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Regioselective hydroxylation of 2-hydroxychalcones by dimethyldioxirane towards polymethoxylated flavonoids

Han-Wei Chu, Huan-Ting Wu and Yean-Jang Lee*

Department of Chemistry, National Changhua University of Education, No. 1 Ching Der Road, Changhua 50058, Taiwan

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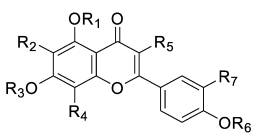
Abstract—The flavone nucleus is part of a large number of natural products and medicinal compounds. In this presentation the novel regioselective hydroxylation of hydroxyarenes with DMD is described. The results showed further that flavonoids with 5-hydroxy group were selectively oxyfunctionalized at the *para*-position C8 carbon atom by DMD. Finally, according to this methodology, the naturally occurring isosinensetin, tangeretin, sinensetin, nobiletin, natsudaidain, gardenin B, 3,3′,4′,5,6,7,8-heptamethoxyflavone, quercetin and its derivatives were synthesized.

1. Introduction

The flavone nucleus is part of a large number of natural products and medicinal compounds.[1] Quercetin (**7**) and kaempferol[2] are known as potential anti-tumor agents and human immunodeficiency virus (HIV) type 1 integrase inhibitors.[3] In addition, the polyphenol constituents of fruits, vegetables, and beverages are important contributors to health benefits including anticancer and antiviral activities and reduce the risk of coronary heart disease and stroke.[4] Recently much attention has focused on the protective biochemical function of naturally occurring antioxidants in biological systems, and on their mechanisms of action. Phenolic compounds were considered to play an important role for the prevention of oxidative damage in living systems.[5] Moreover, in capturing free radicals, their antioxidant activity is highly influenced by the presence of oxygenated groups (hydroxyls, methoxyls) on the aromatic rings. For instance, our previous investigation indicated that the CAPE analogues[6a–c] are therapeutically useful in analogy to the structural feature of an *ortho*-dihydroxy system.[7] In our observations,[6b] the ability of **7** and glycyrrhizin to scavenge free-radicals and block lipid peroxidation raises the possibility that they may act as protective factors against carcinogenesis, and it implies that **7** is better than glycyrrhizin as a chemopreventor against cytotoxicity and genotoxicity on co-exposure of cadmium and AA in V79 cells. Compound **7** is also consistent with structure and activity relationship that the aryl units contain at least one aryl ring required *ortho* bis-hydroxyl groups for significant inhibitory potency of antioxidants. Furthermore, Yano et al. have observed that six polymethoxylated flavonoids, namely, tangeretin (**2**), sinensetin (**3**), nobiletin (**4**), natsudaidain (**5**), gardenin B (**6**), and 3,3′,4′,5,6,7,8-heptamethoxyflavone (**8**), are important candidates for cancer-protective action.[8] In addition, Rio et al.[9] found that quercetogetin may play a protective role against pathogenic attack, and the biological activities of the polymethoxylated flavones are not well understood. Due to the medicinal imperatives, the scarcity of polyhydroxylated or polymethoxylated flavones and the clear need for a reliable supply, we are stimulated to synthesize polymethoxylated flavonoids **1**–**13**.



isosinensetin	**1** R_1=R_2=R_5=H,R_3=R_6=Me,R_4=R_7=OMe	**8** R_1=R_3=R_6=Me,R_2=R_4=R_5=R_7=OMe
tangeretin	**2** R_1=R_3=R_6=Me,R_2=R_4=OMe,R_5=R_7=H	**9** R_1=R_3=R_6=Me,R_2=R_4=H,R_5=R_7=OMe
sinensetin	**3** R_1=R_3=R_6=Me,R_2=R_7=OMe,R_4=R_5=H	**10** R_1=R_3=R_6=Me,R_2=R_4=H,R_5=OH,R_7=OMe
nobiletin	**4** R_1=R_3=R_6=Me,R_2=R_4=R_7=OMe,R_5=H	**11** R_1=R_2=R_4=H,R_3=R_6=Me,R_5=R_7=OMe
natsudaidain	**5** R_1=R_3=R_6=Me,R_2=R_4=R_7=OMe,R_5=OH	**12** R_1=R_2=H,R_3=R_6=Me,R_4=R_5=R_7=OMe
gardenin B	**6** R_1=R_5=R_7=H,R_2=R_4=OMe,R_3=R_6=Me	**13** R_1=R_3=R_6=Me,R_2=H,R_4=R_5=R_7=OMe
quercetin	**7** R_1=R_2=R_3=R_4=R_6=H,R_5=R_7=OH	

Keywords: Flavones; Hydroxylation; Dioxirane.
* Corresponding author. Tel.: +886-4-7232105; fax: +886-4-7211190; e-mail address: leeyj@cc.ncue.edu.tw

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We have developed syntheses of kaempferol and methylated kaempferols,[10] which has been worked on C3-hydroxylation of flavone by dimethyl dioxirane (DMD).[11] There are semisynthetic studies in the literature.[10] The reported results[10] and our preliminary study shows that the flavones can be synthesized from *o*-hydroxyketones or chalcones using the Allan-Robinson[10] or Algar-Flym-Oyamada[10] reaction, but in poor yields. Moreover, compared with other approaches for synthesizing polymethoxylated flavones, the oxidative reaction of the C-3 flavones was proved impossible to effect lithiolation with LDA or LHMDS, $B(OMe)_3$, and H_2O_2. Alternately, oxidative-hydroxylation of DMD has been reported by several groups.[12] Recently Bernini et al. claimed that aromatic ring hydroxylation of flavanones by DMD under acidic media.[13] However, the scope of this process appears to be limited. For example, the free hydroxy group of flavones affects the reaction, and it has a competition pathway between C3 hydroxylation and aromatic rings. Herein we report the regioselective hydroxylation of 2-hydroxylchalcones by DMD towards isosinensetin (**1**), **2**, **3**, **4**, **5**, **6**, **8**, **7** and its derivatives efficiently.

