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Graphical Abstract

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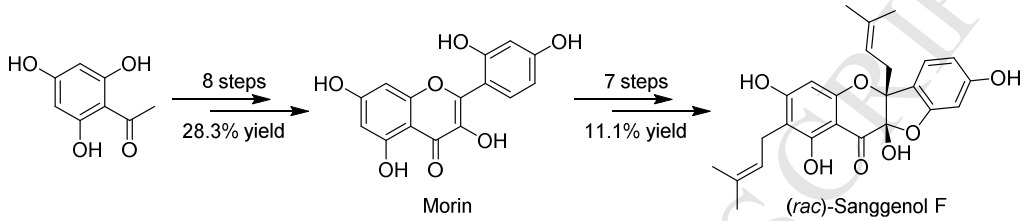

Morin

(*rac*)-Sanggenol F

Tetrahedron
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The total synthesis of (±)-sanggenol F

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ABSTRACT

A concise and efficient total synthesis of sanggenol F (**1**) in racemic form has been completed via a sequence of 15 steps with an overall yield of 3.1%, starting from commercially available 2,4,6-trihydroxyacetophenone. Meanwhile, a semisynthesis of sanggenol F racemate has also been achieved in 11.1% overall yield via 7 steps with naturally-occurring morin (**2**) as the starting material. One step and a stepwise approach were employed to construct the two prenyl side chains at 2- and 6-positions by Claisen rearrangement reaction.

1. Introduction

Sanggenon-type flavanones are a family of 3-hydroxy-2-prenylflavanones with an ether linkage between the C-2′ and C-3 and two contiguous stereogenic oxa-quarternary carbon centers. This group of isoprenylated flavonoids is characteristic constituents of the genus *Morus*,[1] especially 'Sang-Bai-Pi',[1f-j] a traditional Chinese medicine, and have been found to possess improtant and interesting biological activities.[1c,1j,2] Sanggenol F (**1**, Fig. 1), isolated from *Morus nigra* by our group,[1a] is a typical sanggenon-type flavanones, which has been reported to promote adipocyte differentiation and enhance insulin sensitivity in 3T3-L1 cells.[3a-b]

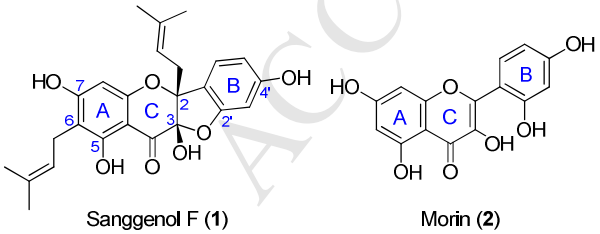

Fig. 1. Structures of sanggenol F (**1**) and morin (**2**).

Despite its favorable biological activities, sanggenol F is difficult to be obtained in significant amounts by isolation because of its low content in the *Morus* plants and the concomitant occurrence of related phenolics that complicate its purification. This drawback remarkably hampered its further bioactivity studies. Therefore, chemical synthesis would be an effective alternative to provide this compound. In a broader sense, further development of efficient and general synthetic approaches to the relevant sanggenon-type flavanones would also be highly desirable. Recently, the semisynthesis of (±)-sanggenol F (**1**) was achieved using naturally-occurring morin (**2**) as the starting material via 9 steps.[4] We herein report the total synthesis of racemic sanggenol F (**1**) by using different stategies via a linear sequence of 15 conventional chemical reaction steps with an overall yield of 3.1%, starting from the commercially available 2,4,6-trihydroxyacetophenone. The semisynthesis of **1** starting from **2** via 7 steps is also described in this paper.

2. Results and discussion

In a retrosynthetic sense (Scheme 1), the construction of two adjacent and fully substituted carbones (2- and 3-positions) can be viewed as the key to the synthesis of sanggenon-type flavanones. We envisioned that (±)-sanggenol F (**1**) may be accessible via an intramolecular hemiketal formation from intermediate **3**, which in turn was to be derived from double Claisen rearrangements of the diether intermediate **4**. This key intermediate **4** might be obtained from a precise modification of the densely functionalized intermediate **2** (morin), by the selective introduction of two 1,1-dimethyl-2-propenyl groups (reverse prenyl group) onto the 3- and 5-hydroxyls, respectively, and MOM protection onto the 2',4'- and 7-hydroxyls. Retrosynthetically, morin (**2**) can be derived from 2,4,6-trihydroxyacetophenone (**6**), via an early reported procedure for the preparation of flavonols which utilized Baker-Venkataraman rearrangement[5] of **5** and subsequent cyclization of the resulting 1,3-diketones, followed by the oxidation of 3-position at the

