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Acid catalyzed stereoselective rearrangement and dimerization of flavenes: synthesis of dependensin

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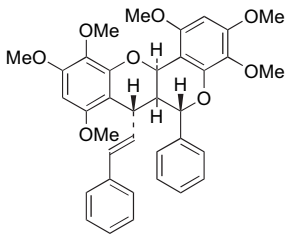
Abstract—Appropriately substituted flavenes undergo stereoselective rearrangement and dimerization when treated with methanolic hydrochloric acid to give benzopyranobenzopyrans. A rationale for the rearrangement is proposed. This synthetic methodology has been used for a high yield synthesis of the natural product dependensin.

1. Introduction

The flavonoids are widely distributed in the plant kingdom. Many natural flavonoids exist as 'dimers' in which two flavonoid molecules are coupled together at various positions. These dimeric flavonoids have been shown to possess a wide range of physiological and biological properties including antioxidant,[1] anticancer,[2] anti-inflammatory[3] and antiviral[4] activities. Some of the major limitations in using these compounds as medicaments include their low abundance in the plant material, tedious methods of extraction and purification and limited availability of biological data. A possible solution to these problems is the development of efficient synthetic methodologies for these compounds.

The dimeric flavonoid dependensin (**1**) was isolated as a racemate from the root bark of the Tanzanian medicinal plant *Uvaria dependens*.[5] The complex polycyclic architecture was delineated by 1D and 2D NMR spectroscopies. Although the biological activity of pure dependensin has not been investigated due to unavailability of material, the crude *Uvaria* extract shows potent anti-malarial activity.



Dependensin (**1**)

There are no reports on the total synthesis of dependensin in the literature. The heterocyclic ring system present in **1** is quite unique and is not found in any other natural product. The polycyclic structure of **1** contains a dense array of functionality and stereochemistry, which includes two fused benzopyran ring systems, four stereocentres and one trans double bond. This unique structural complexity has prompted the development of an efficient synthetic approach in an attempt to develop new agents for the treatment of malaria.

As part of an ongoing investigation into the chemistry of dimeric flavonoids, the synthesis of 4′,7-dihydroxyflavene **2** was required. Attempts to synthesize this compound by alkaline hydrolysis of 4′,7-diacetoxyflavene **3** resulted in the formation of polymeric products. However, it was found that when treated with methanolic hydrochloric acid, diacetoxyflavene **3** undergoes stereoselective rearrangement and dimerization to give the benzopyranobenzopyran **4**, in excellent yield. The corresponding 5-hydroxy and 6-hydroxy substituted flavenes were also synthesized with a view that they might undergo similar rearrangement. However, treatment with hydrochloric acid under similar conditions gave a polymeric product and a complex mixture, respectively.

Based on acid catalyzed dimerization of diacetoxyflavene **3**, it was envisaged that dependensin could be formed in nature by dimerization of a trimethoxyflavene. In order to test this hypothesis the synthesis of dependensin was attempted in a similar way.

2. Results and discussion

2.1. Formation of flavenes

The condensation of resacetophenone **5** with 4-hydroxybenzaldehyde was carried out in the presence of an excess of

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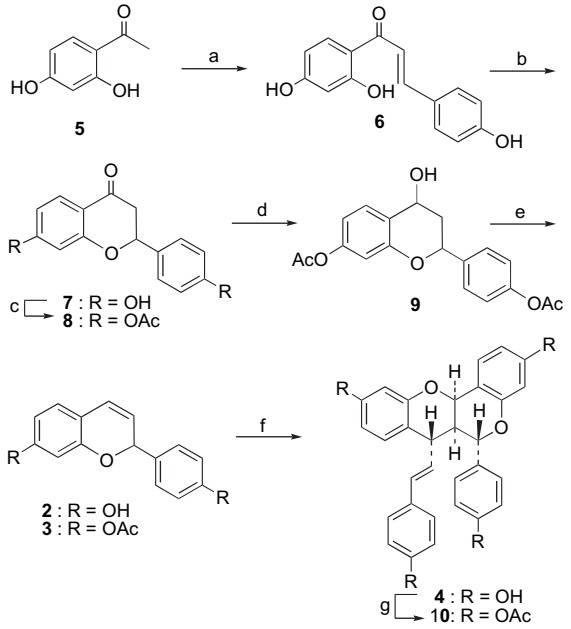
potassium hydroxide to give 4,2′,4′-trihydroxy chalcone **6**.[6] The cyclization of **6** was then effected by heating it with methanolic hydrochloric acid followed by acetylation using excess acetic anhydride and pyridine to give flavanone **8**.

Catalytic hydrogenation of **8** using palladium on charcoal gave *cis*-flavanol **9** in 90% yield (Scheme 1). The stereochemistry of **9** was established on the basis of an NOE observed between H2 and H4. The dehydration of **9** was carried out by heating it in toluene with a catalytic amount of *p*-toluenesulfonic acid to give flavene **3** in 70% yield. When **3** was treated with concd hydrochloric acid in methanol, benzopyranobenzopyran **4** was isolated in 92% yield. The structure of **4** was established on the basis of ^{1}H and ^{13}C, and two-dimensional NMR experiments. The observed important NOEs are as shown in Figure 1. However, attempts to obtain a single crystal of **4** by crystallization from various solvents were unsuccessful. The corresponding tetraacetoxy derivative **10** was also synthesized, but a single crystal of this derivative could not be obtained either.



Scheme 1. Reagents and conditions: (a) 4-hydroxybenzaldehyde, 60% aq KOH, 100 °C, 1.5 h, 65%; (b) concd HCl, MeOH, reflux, 24 h, 62%; (c) Ac_2O, pyridine, 100 °C, 1 h, 76%; (d) H_2, Pd/C, THF, 48 h, rt, 90%; (e) *p*-TSA, toluene, reflux, 2 h, 70%; (f) concd HCl, MeOH, rt, 6 h, 92%; (g) Ac_2O, pyridine, 100 °C, 6 h, 74%.

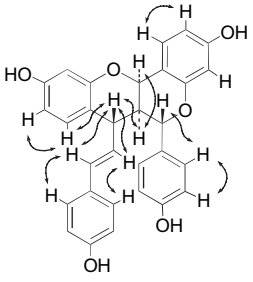
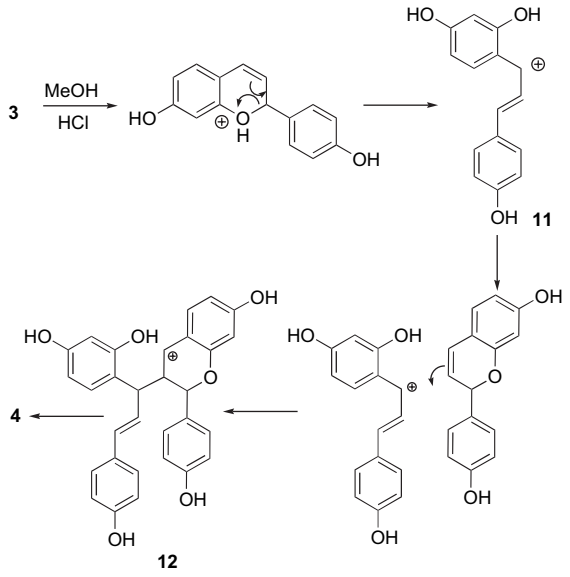


Figure 1. Key NOE correlations for **4**.