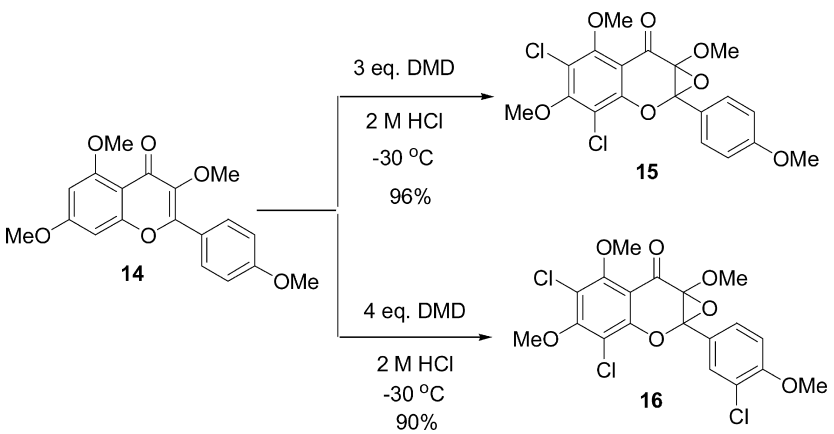
2. Results and discussion

In the beginning of our synthesis, the availability of methylated flavones prompted us to prepare polymethoxylated flavones from this compound. The synthetic compound **14**[10] was treated with 3 or 4 equiv. DMD (0.22 or 0.30 mmol) under 2 M HCl conditions to give the undesired chlorinated products **15** and **16** in excellent yield 96 and 90%, respectively (Scheme 1). The structures were analyzed by ^1H, ^{13}C NMR, and mass spectra. Thus, the utilization of acid media in DMD oxidation reactions on the methylated flavones cannot allow us to synthesize the polymethoxylated flavonoids.

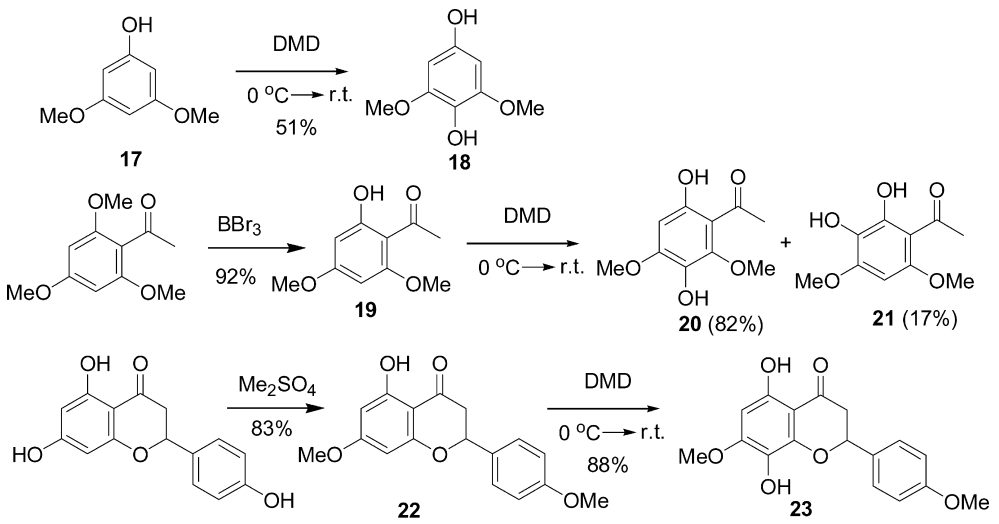
To evaluate this approach to hydroxyflavones, we tested simple aromatic compounds and 5-hydroxyflavonoids (**22**) and examine its versatility (Scheme 2). Insight into the scope of this reaction was initially gained in study with 3,5-dimethoxyphenol **17**. The hydroxybenzene **17** was treated with 1 equiv. DMD for 2 h to provide the dominated regiospecific product **18** in moderate yield 51%. Moreover, it can be smoothly obtained by the hydroxylation of **19** under previous conditions to afford the desired dihydroxyarene **20**. However, the adjacent hydroxyl **21** was accompanied in 17% yield. In a similar fashion, one interesting result had come from the reaction of 5-hydroxyflavanone **22** with DMD to provide the regiospecific hydroxylated product **23** in high yield 88%. The *regio*-structure of **20** was confirmed by use of X-ray crystallographic method.[14] Although, we do not know the detailed mechanism of the regioselective hydroxylation with DMD in the phenols. On the basis of these observations and Adam's[15] studies, the mechanistic route for the formation of the corresponding hydroxyl products involve an epoxide-intermediate **24**[15] at the first stage, and it then undergo a ring opening to obtain the regioselective *ortho*- and *para*-hydroxyl arenes (Scheme 3).

As a consequence of the biological and structural interest in polymethoxyl flavonoids, we initiated using this novel regioselective hydroxylation by DMD to prepare these substances, such as **1**, **7**, *tetra-O*-methylisoscutellarein (**27**), and kaempferols. It is worth noted that this oxyfunctional reaction may occur on the free 5-hydroxy group of flavones. The 5-hydroxy group could play a determining role in favoring C8-position oxyfunctionalized process. The C8 hydroxyl products obtained in this way appear useful starting materials to access polymethoxygenated flavonoids, known to be antioxidant and anti-tumor compounds. The results are shown in Scheme 4, which is manipulated by the treatment of 5-hydroxyflavones, **25**[10] and **26a**,[16] via the sequence of DMD and Me_2SO_4. For instance, compound **25** was readily performed by C8-hydroxylation with 1 equiv. DMD under neutral conditions and followed by methylation with 1 equiv. Me_2SO_4 to obtain the expected **27** in high yield (two steps 85%). Moreover, **26a** was also underway with 1 equiv. DMD to provide the C8-hydroxylation flavone, and followed by methylation to give **1** and **28** in 55 and 38% yield (two steps), respectively. On the other hand, the methylation of **26a** with Me_2SO_4 to provide the methylated flavone **26b** in excellent yield (97%), which could be converted by the sequence of C3-oxidative-hydroxylation and demethylation to afford kaempferol and quercetin derivatives **7**, **9**, **10**, and **11** as well.