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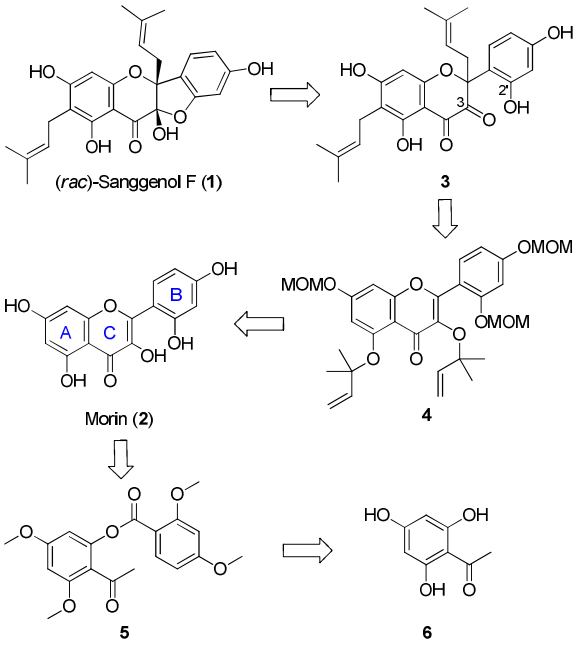
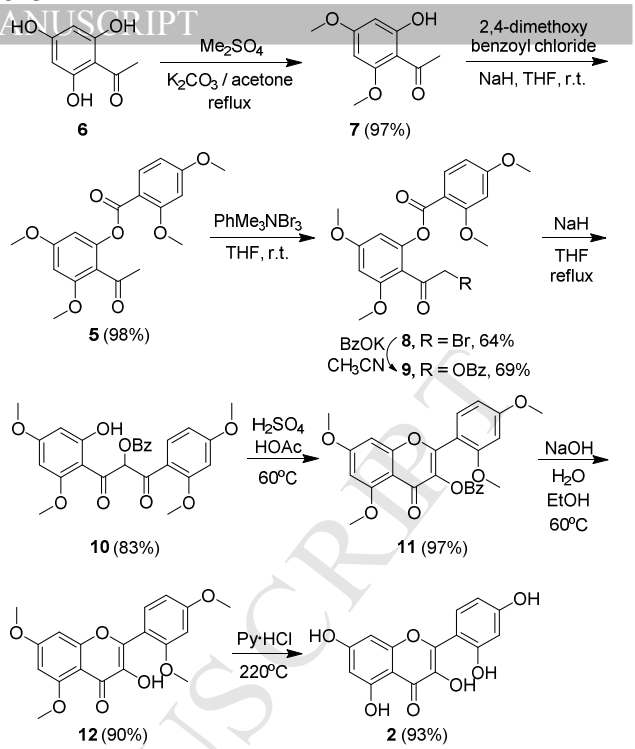
flavone skeleton. The oxidation step required such oxidants as dimethyldioxirane (DMDO) and hypervalent iodine derivatives,[6] that discouraged the scale-up synthesis of flavonols. Brouillard et al.[7] developed an alternative approach to avoid using such oxidants and we examined the feasibility of this approach to synthesize flavonols in the preparation of **2** in this study. Singh group[8] reported the synthesis of **2** starting from the aldol condensation of 2,4-dihydroxybenzaldehyde and **6** without any protection of all hydroxyl groups under the conditions of NaOH/EtOH, but we verified that it doesn't work and the protection is necessary.

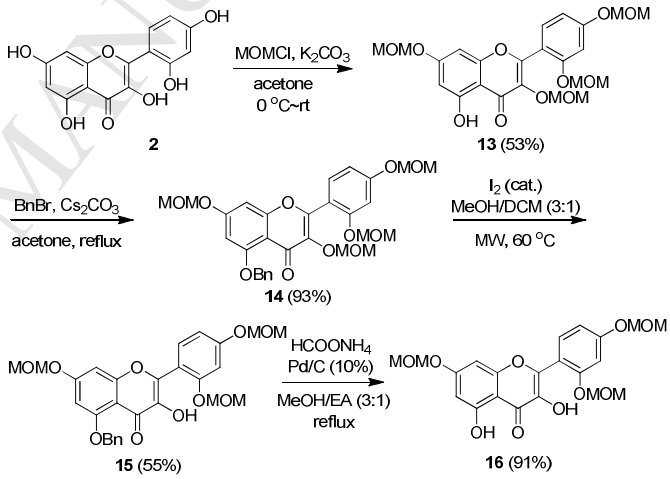


Scheme 1. Retrosynthetic analysis of (±)-sanggenol F (**1**).

As shown in Scheme 2, treatment of 2,4,6-trihydroxyacetophenone (**6**) with Me_2SO_4 and K_2CO_3 in refluxing acetone gave an excellent yield (97%) of 2-hydro-4,6-dimethoxyacetophenone (**7**)[9], which underwent a smooth esterification with 2,4-dimethoxybenzoyl chloride[10] in the presence of NaH in THF to provide ester **5** in 98% yield. Subsequent α-bromination of the ketonic moiety of **5** with phenyltrimethylammonium tribromide (PTT) afforded **8** in a yield of 64%, herein it was found that a batchwise addition of PTT is needed to prevent hydrolysis of the ester **5**. Nucleophilic substitution of bromide in **8** with benzoate was conducted in refluxing acetonitrile, giving rise to **9** in 69% yield. The Baker-Venkataraman rearrangement of **9** proceeded smoothly with NaH in refluxing THF, leading to the isolation of **10** in 83% yield. The subsequent cyclization of **10** in the presence of H_2SO_4/AcOH generated the flavone derivative **11** in an excellent yield (97%). Deprotection of benzoate group in **11** by saponification and compound **12** were obtained in the yield of 90% after purification. It was reported that complete demethylation of isoprenylated flavonoids was tough and low yielding,[10,11] so the intermediate **12** was submitted to demethylation by treating with Py·HCl at 220°C[12] to produce morin (**2**) in 93% yield. So far, the natural product morin was synthesized from **6** via 8 steps in an overall yield of 28.3%.



Scheme 2. Synthesis of morin (**2**).

