 147.8, 151.5, 154.5, 157.6, 177.4, 187.0, 196.7. HRMS (ESI$^+$) m/z=345.0957 [M+H]$^+$ found, $C_{18}H_{17}O_7^+$ required 345.0969.

*4.3.6. Synthesis of 1-(2-hydroxy-3,4-dimethoxyphenyl)-3-(2,5-dibenzyloxy-4-methoxyphenyl)propenone (**54**).* A mixture of 2-hydroxy-3,4-dimethoxyacetophenone **44** (1.35 g, 6.88 mmol), 2,5-dibenzyloxy-4-methoxybenzaldehyde **51** (2.35 g, 6.75 mmol) and KOH (5.03 g, 89.6 mmol) in absolute EtOH (50 mL) was reacted according to GP-A. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc; 5:1) and recrystallized from absolute EtOH to afford **54** (968 mg, 27%) as a bright yellow-orange powdery solid. Mp 178–180 °C. TLC R_f=0.22 (PE/EtOAc; 2:1). IR ν_{max} (neat)/cm^{-1}: 3004w(br) (O–H str), 2937w (C–H str), 2843w (C–H str), 1745w, 1628m (C=O str), 1606w (C=C str), 1552s (C=C str), 1501m (C=C str), 1444s, 1343m, 1265s, 1224s, 1199w, 1129s, 1078s, 1005s. ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.91 (3H, s, –OCH$_3$), 3.92 (3H, s, –OCH$_3$), 3.95 (3H, s, –OCH$_3$), 5.14 (2H, s, –OCH_2Ph), 5.16 (2H, s, –OCH_2Ph), 6.35 (1H, d, J 9.2 Hz, ArH), 6.61 (1H, s, ArH), 7.11 (1H, s, ArH), 7.23 (1H, d, J 9.2 Hz, ArH), 7.32–7.36 (1H, m, ArH), 7.38–7.48 (7H, m, ArH), 7.52 (2H, d, J 7.2 Hz, ArH), 7.58 (1H, d, J 15.2 Hz, –CH=CHCO–), 7.99 (1H, d, J 15.6 Hz, –CH=CHCO–). ^{13}C NMR (500 MHz, CDCl$_3$): δ 56.0, 56.1, 60.6, 71.5, 72.2, 98.4, 102.5, 115.8, 117.5, 119.2, 125.9, 127.5, 128.0, 128.3, 128.6, 128.8, 136.3, 136.6, 137.0, 140.6, 142.3, 153.2, 154.6, 158.1, 158.2, 193.0. HRMS (ESI$^+$) m/z=527.2055 [M+H]$^+$ found, $C_{32}H_{31}O_7^+$ required 527.2064.

*4.3.7. Synthesis of 2′,5′-dibenzyloxy-3,7,8,4′-tetramethoxyflavone (**57**).* A mixture of chalcone **54** (300 mg, 0.570 mmol), 16% NaOH (aq) (1.14 mL) and 15% H_2O_2 (0.570 mL) in MeOH (10 mL) was reacted according to GP-C. The crude product was purified by flash column chromatography (SiO_2, 1% MeOH/CH$_2$Cl$_2$) to afford 2-(2,5-bis(benzyloxy)-4-methoxyphenyl)-3-hydroxy-7,8-dimethoxy-4*H*-chromen-4-one (149 mg, 48%) as a pale yellow powdery solid. To a solution of 2-(2,5-bis(benzyloxy)-4-methoxyphenyl)-3-hydroxy-7,8-dimethoxy-4*H*-chromen-4-one (220 mg, 0.407 mmol) in dry acetone (10 mL) were added anhydrous K_2CO_3 (169 mg, 1.22 mmol) and dimethyl sulfate (0.116 mL, 1.22 mmol). The reaction mixture was heated at reflux with stirring for 3 h under a nitrogen atmosphere. The resulting mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. The crude residue was taken up in EtOAc (30 mL) and the organic layer washed with H_2O (2×20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by flash column chromatography (SiO_2, 1% MeOH/CH$_2$Cl$_2$) to afford **57** (198 mg, 88%) as a yellow oil, which solidified on standing to give a bright yellow crystalline solid. Mp 58–60 °C. TLC R_f=0.48 (1% MeOH/CH$_2$Cl$_2$). IR ν_{max} (neat)/cm^{-1}: 2937w (C–H str), 2840w (C–H str), 1600s (C=O str), 1508s (C=C str), 1442s, 1416w, 1377m, 1285s, 1269s, 1220s, 1196s, 1168s, 1122m, 1084s, 1062w, 1009s. ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.66 (3H, s, –OCH$_3$), 3.81 (3H, s, –OCH$_3$), 3.88 (3H, s, –OCH$_3$), 3.98 (3H, s, –OCH$_3$), 5.13 (2H, s, –OCH_2Ph), 5.13 (2H, s, –OCH_2Ph), 6.65 (1H, s, ArH), 7.03 (1H, d, J 9.0 Hz, ArH), 7.07 (1H, s, ArH), 7.23–7.31 (4H, m, ArH), 7.34–7.37 (4H, m, ArH), 7.43 (2H, d, J 7.5 Hz, ArH), 8.00 (1H, d, J 9.0 Hz, ArH). ^{13}C NMR (500 MHz, CDCl$_3$): δ 56.0, 56.5, 60.4, 61.5, 71.8, 99.9, 109.7, 112.0, 117.1, 119.5, 120.9, 127.2, 127.4, 127.9, 127.9, 128.5, 128.5, 136.7, 136.8, 137.0, 141.2, 142.0, 150.0, 152.0, 152.4, 155.8, 156.0, 174.6. HRMS (ESI$^+$) m/z=555.1995 [M+H]$^+$ found, $C_{33}H_{31}O_8^+$ required 555.2013.

