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PAPER

Tandem one-pot synthesis of flavans by recyclable silica–$HClO_4$ catalyzed Knoevenagel condensation and [4 + 2]-Diels–Alder cycloaddition†‡

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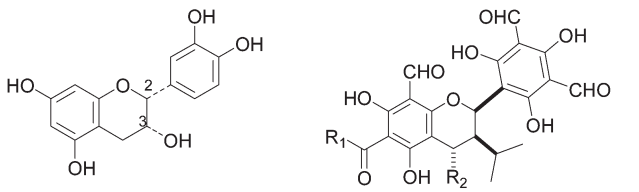
An efficient one-pot multi-component synthesis of flavans using perchloric acid supported on silica as a recyclable heterogeneous catalyst has been described. This is the first report of direct one-step construction of a flavan skeleton from a phenolic precursor. The method involves a Knoevenagel-type condensation leading to *in situ* formation of transient *O*-quinone methide which further undergoes [4 + 2]-Diels–Alder cycloaddition with styrene to yield a flavan skeleton. The method provides easy access to a wide range of bio-active natural products *viz.* flavonoids, anthocyanins and catechins.

Introduction

Flavans are a set of naturally occurring flavonoids possessing a 2-phenyl-3,4-dihydro-2*H*-chromene nucleus. They are widely distributed in the plant kingdom[1] with >17 000 natural flavans isolated so far[2] and many exhibit interesting and useful biological activities.[1,3] Amongst different flavans, flavan-3-ols are most abundant and occur in monomeric, oligomeric and polymeric forms, which are also known as condensed tannins or proanthocyanidins. They exhibit high degree of structural diversity, varying according to the type of constitutive units, type of interflavan linkages, and degree of polymerization. Most widely known flavans are catechins (**1–2**, 2*R*,3*S* and 2*S*,3*R*) and epicatechins (**3–4**, 2*R*,3*R* and 2*S*,3*S*), which occur in plants such as catechu, tea cocoa *etc.* and are known to possess various biological properties such as anticarcinogenic, anti-inflammatory, antioxidant and immunomodulatory properties, inhibition of bone resorption *etc*.[4] Fully substituted monomeric flavans sideroxylonal B (**5**) and grandinal (**6**) have been reported from *Eucalyptus sideroxylon* and *E. grandis*, which exhibited antibacterial activities against Gram-positive bacteria and inhibition of aldose reductase.[5] Recently benzodipyran- and benzotripyran-type compounds have been reported to possess potent angiogenic activities.[6] Structures of flavans **1–6** are shown in Fig. 1.

Flavans have received a considerable amount of attention in the last few decades because of their numerous bioactivities.



(+)-Catechin (**1**): 2R, 3S
(-)-Catechin (**2**): 2S, 3R
(-)-Epicatechin (**3**): 2R,3R
(+)-Epicatechin (**4**): 2S,3S

Sideroxylonal B (**5**): R_1 = H, R_2 = isobutyl
Grandinal (**6**): R_1 = isobutyl, R_2 = H

Fig. 1 Examples of naturally occurring biologically active flavans.

However, due to their structural complexity, very little synthetic work has been reported. Currently available protocols for the synthesis of the flavan skeleton include the Heck-arylation of a chromene intermediate with arenediazonium salt,[7] reaction of tris-*O*-boc formyl phloroglucinol with styrene in the presence of magnesium bromide dietherate and lithium aluminum hydride,[8] reduction of dihydroflavones or dihydroflavonols,[9] and cinnamylation of phenolic compounds with cinnamyl alcohol in the presence of H_3PO_4.[10] Syntheses of the polyfunctional flavans sideroxylonals **5**[11] and grandinal **6**[12] have been reported *via* a cycloaddition reaction between *in situ* generated *O*-quinone methide from *ortho*-alkyl substituted phloroglucinols (using DDQ) and a substituted styrene-type compound. Most of the reported protocols require multiple steps to construct the flavan skeleton; many of them require expensive, hazardous chemicals and anhydrous conditions. Several protocols comprise protection/deprotection steps and use homogeneous catalytic systems. Direct one-step construction of a flavan skeleton is not known in the literature.

In recent years, a great number of short and efficient strategies have been discovered by chemists to facilitate the synthesis of

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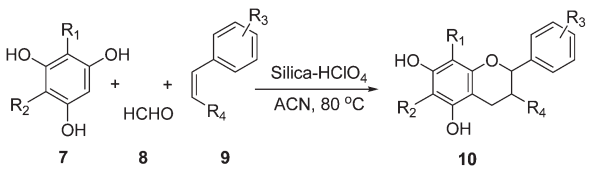


Scheme 1 One-pot MCR approach to flavan synthesis.

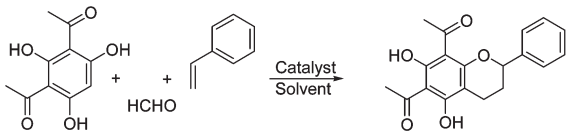
complex natural products.[13] In this regard, several domino 'one-pot' strategies, which consist of merging compatible single bond-forming processes so as to allow multiple bond-forming events between several substrates, a concept generally termed as multi-component reactions (MCRs), are being developed.[14] In the present work, we report the synthesis of flavans directly from phloroglucinol or mono- or disubstituted phloroglucinols **7** using a one-pot MCR between phloroglucinol **7**, formaldehyde **8** and styrene **9** in the presence of a recyclable heterogeneous solid acid catalyst in excellent yields. This one-pot protocol involves a Knoevenagel-type condensation of formaldehyde **8** with phloroglucinol **7** leading to the *in situ* formation of transient *O*-quinone methide, which further undergoes [4 + 2]-Diels–Alder cycloaddition with styrene **9** to yield flavan **10** (Scheme 1).