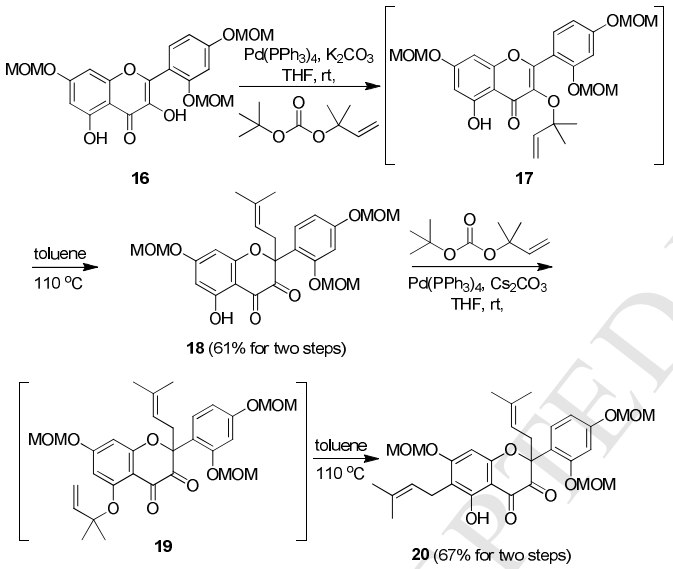


Scheme 3. Synthesis of intermediate **16**

Subsequent efforts were made towards the selective protection of **2**, leaving its 3- and 5-hydroxyl groups for the introduction of two prenyl side chains. After some trials on different protective groups, methoxymethyl (MOM) proved to be the proper choice. As shown in Scheme 3, treatment of morin (**2**) with 8 equivalents of MOMCl and K_2CO_3 in acetone at reflux afforded *tetra*-MOM-protected intermediate **13** in 53% yield, wherein only 5-OH was left intact as a result of its intramolecular hydrogen-bonding interaction with the 4-carbonyl group. With intermediate **13** in hand, we subsequently tried to selectively cleave the 3-MOM moiety, which is vicinal to the 4-carbonyl group, by using I_2 in MeOH.[13] However, treatment of **13** with I_2 in MeOH under reflux has generated an intractable mixture without trace of **16** as identified by LC-MS. We reasoned that the intramolecular hydrogen bond between 5-OH and the 4-carbonyl group in **13** might interfere with the effect of I_2/MeOH. To examine such a possibility, we masked the 5-OH via benzyl group protection, to give a 93% yield of **14** in which hydrogen bond is no longer available. Owing to the poor solubility of **14** in MeOH, we tried I_2/MeOH/CH_2Cl_2 (3:1) for the selective deprotection of 3-MOM group, which generated also a mixture with trace of **15** regardless

of at room temperature or reflux. And gratifyingly, selective removal of the 3-MOM of **14** was achieved with our efforts by microwave heating at 60 °C for 45 minutes in catalytic amount of I_2 with MeOH/CH_2Cl_2 (3:1) as solvent, leading to the formation of **15** in 55% yield. In this case, it was found that prolonging the reaction time or increasing the amount of I_2 would result in a more complex mixture. Subsequent removal of benzyl group of **15** proceeded smoothly under hydrogenolytic conditions ($HCOONH_4$, Pd-C, CH_3OH/EA), providing the desired intermediate **16** in 91% yield.

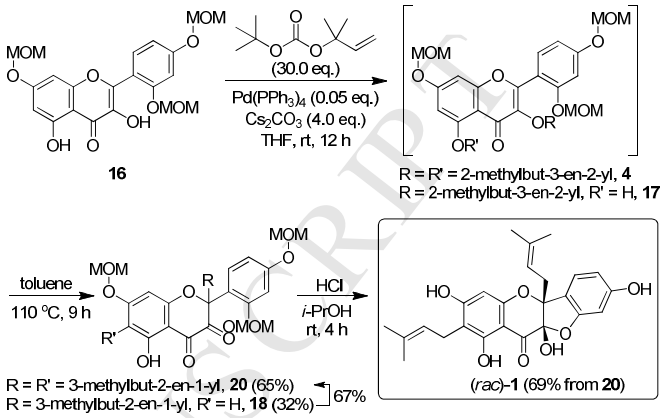
The subsequent introduction of two 1,1-dimethyl-2-propenyl units (reverse prenyl group) onto 3- and 5-hydroxyls of **16** was not trivial as it seems. As shown in Scheme 4, the next efforts were made to obtain two isoprenylated product **20**. Treatment of **16** with an excessive amount (5 eq.) of *t*-butyl(2-methylbut-3-en-2-yl)carbonate under $Pd(PPh_3)_4$ catalysis[14] and K_2CO_3 only gave a mono-alkylated product **17**. No desired di-alkylated compound **4** was detected in this case, presumably as a result of reactivity difference between two hydroxyls at 3- and 5-positions, since the hydrogen bond between the 5-OH and 4-carbonyl might also retard the reaction as before. Interestingly, we found compound **17** was unstable in the process of purification, and it can convert to **18** in silica gel partially (10% detected from LC-MS). So we decided to conduct the next step without further purification.



Scheme 4. Stepwise synthesis of the intermediate **20**.