*4.3.8. Synthesis of 2′,5′-dihydroxy-3,7,8,4′-tetramethoxyflavone—diplotrin A (**6**).* A mixture of flavone **57** (140 mg, 0.252 mmol) and 10% Pd/C (34.7 mg) in MeOH (10 mL) was reacted according to GP-D. The crude product was purified by flash column chromatography (SiO_2, 1% MeOH/CH$_2$Cl$_2$) to afford **6** (83.5 mg, 88%) as a pale yellow powdery solid. Mp 110–112 °C (lit. mp[17] 113 °C). TLC R_f=0.18 (1% MeOH/CH$_2$Cl$_2$). IR ν_{max} (neat)/cm^{-1}: 3507w(br) (O–H str), 3138w(br) (O–H str), 2944w (C–H str), 2846w (C–H str), 1739w, 1607s (C=O str), 1594s (C=C str), 1562m (C=C str), 1511s (C=C str), 1449s, 1428m, 1375m, 1345m, 1286s, 1271w, 1248m, 1198s, 1164s, 1125s, 1085s, 1066m, 1030m, 1001s. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.70 (3H, s, –OCH$_3$), 3.79 (3H, s, –OCH$_3$), 3.83 (3H, s, –OCH$_3$), 3.94 (3H, s, –OCH$_3$), 6.56 (1H, s, ArH), 6.82 (1H, s, ArH), 7.26 (1H, d, J 9.2 Hz, ArH), 7.81 (1H, d, J 8.8 Hz, ArH), 8.61 (1H, s, OH), 9.25 (1H, s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): δ 55.5, 56.5, 59.7, 61.0, 101.0, 108.8, 110.6, 116.1, 118.7, 120.2, 136.2, 138.8, 140.2, 149.0, 149.4, 150.5, 155.9, 156.1, 173.3. HRMS (ESI$^+$) m/z=375.1062 [M+H]$^+$ found, $C_{19}H_{19}O_8^+$ required 375.1074.