It is assumed that initially the flavene **3** undergoes acid catalyzed hydrolysis to give dihydroxyflavene **2**, which is protonated and ring opened to give the stabilized benzylic carbocation **11**. This is attacked by another dihydroxyflavene molecule to generate another benzylic carbocation **12**, which cyclizes stereoselectively to give compound **4** (Scheme 2).

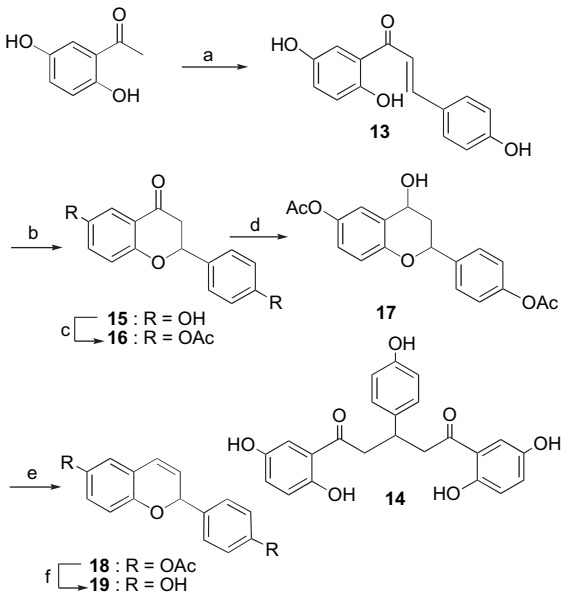


Scheme 2.

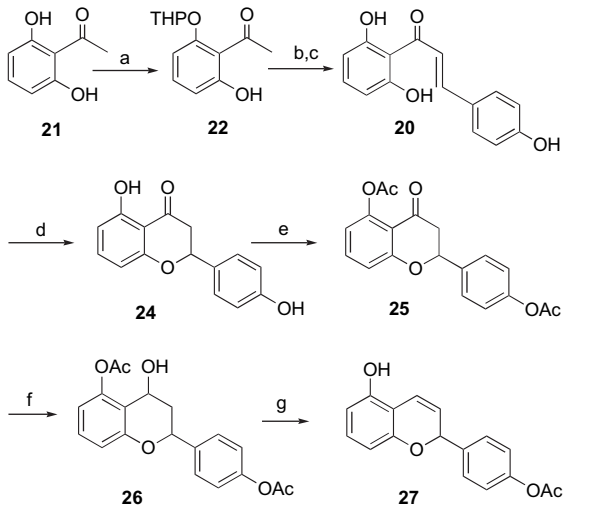
The literature procedure for the synthesis of chalcone **13** involves condensation of 4-hydroxybenzaldehyde and 2′,5′-dihydroxyacetophenone in the presence of 40% potassium hydroxide at room temperature for a period of seven days.[7] Therefore, a procedure outlined for the synthesis of **6** was used for the preparation of chalcone **13**. However, in this case in addition to the desired product **13**, compound **14** formed by Michael addition of 2′,5′-dihydroxyacetophenone to the chalcone **13** was also isolated. The cyclization of **13** to flavanone **15** was effected by refluxing it with methanolic hydrochloric acid in 92% yield. This was followed by acetylation and catalytic hydrogenation using palladium on charcoal to give flavanol **17** in 99% yield. The stereochemistry of the flavanol **17** was found to be predominantly cis (cis:trans: 95:5) based on NOESY experiments. Flavanol **17** was dehydrated by heating it with toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid to give flavene **18** in 95% yield (Scheme 3).

Surprisingly, treatment of **18** with methanolic hydrochloric acid gave a complex mixture. On the contrary, when **18** was treated with aqueous potassium hydroxide solution followed by acidification, dihydroxyflavene **19** was isolated in 47% yield.

Attempts to synthesize chalcone **20** by condensation of 4-hydroxybenzaldehyde with 2′,6′-dihydroxyacetophenone **21** in the presence of excess potassium hydroxide at 100 °C gave a polymeric compound. Furthermore, literature methods for the synthesis of chalcone **20** by condensation of 2′,6′-dihydroxyacetophenone **21** and 4-hydroxybenzaldehyde in the presence of sodium hydroxide[8] or potassium hydroxide[9] at room temperature gave very poor yields.



Scheme 3. Reagents and conditions: (a) 4-hydroxybenzaldehyde, 60% aq KOH, 100 °C, 2 h, 48%; (b) concd HCl, MeOH, reflux, 48 h, 92%; (c) Ac_2O, pyridine, 100 °C, 1 h, 65%; (d) H_2, Pd/C, THF, 48 h, rt, 99%; (e) *p*-TSA, toluene, reflux, 1.5 h, 95%; (f) 1 M KOH, MeOH, rt, 1 h, 47%.



Scheme 4. Reagents and conditions: (a) 3,4-dihydro-2*H*-pyran, *p*-TSA, THF, overnight, rt, 55%; (b) 4-(tetrahydro-2-pyranoxy)benzaldehyde **23**, KOH, EtOH, rt, overnight; (c) 2 M HCl, MeOH, 70 °C, 30 min, 56% (over two steps); (d) NaOAc, EtOH, reflux, 1 h, 92%; (e) Ac_2O, pyridine, 100 °C, 2 h, 94%; (f) $NaBH_4$, MeOH, −15 °C, 2 h, 95%; (g) *p*-TSA, toluene, reflux, 1.5 h, 15%.

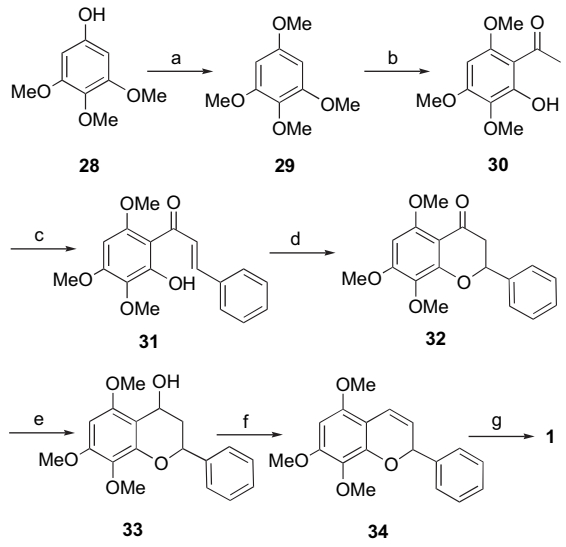
This observation has been confirmed by Takahashi et al.[10] who have reported similar problems with the reported methods. This problem can be overcome by protecting one of the OH groups prior to condensation.[11] Hence, **21** was reacted with 3,4-dihydro-2*H*-pyran in the presence of *p*-toluenesulfonic acid to give 2′-hydroxy-6′-tetrahydropyran-2-yloxyacetophenone **22** in 55% yield. The hydroxyl group of 4-hydroxybenzaldehyde was also protected as the THP ether **23**. The condensation of **22** with **23** was then carried out under standard conditions in the presence of excess potassium hydroxide followed by deprotection to give 2′,6′,4-trihydroxychalcone **20** in 56% overall yield. Attempts to cyclize **20** under acidic conditions (similar to the ones used for cyclization of **6** and **13**) were unsuccessful resulting in the isolation of unreacted starting materials. An alternative method[9] of cyclization using aqueous sodium hydroxide and hydrogen peroxide also gave very poor yields. Surprisingly this cyclization was achieved very effectively when sodium acetate was used as a base to give flavanone **24** in 92% yield (Scheme 4). The high yield and ease of formation of **24** under these mildly alkaline conditions are probably due to the presence of the 6′-hydroxyl group, which stabilizes the intermediate anion by hydrogen bonding. The two hydroxyl groups in the flavanone **24** were then protected by acetylation to give diacetoxyflavanone **25** in 94% yield. Attempts to reduce the flavanone **25** by catalytic hydrogenation using palladium charcoal as catalyst at ambient temperature and at 60 °C were unsuccessful and the starting material was recovered. Attempted reduction by transfer hydrogenation using palladium charcoal and ammonium formate gave multiple products, whereas catalytic hydrogenation using Raney nickel gave only starting material. However, the reduction was successfully effected using sodium borohydride[12] to give the desired *trans*-flavanol **26** in 93% yield. The dehydration of **26** was carried out under standard conditions, using *p*-toluenesulfonic acid, but was also accompanied by hydrolysis of one of the acetoxy groups. This results in poor yields of the flavene **27** and formation of substantial amounts of polymeric material. The deprotection of the *O*-acetyl group at the 5-position can be explained on the basis of neighbouring group participation.