Inspired by a reported procedure on the Claisen rearrangement catalyzed by Lewis acids,[15] we examined both $Sc(OTf)_3$ and $Cu(OTf)_2$ as the catalysts for the Claisen rearrangement reaction of **17**. The results indicated that a moderate yield (35%) of **18** was achieved in the presence of a substoichiometric amount (30 mol%) of $Sc(OTf)_3$, whereas $Cu(OTf)_2$ was found ineffective for promoting the transformation. Finally, Claisen rearrangement of **17** proceeded smoothly in refluxing toluene,[16] to give the mono-prenylated intermediate **18** in 61% yield for the two steps. Then we set out to introduce the second 1,1-dimethyl-2-propenyl unit onto 5-OH of **18**. Treatment of **18** with *t*-butyl(2-methylbut-3-en-2-yl)carbonate and K_2CO_3 under the catalysis of $Pd(PPh_3)_4$ didn't generate **19** at all, even if a longer reaction time gained no improvement. Inspired by the reaction of **13** to produce **14**, we found using Cs_2CO_3 as the base to give **19** more effectively for the prenyl etherification of 5-OH. After Claisen rearrangement of **19**, **20** was obtained in the yield of 67% for two steps.

Then we examined the possibility of di-etherification of **16** to give **20** directly by treating with excess equivalents of *t*-butyl(2-methylbut-3-en-2-yl)carbonate under the catalysis of $Pd(PPh_3)_4$ with Cs_2CO_3 as base (Scheme 5). After a thorough investigation on the optimal conditions, the desired product **4** was furnished accompanied by mono-alkylated product **17** consistently even if *t*-butyl(2-methylbut-3-en-2-yl)carbonate was added upto 30 equivalents (monitored by TLC and LC-MS). Considering the instability of **4** and **17**, Claisen rearrangement of the mixture were carried out in reflux toluene directly and afforded **20** and **18** in yields of 65% and 32%, respectively. The byproduct **18** could be utilized to afford **20** in 67% yield as described in Scheme 4.



Scheme 5. One step synthesis of intermediate **20** and the synthesis of **1**.

It is known that acidic condition is the best choice for not only the deprotection of MOM groups, but also the formation of intramolecular hemiketal. The key intermediate **20** was submitted to different kind of acids such as HCl, CF_3COOH, TsOH, CH_3COOH, $AlCl_3$ and $ZnBr_2$ in alcohol or tetrahydrofuran and all failed to generate the target product **1** except TsOH/CH_3OH with microwave assistance, producing **1** with a poor yield of 15%. Finally, the optimized reaction conditions were verified as the solution of hydrogen chloride gas in isopropanol (2.4 M) under room temperature and (±)-sanggenol F (**1**) was afforded in 69% yield. The sample of this product was fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS, and the data were found to be identical with those of the natural product.

3. Conclusion

In conclusion, (±)-sanggenol F (**1**) and morin (**2**) have been successfully synthesized by a sequence of 15 and 8 steps starting from commercially available 2,4,6-trihydroxyacetophenone (**6**) with an overall yield of 3.1% and 28.3%, respectively. Simutaneously, a semi-synthesis of **1** has been accomplished in 11.1% overall yield with naturally-occurring morin as the starting material via 7 steps. The construction of two prenyl side chains in the target product could be accomplished in one step or a stepwise manner, since the densely functionalized flavonol core necessitates different conditions for the Claisen rearrangements involved. The migration of the prenyl group to the 2- and/or 5-position was readily achieved by traditional heating, obviating the use of an expensive Lewis acid. Moreover, the deprotection of protective groups and the intramolecular hemiketal formation could be accomplished in one step effectively. The synthetic strategy described herein may provide a facile approach to sanggenol-type flavanones, which will definitely facilitate the elaboration and diversification of these interesting compounds for further bioactivity evaluation.

4. Experimental section

4.1. General

Starting materials and reagents were obtained from commercial suppliers and were used without purification unless otherwise stated. Melting points were measured in open capillary tubes using hot stage apparatus and were uncorrected. Reactions were monitored by analytical thin-layer chromatography (TLC) on 0.2 mm silica gel plates, and visualization of the developed chromatogram was enabled by UV absorbance or by using an ethanolic phosphomolybdic acid dip. Flash chromatography was performed using silica gel (300-400 mesh) with the specified solvent system. ^{1}H NMR spectra were recorded at 400 MHz using TMS as an internal standard and ^{13}C NMR spectra were measured at 150 MHz with complete proton decoupling. All chemical shifts are reported in parts per million on the d scale relative to an internal standard of TMS (^{1}H) or the signals of the solvent (^{13}C). Infrared (IR) spectra were recorded neat on KBr tablets with frequencies expressed in cm^{-1}. High-resolution mass spectra (HRMS) were recorded using either electron impact (EI) or electrospray ionization (ESI) techniques.

4.2. 2-Hydroxy-4,6-dimethoxyacetophenone (7)

To a refluxing solution of 2,4,6-trihydroxyacetophenone-monohydrate (**6**, 10 g, 59.5 mmol) and K_2CO_3 (16.5 g, 119 mmol) in acetone (150 mL), $(CH_3)_2SO_4$ was added at three-hour intervals (3 × 3.76 mL, 119 mmol). The solution was filtered and the solvent was evaporated to afford **7** (11.3 g, 97%) as a yellow solid. mp 74-75 °C (Lit[17]: 73-76 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (d, J = 2.0 Hz, 1H, Ar-H), 5.92 (d, J = 2.0 Hz, 1H, Ar-H), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.61 (s, 3H, $COCH_3$). IR (neat): ν 2970, 2833, 1617, 1440, 1157, 895, 597 cm^{-1}.