Results and discussion

Initially, an experimental exploration of reaction parameters, including catalyst, solvent, temperature and reaction time, was conducted using the model MCR between 2,4-diacetyl phloroglucinol (**7c**), formaldehyde (**8**) and styrene (**9a**) (Table 1). Catalyst-free MCR was first attempted by varying the solvent, reaction temperature and time, however no product was formed. The catalytic effect of various cation-exchange resins and silica based acid catalysts[15–17] was investigated. Amberlyst-15 and Amberlite catalysts led to the formation of flavan **10c** in 50% yield. A brief examination of solvents showed ACN to be a suitable solvent (entries 1 *vs.* 4 and 5), which was selected for further optimization studies. After numerous trials, we eventually found that all three silica based catalysts, silica–I_2, silica–$FeCl_3$ and silica–$HClO_4$ are competent, affording the flavan **10c** in >55% yield (entries 7–9). Further optimization revealed that the reaction could proceed smoothly by decreasing the catalyst loading as low as 10% w/w (entry 14); however, 50% w/w silica–$HClO_4$ appeared to be superior in terms of efficiency and reaction time.

The catalyst was reused repeatedly to prove its heterogeneous nature and its recyclability. The MCR between **7c**, **8** and **9a** in the presence of silica–$HClO_4$ (50% w/w) led to formation of flavan **10c** in 84, 65, 58 and 48% in 3 h reaction time over four cycles respectively. However, when the reaction time was increased to 8, 12 and 16 h for cycles 2–4, product yields were improved to 78, 70 and 65% respectively. In order to understand the reason for the decreased catalytic activity of the silica–$HClO_4$ catalyst after its use, we determined the total acidity of fresh and used catalysts (after first use) by ammonia-TPD experiments. The total acidity of the fresh catalyst was found to be 10.95 mmol NH_3/g, however it decreased to 7.6 mmol NH_3/g after the first use. This decreased acidity is a clear indication of the catalyst leaching after use, which justifies the reason for decrease in the product yield from 84% (fresh catalyst) to 65% (first recycle). However, the catalyst could be recycled up to three times producing >50% yield of the desired flavan.

Table 1 Solvent and catalyst optimization studies[a]



Entry	Catalyst (% w/w)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	Amberlyst-15 (50)	ACN	80	3	50
2	Amberlite-IR-50 (50)	ACN	80	3	50
3	Amberlite-IR-140 (50)	ACN	80	3	50
4	Amberlyst-15 (50)	H_2O	100	3	20
5	Amberlyst-15 (50)	Dioxane	100	6	30
6	Silica gel (50)	ACN	80	6	0
7	Silica–I_2 (50)	ACN	80	3	55
8	Silica–$FeCl_3$ (50)	ACN	80	3	60
9	Silica–$HClO_4$ (50)	ACN	80	3	84
10	Silica–$HClO_4$ (50)	H_2O	100	3	50
11	Silica–$HClO_4$ (50)	Dioxane	100	3	50
12	Silica–$HClO_4$ (20)	ACN	80	3	70
13	Silica–$HClO_4$ (10)	ACN	80	3	50
14	Silica–$HClO_4$ (10)	ACN	80	12	80
15	Silica–$HClO_4$ (5)	ACN	80	3	35
16	$HClO_4$ (100)	ACN	70	3	20
17	$HClO_4$ (100)	ACN	70	10	60
18	$HClO_4$	$HClO_4$	70	3	0

[a] Reagents and conditions: **7c** (1 mmol), **8** (3 mmol), **9a** (1.5 mmol) and catalyst. [b] Isolated yields.

We also performed a control experiment with neat $HClO_4$ instead of silica–$HClO_4$ catalyst. When 100 mol% of $HClO_4$ in ACN solvent was used, 20% product yield was formed after 3 h reflux (entry 16), however after reflux for 10 h, 60% of the desired flavan **10c** was formed (entry 17). The reaction when performed in neat $HClO_4$ (excess) without ACN did not proceed (entry 18). These results indicated that apart from the ease of product isolation and its recyclable nature, silica–$HClO_4$ catalyst is also much more efficient in comparison to neat $HClO_4$.

Next, we studied the scope of the MCR. Phloroglucinol (**7a**) and its mono- (**7b**) and disubstituted analogs (**7c–7e**),[18,19] styrene (**9a**), 4-methyl styrene (**9b**), 4-*tert*-butyl styrene (**9c**), 2-vinyl naphthalene (**9d**) and isosaffrol (**9e**) were investigated (Table 2). Under optimized reaction conditions, MCR of phloroglucinol (**7a**) with **8** and **9a** led to the formation of hexahydrobenzotripyran **10a** in 35% yield (entry 1). Similarly, monosubstituted phloroglucinol **7b** (entry 2) produced tetrahydrodipyran **10b** in 52% yield. Like 2,4-diacetyl phloroglucinol **7c** (entry 3), other disubstituted phloroglucinols **7d** and **7e** also produced desired flavans **10d** and **10e** in excellent yields (entries 4 and 5). 4-Methyl styrene **9b**, 4-*tert*-butyl styrene **9c** as well as 2-vinyl naphthalene **9d** participated well in this reaction, producing desired flavans in good yields (entries 6–10). The MCR protocol also worked well with the β-substituted styrene isosaffrol (**9e**). Reaction of **7c** with isosaffrol (**9e**) produced 3-methyl substituted flavan **10k** in 88% yield (entry 11). It is evident from Table 2 that disubstituted phloroglucinols showed better