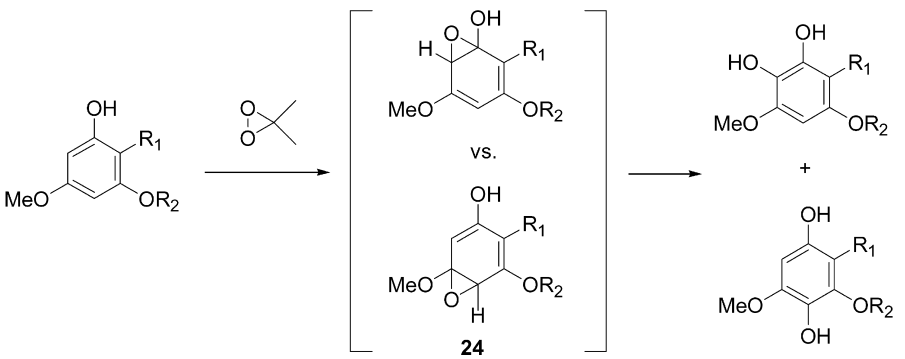
With the 5-hydroxy flavone **11** in hand, it can readily proceed with the regioselective oxidative-hydroxylation by DMD to afford the desired product **29** in high yield 89%



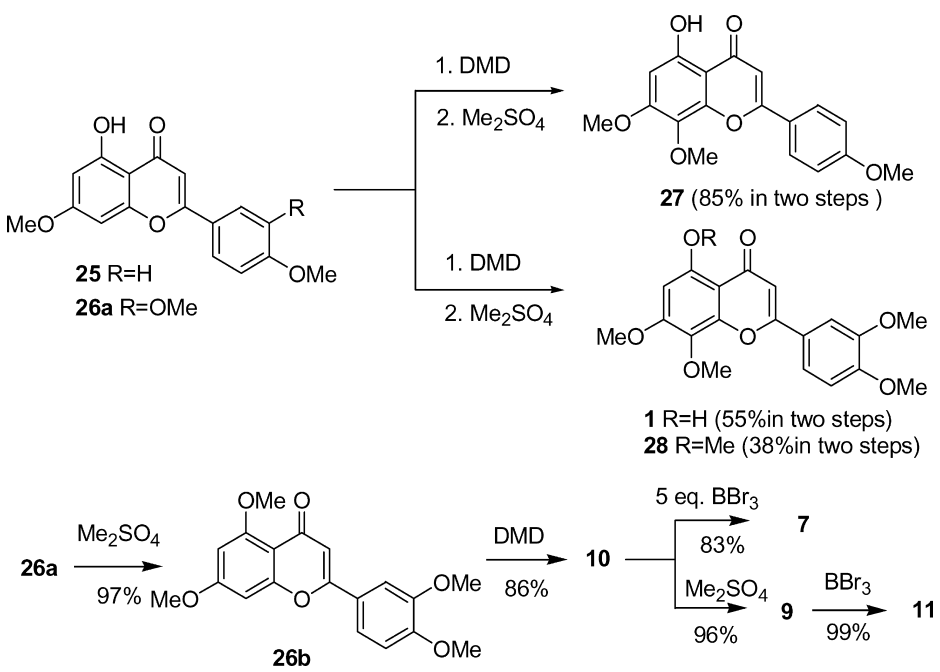
Scheme 1.



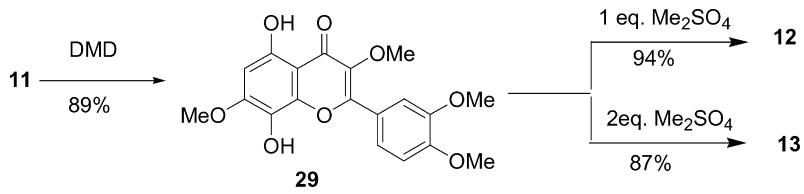
Scheme 2.



Scheme 3.



Scheme 4.

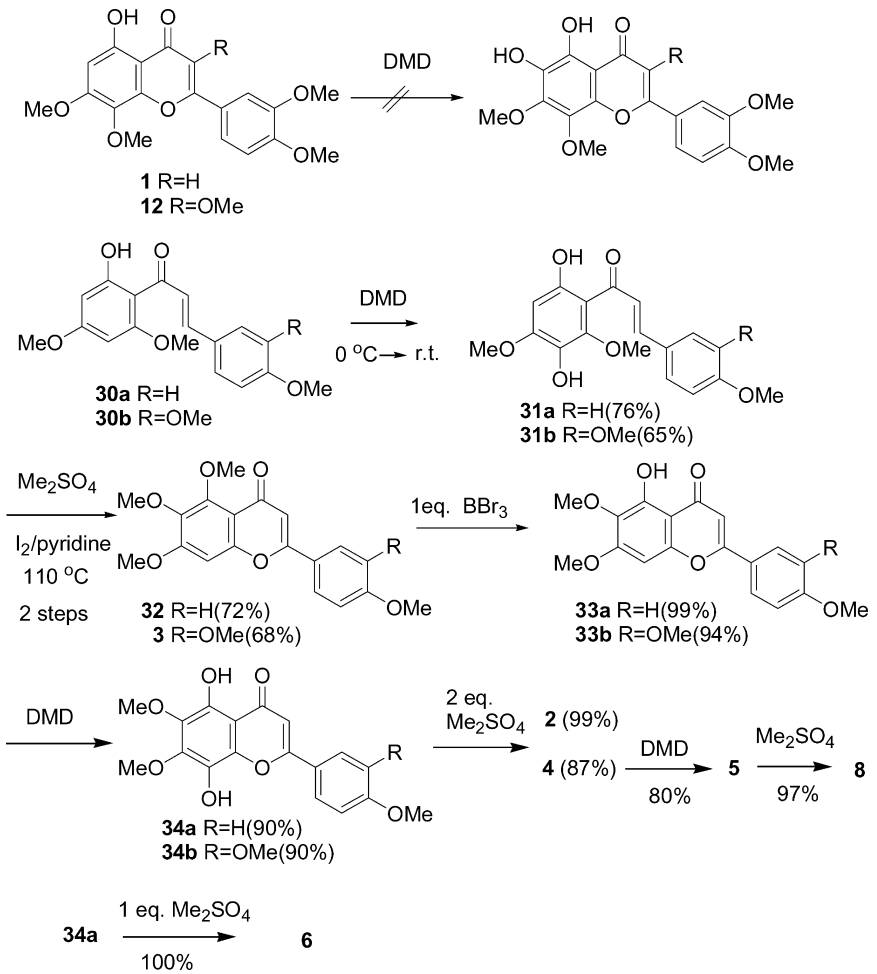


Scheme 5.