2.2. Synthesis of dependensin 1

Reaction of 3,4,5-trimethoxyphenol **28** with methyl iodide and potassium carbonate in acetone gave 1,3,4,5-tetramethoxybenzene **29** in 96% yield. Acetylation following the literature procedure[13] involving aluminium chloride and acetyl chloride gave acetophenone **30** in 56% yield, which was converted to chalcone **31** in 95% yield by reaction with benzaldehyde and potassium hydroxide in aqueous ethanol.

The cyclization of the chalcone **31** to flavanone **32** was achieved in 63% yield by refluxing with methanolic hydrochloric acid. Attempts to reduce flavanone **32** by hydrogenation with palladium on charcoal were not successful. The reaction was sluggish (ca. 5–7 days) and the product was a complex mixture. However, reduction using sodium borohydride in (1:1) THF and methanol gave *cis*-flavanol **33** as a sticky solid in 95% yield. The stereochemistry was established on the basis of the NOE between H2 and H4. Compound **33** was found to be unstable, and was quickly converted by dehydration with *p*-toluenesulfonic acid in refluxing toluene into the related flavene **34**, which on treatment with methanolic hydrochloric acid gave dependensin **1** in 72% yield (Scheme 5).

The structure and stereochemistry of dependensin were established on the basis of 1D and 2D NMR spectroscopies and reported spectroscopic data.



Scheme 5. Reagents and conditions: (a) MeI, K_2CO_3, acetone, 24 h, 96%; (b) $AlCl_3$, AcCl, Et_2O, 0 °C to rt, overnight, 56%; (c) benzaldehyde, KOH, EtOH, overnight, 95%; (d) concd HCl, MeOH, 40 h, reflux, 63%; (e) $NaBH_4$, THF/MeOH, 0 °C, 1 h, 95%; (f) *p*-TSA, toluene, reflux, 15 min, 80%; (g) concd HCl, MeOH, rt, overnight, 72%.

3. Conclusion

4′,7-Dihydroxyflav-3-ene **2** undergoes stereoselective rearrangement and dimerization on treatment with methanolic hydrochloric acid to give benzopyranobenzopyran. However, the corresponding 4′,5- or 4′,6-dihydroxy substituted flavenes do not rearrange and dimerize under similar conditions. This synthetic methodology has been used for an efficient synthesis of the natural product dependensin.

4. Experimental

4.1. General

All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on Bruker DPX300 (300 MHz) and Bruker DPX600 (600 MHz) spectrometers. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI). Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 60GF_{254}.

4.1.1. 4,2′,4′-Trihydroxychalcone (6). To a mixture of **5** (6.8 g, 44.7 mmol), 4-hydroxybenzaldehyde (5.6 g, 45.9 mmol) and ethanol (5.6 mL) was added aqueous potassium hydroxide (41.6 mL, 60% w/w). The resulting suspension was heated at 100 °C for 1.5 h and then kept overnight at room temperature. The reaction mixture was poured onto ice (100 g) and acidified to pH 4 using concd hydrochloric acid. The precipitated yellow solid was filtered, washed with water (200 mL) and air dried to give **6** as a yellow solid (7.5 g, 65%). Mp: 200 °C (from methanol/water) lit.[14] 200–201 °C; IR (KBr) 3383, 1627, 1605, 1513, 1225, 1211, 1143 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.35 (d, J=2.3 Hz, 1H), 6.45 (dd, J=2.3, 9.0 Hz, 1H), 6.91 (d, J=8.7 Hz, 2H), 7.72 (d, J=8.7 Hz, 2H), 7.74 (d, J=16.2 Hz, 1H), 7.83 (d, J=16.2 Hz, 1H), 8.1 (d, J=9.0 Hz, 1H), 9.1 (br, 2H), 13.59 (s, 1H); ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 102.5, 107.7, 113.6, 115.8, 117.4, 126.6, 130.8, 132.3, 144.1, 160.0, 164.6, 166.6, 191.9.

4.1.2. 4′,7-Dihydroxyflavanone (7). A suspension of **6** (3 g, 11.7 mmol) in methanol (50 mL) and concd hydrochloric acid (25 mL) was refluxed for 24 h. Methanol was removed under vacuum and the resulting dark solution was diluted with water (150 mL). The product was extracted with ethyl acetate (100 mL×3), dried over anhydrous sodium sulfate and the solvent evaporated under vacuum. The crude product was chromatographed using light petroleum/ethyl acetate (50:50) as eluent to yield the title compound as a pale yellow solid (1.86 g, 62%). Mp: 195–197 °C (from benzene/light petroleum) lit.[14] 195–196 °C; R_f (50% ethyl acetate/light petroleum) 0.35; IR (KBr) 3377, 1656, 1601, 1516, 1465, 1234, 1163 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 2.66 (dd, J=3, 16.8 Hz, 1H), 3.03 (dd, J=13.0, 16.8 Hz, 1H), 5.44 (dd, J=3, 13.0 Hz, 1H), 6.41 (d, J=2.3 Hz, 1H), 6.56 (dd, J=2.3, 8.7 Hz, 1H), 6.88 (d, J=8.7 Hz, 2H), 7.38 (d, J=8.7 Hz, 2H), 7.71 (d, J=8.7 Hz, 1H), 8.45 (br, 1H), 9.3 (br, 1H); ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 43.7, 79.5, 102.7, 110.2, 114.3, 115.2, 128.0, 128.5, 130.3, 157.5, 163.5, 164.2, 189.6.

4.1.3. 4′,7-Diacetoxyflavanone (8). A mixture of **7** (500 mg, 1.95 mmol), pyridine (0.6 mL) and acetic anhydride (3 mL) was heated with stirring at 100 °C for 1 h. The reaction mixture was cooled to room temperature. After 2 h the precipitated white solid was filtered and washed with methanol–water (10 mL, 50:50) and air dried (510 mg, 76%). Mp: 192–194 °C, lit.[15] 195–198 °C; IR (KBr) 1763, 1742, 1693, 1609, 1511, 1441, 1425, 1370, 1282, 1246, 1196, 1142, 1118, 1063, 1013, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.30 (s, 3H), 2.31 (s, 3H), 2.88 (dd, J=3.0, 16.8 Hz, 1H), 3.05 (dd, J=13.0, 16.8 Hz, 1H), 5.49 (dd, J=3.0, 13 Hz, 1H), 6.81 (dd, J=2.3, 8.3 Hz, 1H), 6.82 (d, J=2.3 Hz, 1H), 7.16 (d, J=8.3 Hz, 2H), 7.48 (d, J=8.3 Hz, 2H), 7.95 (d, J=8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.6 MHz,): δ 19.9, 20.0, 43.7, 79.4, 111.0, 115.6, 118.7, 121.9, 127.5, 127.7, 136.5, 151.1, 156.7, 162.2, 168.1, 168.6, 189.7.