Table 2 One-pot synthesis of flavans **10** from phloroglucinols **7**[a]

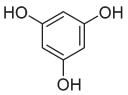
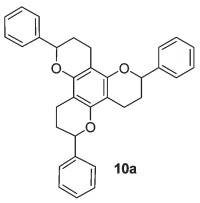
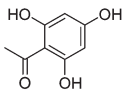
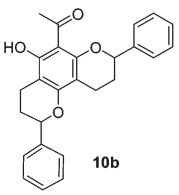
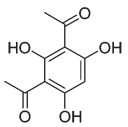
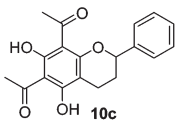
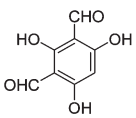
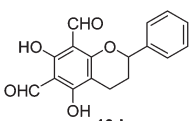
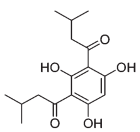
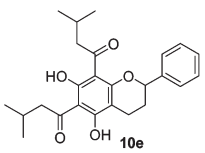
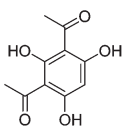
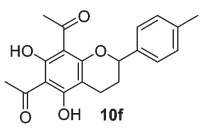
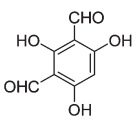
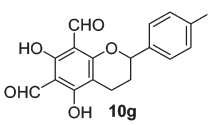
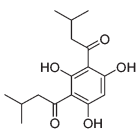
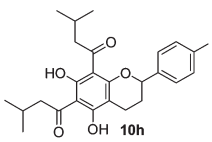
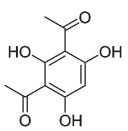
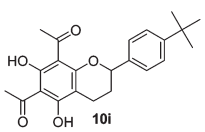
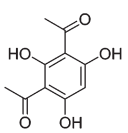
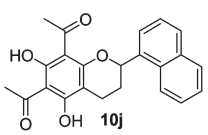
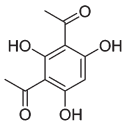
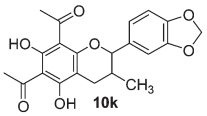
Entry	Phloroglucinol **7**	Styrene **9**	Flavan **10**	Time (h)	Yield[b] (%)
1	 **7a**	 **9a**	 **10a**	6.0	35
2	 **7b**	 **9a**	 **10b**	6.0	52
3	 **7c**	 **9a**	 **10c**	1.5	84
4	 **7d**	 **9a**	 **10d**	4.0	76
5	 **7e**	 **9a**	 **10e**	1.5	86
6	 **7c**	 **9b**	 **10f**	1.0	92
7	 **7d**	 **9b**	 **10g**	3.0	87
8	 **7e**	 **9b**	 **10h**	1.0	92
9	 **7c**	 **9c**	 **10i**	1.0	94
10	 **7c**	 **9d**	 **10j**	1.0	92

Table 2 *(Contd.)*

Entry	Phloroglucinol **7**	Styrene **9**	Flavan **10**	Time (h)	Yield[b] (%)
11	 **7c**	 **9e**	 **10k**	1.5	88

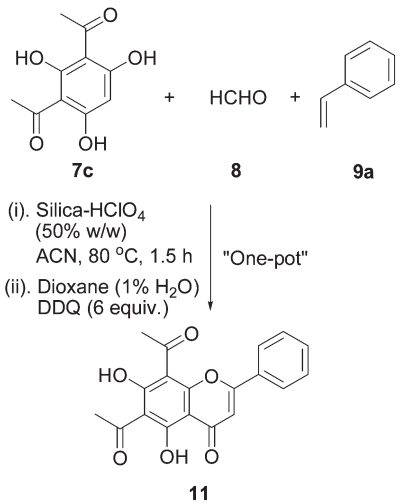
[a] Reagents and conditions: **7** (1 mmol), **8** (3 mmol), **9** (1.5 mmol) and silica–$HClO_4$ catalyst (50% w/w) in ACN at 80 °C. [b] Isolated yields.

reactivity in the MCR compared with mono-substituted followed by non-substituted phloroglucinol. Amongst different styrenes used, 4-methyl **9b** and *tert*-butyl **9c** styrenes produced higher yields compared with non-substituted styrene **9a**.

All synthesized flavans have been fully characterized using melting point, ^{1}H NMR, ^{13}C NMR, MS, IR and HRMS data. The CH proton at the C_2 position shows the typical 'dd (J = 2–6 and 8–15 Hz)' signal in the ^{1}H NMR spectrum, which is consistent with literature values.[20] The H_2 proton of flavan **10k** showed J_{2-3} = 9.9 Hz, indicating 2,3-*trans* relative stereochemistry. 2,3-*Trans* relative stereochemistry was further confirmed by NOESY experiments. The applicability of the MCR protocol for substituted flavan **10k** indicates its promise in the total synthesis of a variety of biologically important 3-substituted flavans (*e.g.* grandinal, catechins).