(Scheme 5). Sequentially, the dihydroxyl flavone **29** was treated with Me_2SO_4 to achieve the natural occurring product **12** in high yield (two steps 84% from **11**). The result also observed that **11** was transformed by the treatment of DMD and followed by methylation with 2 equiv. Me_2SO_4 to produce the polymethylated flavone **13** in good yield (two steps 77%).

Finally, we applied our strategy to the synthesis of the polymethoxyflavones **2**–**8**. Attempts to obtain 5,6-dihydroxyflavones from 5-hydroxyflavones with DMD and subsequent methylation with Me_2SO_4 (Scheme 6) were unsuccessful, and resulted in the B-ring opening and oxidative-degradation products, chalcones, ketones and aldehydes from 5-hydroxyflavones. An alternative procedure involving regioselective hydroxylation of 2-hydroxychalcones **30a** or **30b**, followed by a methylation and an oxidative-cyclization reaction on the resulting dihydroxychalcones **31a** or **31b** using Me_2SO_4 and I_2/pyridine gave good yields of the corresponding naturally occurring *tetra-O*-methylscutellarein **32** and **3**, respectively. The *regio*-structures of **31a**, **31b** and **32** were identified by use of X-ray crystallographic method.[14] With the key intermediates **3** and **32** in hand, it is manipulated by the treatment of polymethoxyflavones, **3** and **32**, via the sequence of BBr_3, DMD, and Me_2SO_4. For example, compounds, **3** and **32**, were readily employed by C5-demethylation with 1 equiv. BBr_3, and followed by the regioselective hydroxylation and methylation with DMD and Me_2SO_4 under standard conditions to obtain the naturally occurring **2**, **4** and **6** in a high yield 88, 74 and 89% (three steps from **3** and **32**), respectively. Furthermore, compound **4** could be converted by the sequence of C3-hydroxylation and methylation to afford **5** and **8** as well.

In summary, we have developed the versatility of DMD in



Scheme 6.

C3- and C8-hydroxylation of flavones and provided a practical method to synthesize the naturally occurring methylated flavones **1**–**13** starting with commercially available aldehyde. In addition, the key intermediates **3** and **32**, polymethoxyflavones, have efficiently been synthesized by cross-aldol condensation, DMD regioselective hydroxylation and I_2 oxidative promoting-cyclization. However, the regioselective C8-hydroxylation of aromatic ring, 5-hydroxyflavone, is predominated over the conjugated C3- or C6-position of flavones. Therefore, the mechanistic studies should be addressed in near future. Further polymethylated or polyhydroxylated flavones are currently underway to employ this strategy for supplying biological assays.

3. Experimental[17]

3.1. General procedure for hydroxylation with DMD

The required amount (5.0–150 mL) of the DMD (prepared according to Adam's method[11]) in acetone (0.01–0.05 M) was added rapidly to a cooled solution of flavones or aromatic compound under neutral conditions. Stirring was continued for various time, the reaction was monitored by TLC analysis. The solvent was removed and the residue was subjected to column chromatography to give the corresponding oxygenated or chlorinated products.

3.1.1. 1a,7a-Dihydro-3,5-dichloro-4,6-dimethoxy-1a-(4-methoxyphenyl)-7a-methoxy-7*H*-oxireno[b][1]benzopyran-7-one (15). A solution of **14** (25 mg, 0.073 mmol) in CH_2Cl_2 was cooled down to −30 °C under 2 M HCl (4.0 mmol), and then treated with DMD (22 mL, 0.22 mmol) for stirring 1 min. The solvent was removed in vacuo, and the residue was subjected to column chromatography (CH_2Cl_2/ether 2:1) to obtain the chlorinated product **15** (30 mg, 96%) as a white solid: mp 119–121 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 3.53, 3.89, 4.03 and 4.19 (3H each, s, OMex4), 6.96 and 8.26 (2H each, d, J=9.0 Hz, 2,6-H, 3,5-H); ^{13}C NMR ($CDCl_3$) δ 53.4, 55.5, 61.3, 63.1, 107.0, 108.9, 109.0, 113.7, 115.7, 125.7, 133.4, 153.8, 161.7, 164.4, 165.8, 187.6, 189.8; HRMS (FAB+H) calcd for $C_{19}H_{17}O_7Cl_2$: 427.0351 [M+H], found: m/z 427.0351 $[M+H]^+$.

3.1.2. 1a,7a-Dihydro-3,5-dichloro-4,6-dimethoxy-1a-(3-chloro-4-methoxyphenyl)-7a-methoxy-7*H*-oxireno[b][1]benzopyran-7-one (16). Followed by previous procedures and conditions, a solution of **14** (25 mg, 0.073 mmol) in CH_2Cl_2 was treated with DMD (30 mL, 0.30 mmol) for stirring 1 min. The solvent was removed in vacuo, and the residue was subjected to column chromatography (CH_2Cl_2/ether 2:1) to obtain the chlorinated product **16** (30 mg, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.53, 3.99, 4.03 and 4.19 (3H each, s, OMex4), 7.01 (1H, d, J=8.5 Hz, 5-H), 8.24 (1H, d, J=8.5 Hz, 6-H), 8.27 (1H, s, 2-H); ^{13}C NMR ($CDCl_3$) δ 53.5, 56.4, 61.3, 63.1, 107.0, 108.7, 108.7, 111.1, 115.9, 122.8, 126.2, 131.9, 132.9, 153.8, 159.6, 161.8, 165.7, 186.9, 189.4.

3.1.3. 2,6-Dimethoxybenzene-1,4-diol (18). The compound **17** (150 mg, 0.97 mmol) in CH_2Cl_2 was added DMD (5.0 mL) for stirring 50 min from 0 °C to room temperature. The purification was employed by column chromatography (hexane/ether 2:1) to provide the desired dihydroxy benzene **18** (84 mg, 51%) as a yellow solid: mp 253–255 °C (acetone) (lit.[18] mp 149 °C).