4.3. 2-Acetyl-3,5-dimethoxyphenyl 2,4-dimethoxybenzoate (5)

To a solution of **7** (11.3 g, 57.63 mmol) in THF (30 mL), NaH (60%, 3.46 g, 86.45 mmol) was added at 0°C. After stirring the mixture for 5 min, 2,4-dimethoxybenzoyl chloride (13.9 g, 69.16 mmol) was added dropwise. The resulting solution was slowly warmed to room temperature over a period of 3 h and then poured into ice water (30 mL), followed by extraction with EtOAc (3 × 30 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was then purified by silica gel column chromatography (PE/EA 10:1) to afford **5** (20.33 g, 98%) as a white solid, mp 105-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.8 Hz, 1H, Ar-H), 6.55 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 6.50 (d, J = 2.0 Hz, 1H, Ar-H), 6.38 (s, 2H, Ar-H), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3) , 2.47 (s, 3H, $COCH_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.8, 164.9, 163.1, 162.1, 161.9, 158.7, 149.7, 134.7, 117.5, 110.8, 104.7, 100.1, 98.9, 96.4, 56.0, 55.8, 55.6, 55.5, 31.9. IR (neat): ν 2943, 1737, 1610, 1157, 1096, 830, 761 cm^{-1}. MS (ESI): $[M+H]^+$: 361.1. HRMS (ESI) calcd mass for $C_{19}H_{20}NaO_7$ $[M+Na]^+$ 383.1106, found 383.1101.

4.4. 2-(2-Bromoacetyl)-3,5-dimethoxyphenyl 2,4-dimethoxybenzoate (8)

To a solution of **5** (1.8 g, 5 mmol) in dry THF (100 mL) was added PTT (2.1 g, 5.5 mmol) in portions. The reaction mixture was stirred at room temperature for 2 h, and was then poured into water (40 mL) and concentrated in vacuo, then extracted with CH_2Cl_2 (3 × 80 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (15% EtOAc/PE) to afford **8** (1.4 g, 64%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.8 Hz, 1H, Ar-H), 6.55 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 6.50 (d, J = 2.0 Hz, 1H, Ar-H), 6.45 (d, J = 2.0 Hz, 1H, Ar-H), 6.38 (d, J = 2.0 Hz, 1H, Ar-H), 4.44 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 191.9, 165.1, 163.1, 162.9, 162.3, 159.1, 151.0, 134.9, 113.8, 110.7, 105.0, 100.9, 99.1, 96.4, 56.1, 56.1, 55.7, 55.6, 37.0. IR (neat): ν 2947, 1729, 1609, 1296, 1113, 823, 597 cm^{-1}. HRMS (ESI) calcd mass for $C_{19}H_{19}BrNaO_7$ $[M+Na]^+$ 461.0222, found 461.0206.

4.5. 2-(2-(Benzoyloxy)acetyl)-3,5-dimethoxyphenyl 2,4-dimethoxybenzoate (9)

A mixture of **8** (2.03 g, 4.63 mmol) and BzOK (1.5 g, 9.26 mmol) was stirred in CH_3CN (20 mL) at refluxing temperature for 48 h. The mixture was diluted with H_2O (50 mL), followed by extraction with EtOAc (3 × 30 mL). The combined organic phase was then washed with water (3 × 10 mL) and brine (10 mL). After concentration in vacuo, the residue was purified by silica gel column chromatography (25% EtOAc/PE) to afford **9** (1.53 g, 69%) as a white solid. mp 42-43 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 3H, Ar-H), 7.54 (br t, J = 7.5 Hz, 1H, Ar-H), 7.41 (br t, J = 7.5 Hz, 2H, Ar-H), 6.51 (dd, J = 8.7, 2.2 Hz, 1H, Ar-H), 6.49 (d, J = 2.2 Hz, 1H, Ar-H), 6.46 (d, J = 2.0 Hz, 1H, Ar-H), 6.37 (d, J = 2.0 Hz, 1H, Ar-H), 5.28 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.0, 165.8, 165.0, 163.1, 162.9, 162.3, 159.6, 151.3, 135.1, 133.0, 129.9, 129.9, 128.3, 128.3, 113.7, 111.0, 104.9, 101.0, 99.0, 96.3, 69.6, 56.0, 56.0, 55.7, 55.5. IR (neat): ν 2923, 1727, 1609, 1419, 1213, 830, 712 cm^{-1}. HRMS (ESI) calcd mass for $C_{26}NH_{28}O_9$ $[M+NH_4]^+$ 498.1759, found 498.1757.

4.6. 1-(2,4-Dimethoxyphenyl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxo-propan-2-yl benzoate (10)

To a suspension of NaH (60%, 53 mg, 1.26 mmol) in dry THF (20 mL) was added **9** (400 mg, 0.83 mmol). The mixture was refluxed for 2 h with stirring. The cooled mixture was poured into ice water (20 mL) and concentrated in vacuo, extracted with EtOAc (3 × 40 mL). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The residue was then purified by silica gel column chromatography (15% EtOAc/PE) to afford **10** (330 mg, 83%) as a white solid. mp 66-67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.35 (s, 1H, Ar-OH), 8.09 (br d, J = 8.8 Hz, 3H, Ar-H), 7.56 (br t, J = 7.6 Hz, 1H, Ar-H), 7.44 (s, 1H, CH), 7.41 (br t, J = 7.6 Hz, 2H, Ar-H), 6.61 (dd, J = 8.8, 2.4 Hz, 1H, Ar-H), 6.42 (d, J = 2.4 Hz, 1H, Ar-H), 6.11 (d, J = 2.4 Hz, 1H, Ar-H), 5.87 (d, J = 2.4 Hz, 1H, Ar-H), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.4, 189.0, 168.0, 166.8, 165.7, 165.6, 162.0, 161.1, 133.8, 133.2, 130.1, 130.1, 129.6, 128.4, 128.4, 118.0, 106.1, 104.7, 98.3, 94.0, 91.0, 81.8, 55.7, 55.7, 55.5, 55.4. IR (neat): ν 2925, 1725, 1596, 1420, 1160, 823, 711 cm^{-1}. MS (ESI): $[M+H]^+$: 481.1. HRMS (ESI) calcd mass for $C_{26}H_{25}O_9$ $[M+H]^+$ 481.1493, found 481.1496.