*4.3.9. Synthesis of 1-(2-hydroxy-3,4-dimethoxyphenyl)-3-(3-benzyloxy-4-methoxyphenyl)propenone (**55**).* A mixture of 2-hydroxy-3,4-dimethoxyacetophenone **44** (1.00 g, 5.10 mmol), 3-(benzyloxy)-4-methoxybenzaldehyde **52** (1.25 g, 5.16 mmol) and KOH (3.68 g, 65.6 mmol) in absolute EtOH (50 mL) was reacted according to GP-A. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc; 5:1) and recrystallized from absolute EtOH to afford **55** (1.10 g, 51%) as a bright yellow fluffy solid. Mp 148–150 °C. TLC R_f=0.45 (PE/EtOAc; 1:1). IR ν_{max} (neat)/cm^{-1}: 3006w(br) (O–H str), 2948w (C–H str), 2841w (C–H str), 1737w, 1635m (C=O str), 1596w (C=C str), 1561m (C=C str), 1504s (C=C str), 1455w, 1438w, 1427m, 1370m, 1352w, 1306m, 1293w, 1257s, 1220m, 1163w, 1129s, 1076s, 1021w, 1005s. ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.93 (3H, s, –OCH$_3$), 3.96 (3H, s, –OCH$_3$), 3.97 (3H, s, –OCH$_3$), 5.23 (2H, s, –OCH_2Ph), 6.55 (1H, d, J 8.8 Hz, ArH), 6.94 (1H, d, J 8.4 Hz, ArH), 7.20 (1H, d, J 2.0 Hz, ArH), 7.26–7.28 (1H, m, ArH), 7.33–7.37 (2H, m, ArH), 7.42 (2H, t, J 7.6 Hz, ArH), 7.50 (2H, d, J 6.8 Hz, ArH), 7.65 (1H, d, J 8.8 Hz, –CH=CHCO–), 7.81 (1H, d, J 15.2 Hz, –CH=CHCO–). ^{13}C NMR (500 MHz, CDCl$_3$): δ 56.1, 56.1, 60.7, 71.3, 102.7, 111.6, 113.4, 115.6, 117.9, 123.7, 125.8, 127.4, 127.6, 128.1, 128.7, 136.7, 144.8, 148.4, 152.3, 158.3, 158.4, 192.3. HRMS (ESI$^+$) m/z=421.1652 [M+H]$^+$ found, $C_{25}H_{25}O_6^+$ required 421.1646.

*4.3.10. Synthesis of 3′-benzyloxy-3,7,8,4′-tetramethoxyflavone (**58**).* A mixture of chalcone **55** (812 mg, 1.93 mmol), 16% NaOH (aq) (3.86 mL) and 15% H_2O_2 (1.93 mL) in MeOH (10 mL) was reacted according to GP-C. The crude product was purified by flash column chromatography (SiO_2, 1% MeOH/CH$_2$Cl$_2$) to afford 2-(3-(benzyloxy)-4-methoxyphenyl)-3-hydroxy-7,8-dimethoxy-4*H*-chromen-4-one (448 mg, 53%) as a pale yellow-green powdery solid. To a solution of 2-(3-(benzyloxy)-4-methoxyphenyl)-3-hydroxy-7,8-dimethoxy-4*H*-chromen-4-one (302 mg, 0.694 mmol) in dry acetone (10 mL) were added anhydrous K_2CO_3 (288 mg, 2.08 mmol) and dimethyl sulfate (0.198 mL, 2.08 mmol). The reaction mixture was heated at reflux with stirring for 3 h under a nitrogen atmosphere. The resulting mixture was allowed to cool to room temperature, filtered under suction, washed with additional acetone (3×10 mL) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 1% MeOH/

CH_2Cl_2) to afford **58** (308 mg, 99%) as a pale yellow powdery solid. Mp 168–170 °C. TLC R_f=0.30 (1% MeOH/CH_2Cl_2). IR ν_{max} (neat)/cm^{-1}: 2982w (C–H str), 2939w (C–H str), 2842w (C–H str), 1741w, 1637s (C=O str), 1596s (C=C str), 1566m (C=C str), 1506s (C=C str), 1457s, 1435s, 1425m, 1381s, 1334m, 1287s, 1270m, 1259s, 1234w, 1206s, 1187w, 1167m, 1144s, 1083s, 1062s, 1041w, 1014s. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (3H, s, –OCH_3), 3.97 (3H, s, –OCH_3), 3.99 (3H, s, –OCH_3), 4.00 (3H, s, –OCH_3), 5.27 (2H, s, –O*CH*$_2$Ph), 7.03 (1H, d, *J* 9.5 Hz, ArH), 7.05 (1H, d, *J* 9.0 Hz, ArH), 7.31 (1H, t, *J* 7.5 Hz, ArH), 7.39 (2H, t, *J* 8.0 Hz, ArH), 7.49 (2H, t, *J* 8.0 Hz, ArH), 7.84 (1H, dd, *J* 8.5, 2.5 Hz, ArH), 7.87 (1H, d, *J* 2.0 Hz, ArH), 7.96 (1H, d, *J* 8.5 Hz, ArH). ^{13}C NMR (500 MHz, $CDCl_3$): δ 56.0, 56.4, 59.8, 61.5, 70.8, 109.7, 111.3, 113.8, 119.0, 121.0, 122.4, 123.5, 127.1, 127.9, 128.6, 136.6, 136.7, 140.4, 147.7, 149.4, 151.7, 154.8, 156.2, 174.6. HRMS (ESI$^+$) *m*/*z*=449.1584 $[M+H]^+$ found, $C_{26}H_{25}O_7^+$ required 449.1595.