3.1.4. 3,6-Dihydroxy-2,4-dimethoxyacetophenone (20) and 2,3-dihydroxy-4,6-dimethoxyacetophenone (21). A solution of synthetic 2,4,6-trimethoxyacetophenone[10] (200 mg, 0.95 mmol) in CH_2Cl_2 was added BBr_3 (1 M, 1.0 mL, 1.0 mmol) solution dropwise at room temperature. The mixture was stirred under a nitrogen atmosphere for 20 min. The resulting solution was quenched by adding 4 M KOH (2.0 mL), and followed by extraction with CH_2Cl_2. The solvent was removed in vacuo to give a solid mixture which was subjected to column chromatography (SiO_2, hexane/ether 2:1) to obtain **19** (172 mg, 92%) as a white needle solid: mp 80–81 °C (hexane) (lit.[19a] mp 83–85 °C). According to previous general procedure for hydroxylation, the synthetic **19** (150 mg, 0.76 mmol) was treated with DMD (45 mL, 0.85 mmol) for stirring 10 min. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to provide the products **20** (133 mg, 82%) and **21** (27 mg, 17%), respectively. **20**: mp 156–158 °C (hexane) (lit.[19b] mp 162–162.5 °C); **21**: mp 161 °C (hexane) (lit.[19b] mp 161–165.5 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.63 (3H, s, CH_3), 3.88 and 3.96 (3H each, s, OMex2), 6.01 (1H, s, 5-H).

3.1.5. 2,3-Dihydro-5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyranone (22). To a mixture of 4,5,7-trihydroxyflavanone (500 mg, 1.8 mmol) and K_2CO_3 (2 equiv. 500 mg) in acetone (50 mL) was added Me_2SO_4 (0.40 mL, 4.2 mmol) dropwise at room temperature, and then refluxed for 6 h. The resulting solution was cooled and was added to H_2O (10 mL), and extracted with CH_2Cl_2 (3×100 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to afford the desired product **22** (459 mg, 83%) as a white solid: mp 167–168 °C (CH_2Cl_2) (lit.[20a] mp 164 °C).

3.1.6. 2,3-Dihydro-5,8-dihydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyranone (23). A solution of **22** (50 mg, 0.17 mmol) in CH_2Cl_2 was introduced with DMD (0.30 mL, 0.34 mmol) for 20 min to give the regioselective product **23** (47 mg, 88%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.88 (1H, dd, J=16.6, 3.8 Hz, 3-H), 3.11 (1H, dd, J=16.6, 12.5 Hz, 3-H), 3.82 (3H each, s, OMex2), 5.64 (1H, dd, J=12.5, 3.8 Hz, 2-H), 5.89 (1H, s, 6-H), 6.95 and 7.36 (2H each, d, J=8.7 Hz, 2,6-H, 3,5-H).

3.1.7. 5-Hydroxy-7-methoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (26a). The **26a** was synthesized by our previous procedure[10] from **30b** (1.75 g, 5.1 mmol) in overall yield 97% (two steps) as a yellow solid: mp 169 °C (CH_2Cl_2) (lit.[20b] mp 161–162 °C).

3.1.8. 5-Hydroxy-7,8-dimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (27). The 5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyrone (**25**) was prepared according to our previous procedure.[10] A solution of **25** (150 mg, 0.50 mmol) in CH_2Cl_2 was added DMD (40 mL,

0.8 mmol) for 2 h to provide the desired 5,8-dihydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyrone (141 mg, 89%) as a solid: mp 269–271 °C (acetone) (lit.[21] mp 214–215 °C); ^{1}H NMR (200 MHz, DMSO) δ 3.96 and 4.00 (3H each, s, OMex2), 6.65 (1H, s, 6-H), 6.98 (1H, s, 3-H), 7.23 and 8.22 (2H each, d, J=8.8 Hz, 2,6-H, 3,5-H), 9.01 (1H, s, OH); HRMS (EI) calcd for $C_{17}H_{14}O_6$: 314.0790 [M], found: 314.0783 [M]$^+$. To a mixture of dihydroxyflavone (180 mg, 0.57 mmol) and K_2CO_3 (1.5 equiv. 120 mg) in acetone (10 mL) was added Me_2SO_4 (54 μL, 0.57 mmol) dropwise at room temperature, and then refluxed for 3 h. The resulting solution was cooled and was added H_2O (2 mL), and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2) to afford the desired product **27** (180 mg, 96%) as a white solid: mp 220.5 °C (CH_2Cl_2) (lit.[22] mp 220–221 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90, 3.94, and 3.95 (3H each, s, OMex3), 6.43 (1H, s, 6-H), 6.59 (1H, s, 3-H), 7.03 and 7.91 (2H each, d, J=8.8 Hz, 2,6-H, 3,5-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.5, 56.3, 61.6, 95.7, 103.8, 104.8, 114.5, 123.5, 128.1, 128.9, 149.4, 157.5, 158.4, 162.7, 163.9, 182.6.

3.1.9. 5,7,8-Trimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (28) and isosinensetin (1). A solution of **26a** (100 mg, 0.30 mmol) in CH_2Cl_2 was treated with DMD (15 mL, 0.30 mmol) for 20 min to give the regioselective product 5,8-dihydroxy-7-methoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (98 mg, 93%) as a yellow solid: mp 254–256 °C (acetone) (lit.[23a] mp 250–251 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.97 and 3.99 (3H each, s, OMex3), 6.44 (1H, s, 6-H), 6.58 (1H, s, 3-H), 6.99 and 7.65 (1H each, d, J=8.4 Hz, 5,6-H), 7.51 (1H, s, 2-H). To a mixture of dihydroxyflavone (90 mg, 0.26 mmol) and K_2CO_3 (1.5 equiv. 54 mg) in acetone (5.0 mL) was added Me_2SO_4 (30 μL, 0.32 mmol) dropwise at room temperature, and then refluxed for 1 h. The resulting solution was cooled and was added H_2O (1 mL), and extracted with CH_2Cl_2 (3×10 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to afford the desired products **1** (55 mg, 59%) as a yellow solid and **28** (40 mg, 41%) as a white solid. **28**: mp 190–192 °C (acetone) (lit.[23b] mp 199–200 °C); HRMS (EI) calcd for $C_{20}H_{20}O_7$: 372.1209 [M], found: m/z 372.1216 [M]$^+$; **1**: mp 199–201 °C (CH_2Cl_2) (lit.[24] mp 207–208 °C); HRMS (EI) calcd for $C_{19}H_{18}O_7$: 358.1053 [M], found: 358.1051 [M]$^+$.