4.7. 2-(2,4-Dimethoxyphenyl)-5,7-dimethoxy-3-benzoyloxy-4*H*-chromen-4-one (11)

To a solution of **10** (330 mg, 0.69 mmol) in AcOH (20 mL) was added conc. H_2SO_4 (0.2 mL). The reaction mixture was stirred at 60 °C for 2 h, and was then poured into ice water (10 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The residue was then purified by silica gel column chromatography (50% EtOAc/PE) to afford **11** (309 mg, 97%) as a white solid, mp 212-213 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br d, J = 8.0 Hz, 2H, Ar-H), 7.55 (br t, J = 8.0 Hz, 1H, Ar-H), 7.48 (d, J = 8.8

Hz, 1H, Ar-H), 7.41 (br t, *J* = 8.0 Hz, 2H, Ar-H), 6.55 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar-H), 6.49 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.46 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.36 (d, *J* = 2.0 Hz, 1H, Ar-H), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 164.1, 164.0, 163.1, 161.4, 159.8, 158.8, 153.2, 135.3, 133.1, 131.4, 130.3, 130.3, 129.5, 128.3, 128.3, 111.9, 109.3, 104.9, 98.7, 96.0, 92.7, 56.3, 55.7, 55.6, 55.5. IR (neat): *v* 3433, 2922, 1745, 1610, 1457, 831, 706 cm^{-1}. MS (ESI): $[M+H]^+$: 463.1. HRMS (ESI) calcd for $C_{26}H_{23}O_8$ $[M+H]^+$ 463.1393, found 463.1386.

4.8. 2-(2,4-Dimethoxyphenyl)-3-hydroxy-5,7-dimethoxy-4*H*-chromen-4-one (12)

To a solution of **11** (20 mg, 0.043 mmol) in ethanol (2 mL), 5% aqueous sodium hydroxide solution was added dropwise. The reaction mixture was stirred at 60 °C for 2 h, and was then acidified by 1 *M* HCl, extracted with EtOAc (3 × 5 mL). The organic phase was washed with $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. The residue was then purified by silica gel column chromatography (50% EtOAc/PE) to afford **12** (14 mg, 90%) as a white solid. mp 156-157 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H, Ar-OH), 7.36 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.69 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.64 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-H), 6.61 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.47 (d, *J* = 2.0 Hz, 1H, Ar-H), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.7, 164.0, 162.6, 160.7, 159.2, 158.9, 143.6, 139.3, 132.4, 112.8, 107.4, 105.6, 99.3, 96.1, 93.2, 56.7, 56.4, 56.3, 56.0. IR (neat): *v* 3191, 2920, 1620, 1412, 1023, 816, 726 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{19}O_7$ $[M+H]^+$ 359.1125, found 359.1127.

4.9. 2-(2,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one (morin, 2)

The mixture of **12** (79 mg, 0.22 mmol) and Py·HCl (750 mg, 7.2 mmol) in a 50 mL sealed tube was heated to 220 °C for 15 minutes with stirring, then acidified by 1 *M* HCl, extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The residue was then purified by silica gel column chromatography (20% CH_2Cl_2/MeOH) to afford **2** (62 mg, 93%) as a brown solid. mp 286-287 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H, Ar-OH), 10.71 (s, 1H, Ar-OH), 9.78 (s, 1H, Ar-OH), 9.72 (s, 1H, Ar-OH), 8.89 (s, 1H, Ar-OH), 7.22 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.40 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.35 (dd, *J* = 8.4, 2.0 Hz, 1H, Ar-H), 6.30 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.18 (d, *J* = 2.0 Hz, 1H, Ar-H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.7, 164.2, 161.4, 160.9, 157.3, 157.2, 149.5, 136.6, 132.1, 109.7, 107.3, 104.0, 103.4, 98.5, 93.8. IR (neat): *v* 3526, 2917, 1661, 1179, 833, 796, 637 cm^{-1}. HRMS (EI) calcd mass for $C_{15}H_{10}O_7^+$ 302.0427, found 302.0431.