4.1.4. *cis*-4′,7-Diacetoxyflavan-4-ol (9). To a solution of **8** (700 mg, 2.05 mmol) in THF (28 mL) was added 10% palladium on charcoal (200 mg). The mixture was hydrogenated at room temperature and atmospheric pressure for 48 h and filtered through a pad of Celite®. Evaporation of the solvent under vacuum afforded **7** (630 mg, 90%) as a white solid. Mp: 156–158 °C (from methanol); IR (KBr) 3471, 1756, 1738, 1613, 1588, 1494, 1425, 1371, 1219, 1196, 1142, 1117, 1017, 968, 914, 832 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (ddd, J=10.4, 11.7, 13.2 Hz, 1H), 2.28 (s, 3H), 2.30 (s, 3H), 2.51 (ddd, J=1.9, 6.4, 13.2 Hz, 1H), 5.07 (dd, J=6.4, 10.4 Hz, 1H), 5.18 (dd, J=1.9, 11.7 Hz,

1H), 6.62 (d, J=2.3 Hz, 1H), 6.72 (dd, J=2.3, 8.7 Hz, 1H), 7.12 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7 Hz, 2H), 7.52 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 20.9, 21.0, 39.7, 65.3, 109.8, 114.3, 121.7, 123.5, 127.1, 127.7, 137.7, 150.4, 150.9, 155.0, 169.4; Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.65; H, 5.29. Found: C, 66.35; H, 5.35; HRMS (ESI) m/z 365.0995 (MNa^+, $C_{19}H_{18}O_6Na$, requires 365.0996).

4.1.5. 4′,7-Diacetoxyflav-3-ene (3). A mixture of *p*-toluenesulfonic acid (120 mg) and toluene (750 mL) was heated to reflux for 45 min with Dean–Stark apparatus to remove traces of water. Diacetoxyflavan-4-ol **9** (1.8 g, 5.26 mmol) was added and the heating was continued for a further 2 h. The reaction mixture was cooled to room temperature and washed with water (200 mL×2). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Column chromatography using ethyl acetate/light petroleum (25:75) afforded **3** (1.2 g, 70%) as colourless crystals. Mp: 110–112 °C (methanol); R_f (25% ethyl acetate/light petroleum) 0.48; IR (KBr) 1756, 1497, 1372, 1218, 1202, 1191, 1139, 1115, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.25 (s, 3H), 2.29 (s, 3H), 5.75 (dd, J=3.4, 9.8 Hz, 1H), 5.91 (dd, J=1.1, 3.4 Hz, 1H), 6.51 (dd, J=1.1, 9.8 Hz, 1H), 6.53 (d, J=2.3 Hz, 1H), 6.61 (dd, J=2.3, 7.9 Hz, 1H), 6.98 (d, J=7.9 Hz, 1H), 7.09 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 21.0, 76.6, 109.6, 114.2, 118.9, 121.7, 123.4, 123.9, 126.9, 128.2, 138.0, 150.6, 151.3, 153.7, 169.0, 169.3; Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.55; H, 4.97; HRMS (ESI) m/z 347.0893 (MNa^+, $C_{19}H_{16}O_5Na$, requires 347.0890).

4.1.6. 6a,12a-Dihydro-3,10-dihydroxy-6-(4′-hydroxyphenyl)-7-[(1*E*)-2-(4″-hydroxyphenylethenyl)]-6*H*,7*H*-[1]benzopyrano[4,3-*b*][1]benzopyran (4). To a suspension of **3** (350 mg, 1.08 mmol) in methanol (35 mL) was added 10 M HCl (2.7 mL). The mixture was stirred under an argon atmosphere for 6 h. Methanol was evaporated off at 30 °C under vacuum and the residue was taken up in ethyl acetate (50 mL). The organic layer was washed with water (25 mL×2), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (70:30) as eluent to yield **4** (240 mg, 92%) as a light red solid. Mp: 190–192 °C (ethyl acetate/light petroleum); R_f (70% ethyl acetate/light petroleum) 0.45; IR (KBr) 3407, 2958, 1616, 1511, 1458, 1230, 1159, 1119, 1017, 696, 836 cm^{-1}. ^{1}H NMR (acetone-d_6, 600 MHz): δ 2.51 (ddd, J=2.1, 2.4, 10.9 Hz, 1H), 3.11 (dd, J=2.1, 6.7 Hz, 1H), 4.89 (d, J=10.9 Hz, 1H), 5.08 (d, J=2.4 Hz, 1H), 6.02 (d, J=15.7 Hz, 1H), 6.24 (dd, J=6.7, 15.7 Hz, 1H), 6.33 (d, J=2.3 Hz, 1H), 6.33 (d, J=2.4 Hz, 1H), 6.41 (dd, J=2.4, 8.3 Hz, 1H), 6.48 (dd, J=2.3, 8.3 Hz, 1H), 6.74 (d, J=8.6 Hz, 2H), 6.77 (d, J=8.3 Hz, 1H), 6.89 (d, J=8.5 Hz, 2H), 7.19 (d, J=8.6 Hz, 2H), 7.2 (d, J=8.5 Hz, 2H), 7.25 (d, J=8.3 Hz, 1H), 8.31 (br s, 2H), 8.52 (br s, 2H); ^{13}C NMR (acetone-d_6, 150 MHz): δ 38.7, 41.6, 67.6, 77.0, 102.9, 103.2, 108.6, 109.1, 112.2, 113.7 (2×115.7), 127.9, 129.2, 129.4, 130.3, 130.9, 131.3, 131.5, 132.0, 154.1, 156.5, 157.3, 157.9, 158.1, 159.7; HRMS (ESI) m/z 503.1478 (MNa^+, $C_{30}H_{24}O_6Na$, requires 503.1465).

4.1.7. 6a,12a-Dihydro-3,10-diacetoxy-6-(4′-acetoxyphenyl)-7-[(1*E*)-2-(4″-acetoxyphenylethenyl)]-6*H*,7*H*-[1]benzopyrano[4,3-*b*][1]benzopyran (10). A mixture of compound **4** (50 mg, 0.104 mmol), acetic anhydride (1 mL) and pyridine (0.5 mL) was heated at 100 °C for 6 h. The reaction mixture was cooled to room temperature and poured over cold water (50 mL). The white solid was filtered, washed with water (10 mL) and dried (50 mg, 74%). Mp: 140–142 °C (ethyl acetate/light petroleum); IR (KBr) 2923, 1762, 1616, 1498, 1369, 1209, 1144, 1115, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (s, 3H), 2.28 (s, 6H), 2.31 (s, 3H), 2.49 (ddd, J=2.3, 3.0, 9.8 Hz, 1H), 3.24 (dd, J=2.3 6.4 Hz, 1H), 5.08 (d, J=3.0 Hz, 1H), 5.08 (d, J=9.8 Hz, 1H), 6.07 (d, J=15.8 Hz, 1H), 6.16 (dd, J=6.4, 15.8 Hz, 1H), 6.67 (dd, J=2.3, 8.3 Hz, 1H), 6.69 (d, J=2.3 Hz, 1H), 6.69 (d, J=2.3 Hz, 1H), 6.73 (dd, J=2.3, 8.3 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 6.99 (d, J=8.6 Hz, 2H), 7.14 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.6 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H), 7.39 (d, J=8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 21.0, 37.9, 40.9, 66.9, 76.2, 110.2, 110.2, 114.3, 114.5, 117.6, 118.4, 121.6, 121.8, 127.2, 128.2, 130.8, 131.0, 131.5, 132.3, 134.2, 135.8, 150.0, 150.6, 150.9, 152.2, 153.0, 155.1, 169.1, 169.1, 169.1, 169.2; Anal. Calcd for $C_{38}H_{32}O_{10}$: C, 70.36; H, 4.97. Found: C, 70.41; H, 5.27.