Further, the utility of this protocol was explored for flavonoid synthesis. Flavan **10c** on treatment with DDQ in dioxane (1% water) led to the formation of the corresponding flavone **11** in 75% yield. Next, we attempted a one-pot conversion of disubstituted phloroglucinol **7c** to flavone **11**. The mixture of **7c**, **8**, **9a** and silica–$HClO_4$ in acetonitrile was refluxed for 1.5 h, followed by addition of DDQ (4 equiv.). The reaction was allowed to reflux for 6 h, which led to the formation of the desired flavone **11**, but only in 10% yield. After further optimization studies, we found that the flavan **10** synthesis works well in ACN solvent; however the oxidation/dehydrogenation reaction requires a dioxane solvent. Thus an optimized one-pot protocol for flavone synthesis directly from phloroglucinols **7** includes evaporation of ACN after flavan **10c** formation, followed by addition of DDQ and dioxane (1% water) in the same pot, which leads to the formation of flavone **11** in 65% yield (Fig. 2).

The formation of flavone **11** *via* the one-pot protocol from phloroglucinol precursor **7c** involves a cascade of 4 reactions, namely a Knoevenagel-type condensation, a [4 + 2] Diels–Alder cycloaddition, DDQ-mediated oxidation and DDQ-mediated dehydrogenation. The plausible mechanism for this one-pot MCR is depicted in Fig. 3. Under acidic conditions, formaldehyde is protonated (structure **I**) which enhances its electrophilicity. 2,4-Disubstituted phloroglucinol being an active hydrogen species, it undergoes a Knoevenagel-type condensation with protonated formaldehyde, producing transient *O*-quinone methide **III**. This *O*-quinone methide **III** quickly undergoes a [4 + 2]-Diels–Alder cycloaddition reaction with dienophile **9a** to produce flavan **10c**. Further DDQ-mediated oxidation of the benzylic CH_2 produces 2,3-dihydro flavone **VIII**. Here, activation of the benzylic CH_2 of flavan **10c** occurs *via* hydride ion abstraction by DDQ.[21,22] 2,3-Dihydroflavone **VIII** further undergoes DDQ-mediated dehydrogenation leading to the formation of flavone **11** (Fig. 3).



7c **8** **9a** **11**

Fig. 2 One-pot synthesis of flavone **11** from phloroglucinol **7c**.

Conclusion

In summary, we have developed a very simple and economical tandem one-pot protocol for synthesis of flavans **10** and flavones **11** directly from substituted phloroglucinol precursors. Key features of our developed methodology are (a) no protection/deprotection steps required; (b) an inexpensive, easy to prepare, non-hazardous, easy to separate from reaction mixture, reusable catalyst and (c) a diversity-oriented synthesis. The developed protocol provides a shorter route to access a variety of flavan natural products such as catechins, flavonoids, anthocyanins, grandinal *etc.* using the appropriate dienophile, aldehyde and phloroglucinol precursor.

Experimental section

General

All chemicals were obtained from Sigma-Aldrich Company and used as received. ^{1}H, ^{13}C and DEPT NMR spectra were recorded on Brucker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent

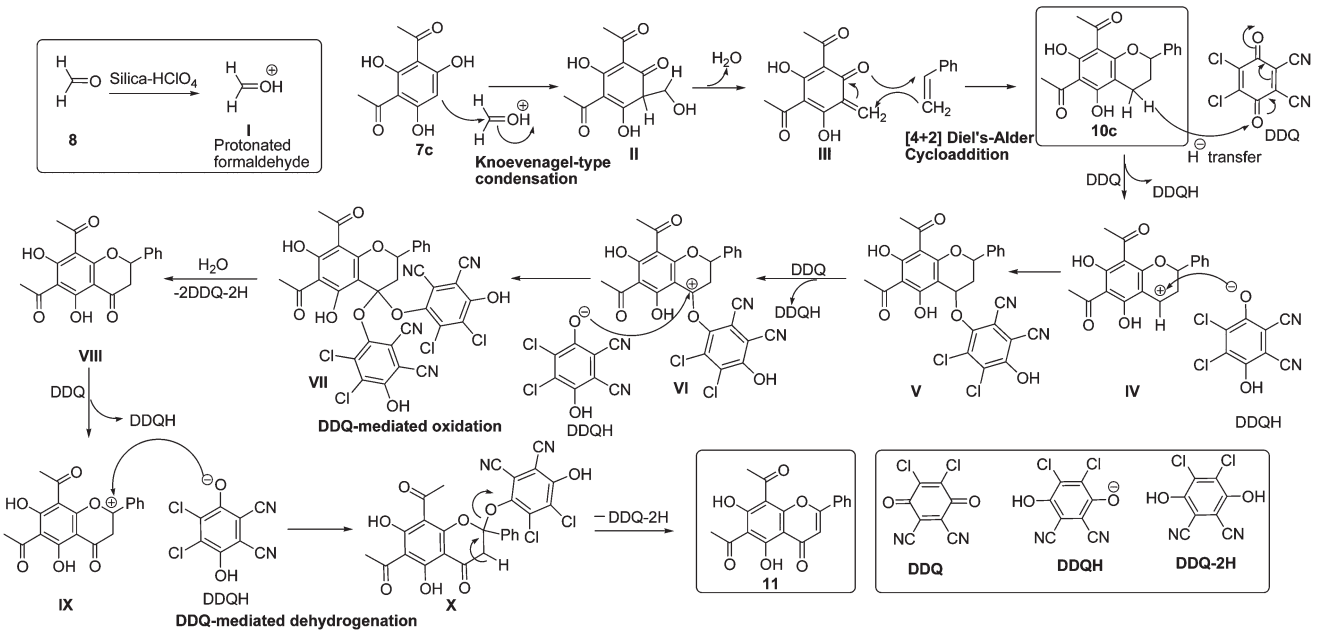


Fig. 3 Plausible mechanism of the one-pot multi-component synthesis of flavan **10c** and flavone **11**.