4.10. 2-(2,4-Bis(methoxymethoxy)phenyl)-5-hydroxy-3,7-bis(methoxymethoxy)-4*H*-chromen-4-one (13)

A solution of **2** (60 mg, 0.20 mmol) and K_2CO_3 (220 mg, 1.60 mmol) in acetone (10 mL), MOMCl (0.12 mL, 1.60 mmol) was added slowly at 0 °C. After stirring for 10 min under this temperature, the reaction mixture was then stirred for 5 h at room temperature. Water (5 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was then purified by silica gel column chromatography (15% EtOAc/PE) to afford **13** (50 mg, 53%) as a yellow granular solid. mp 101-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.56 (s, 1H, Ar-OH), 7.43 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.94 (br s, 1H, Ar-H), 6.81 (dd, *J* = 8.5, 1.8 Hz, 1H, Ar-H), 6.54 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.47 (d, *J* = 2.0 Hz, 1H, Ar-H), 5.22 (s, 2H, -OCH_2O-), 5.21 (s, 2H, -OCH_2O-), 5.19 (s, 2H, -OCH_2O-), 5.01 (s, 2H, -OCH_2O-), 3.50 (s, 3H, OCH_3), 3.48 (s, 6H, 2×OCH_3), 2.98 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.6, 162.9, 162.1, 160.3, 157.6, 157.3, 156.6, 136.7, 132.0, 114.3, 108.7, 107.0, 103.7, 99.5, 97.6, 94.7, 94.4, 94.3, 94.2, 56.6, 56.4, 56.3, 56.2. IR (neat): *v* 2915, 1656, 1595, 1493, 1243, 1075, 812 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{27}O_{11}$ $[M+H]^+$ 479.1548, found 479.1556.

4.11. 5-(Benzyloxy)-2-(2,4-bis(methoxymethoxy)phenyl)-3,7-bis(methoxymethoxy)-4*H*-chromen-4-one (14)

To a solution of **13** (20 mg, 0.0410 mmol) in acetone (30 mL), Cs_2CO_3 (27 mg, 0.082 mmol) and BnBr (0.01 mL, 0.082 mmol) were added. After stirring for 4 h under reflux, water (5 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (30% EtOAc/PE) to afford **14** (22 mg, 93%) as a white solid. mp 106-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (br d, *J* = 7.5 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.40 (br t, *J* = 7.5 Hz, 2H, Ar-H), 7.30 (br t, *J* = 7.5 Hz,1H, Ar-H), 6.93 (br s, 1H, Ar-H), 6.80 (br d, *J* = 8.5 Hz, 1H, Ar-H), 6.63 (br s, 1H, Ar-H), 6.50 (br s, 1H, Ar-H), 5.27 (s, 2H, -OCH_2Ph), 5.21 (s, 2H, -OCH_2O-), 5.18 (s, 4H, 2×-OCH_2O-), 5.05 (s, 2H, -OCH_2O-), 3.49 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.92 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.6, 161.2, 160.0, 159.9, 159.2, 156.6, 154.3, 138.9, 136.4, 132.1, 128.6, 128.6, 127.7, 126.8, 126.8, 114.9, 110.8, 108.7, 103.7, 98.3, 97.5, 96.0, 94.7, 94.4, 94.4, 70.8, 56.4, 56.4, 56.2, 56.2. IR (neat): *v* 1636, 1610, 1430, 1195, 1002 cm^{-1}. HRMS (ESI) calcd for $C_{30}H_{33}O_{11}$ $[M+H]^+$ 569.2017, found 569.2034.

4.12. 5-(Benzyloxy)-2-(2,4-bis(methoxymethoxy)phenyl)-3-hydroxy-7-(methoxymethoxy)-4*H*-chromen-4-one (15)

The solution of **14** (415 mg, 0.73 mmol) and I_2 (4 mg, 0.016 mmol) in 2 mL CH_3OH / CH_2Cl_2 (18 mL, 3:1) was microwaved at 60°C for45 minutes, and was then quenched with aq. water (1 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL), and the combined extracts was washed with water and brine and concentrated in vacuo. The residue was then purified by silica gel column chromatography (15% EtOAc/PE) to afford **15** (210 mg, 55%) as a white needle. mp 153-154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (br d, *J* = 7.6 Hz, 2H, Ar-H), 7.49 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.43 (br t, *J* = 7.6 Hz, 2H, Ar-H), 7.33 (br t, *J* = 7.6 Hz, 1H, Ar-H), 6.94 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.83 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar-H), 6.79 (s, 1H, =C-OH), 6.68 (br s, 1H, Ar-H), 6.52 (br s, 1H, Ar-H), 5.28 (s, 2H, -OCH_2Ar), 5.22 (s, 2H, -OCH_2O-), 5.21 (s, 2H, -OCH_2O-), 5.18 (s, 2H, -OCH_2O-), 3.50 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 161.5, 160.1, 159.6, 159.3, 156.4, 142.5, 138.8, 136.3, 131.5, 128.7, 128.7, 127.8, 126.8, 126.8, 114.4, 109.1, 107.8, 104.1, 97.7, 95.9, 95.0, 94.4, 94.4, 70.8, 56.5, 56.3, 56.2. IR (neat): *v* 3347, 2920, 1611, 1437, 1196, 912, 632 cm^{-1}. HRMS (ESI) calcd for $C_{28}H_{29}O_{10}$ $[M+H]^+$ 525.1755, found 525.1768.