*4.3.11. Synthesis of 3′-hydroxy-3,7,8,4′-tetramethoxyflavone—diplotrin B (**7**).* A mixture of flavone **58** (28.3 mg, 0.0631 mmol) and 10% Pd/C (20.0 mg) in MeOH (10 mL) was reacted according to GP-D. The crude product was purified by flash column chromatography (SiO_2, 1% MeOH/CH_2Cl_2) to afford **7** (11.8 mg, 52%) as a pale yellow powdery solid. Mp 160–162 °C (lit. mp[17] 159 °C). TLC R_f=0.16 (1% MeOH/CH_2Cl_2). IR ν_{max} (neat)/cm^{-1}: 3366w(br) (O–H str), 2920w (C–H str), 2850w (C–H str), 1593s (C=O str), 1554m (C=C str), 1512s (C=C str), 1456w, 1434s, 1388m, 1288s, 1208m, 1179w, 1132m, 1088s, 1064m, 1023s. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (3H, s, –OCH_3), 4.00 (3H, s, –OCH_3), 4.01 (3H, s, –OCH_3), 4.03 (3H, s, –OCH_3), 5.73 (1H, br s, OH), 7.00–7.06 (2H, m, ArH), 7.79–7.82 (2H, m, ArH), 7.99 (1H, d, *J* 9.2 Hz, ArH). ^{13}C NMR (500 MHz, $CDCl_3$): δ 56.0, 56.5, 60.0, 61.6, 110.1, 110.4, 114.6, 118.7, 121.1, 121.7, 124.1, 136.7, 140.5, 145.5, 148.7, 149.6, 155.6, 156.5, 175.2. HRMS (ESI$^+$) *m*/*z*=359.1117 $[M+H]^+$ found, $C_{19}H_{19}O_7^+$ required 359.1125.

*4.3.12. Synthesis of 1-(2-hydroxy-4-methoxyphenyl)-3-(2-benzyloxy-4,5-dimethoxyphenyl)propenone (**56**).* A mixture of 2-hydroxy-4-methoxyacetophenone **45** (2.07 g, 12.5 mmol), 2-benzyloxy-4,5-dimethoxybenzaldehyde **53** (3.30 g, 12.1 mmol) and KOH (8.83 g, 157 mmol) in absolute EtOH (50 mL) was reacted according to GP-A. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc; 5:1) and recrystallized from absolute EtOH to afford **56** (786 mg, 15%) as a bright yellow-orange fluffy solid. Mp 208–210 °C. TLC R_f=0.26 (PE/EtOAc; 2:1). IR ν_{max} (neat)/cm^{-1}: 3001w(br) (O–H str), 2943w (C–H str), 2905w (C–H str), 2827w (C–H str), 1611m (C=O str), 1578w (C=C str), 1553m (C=C str), 1526w (C=C str), 1505m (C=C str), 1465m, 1437m, 1402w, 1392w, 1350s, 1258m, 1232m, 1215m, 1201s, 1147s, 1121s, 1051w, 1021s. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (3H, s, –OCH_3), 3.91 (3H, s, –OCH_3), 3.93 (3H, s, –OCH_3), 5.16 (2H, s, –O*CH*$_2$Ph), 6.30 (1H, dd, *J* 9.0, 3.0 Hz, ArH), 6.44 (1H, d, *J* 2.5 Hz, ArH), 6.62 (1H, s, ArH), 7.07 (1H, s, ArH), 7.37 (1H, d, *J* 9.0 Hz, ArH), 7.41–7.48 (3H, m, ArH), 7.52 (1H, d, *J* 1.5 Hz, ArH), 7.54 (1H, d, *J* 1.5 Hz, ArH), 7.69 (1H, d, *J* 15.5 Hz, –*CH*=CHCO–), 8.02 (1H, d, *J* 15.5 Hz, –CH=*CH*CO–). ^{13}C NMR (500 MHz, $CDCl_3$): δ 55.5, 56.1, 56.5, 71.6, 98.2, 100.7, 107.5, 114.0, 114.3, 115.8, 119.5, 128.1, 128.4, 128.8, 131.1, 136.3, 140.6, 143.4, 152.1, 154.2, 165.7, 166.5, 192.5. HRMS (ESI$^+$) *m*/*z*=421.1652 $[M+H]^+$ found, $C_{25}H_{25}O_6^+$ required 421.1651.