($CDCl_3$, 7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz or 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$, 77 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on a Perkin-Elmer IR spectrophotometer. Melting points were recorded on a digital melting point apparatus.

Procedures for preparation of silica catalysts. (a) Silica–I_2:[16] commercial iodine (1 g) and silica gel (#230–400) (1 g) were placed in a culture tube and mixed thoroughly for 30 min. The prepared catalyst was kept in the closed tube. (b) Silica–$FeCl_3$:[17] to a solution of $FeCl_3{\cdot}6H_2O$ (1.2 g) in acetone (20 mL) was added silica gel (10 g, #230–400) at room temperature. The solvent was evaporated under reduced pressure and the resulting yellow powder was kept in a closed container. (c) Silica–$HClO_4$:[15] perchloric acid (1.25 g, as a 70% aqueous solution) was added to a suspension of silica gel (23.75 g, #230–400) in Et_2O. The mixture was concentrated and the residue heated at 100 °C for 72 h under vacuum to afford $HClO_4$–SiO_2 as a free flowing powder.

Procedure for determination of the acidity of silica–$HClO_4$ catalyst. The acidity of the catalyst before and after use was determined by a CHEMBET-3000 TPD/TPR/TPO instrument, containing a quartz reactor and TCD detector. Prior to TPD studies, samples were pre-treated at 250 °C for 2 h with a continuous flow of pure nitrogen (99.9%), and then cooled to room temperature. After pre-treatment, samples were saturated with NH_3 gas until they reached saturated adsorption. The temperature was increased to 80 °C and kept there for 2 h, while a helium flow of 20 cm^3 min^{-1} was applied to remove the physisorbed ammonia. Finally the system was heated from 80 °C to 1000 °C at a rate of 10 °C min^{-1} and desorbed gas monitored with TCD detector. All the flow rates were maintained at normal temperature and pressure.

Procedure for preparation of 1-acetyl phloroglucinol (7b). A solution of phloroglucinol (**7a**, 10 g, 79.36 mmol) and anhydrous aluminum chloride (21.7 g, 237.9 mmol) in carbon disulphide (100 mL) was stirred at room temperature for 20 min. Nitrobenzene (150 mL) was added and temperature of the reaction mixture was allowed to increase to 50 °C. Acyl chloride (18.6 mL, 237.9 mmol) was added and the reaction mixture was stirred for a further 30 min. On cooling, the reaction mixture was diluted with ethyl acetate. Water was added to the resultant mixture leading to the formation of a white precipitate in the aqueous layer. The organic layer was decanted off and the remaining solid residue was washed 5–6 times with ethyl acetate. The combined ethyl acetate layer was evaporated under reduced pressure and the remaining viscous oil was purified by silica gel column chromatography using hexane–EtOAc as eluent to yield monoacetyl phloroglucinol **7b** (9.5 g). Yield: 72%; cream colored solid; mp. 134–136 °C; ^1H NMR (CD_3OD, 400 MHz): δ 5.80 (s, 2H), 2.60 (s, 3H); ESI-MS: *m/z* 169 $[M + 1]^+$.[19]

General procedure for preparation of diacyl phloroglucinols 7c and 7e. A solution of phloroglucinol (**7a**, 10 g, 79.36 mmol) and acetic acid or isovaleric acid (3 equiv.) in BF_3-etherate (100 mL) were refluxed at 100 °C for 2.5 h. The reaction mixture was cooled to room temperature, poured into crushed ice and extracted with ethyl acetate (100 mL × 3). Combined organic layers were evaporated on a rotary evaporator. The crude product was purified by silica gel (#100–200) column chromatography to yield diacyl phloroglucinols **7c** (11.6 g) and **7e** (17.2 g). 1,3-Diacetyl-2,4,6-trihydroxybenzene (**7c**): Yield: 70%; cream colored solid; mp. 172–174 °C; ^1H NMR

(CD_3OD, 400 MHz): δ 5.84 (s, 1H), 2.65 (s, 6H); ESI-MS: *m/z* 211 $[M + 1]^+$. 1,3-Di-(3-methyl-butanoyl)-2,4,6-trihydroxybenzene (**7e**): Yield: 75%; yellow solid; mp. 114–116 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.85 (s, 1H), 2.99 (d, J = 6.7 Hz, 4H), 2.26 (m, 2H), 0.99 (d, J = 6.7 Hz, 12H); ESI-MS: *m/z* 295 $[M + 1]^+$.[23]

Procedure for preparation of 2,4-diformyl phloroglucinol (7d). Phosphoryl chloride (1.6 mL, 16.7 mmol) was added drop-wise to DMF (1.3 mL, 16.7 mmol) with strong stirring at room temperature under a nitrogen atmosphere. Stirring was continued for 30 min. This Vilsmeier reagent was then slowly added to a stirred solution of anhydrous phloroglucinol (**7a**, 1 g, 7.9 mmol) in dioxane (5 mL) at room temperature under a nitrogen atmosphere. This solution was then stirred at room temperature for 12 h, whereupon it turned into a yellow amorphous solid. This solid mixture was cooled to 0 °C before being added to ice-water slurry (~40 mL). The solution was allowed to slowly warm to room temperature and stirring was continued for a further 4 h, during which time a cream precipitate formed. This precipitate was then filtered off and washed with more water, to give 2,4-diformyl phloroglucinol **7d** (1.22 g). Yield: 85%; cream colored solid; mp. 218–220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.09 (s, 2H), 5.83 (s, 1H); ESI-MS: *m/z* 183 $[M + 1]^+$.[20]

General procedure for one-pot multi-component synthesis of flavans 10a–k. To a solution of substituted phloroglucinol (**7**, 100 mg) in acetonitrile were added formaldehyde (**8**, 3 equiv.), substituted styrene (**9**, 1.5 mmol) and silica–$HClO_4$ (50% w/w). The mixture was then refluxed at 80 °C for 1–6 h. Completion of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and was filtered through Whatman filter paper. The filtrate was concentrated on a rotary evaporator to give the crude product. Crude products were purified by silica gel (#100–200) column chromatography to give flavans **10a–k** in 35–92% yield.