3.1.10. Quercetin (7). To a suspension of **26a** (1.5 g, 4.6 mmol) and K_2CO_3 (1.5 equiv. 0.95 g) in acetone (50 mL) was added Me_2SO_4 (0.65 mL, 6.9 mmol) dropwise at room temperature, and then refluxed for 2 h. The resulting solution was cooled and was added H_2O (10 mL), and extracted with CH_2Cl_2 (3×200 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 2:1) to give the desired tetramethoxylflavone **26b** (1.5 g, 97%) as a white solid: mp 190–192 °C (CH_2Cl_2) (lit.[25a] mp 188–190 °C). The amount of DMD (50 mL) was added rapidly under N_2 to a cooled solution of methylated flavone **26b** (0.40 g, 1.2 mmol) in dried CH_2Cl_2 (50 mL). Stirring was continued for 30 min. The solvent was removed and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to provide the corresponding 3-hydroxy-5,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (**10**) (0.36 g, 86%) as a yellow solid: mp 184–186 °C (CH_2Cl_2) (lit.[26] mp 197–198 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.89, 3.92, 3.97, and 4.03 (3H each, s, OMex4), 6.33 and 6.53 (1H each, d, J=2.1 Hz, 6,8-H), 6.98 (1H, d, J=9.1 Hz, 5-H), 6.95 (1H, d, J=9.1 Hz, 6-H), 7.81 (1H, s, 2-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.5, 56.6, 56.7, 57.5, 93.1, 96.3, 106.8, 111.0, 111.5, 121.3, 124.4, 138.2, 142.8, 149.5, 150.9, 159.5, 161.2, 165.0, 172.5.

A sealed tube of **10** (0.30 g, 0.84 mmol) and BBr_3 (5 equiv. 1 M, 4.2 mL) in CH_2Cl_2 (10 mL) was refluxed for 6 h, and then cooled to room temperature. The brown mixture was dissolved in MeOH and subjected to column chromatography (SiO_2, EtOAc/CH_2Cl_2 1:4) to obtain **7** (0.21 g, 83%) as a yellow solid: mp 320 °C (acetone) (lit.[25b] mp 318–320 °C); ^{1}H NMR (300 MHz, $(CD_3)_2CO$+DMSO) δ 6.22 and 7.78 (1H each, d, J=2.1 Hz, 6,8-H), 6.46 (1H, d, J=1.8 Hz, 2′-H), 6.95 (1H, d, J=8.4 Hz, 5′-H), 7.64 (1H, dd, J=8.4, 2.1 Hz, 6′-H); ^{13}C NMR (75.47 MHz, $(CD_3)_2$-CO+DMSO) δ 92.6, 97.4, 102.2, 114.0, 114.4, 119.5, 121.8, 134.9, 144.2, 145.3, 146.7, 155.9, 160.4, 163.5, 174.8.

3.1.11. 3,5,7-Trimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (9). To a mixture of **10** (1.0 g, 2.8 mmol) and K_2CO_3 (1.2 equiv. 0.46 g) in acetone (80 mL) was added Me_2SO_4 (0.32 mL, 3.3 mmol) dropwise at room temperature, and then refluxed for 1 h. The resulting solution was cooled and was added H_2O (10 mL), and extracted with CH_2Cl_2 (3×200 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired pentamethoxylflavone **9** (1.0 g, 96%) as a white solid: mp 154–155 °C (acetone) (lit.[27] mp 153–154 °C).

3.1.12. 5-Hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (11). A solution of **9** (1.0 g, 2.7 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 2.7 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the corresponding **11** (0.95 g, 99%) as a yellow solid: mp 158–159 °C (CH_2Cl_2) (lit.[28] mp 160–161 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.85 and 3.96 (3H each, s, OMex4), 6.30 and 6.40 (1H each, d, J=2.1 Hz, 6,8-H), 6.96 (1H, d, J=8.5 Hz, 5-H), 7.66 (1H, s, 2-H), 7.72 (1H, d, J=8.5 Hz, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$) 56.4, 56.6, 56.6, 60.7, 92.7, 98.4, 106.6, 111.4, 111.8, 122.7, 123.5, 139.5, 149.3, 152.0, 156.3, 157.2, 162.5, 166.0, 179.3.

3.1.13. 5,8-Dihydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (29). The **11** (0.30 g, 0.84 mmol) in CH_2Cl_2 was added with DMD (25 mL, 1.0 mmol) for 50 min to obtain the regioselective product **29** (0.28 g, 89%) as a yellow solid: mp 238–240 °C (acetone) (lit.[29] mp 240–242 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.87, 3.88, 3.97, and 3.98 (3H each, s, OMex4), 6.44 (1H, s, 6-H), 7.00 (1H, d, J=8.5 Hz, 5′-H), 7.79 (1H, d, J=1.9 Hz, 2′-H), 7.80 (1H, dd,

J=8.5, 1.9 Hz, 6′-H); HRMS (EI) calcd for $C_{19}H_{18}O_8$: 374.1004 [M], found: m/z 374.1002 $[M]^+$.

3.1.14. 5-Hydroxy-3,7,8-trimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (12). To a mixture of **29** (0.24 g, 0.64 mmol) and K_2CO_3 (1.0 equiv. 89 mg) in acetone/CH_2Cl_2 (1:1 50 mL) was added Me_2SO_4 (61 μL, 0.63 mmol) dropwise at room temperature, and then refluxed for 4 h. The resulting solution was cooled and was added H_2O (1.0 mL), and extracted with CH_2Cl_2 (3×100 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **12** (0.23 g, 94%) as a yellow solid: mp 152–155 °C (CH_2Cl_2) (lit.[30a] mp 161–162 °C); HRMS (FAB+H) calcd for $C_{20}H_{21}O_8$: 389.1236 [M+H], found: m/z 389.1233 $[M+H]^+$.