4.1.8. 4,2′,5′-Trihydroxychalcone (13). To a mixture of 2,5-dihydroxyacetophenone (1.36 g, 8.94 mmol), 4-hydroxybenzaldehyde (1.12 g, 9.1 mmol) and ethanol (1.12 mL) was added potassium hydroxide solution (8 mL, 60% w/w). The dark mixture was heated at 100 °C for 2 h. TLC analysis showed formation of two products. The reaction mixture was cooled to room temperature and poured over ice cold water (30 mL). The mixture was acidified to pH 5 with concd hydrochloric acid (ca. 13 mL). The solid was filtered, washed with water (50 mL) and dried at 80 °C. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (40:60) as eluent to yield title compound **13** (1.1 g, 48%) as yellow solid. Mp: 228–230 °C, lit.[7] 223–235 °C; R_f (40% ethyl acetate/light petroleum) 0.4; IR (KBr) 3358, 3174, 1705, 1636, 1599, 1583, 1541, 1516, 1437, 1369, 1321, 1289, 1268, 1186, 1168, 821 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.79 (d, J=8.6 Hz, 1H), 6.91 (d, J=8.6 Hz, 2H), 7.05 (dd, J=3.0, 8.6 Hz, 1H), 7.52 (d, J=3.0 Hz, 1H), 7.68 (d, J=15.1 Hz, 1H), 7.72 (d, J=8.6 Hz, 2H), 7.84 (d, J=15.1 Hz, 1H), 8.03 (s, 1H), 8.98 (s, 1H), 12.40 (s, 1H). Further elution gave compound **14** as pale yellow solid (350 mg, 20%).

4.1.9. 1,5-Bis(2,5-dihydroxyphenyl)-3-(4-hydroxyphenyl) pentane-1,5-dione (14). Mp: 179–181 °C; R_f (40% ethyl acetate/light petroleum) 0.22; IR (KBr) 3404, 1642, 1629, 1609, 1485, 1232, 1198, 1176, 999, 792 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.42 (dd, J=7.5, 16.6 Hz, 2H), 3.52 (dd, J=6.4, 16.6 Hz, 2H), 3.99 (dt, J=6.4, 7.5 Hz, 1H), 6.71 (d, J=8.6 Hz, 2H), 6.76 (d, J=9.0 Hz, 2H), 7.06 (dd, J=3.0, 9.0 Hz, 2H), 7.21 (d, J=8.6 Hz, 2H), 7.40 (d, J=3.0 Hz, 2H), 8.07 (s, 2H), 8.08 (s, 1H), 11.65 (s, 2H); ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 36.2, 44.6, 114.7, 115.0, 118.3, 119.3, 124.7, 128.5, 134.1, 149.3, 154.9, 155.8, 205.1; HRMS (ESI) m/z 431.1099 (MNa^+, $C_{23}H_{20}O_7Na$, requires 431.1101).

4.1.10. 4′,6-Dihydroxyflavanone (15). A mixture of **13** (2.5 g, 9.76 mmol), methanol (125 mL) and concd hydrochloric acid (10 mL) was refluxed for 48 h. The reaction mixture concentrated under vacuum to 20 mL and diluted with water (100 mL). The product was filtered, washed with water and dried. The title compound was obtained as a pale yellow solid (2.33 g, 92%). Mp: 235–237 °C, lit.[7] 230 °C; IR (KBr) 3500–2500, 3331, 1669, 1617, 1476, 1374, 1318, 1214, 1135, 837, 777 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz): δ 2.71 (dd, J=2.6, 17.0 Hz, 1H), 3.07 (dd, J=13.2, 17.0 Hz, 1H), 5.4 (dd, J=2.6, 13.2 Hz, 1H), 6.88 (d, J=6.8 Hz, 2H), 6.89 (d, J=8.6, 1H), 7.07 (dd, J=3.4, 8.6 Hz, 1H), 7.23 (d, J=3.4 Hz, 1H), 7.38 (d, J=6.8 Hz, 2H), 8.34 (s, 1H), 8.51 (s, 1H); ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 44.0, 79.3, 110.2, 115.1, 118.9, 121.1, 124.1, 127.9, 130.4, 151.5, 155.3, 157.6, 191.4.

4.1.11. 4′,6-Diacetoxyflavanone (16). A mixture of **15** (2.3 g, 9.0 mmol), acetic anhydride (14 mL) and pyridine (2.3 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to room temperature and maintained there for 2 h. The precipitated white solid was filtered and washed with methanol–water (50 mL, 1:1) and dried to give the title compound as a white solid (2 g, 65%). Mp: 181–183 °C (methanol); IR (KBr) 1768, 1748, 1683, 1613, 1485, 1365, 1280, 1226, 1197, 1181, 1013, 920, 907 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 3H), 2.31 (s, 3H), 2.88 (dd, J=3.0, 16.9 Hz, 1H), 3.05 (dd, J=13.2, 16.9 Hz, 1H), 5.47 (dd, J=3.0, 13.2 Hz, 1H), 7.06 (d, J=8.7 Hz, 1H), 7.16 (d, J=8.7 Hz, 2H), 7.23 (dd, J=2.6, 8.7 Hz, 1H), 7.49 (d, J=8.7 Hz, 2H), 7.61 (d, J=2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 20.8, 21.0, 44.3, 79.2, 119.1, 119.2, 121.1, 121.1, 127.2, 129.8, 135.9, 144.8, 150.8, 158.9, 169.2, 169.4, 190.8; Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.73. Found: C, 67.25; H, 4.78; HRMS (ESI) m/z 363.0834 (M+Na^+, $C_{19}H_{16}O_6Na$, requires 363.0839).

4.1.12. *cis*-4′,6-Diacetoxyflavan-4-ol (17). To a solution of **16** (2 g, 5.88 mmol) in THF (80 mL) was added 10% palladium on charcoal (200 mg). The mixture was hydrogenated at room temperature and atmospheric pressure for 48 h. The catalyst was filtered off through Celite® and the bed was washed with dichloromethane (25 mL×2). Evaporation of the filtrate under vacuum afforded **17** (2 g, 99%) as a white solid. Mp: 142–143 °C (methanol); IR (KBr) 3464, 1755, 1483, 1367, 1223, 1395, 1018, 898, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.04 (ddd, J=4.5, 11.7, 13.2 Hz, 1H), 2.27 (s, 3H), 2.30 (s, 3H), 2.44 (ddd, J=1.9, 6.0, 13.2 Hz, 1H), 5.01 (dd, J=4.5, 6.0 Hz, 1H), 5.13 (dd, J=1.9, 11.7 Hz, 1H), 6.84 (d, J=8.3 Hz, 1H), 6.89 (dd, J=2.3, 8.3 Hz, 1H), 7.11 (d, J=8.7 Hz, 2H), 7.22 (d, J=2.3 Hz, 1H), 7.41 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 20.9, 21.0, 39.6, 65.5, 76.5, 117.3, 119.7, 121.7, 122.2, 126.5, 127.2, 137.8, 144.3, 150.4, 151.9, 169.3, 170.0; Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.65; H, 5.29. Found: C, 67.14; H, 5.37; HRMS (ESI) m/z 365.0999 (M+Na^+, $C_{19}H_{18}O_6Na$, requires 365.0996).