*Tris-(2-phenyl-2,3-dihydro benzopyran) (**10a**, Table 2, entry 1).* 131 mg; yield: 35%; white sticky solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46–7.31 (m, 15H), 5.07–5.00 (m, 3H), 2.85 (m, 3H), 2.74 (m, 3H), 2.23 (m, 3H), 2.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.28, 151.18, 142.39, 142.32, 142.29, 128.38, 127.51, 125.79, 125.76, 102.17, 102.15, 77.42, 29.81, 29.79, 29.67, 19.45, 19.44, 19.36; IR ($CHCl_3$): ν_{max} 3451, 3030, 3064, 2925, 2852, 1732, 1614, 1496, 1443, 1310, 1218, 1126, 1085 cm^{-1}; ESI-MS: *m/z* 475 $[M + 1]^+$; HRMS: *m/z* 475.2266 calcd for $C_{33}H_{30}O_3 + H^+$ (475.2268).

*8-Acetyl-bis-(2-phenyl-2,3-dihydro benzopyran) (**10b**, Table 2, entry 2).* 123 mg; yield: 52%; white sticky mass; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 14.23 (s, 1H), 7.39 (m, 10H), 5.09 (m, 2H), 2.80–2.69 (m, 4H), 2.57 (s, 3H), 2.32 (m, 2H), 2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.44, 162.37, 159.08, 155.99, 141.22, 141.12, 128.60, 128.55, 126.02, 125.71, 105.25, 102.20, 101.14, 78.78, 78.72, 33.47, 29.31, 29.12, 19.27, 18.59; IR ($CHCl_3$): ν_{max} 3450, 2927, 1615, 1424, 1369, 1276, 1131, 1105 cm^{-1}; ESI-MS: *m/z* 401 $[M + 1]^+$; HRMS: *m/z* 401.1732 calcd for $C_{26}H_{24}O_4 + H^+$ (401.1753).

*6,8-Diacetyl-5,7-dihydroxyflavan (**10c**, Table 2, entry 3).* 130 mg; yield: 84%; white crystalline solid; m.p. 101–103 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 16.15 (s, 1H), 15.18 (s, 1H), 7.40 (m, 5H), 5.15 (dd, J = 2.3, 10.4 Hz, 1H), 2.76 (m, 1H), 2.72 (s, 3H), 2.66 (m, 1H), 2.53 (s, 3H), 2.24 (m, 1H), 2.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 204.5, 203.4, 171.6, 170.9, 162.6, 140.0, 128.8, 128.5, 127.8, 125.8, 104.6, 103.9, 101.1, 79.99, 33.34, 33.10, 28.54, 18.49; IR ($CHCl_3$): ν_{max} 3400, 2924, 1615, 1423, 1364, 1169, 1105, 1024 cm^{-1}; ESI-MS: *m/z* 327 $[M + 1]^+$; HRMS: *m/z* 349.1045 calcd for $C_{19}H_{18}O_5 + Na^+$ (349.1015).

*6,8-Diformyl-5,7-dihydroxyflavan (**10d**, Table 2, entry 4).* 124 mg; yield: 76%; light yellow solid; m.p. 236–238 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 13.51 (s, 1H), 13.30 (s, 1H), 10.19 (s, 1H), 10.07 (s, 1H), 7.39 (m, 5H), 5.22 (dd, J = 6.0, 15 Hz, 1H), 2.76 (m, 1H), 2.66 (m, 1H), 2.31 (m, 1H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.0, 191.9, 169.0, 168.0, 164.0, 139.6, 128.8, 128.5, 125.8, 104.1, 103.9, 101.2, 79.7, 28.3, 17.6; IR ($CHCl_3$): ν_{max} 2924, 1640, 1442, 1305, 1154 cm^{-1}; ESI-MS: *m/z* 299 $[M + 1]^+$; HRMS: *m/z* 299.0888 calcd for $C_{17}H_{14}O_5 + H^+$ (299.0918).

*6,8-Di-(3-methylbutyryl)-5,7-dihydroxyflavan (**10e**, Table 2, entry 5).* 119 mg; yield: 86%; light yellow solid; m.p. 117–119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 16.39 (s, 1H), 15.37 (s, 1H), 7.42 (m, 5H), 5.09 (dd, J = 2.3, 10.7 Hz, 1H), 3.03 (d, J = 6.8 Hz, 2H), 2.82 (d, J = 6.7 Hz, 2H), 2.62 (m, 2H), 2.28 (m, 2H), 2.04 (m, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.72 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.0, 206,0, 170.1, 169.7, 162.3, 139.8, 128.7, 128.6, 126.4, 104.7, 103.8, 101.1, 80.2, 53.1, 53.0, 28.2, 25.6, 25.1, 22.8, 22.7, 22.4, 22.3, 18.8; IR ($CHCl_3$): ν_{max} 3400, 2956, 2926, 1614, 1417, 1294, 1192, 1161, 1023 cm^{-1}; ESI-MS: *m/z* 411 $[M + 1]^+$; HRMS: *m/z* 411.2139 calcd for $C_{25}H_{30}O_5 + H^+$ (411.2166).