*4.3.13. Synthesis of 2′-benzyloxy-7,4′,5′-trimethoxyflavone (**59**).* To a stirred solution of chalcone **56** (209 mg, 0.498 mmol) in DMSO (10 mL) was added a catalytic amount of iodine (12.6 mg, 0.0498 mmol). The reaction mixture was heated to 130 °C with stirring for 3 h under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and satd $NaHSO_3$ solution (20 mL) was added. The resulting mixture was extracted with $CHCl_3$ (3×50 mL) and the combined organic layers were washed with H_2O (2×50 mL), brine (2×50 mL), dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc; 2:1) to afford **59** (197 mg, 41%) as a pale yellow powdery solid. Mp 167–169 °C. TLC R_f=0.24 (PE/EtOAc; 1:1). IR ν_{max} (neat)/cm^{-1}: 2920w (C–H str), 2836w (C–H str), 1739w, 1635m (C=O str), 1613s (C=C str), 1578m (C=C str), 1563m (C=C str), 1522s (C=C str), 1434s, 1399w, 1387m, 1358s, 1264s, 1249s, 1219s, 1207s, 1197s, 1164s, 1150s, 1088m, 1035m. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (3H, s, –OCH_3), 3.92 (3H, s, –OCH_3), 3.94 (3H, s, –OCH_3), 5.22 (2H, s, –O*CH*$_2$Ph), 6.62 (1H, s, ArH), 6.89 (1H, d, *J* 2.5 Hz, ArH), 6.98 (1H, dd, *J* 9.0, 2.0 Hz, ArH), 7.10 (1H, s, CH), 7.30–7.33 (1H, m, ArH), 7.35–7.38 (3H, m, ArH), 7.42 (2H, d, *J* 7.0 Hz, ArH), 8.14 (1H, d, *J* 9.0 Hz, ArH). ^{13}C NMR (500 MHz, $CDCl_3$): δ 55.8, 56.0, 56.7, 71.9, 99.7, 100.2, 111.5, 111.9, 113.1, 114.2, 117.6, 127.0, 127.2, 128.2, 128.7, 136.3, 143.5, 152.2, 152.4, 158.1, 161.0, 164.0, 178.1. HRMS (ESI$^+$) *m*/*z*=419.1477 $[M+H]^+$ found, $C_{25}H_{23}O_6^+$ required 419.1489.

*4.3.14. Synthesis of 2′-hydroxy-7,4′,5′-trimethoxyflavone—diplotrin C (**8**).* A mixture of flavone **59** (101 mg, 0.242 mmol) and 10% Pd/C (20.7 mg) in MeOH (10 mL) was reacted according to GP-D. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc; 1:1) and recrystallized from MeOH to afford **8** (59.4 mg, 75%) as a pale yellow powdery solid. Mp 168–170 °C (lit. mp[17] 170 °C). TLC R_f=0.23 (PE/EtOAc; 1:3). IR ν_{max} (neat)/cm^{-1}: 3136w(br) (O–H str), 2961w (C–H str), 2920w (C–H str), 2851w (C–H str), 1737w, 1611s (C=O str), 1587m (C=C str), 1551s (C=C str), 1519m (C=C str), 1505m (C=C str), 1442m, 1401s, 1379s, 1251m, 1213m, 1198s, 1158s, 1103m, 1031s. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.80 (3H, s, –OCH_3), 3.81 (3H, s, –OCH_3), 3.92 (3H, s, –OCH_3), 6.65 (1H, s, ArH), 7.03 (1H, dd, *J* 8.8, 2.4 Hz, ArH), 7.08 (1H, s, ArH), 7.32 (1H, d, *J* 2.4 Hz, ArH), 7.47 (1H, s, ArH), 7.91 (1H, d, *J* 8.8 Hz, ArH), 10.48 (1H, br s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): δ 55.5, 56.1, 56.6, 100.9, 101.1, 108.2, 109.5, 111.3, 114.3, 116.9, 126.0, 142.1, 152.4, 152.5, 157.5, 160.2, 163.6, 176.5. HRMS (ESI$^+$) *m*/*z*=329.1006 $[M+H]^+$ found, $C_{18}H_{17}O_6^+$ required 329.1020.

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Supplementary data

Copies of the ^{1}H NMR and ^{13}C NMR spectra of the synthesized natural products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.02.017.

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