3.1.15. 3,5,7,8-Tetramethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (13). Followed by previous conditions from **29** (0.39 g, 1.0 mmol), K_2CO_3 (5.0 equiv. 0.73 g), and Me_2SO_4 (0.30 mL, 3.2 mmol) in acetone/CH_2Cl_2 (1:1 50 mL) to generate the corresponding **13** (0.36 g, 87%) as a white solid: mp 166–167 °C (acetone) (lit.[30b] mp 170 °C); HRMS (FAB+H) calcd for $C_{21}H_{23}O_8$: 403.1393 [M+H], found: m/z 403.1396 $[M+H]^+$.

3.1.16. 1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)propenone (30a). The chalcone **30a** was synthesized by the known procedure.[10]

3.1.17. 1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (30b). According to our previous procedures, a mixture of 2,4,6-trimethoxyacetophenone (4.3 g, 20 mmol) and 3,4-dimethoxybenzaldehyde (3.9 g, 23 mmol) in ethanol (200 mL) was stirred at room temperature for 20 min. A solution of 50% KOH (80 mL) was added dropwise, and then stirred at room temperature for 3 h. The resulting solution was neutralized by addition of 4 M HCl and extracted with CH_2Cl_2 (3×300 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, EtOAc/CH_2Cl_2 1:4) to give the desired 1-(2,4,6-trimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (7.1 g, 99%) as a yellow solid: mp 117 °C (CH_2Cl_2) (lit.[31a] mp 117 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.79, 3.80, 3.86, 3.90, and 3.91 (3H each, s, OMex5), 6.17 (2H, s, 3,5-H), 6.84 and 7.29 (1H each, d, J=16.0 Hz, 2,3-C=H), 6.85 and 7.09 (1H each, d, J=8.0 Hz, 5′,6′-H), 7.07 (1H, s, 2′-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.3, 55.8, 55.8, 55.8, 90.6, 109.8, 110.9, 111.7, 122.8, 127.0, 127.7, 144.5, 149.0, 151.0, 158.5, 162.1, 194.3. A solution of 1-(2,4,6-trimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (2.4 g, 6.7 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 6.7 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to provide the corresponding **30b** (2.0 g, 90%) as a orange yellow solid: mp 154–156 °C (ether) (lit.[31b] mp 135–137 °C).

3.1.18. 1-(2,5-Dihydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)propenone (31a). The solution of **30a** (0.25 g, 0.80 mmol) in CH_2Cl_2 was added with DMD (45 mL, 0.90 mmol) for 1 h to give the regioselective product **31a** (0.20 g, 76%) as a red orange solid: mp 128–130 °C (hexane) (lit.[31c] mp 141–142 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.86, 3.87, and 3.94 (3H each, s, OMex3), 6.33 (1H, s, 3-H), 6.94 and 7.60 (2H each, d, J=8.8 Hz, 2′,6′-H, 3′,5′-H), 7.86 (1H each, s, 2,3-C=H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.4, 56.3, 61.8, 96.2, 108.6, 114.4, 123.6, 128.0, 130.2, 131.7, 143.5, 146.8, 154.1, 159.6, 161.6, 192.5; HRMS (EI) calcd for $C_{18}H_{18}O_6$: 330.1103 [M], found: m/z 330.1110 $[M]^+$.

3.1.19. 1-(2,5-Dihydroxy-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (31b). Followed by general procedure for hydroxylation, a solution of **30b** (0.25 g, 0.73 mmol) in CH_2Cl_2 was added with DMD (40 mL, 0.80 mmol) for 1 h to produce the regioselective dihydroxychalcone **31b** (0.17 g, 65%) as a orange yellow solid: mp 171–172 °C (ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.87, 3.93, and 3.94 (3H each, s, OMex3), 6.33 (1H, s, 3-H), 6.91 (1H, d, J=8.3 Hz, 5′-H), 7.17 (1H, d, J=1.3 Hz, 2′-H), 7.24 (1H, dd, J=8.3, 2.0 Hz, 6′-H), 7.85 (1H each, s, 2,3-C=H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.4, 56.8, 62.3, 96.7, 109.1, 110.5, 111.7, 123.7, 124.4, 128.8, 132.4, 144.3, 147.4, 149.8, 151.9, 154.8, 160.1, 193.0; HRMS (EI) calcd for $C_{19}H_{20}O_7$: 360.1209 [M], found: m/z 360.1205 $[M]^+$.

3.1.20. 5,6,7-Trimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (32). A mixture of **31a** (0.24 g, 0.73 mmol) and K_2CO_3 (1.2 equiv. 0.12 g) in acetone (50 mL) was added Me_2SO_4 (68 μL, 0.73 mmol), and then refluxed for 4 h. The resulting solution was cooled and added H_2O (1.0 mL), and extracted with CH_2Cl_2 (3×100 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the corresponding 1-(6-hydroxy-2,3,4-trimethoxyphenyl)-3-(4-methoxyphenyl)propenone (0.24 g, 95%) as a yellow solid: mp 139–141 °C (hexane) (lit.[32] mp 142 °C); HRMS (EI) calcd for $C_{19}H_{20}O_6$: 344.1260 [M], found: m/z 344.1255 $[M]^+$. To a mixture of hydroxychalcone (0.24 g, 0.69 mmol) and I_2 (1 equiv. 0.69 mmol) in pyridine (10 mL) was refluxed for 4 h. After cooling, the solid was filtered and the filtrate was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to obtain the desired product **32** (0.18 g, 76%) as a white solid: mp 134–135 °C (hexane) (lit.[32] mp 141–142 °C); HRMS (EI) calcd for $C_{19}H_{18}O_6$: 342.1103 [M], found: m/z 342.1101 $[M]^+$.

3.1.21. Sinensetin (3). According to the previous preparation of **32**, a mixture of **31b** (0.25 g, 0.69 mmol) and K_2CO_3 (1.1 equiv. 0.11 g) in acetone (25 mL) was added Me_2SO_4 (70 μL, 0.74 mmol), and then refluxed for 6 h to afford the desired 1-(6-hydroxy-2,3,4-trimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propenone (0.16 g, 95%) as a yellow solid: mp 135–136 °C (ether) (lit.[32] mp 140–142 °C); HRMS (EI) calcd for $C_{20}H_{22}O_7$: 374.1366 [M], found: m/z 374.1359 $[M]^+$. A mixture of hydroxychalcone (0.25 g, 0.67 mmol) and I_2 (1.1 equiv. 0.75 mmol) in pyridine (5 mL) was refluxed for 8 h. After cooling, the solid was filtered and the filtrate was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to obtain sinensetin **3** (0.16 g, 71%) as a white solid: mp 174–176 °C (acetone)

(lit.[22] mp 176–177 °C); HRMS (EI) calcd for $C_{20}H_{20}O_7$: 372.1209 [M], found: *m/z* 372.1219 $[M]^+$.