*6,8-Diacetyl-5,7-dihydroxy-4'-methyl-flavan (**10f**, Table 2, entry 6).* 148 mg; yield: 92%; white crystalline solid; m.p. 157–159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 16.15 (s, 1H), 15.16 (s, 1H), 7.29–7.20 (m, 4H), 5.13 (dd, J = 2.0, 10.4 Hz, 1H), 2.81 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 2.52 (s, 3H), 2.40 (s, 3H), 2.26 (m, 1H), 2.07 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.5, 203.5, 170.0, 169.5, 162.7, 138.3, 137.0, 129.4, 126.1, 104.5, 103.9, 101.1, 79.9, 33.3, 33.1, 29.7, 28.5, 21.2, 18.6; IR ($CHCl_3$): ν_{max} 3400, 2921, 2851, 1620, 1591, 1422, 1365, 1169, 1109 cm^{-1}; ESI-MS: *m/z* 341 $[M + 1]^+$, 363 $[M + Na]^+$; HRMS: *m/z* 341.1385 calcd for $C_{20}H_{20}O_5 + H^+$ (341.1389).

*6,8-Diformyl-5,7-dihydroxy-4'-methyl-flavan (**10g**, Table 2, entry 7).* 149 mg; yield: 87%; white crystalline solid; m.p. 115–117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.49 (s, 1H), 13.30 (s, 1H), 10.19 (s, 1H), 10.06 (s, 1H), 7.28–7.22 (m, 4H), 5.18 (d, J = 10 Hz, 1H), 2.76 (m, 1H), 2.64 (m, 1H), 2.40 (s, 3H), 2.30 (m, 1H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.0, 191.8, 168.9, 168.0, 164.1, 138.4, 136.6, 129.4, 129.1, 125.8, 125.7, 104.0, 103.9, 101.2, 79.7, 28.2, 21.2, 17.6; IR ($CHCl_3$): ν_{max} 2924, 1643, 1443, 1306, 1272, 1182, 1154 cm^{-1}; ESI-MS: *m/z* 313 $[M + 1]^+$, 335 $[M + Na]^+$; HRMS: *m/z* 313.1072 calcd for $C_{18}H_{16}O_5 + H^+$ (313.1076).

*6,8-Di-(3-methyl-butyryl)-5,7-dihydroxy-4'-methyl-flavan (**10h**, Table 2, entry 8).* 132 mg; yield: 92%; light greyish crystalline solid; m.p. 100–102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 16.38 (s, 1H), 15.36 (s, 1H), 7.30 (d, J = 7.7 Hz, 2H), 7.23 (d, J = 7.7 Hz, 2H), 5.07 (d, J = 10.5 Hz, 1H), 3.03 (d, J = 6.7 Hz, 2H), 2.84 (m, 2H), 2.68 (m, 2H), 2.38 (s, 3H), 2.16 (m, 2H),

2.06 (m, 2H), 0.99 (d, J = 6.2 Hz, 6H), 0.74 (d, J = 6.3 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.9, 206.0, 170.1, 169.6, 162.3, 138.4, 136.8, 129.3, 126.3, 104.6, 103.8, 101.1, 80.0, 53.1, 53.0, 28.2, 25.6, 25.0, 22.4, 22.3, 21.2, 18.8; IR ($CHCl_3$): ν_{max} 2957, 2929, 2870, 1614, 1435, 1367, 1294, 1193, 1161, 1126 cm^{-1}; ESI-MS: m/z 425 $[M + 1]^+$, 447 $[M + Na]^+$; HRMS: m/z 425.2323 calcd for $C_{26}H_{32}O_5 + H^+$ (425.2323).

*6,8-Diacetyl-5,7-dihydroxy-4′-*tert*-butyl-flavan (**10i**, Table 2, entry 9).* 170 mg; yield: 92%; light yellow crystalline solid; m.p. 119–121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 16.15 (s, 1H), 15.16 (s, 1H), 7.44 (d, J = 6.8 Hz, 2H), 7.32 (d, J = 6.8 Hz, 2H), 5.16 (dd, J = 2.0, 10.0 Hz, 1H), 2.80 (m, 1H), 2.76 (s, 3H), 2.64 (m, 1H), 2.52 (s, 3H), 2.27 (m, 1H), 2.08 (m, 1H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 204.4, 203.5, 170.0, 169.5, 162.7, 151.4, 136.9, 125.7, 125.6, 104.5, 103.9, 101.1, 79.8, 34.6, 33.4, 33.0, 31.3, 28.5, 18.5; IR ($CHCl_3$): ν_{max} 3401, 2961, 1615, 1424, 1364, 1292, 1169, 1104 cm^{-1}; ESI-MS: m/z 383 $[M + 1]^+$, 405 $[M + Na]^+$; HRMS: m/z 383.1882 calcd for $C_{23}H_{26}O_5 + H^+$ (383.1853).