4.1.13. 4′,6-Diacetoxyflav-3-ene (18). A mixture of *p*-toluenesulfonic acid monohydrate (66 mg, 0.35 mmol) and toluene (425 mL) was heated to reflux for 45 min with a Dean–Stark apparatus to remove traces of water. Compound **17** was added and the heating was continued for 1.5 h. The reaction mixture was cooled to room temperature and washed with satd sodium bicarbonate solution (100 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated off under vacuum. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (25:75) as eluent to yield title compound (900 mg, 95%) as white solid. Mp: 97–99 °C; R_f (25% ethyl acetate/light petroleum) 0.4; IR (KBr) 3064, 1752, 1743, 1483, 1370, 1207, 1193, 1165, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.26 (s, 3H), 2.28 (s, 3H), 5.8 (dd, J=3.4, 10.1 Hz, 1H), 5.90 (dd, J=1.9, 3.4 Hz, 1H), 6.48 (dd, J=1.9, 10.1 Hz, 1H), 6.75 (d, J=8.7 Hz, 1H), 6.76 (d, J=3.0 Hz, 1H), 6.81 (dd, J=3.0, 8.7 Hz, 1H), 7.09 (d, J=8.7 Hz, 2H), 7.45 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 20.9, 21.0, 76.6, 116.5, 119.3, 121.7, 121.7, 122.0, 123.6, 125.4, 128.2, 137.9, 144.4, 150.4, 150.6, 169.2, 169.6; Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.11; H, 5.10; HRMS (ESI) m/z 347.0893 (M+Na^+, $C_{19}H_{16}O_5Na$, requires 347.0890).

4.1.14. 4′,6-Dihydroxyflav-3-ene (19). To a suspension of **18** (100 mg, 0.3 mmol) in methanol (5 mL) was added 1 M potassium hydroxide solution (25 drops). The mixture was stirred under an argon atmosphere for 1 h. The reaction mixture was neutralized by adding 1 M acetic acid solution (25 drops). Water (25 mL) was added and the mixture was extracted with ethyl acetate (25 mL×3). The combined organic extract was washed with satd sodium bicarbonate solution (25 mL), dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was purified by preparative thin layer chromatography using ethyl acetate/light petroleum (1:1) as mobile phase. The title compound was obtained as a pink solid (35 mg, 47%). Mp: 140–142 °C; R_f (50% ethyl acetate/light petroleum) 0.35; IR (KBr) 3656–3002, 1517, 1486, 1278, 1250, 1213, 1033, 836, 775 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz): δ 5.71 (dd, J=1.5, 3.4 Hz, 1H), 5.85 (dd, J=3.4, 9.8 Hz, 1H), 6.55 (m, 4H), 6.79 (d, J=8.6 Hz, 2H), 7.26 (d, J=8.6 Hz, 2H), 8.15 (br, 2H); ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 76.1, 112.7, 115.0, 115.4, 116.1, 123.7, 126.0, 128.5, 131.8, 146.0, 151.4, 157.4; HRMS (ESI) m/z 263.0681 (M+Na^+, $C_{15}H_{12}O_3Na$, requires 263.0681).

4.1.15. 2′-Hydroxy-6′-tetrahydropyranyl-2-oxyacetophenone (22). *p*-Toluenesulfonic acid (30 mg, 0.15 mmol) was added to a mixture of **21** (3.02 g, 19.86 mmol), 3,4-dihydro-2*H*-pyran (10 mL) and dry THF (15 mL). The mixture was stirred under an argon atmosphere overnight. The reaction mixture was poured into satd sodium bicarbonate solution (50 mL) and stirred for 5 min. Light petroleum (100 mL) was added and the layers were separated. The organic layer was washed with 2 M sodium hydroxide (50 mL×2). The pH of the aqueous layer was adjusted to 8 using 1 M hydrochloric acid and again the product was extracted with light petroleum (50 mL×3), dried with anhydrous sodium sulfate and the solvent was partially removed under vacuum. The solution was kept in the refrigerator overnight and filtered. The title compound was obtained as pale yellow crystals[11] (unstable) (2.6 g, 55%). ^1H NMR (acetone-d_6, 300 MHz): δ 1.7–1.9 (m, 6H), 2.71 (s, 3H), 3.72 (m, 2H), 5.5 (m, 1H), 6.51 (d, J=8.2 Hz, 1H), 6.60 (d, J=8.2 Hz, 1H), 7.32 (t, J=8.2 Hz, 1H), 13.14 (s, 1H). ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 19.0, 24.9, 30.2,

33.6, 62.2, 97.3, 104.6, 111.2, 111.7, 136.0, 159.0, 164.3, 204.9.

4.1.16. 4-(Tetrahydro-2-pyranoxy)benzaldehyde (23). *p*-Toluenesulfonic acid (30 mg, 0.15 mmol) was added to a solution of 4-hydroxybenzaldehyde (2.4 g, 19.67 mmol) in 3,4-dihydro-2*H*-pyran (10 mL) and dry THF (15 mL). The mixture was stirred under an argon atmosphere overnight. The reaction was quenched by pouring into satd sodium bicarbonate solution (25 mL) followed by stirring for 5 min. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under vacuum at room temperature. The crude product was chromatographed using dichloromethane/light petroleum (33:66) as eluent to yield **23** as yellowish oil[16] (3.2 g, 80%). R_f (33% dichloromethane/light petroleum) 0.33; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (m, 3H), 1.66 (m, 3H), 3.36 (m, 1H), 3.57 (m, 1H), 5.27 (t, J=2.8, 1H), 6.90 (d, J=8.8 Hz, 2H), 7.56 (d, J=8.8 Hz, 2H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 17.7, 24.3, 29.3, 61.2, 95.4, 116.0, 129.7, 131.0, 161.5, 190.1.

4.1.17. 2′,4,6′-Trihydroxy chalcone (20). To a solution of **22** (0.77 g, 3.26 mmol) and **23** (0.73 g, 3.58 mmol) in absolute ethanol (3 mL) was added solution of potassium hydroxide (3 g) in water (2 mL). The mixture was stirred at ambient temperature overnight, poured into water (150 mL) and acidified to pH 5. The product was extracted with ethyl acetate (25 mL×3), dried over sodium sulfate and evaporated under vacuum. The crude product (1.5 g) was dissolved in methanol (30 mL), hydrochloric acid (10 mL, 2 M) was added and the mixture was heated at 70 °C for 30 min. The reaction was poured into water (150 mL) and extracted with ethyl acetate (25 mL×4). The combined organic extract was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (50:50) as eluent to yield the title compound (470 mg, 56%) as orange needles. Mp: 214–216 °C, lit.[10] 215–216 °C; R_f (50% ethyl acetate/light petroleum) 0.39; IR (KBr) 3363, 3235, 1632, 1581, 1511, 1499, 1453, 1205, 1169, 1009, 822, 746 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.44 (d, J=8.3 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 7.25 (t, J=8.3 Hz, 1H), 7.59 (d, J=8.7 Hz, 2H), 7.80 (d, J=15.5 Hz, 1H), 8.08 (d, J=15.5 Hz, 1H), 8.99 (s, 1H), 11.55 (s, 2H); ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 107.6, 115.9, 124.2, 126.9, 130.5, 135.7, 143.4, 160.0, 162.1, 194.3.