3.1.22. Tangeretin (2). A solution of **32** (0.10 g, 0.29 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 0.29 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the corresponding 5-hydroxy-6,7-dimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (**33a**) (0.095 g, 99%) as a light yellow solid: mp 185–187 °C (CH_2Cl_2) (lit.[22] mp 185–186 °C); HRMS (EI) calcd for $C_{18}H_{18}O_6$: 328.0947 [M], found: *m/z* 328.0941 $[M]^+$. Followed by general procedure for hydroxylation, a solution of 5-hydroxyflavone **33a** (0.090 g, 0.27 mmol) was added with DMD (15 mL, 0.30 mmol) for 20 min to provide the regioselective 5,8-dihydroxy-6,7-dimethoxy-2-(4-methoxyphenyl)-4-benzopyrone (**34a**) (0.085 g, 90%) as a brown yellow solid: mp 194–196 °C (acetone) (lit.[33] mp 199–200 °C); HRMS (EI) calcd for $C_{18}H_{16}O_7$: 344.0896 [M], found: *m/z* 344.0895 $[M]^+$. To a mixture of dihydroxyflavone **34a** (0.075 g, 0.22 mmol) and K_2CO_3 (2.5 equiv. 0.076 g) in acetone/CH_2Cl_2 (1:1 10 mL) was added Me_2SO_4 (52 μL, 0.55 mmol) at room temperature, and then refluxed for 4 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **2** (0.080 g, 99%) as a white solid: mp 152.5–153 °C (hexane) (lit.[22] mp 153–154 °C); HRMS (EI) calcd for $C_{20}H_{20}O_7$: 372.1209 [M], found: *m/z* 372.1207 $[M]^+$; Anal. calcd for $C_{20}H_{20}O_7$: C 64.51; H 5.41; O 30.08. Found: C 64.22; H 5.81; O 29.91.

3.1.23. Nobiletin (4). To a solution of **3** (0.18 g, 0.48 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C for 30 min, and added BBr_3 (1 equiv. 1 M 0.48 mL) into the solution dropwise. The brown mixture was stirred at 0 °C for 30 min, and then MeOH was introduced for quenching the reaction. The solvent was removed in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 1:1) to afford the corresponding 5-hydroxy-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (**33b**) (0.16 g, 94%) as a light yellow solid: mp 190–192 °C (CH_2Cl_2) (lit.[22] mp 190–191 °C); HRMS (EI) calcd for $C_{19}H_{18}O_7$: 358.1053 [M], found: *m/z* 358.1057 $[M]^+$. Followed by general procedure for hydroxylation, a solution of 5-hydroxyflavone **33b** (0.16 g, 0.45 mmol) was added with DMD (25 mL, 0.50 mmol) for 20 min to provide the regioselective 5,8-dihydroxy-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (**34b**) (0.15 g, 90%) as a brown yellow solid: mp 199–201 °C (acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 3.97–4.15 (3H each, s, OMex4), 6.59 (1H, s, 3-H), 6.99 (1H, d, *J*=8.7 Hz, 5-H), 7.42 (1H, d, *J*=1.8 Hz, 2-H), 7.60 (1H, dd, *J*=8.4, 2.1 Hz, 6-H). To a mixture of dihydroxyflavone **34b** (0.15 g, 0.40 mmol) and K_2CO_3 (2.5 equiv. 0.14 g) in acetone/CH_2Cl_2 (1:1 10 mL) was added Me_2SO_4 (95 μL, 1.0 mmol) at room temperature, and then refluxed for 6 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **4** (0.14 g, 87%) as a white solid: mp 137–137.5 °C (acetone) (lit.[22] mp 138 °C); HRMS (EI) calcd for $C_{21}H_{22}O_8$: 402.1315 [M], found: *m/z* 402.1323 $[M]^+$.

3.1.24. Natsudaidain (5). A solution of **4** (78 mg, 0.20 mmol) was added with DMD (2.0 mL, 0.40 mmol) for 10 min to give the 3-hydroxylflavone **5** (28 mg, 80%) as a white solid: mp 130.9 °C (CH_2Cl_2) (lit.[30] mp 141–143 °C); HRMS (EI) calcd for $C_{21}H_{22}O_9$: 418.1264 [M], found: *m/z* 418.1272 $[M]^+$.

3.1.25. 3,5,6,7,8-Pentamethoxy-2-(3,4-dimethoxyphenyl)-4-benzopyrone (8). A mixture of **5** (40 mg, 0.11 mmol) and K_2CO_3 (1.0 equiv. 15 mg) in acetone (5 mL) was added Me_2SO_4 (13 μL, 0.13 mmol) at room temperature, and then refluxed for 1 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×10 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to afford the desired **8** (46 mg, 97%) as a white solid: mp 129–130 °C (acetone) (lit.[24] mp 130–131 °C); HRMS (EI) calcd for $C_{22}H_{24}O_9$: 432.1420 [M], found: *m/z* 432.1416 $[M]^+$.

3.1.26. Gardenin B (6). To a mixture of **34a** (0.15 g, 0.44 mmol) and K_2CO_3 (1.0 equiv. 60 mg) in acetone/CH_2Cl_2 (1:1 10 mL) was added Me_2SO_4 (43 μL, 0.45 mmol) at room temperature, and then refluxed for 1 h. The resulting solution was cooled, and extracted with CH_2Cl_2 (3×20 mL). The organic layer was concentrated in vacuo, and the residue was subjected to column chromatography (SiO_2, CH_2Cl_2/ether 4:1) to give the desired **6** (0.16 g, 100%) as a yellow solid: mp 176 °C (ether) (lit.[22] mp 176–178 °C); MS (EI) *m/z* 211.1 (14.4), 343.3 (100), 358.4 (M^+, 94).

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