*6,8-Diacetyl-3,4-dihydro-2-(naphthalen-1-yl)-2*H*-chromene-5,7-diol (**10j**, Table 2, entry 10).* 164 mg; yield: 92%; white crystalline solid; m.p. 161–163 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 16.20 (s, 1H), 15.22 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 6.6 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.58 (m, 3H), 5.91 (d, J = 10.4 Hz, 1H), 2.44 (m, 1H), 2.38 (m, 1H), 2.36 (s, 3H), 2.22 (s, 3H), 2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.6, 203.5, 170.1, 169.6, 162.8, 135.2, 133.9, 130.3, 129.2, 129.1, 126.6, 125.9, 125.4, 123.6, 122.7, 104.7, 104.0, 101.3, 77.2, 33.2, 33.1, 27.5, 18.9; IR ($CHCl_3$): ν_{max} 3400, 2923, 2852, 1615, 1423, 1364, 1293, 1172, 1105 cm^{-1}; ESI-MS: m/z 377 $[M + 1]^+$, 399 $[M + Na]^+$; HRMS: m/z 377.1384 calcd for $C_{23}H_{20}O_5 + H^+$ (377.1384).

*6,8-Diacetyl-3,4-dihydro-2-(3,4-methylene-dioxy-phenyl)-3-methyl-2*H*-chromene-5,7-diol (**10k**, Table 2, entry 11).* 160 mg; yield: 88%; white sticky solid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 16.12 (s, 1H), 15.16 (s, 1H), 6.85 (m, 3H), 6.01 (s, 2H), 4.59 (d, J = 9.9 Hz, 1H), 2.93 (dd, J = 5.0, 14.5 Hz, 1H), 2.73 (s, 3H), 2.45 (s, 3H), 2.25 (dd, J = 11.2, 16.5 Hz, 1H), 2.08 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.5 (–CO), 203.5 (–CO), 170.0 (C7), 169.2 (C5), 162.4 (C8a), 148.1 (C4′), 147.9 (C4′), 147.8 (C5′), 133.5 (C5′), 133.5 (C1′), 133.3 (C1′), 121.2 (C6′), 121.1 (C6′), 108.2 (C2′), 108.0 (C2′), 107.6 (C3′), 107.0 (C4a), 104.5 (C6), 103.7 (C8), 101.3 (O–CH_2–O), 101.2 (O–CH_2–O), 86.0 (C2), 85.8 (C2), 33.2 (COCH_3), 33.1 (COCH_3), 32.0 (C3), 27.2 (C4), 17.5 (CH–CH_3); IR ($CHCl_3$): ν_{max} 2927, 1618, 1505, 1445, 1425, 1381, 1364, 1247, 1175, 1039 cm^{-1}; ESI-MS: m/z 385 $[M + 1]^+$; HRMS: m/z 385.1255 calcd for $C_{21}H_{20}O_7 + H^+$ (385.1282).

Synthesis of flavone 11 from flavan 10c. To the solution of 5,7-dihydroxy-6,8-diacetyl-flavan (**10c**, 100 mg, 0.306 mmol) in dioxane (1% H_2O) was added DDQ (0.278 mg, 1.2 mmol). The resulting mixture was refluxed at 100 °C for 16 h. The reaction mixture was allowed to cool to room temperature and then filtered through Whatman filter paper. Filtrate was concentrated on a rotary evaporator to give the crude product, which on silica gel (#100–200) column chromatography gave flavone **11** (78 mg) in 75% yield. 6,8-Diacetyl-5,7-dihydroxyflavone (**11**, Fig. 2): white sticky solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 16.04 (s, 1H), 15.72 (s, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.67 (m, 2H), 7.64 (t, J = 7.8 Hz, 2H), 2.94 (s, 3H), 2.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.9, 201.3, 182.6, 171.4, 167.9, 159.5, 151.4, 137.0, 133.0, 129.1, 128.7, 115.5, 110.9, 107.0, 100.6, 32.8, 30.9; IR ($CHCl_3$): ν_{max} 3400, 2923, 2852, 1614, 1611, 1455, 1372, 1304, 1172 cm^{-1}; ESI-MS: m/z 339 $[M + 1]^+$, 361 $[M + Na]^+$; HRMS: m/z 339.0878 calcd for $C_{19}H_{14}O_6 + H^+$ (339.0863).

Procedure for one-pot synthesis of 6,8-diacetyl-5,7-dihydroxyflavone (11) from phloroglucinol precursor 7. To the solution of 2,4-diacetyl phloroglucinol (**7c**, 100 mg, 0.476 mmol) in acetonitrile were added formaldehyde (**8**, 3 equiv.), styrene (**9a**, 0.074 g, 0.714 mmol) and silica–$HClO_4$ (0.05 g, 50% w/w). The mixture was then refluxed at 80 °C for 1.5 h. Completion of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was evaporated on a rotary evaporator to dryness. Dioxane (5 mL), water (10 μL, 5% of dioxane) and DDQ (0.649 g, 2.856 mmol) were then added to the dry reaction mixture and it was refluxed at 100 °C for 16 h. The reaction mixture was allowed to cool to room temperature and then filtered through Whatman filter paper. The filtrate was concentrated on a rotary evaporator to give the crude product, which on silica gel (#100–200) column chromatography gave flavone **11** (104 mg) in 65% yield.

Recyclability studies of silica–$HClO_4$ catalyst. To a solution of 2,4-diacetyl phloroglucinol (**7c**, 500 mg, 2.38 mmol) in acetonitrile (10 mL) were added formaldehyde (**8**, 3 equiv.), styrene (**9**, 3.57 mmol) and silica–$HClO_4$ (250 mg, 50% w/w). The mixture was then refluxed at 80 °C for 1.5 h. After completion of the reaction, the catalyst was recovered by filtration followed by washing with acetonitrile. The recovered catalyst was dried in an oven and reused in the next cycle. The catalyst was recycled 3 times and the amount of catalyst recovered and percentage yield of the flavan **10c** were determined.

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