4.1.18. 4′,5-Dihydroxyflavanone (24). A mixture of **20** (1.3 g, 5.07 mmol), sodium acetate (1.3 g, 15.8 mmol) and ethanol (26 mL) was refluxed for 1 h. The reaction mixture was cooled to room temperature, poured into water (100 mL) and acidified to pH 5 using 1 M hydrochloric acid. The white solid was filtered, washed with water and air dried to give **24** (1.2 g, 92%) as colourless needles. Mp: 205–207 °C (methanol) lit.[17] 206–207 °C; IR (KBr) 3415, 3257, 1632, 1618, 1460, 1371, 1218, 1209, 1057, 837, 714 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 2.83 (dd, J=3.0, 17.0 Hz, 1H), 3.29 (dd, J=12.8, 17.0 Hz, 1H), 5.52 (dd, J=3.0, 12.8 Hz, 1H), 6.47 (2×d, J=8.3 Hz, 2H), 6.89 (d, J=8.6 Hz, 2H), 7.41 (d, J=8.6 Hz, 2H), 7.43 (t, J=8.3 Hz, 1H), 8.50 (s, 1H), 11.79 (s, 1H); ^{13}C NMR (acetone-d_6, 75.6 MHz): δ 43.0, 78.9, 107.3, 107.9, 108.7, 115.2, 128.0, 129.6, 138.1, 157.8, 161.9, 162.0, 199.0.

4.1.19. 4′,5-Diacetoxyflavanone (25). A mixture of **24** (1.2 g, 4.68 mmol), acetic anhydride (7.2 mL, 76.2 mmol) and pyridine (1.2 mL, 14.9 mmol) was heated with stirring at 100 °C for 2 h. The reaction mixture was cooled to room temperature and poured over a mixture of hydrochloric acid (2 M, 50 mL) and ice (100 g). The mixture was stirred for 10 min and filtered. The solid was washed with water (50 mL) and air dried to give the title compound as white solid (1.5 g, 94%). Mp: 134–135 °C, lit.[9] 114 °C (methanol); IR (KBr) 1764, 1745, 1682, 1616, 1467, 1370, 1222, 1190, 1046, 911 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 3H) and 2.39 (s, 3H), 2.78 (dd, J=2.3, 16.6 Hz, 1H), 3.04 (dd, J=13.2, 16. 6 Hz, 1H), 5.48 (dd, J=2.3, 13.2 Hz, 1H), 6.7 (d, J=7.9 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 7.15 (d, J=8.67, 2H), 7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 21.0, 45.3, 78.7, 106.7, 113.8, 116.2, 122.0, 127.3, 135.8, 150.1, 150.9, 162.4, 169.2, 169.6, 172.7, 189.8; Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.73. Found: C, 67.18; H, 4.66.

4.1.20. *trans*-4′,5-Diacetoxyflavanol (26). A suspension of **25** (900 mg, 2.64 mmol) and methanol (40 mL) was stirred at room temperature for 10 min. The mixture was cooled to −15 °C using salt and ice bath under an argon atmosphere and powdered sodium borohydride (580 mg, 15.33 mmol) was added in portions over 15 min. The mixture was stirred at −15 to −10 °C for 1.5 h, then quenched by dropwise addition of acetic acid (65 drops) over 15 min and poured into ice–water (200 mL). The solid was filtered and washed with water (50 mL). The title compound was obtained as a white solid (850 mg, 93%). Mp: >320 °C (acetone); IR (KBr) 3230, 1757, 1697, 1593, 1466, 1371, 1268, 1199, 1176, 1051, 1035, 916, 786 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.15 and 2.3 (m, 2H), 2.18 and 2.31 (2×s, 6H), 3.34 (dd, J=2.3, 12.4 Hz, 1H), 5.98 (t, J=2.8 Hz, 1H), 6.52 and 6.53 (2×d, J=7.9 Hz, 2H), 7.14 (d, J=8.6, 2H), 7.19 (t, J=7.9 Hz, 1H), 7.49 (d, J=8.6 Hz, 2H), 8.32 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 21.0, 21.3, 35.3, 63.8, 72.0, 106.9, 108.8, 109.1, 121.7, 127.3, 131.7, 137.8, 150.5, 156.0, 156.1, 169.3, 173.9; Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.65; H, 5.29. Found: C, 66.44; H, 5.45.

4.1.21. 4′-Acetoxy-5-hydroxyflav-3-ene (27). This was prepared by the procedure used for preparation of **18** (80 mg, 15%) as off-white solid. IR (KBr) 3437, 1756, 1736, 1613, 1463, 1369, 1196, 1067, 1015, 913, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.47 (br s, 1H), 5.75 (dd, J=3.4, 9.8 Hz, 1H), 5.84 (dd, J=1.7, 3.4 Hz, 1H), 6.27 (d, J=7.9 Hz, 1H), 6.39 (d, J=8.3 Hz, 1H), 6.85 (dd, J=1.7, 9.8 Hz, 1H), 6.92 (dd J=7.9, 8.3 Hz, 1H), 7.08 (d, J=8.7 Hz, 2H), 7.46 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 21.0, 76.0, 108.2, 108.7, 109.6, 118.6, 121.6, 122.7, 128.2, 129.3, 138.3, 150.4, 151.6, 153.9, 169.6. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.26; H, 5.10.

4.1.22. 1,2,3,5-Tetramethoxybenzene (29). To a suspension of 3,4,5-trimethoxyphenol (3 g, 16.3 mmol), potassium carbonate (3 g, 21.7 mmol) in acetone (75 mL) was added methyl iodide (2 mL, 32.1 mmol). The mixture was heated

to reflux for 24 h with addition of methyl iodide (2 mL, 32.1 mmol) after every 6 h. Acetone was distilled off under vacuum and the residue was dissolved in water (40 mL) and extracted with dichloromethane (25 mL×3). The combined organic extracts were dried over sodium sulfate and solvent concentrated under vacuum to give 1,3,4,5-tetramethoxybenzene **29** (3.1 g, 96%). Mp: 46 °C, lit.[18] 47 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 3H), 3.784 (s, 3H), 3.84 (s, 6H), 6.15 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 55.4, 56.0, 60.9, 91.7, 132.3, 153.6, 156.2.

4.1.23. 2-Hydroxy-3,4,6-trimethoxyacetophenone (30). A solution of **29** (3 g, 15.1 mmol) in dry ether (15 mL) was cooled to 0 °C under an argon atmosphere. Aluminium chloride (3 g, 22.5 mmol) was added in portions followed by addition of acetyl chloride (3 mL, 42.2 mmol) over 5 min. The reaction mixture was stirred at 0 °C for 3 h and then kept overnight at room temperature. The reaction was quenched by addition of a mixture of concd hydrochloric acid (5 mL) and ice (50 g). The precipitated solid was filtered and washed with water (50 mL) and dried. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (30:70) as eluent to yield the title compound **30** (1.9 g, 56%). Mp: 114–115 °C, lit.[13] 112–113 °C; R_f (30% ethyl acetate/light petroleum) 0.39; IR (KBr) 3500 br, 2933, 1625, 1588, 1471, 1421, 1360, 1295, 1278, 1233, 1212, 1126, 1025, 991, 791 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.61 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 5.96 (s, 1H), 13.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 33.0, 55.5, 55.9, 60.6, 86.4, 106.3, 130.5, 158.3, 158.7, 158.9, 203.6.

4.1.24. 2′-Hydroxy-3′,4′,6′-trimethoxychalcone (31). To a stirred mixture of **30** (1.8 g, 7.96 mmol), benzaldehyde (1.2 g, 11.3 mmol) and ethanol (60 mL) was added a solution of potassium hydroxide (15 g) in water (15 mL). The reaction mixture was stirred overnight under an argon atmosphere. Crushed ice (100 g) was added and the mixture was acidified to pH 3 with concd hydrochloric acid. The precipitated solid was filtered, washed with water and dried to give chalcone **31** (2.37 g, 95%). Mp: 141–142 °C, lit.[19] 138 °C; IR (KBr) 3447, 1625, 1558, 1420, 1330, 1245, 1206, 1124, 1009, 793 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 3H), 3.95 (s, 6H), 6.02 (s, 1H), 7.4 (m, 3H), 7.61 (m, 2H), 7.88 (d, J=15.3 Hz, 1H), 7.87 (d, J=15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 55.9, 56.0, 60.6, 87.1, 106.9, 127.4, 128.3, 128.8, 130.0, 130.9, 135.4, 142.5, 158.4, 158.5, 159.3, 193.2.

4.1.25. 5,7,8-Trimethoxyflavanone (32). A mixture of chalcone **31** (2.4 g, 7.6 mmol), methanol (120 mL) and concd hydrochloric acid (60 mL) was refluxed for 40 h. Methanol was distilled off under vacuum and the residue was diluted with ice water (200 mL). The solid was filtered, washed with water (100 mL) and dried. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (50:50) as eluent to yield starting material **31** (0.5 g, 21%). R_f (50% ethyl acetate/light petroleum) 0.65; further elution with pure ethyl acetate gave the title compound **32** (1.52 g, 63%). Mp: 163–165 °C, lit.[20] 167–168 °C; R_f (50% ethyl acetate/light petroleum) 0.5; IR (KBr) 3007, 2937, 1682, 1598, 1569, 1346, 1276, 1124, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.86 (dd, J=3.4, 16.6 Hz, 1H), 3.0 (dd, J=12.0, 16.6 Hz, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 5.46 (dd, J=3.4, 12.0 Hz, 1H), 6.13 (s, 1H), 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 45.5, 56.0, 56.1, 61.1, 78.9, 89.4, 106.3, 125.9, 128.4, 128.6, 131.0, 138.8, 156.2, 157.8, 158.7, 189.2.

4.1.26. *cis*-5,7,8-Trimethoxyflavan-4-ol (33). A solution of **32** (250 mg, 7.96 mmol) in a mixture of methanol–THF (20 mL, 50:50) was cooled to 10 °C. Sodium borohydride (200 mg) was added in portions and the mixture was stirred at the same temperature for a further 1 h. The reaction was quenched by dropwise addition of acetic acid solution (10%, 4 mL), followed by stirring for 5 min. The reaction mixture was diluted with sodium chloride solution (10%, 100 mL) and the product extracted with ethyl acetate (25 mL×4). The solvent was distilled off and the residue was redissolved in ethyl acetate (25 mL), the extract dried over anhydrous sodium sulfate and concentrated to give the title compound as sticky solid (240 mg, 95%). Attempts to solidify the product by trituration with various solvents and cooling failed. The product was found to be unstable and hence was quickly used in the next reaction. IR (chloroform) 3500–2800, 3017, 1610, 1502, 1466, 1137, 1118, 1042 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 2.21 (ddd, J=9.4, 11.7, 13.5 Hz, 1H), 2.53 (ddd, J=1.8, 7.1, 13.5 Hz, 1H), 3.79 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 5.07 (dd, J=1.8, 11.7 Hz, 1H), 5.26 (dd, J=7.1, 9.4 Hz, 1H), 6.16 (s, 1H), 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 38.5, 55.1, 55.7, 59.8, 62.7, 76.9, 90.1, 125.9, 127.7, 128.3, 131.9, 141.2, 149.5, 152.9, 154.3; HRMS (ESI) m/z 339.1205 (M+Na$^+$, $C_{18}H_{20}O_5Na$, requires 339.1203).

4.1.27. 5,7,8-Trimethoxyflav-3-ene (34). A mixture of *p*-toluenesulfonic acid (16 mg) in toluene (120 mL) was heated to reflux for 1 h with azeotropic removal of water. A solution of **33** (240 mg, 0.75 mmol) in dichloromethane (2 mL) was added over 2 min and heating was continued for 15 min. The reaction mixture was cooled to room temperature and washed with satd sodium bicarbonate solution (25 mL×2). The toluene layer was dried over anhydrous sodium sulfate and the solvent evaporated under vacuum. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (20:80) as eluent to yield the title compound **34** (180 mg, 80%) as an oil. The product was found to be unstable,[5] and hence was quickly analyzed and used in the next step. R_f (20% ethyl acetate/light petroleum) 0.3; IR (neat) 2933, 1606, 1503, 1464, 1455, 1136, 1116 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.65 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 5.69 (dd, J=3.8, 10.1 Hz, 1H), 5.88 (dd, J=1.5, 3.8 Hz, 1H), 6.05 (s, 1H), 6.83 (dd, J=1.5, 10.1 Hz, 1H), 7.34 and 7.48 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 55.8, 56.1, 61.0, 89.4, 105.3, 118.6, 120.3, 126.9, 128.1, 128.4, 131.8, 140.4, 146.8, 151.1, 153.6.

4.1.28. 6a,12a-Dihydro-1,3,4,8,10,11-hexamethoxy-6-phenyl-7-[(1*E*)-2-phenylethenyl]-6*H*,7*H*-[1]benzopyrano[4,3-*b*][1]benzopyran (dependensin) (1). To a solution of **34** (500 mg, 1.67 mmol) in methanol (50 mL) was added concd hydrochloric acid (10 M, 4 mL). The mixture was stirred overnight at room temperature. Methanol was removed under vacuum and the product was dissolved in ethyl acetate, dried over anhydrous sodium sulfate and

concentrated. The crude product was chromatographed over silica gel using ethyl acetate/light petroleum (50:50) as eluent to yield title compound **1** (360 mg, 72%) as a white solid. The analytical sample was prepared by crystallization from methanol. Mp: 197–199 °C; R_f (50% ethyl acetate/light petroleum) 0.58; IR (KBr) 2933, 1609, 1501, 1455, 1204, 1140, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.31 (ddd, J=1.9, 2.6, 11.3 Hz, 1H), 3.35 (ddd, J=1.5, 1.9, 5.7 Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.96 (d, J=11.3 Hz, 1H), 5.40 (d, J=2.6 Hz, 1H), 5.99 (dd, J=1.5, 15.8 Hz, 1H), 6.15 (s, 1H), 6.17 (s, 1H), 6.17 (dd, J=5.7, 15.8 Hz, 1H), 7.1–7.4 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 33.4, 41.5, 56.3, 56.4, 56.8, 56.9, 61.3, 61.5, 63.0, 77.2, 89.6, 89.9, 103.4, 104.9, 126.6, 127.5, 127.8, 128.8×2, 128.9, 131.0, 131.9, 132.9, 137.7, 139.3, 147.6, 149.9, 152.5, 153.9, 154.5, 155.2; Anal. Calcd for $C_{36}H_{36}O_8$: C, 72.46; H, 6.10. Found: C, 72.26; H, 6.10; MS (ESI) m/z 619.21 ($M+Na^+$, $C_{36}H_{36}O_8Na$, requires 619.23).

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