4.13. 2-(2,4-Bis(methoxymethoxy)phenyl)-3,5-dihydroxy-7-(methoxymethoxy)-4*H*-chromen-4-one (16)

To a solution of **15** (155 mg, 0.30 mmol) and $HCOONH_4$ (19 mg, 1.20 mmol) in 20 mL EtOAc/MeOH (1:3), Pd/C (16 mg, 10 wt%) was added. The mixture was stirred under reflux for 1 h. The Pd/C solids were removed by filtration through a plug of celite. Water (5 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine, dried over Na_2SO_4. The solvent was removed on the rotary evaporator and the residue was then purified by silica gel column

chromatography (12% EtOAc/PE) to afford **16** (118 mg, 91%) as a yellow granular solid. mp 159-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.87 (s, 1H, Ar-OH), 7.49 (d, J = 8.6 Hz, 1H, Ar-H), 6.97 (d, J = 2.0 Hz, 1H, Ar-H), 6.85 (dd, J = 8.6, 2.0 Hz, 1H, Ar-H), 6.58 (d, J = 2.0 Hz, 1H, Ar-H), 6.49 (d, J = 2.0 Hz, 1H, Ar-H), 6.13 (s, 1H, =C-OH), 5.23 (s, 2H, -OCH_2O-), 5.22 (s, 2H, -OCH_2O-), 5.21 (s, 2H, -OCH_2O-), 3.50 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.7, 163.1, 161.1, 160.4, 157.4, 156.3, 146.5, 136.9, 131.5, 113.9, 109.2, 105.2, 104.0, 99.3, 95.0, 94.4, 94.4, 94.3, 56.4, 56.4, 56.3. IR (neat): v 3675, 3387, 2988, 2914, 1594, 1250, 1196, 1132, 1076, 892 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{23}O_{10}$ $[M+H]^+$ 435.1286, found 435.1282.

4.14. 2-(2,4-Bis(methoxymethoxy)phenyl)-5-hydroxy-7-(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)chroman-3,4-dione (18)

To a Schlenk flask dried and degassed by argon was added **16** (282 mg, 0.65 mmol) and K_2CO_3 (179 mg, 1.29 mmol), followed by dry THF (10 mL). To the solution was added *tert*-buty-2-methylbut-3-en-2-yl carbonate (0.18 mL, 2.6 mmol) via syringe, followed by $Pd(PPh_3)_4$ (39.5 mg, 0.034 mmol). The reaction was stirred at room temperature under argon for 1 h and then water (5 mL) was added, extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The resultant oil was dissolved in 10 mL toluene and heated to 110 °C with stirring for 2 h. The solvent was removed on the rotary evaporator and the residue was then purified by silica gel column chromatography (12 % EtOAc/PE) to afford **18** (200 mg, 61% for two steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 1H，Ar-OH), 7.44 (d, J = 9.2 Hz, 1H, Ar-H), 6.75–6.72 (m, 2H, Ar-H), 6.19 (d, J = 2.0 Hz, 1H, Ar-H), 6.09 (d, J = 2.0 Hz, 1H，Ar-H), 5.19 (s, 2H，-OCH_2O-), 5.16 (s, 2H，-OCH_2O-), 5.11 (t, J = 7.5 Hz, 1H, -CH_2CH=), 4.92 (d, J = 7.2 Hz, 1H, -OCH_2O-), 4.86 (d, J = 7.2 Hz, 1H, -OCH_2O-), 3.47 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 3.12 (d, J = 7.5 Hz, 2H, -CH_2CH=), 1.57 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.2, 176.5, 167.5, 165.5, 162.9, 159.2, 154.9, 138.3, 127.7, 122.5, 115.5, 108.5, 105.6, 103.0, 96.6, 95.4, 94.4, 94.1, 94.1, 89.8, 56.6, 56.3, 56.2, 36.3, 25.8, 18.0. IR (neat): v 2969, 2919, 1640, 1568, 1449, 1219, 1147, 1076, 923 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{31}O_{10}$ $[M+H]^+$ 503.1912, found 503.191.

4.15. 2-(2,4-Bis(methoxymethoxy)phenyl)-5-hydroxy-7-(methoxymethoxy)-2,6-bis(3-methylbut-2-en-1-yl)chroman-3,4-dione (20)

To a Schlenk flask dried and degassed by argon was added **18** (70 mg, 0.14 mmol), Cs_2CO_3 (90 mg, 0.28 mmol) and dry THF (5 mL). To the solution was added *tert*-buty-2-methylbut-3-en-2-yl carbonate (0.10 mL, 1.4 mmol) via syringe, followed by $Pd(PPh_3)_4$ (10 mg, 0.007 mmol). The reaction was stirred at room temperature under argon for 2 h and then water (5 mL) was added, extracted with EtOAc (3 × 5 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The resultant oil was dissolved in 5 mL toluene and heated to 110 °C with stirring for 2 h. The solvent was removed on the rotary evaporator and the residue was then purified by silica gel column chromatography (6% EtOAc/PE) to afford **20** (53 mg, 67% for two steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.93 (s, 1H，Ar-OH), 7.43 (d, J = 8.8 Hz, 1H, Ar-H), 6.74–6.72 (m, 2H, Ar-H), 6.17 (s, 1H，Ar-H), 5.22 (s, 2H，-OCH_2O-), 5.17 (t, J = 7.2 Hz, 1H, -CH_2CH=), 5.15 (s, 2H，-OCH_2O-), 5.11 (t, J = 7.2 Hz, 1H, -CH_2CH=), 4.92 (d, J = 6.8 Hz, 1H, -OCH_2O-), 4.86 (d, J = 6.8 Hz, 1H, -OCH_2O-), 3.46 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.29 (d, J = 7.2 Hz, 2H, -CH_2CH=), 3.15 (s, 3H, OCH_3), 3.10 (d, J = 7.2 Hz, 2H, -CH_2CH=), 1.78 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.56 (s, 6H, 2×CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.4, 176.6, 165.1, 161.7, 161.3, 159.1, 154.9, 138.0, 131.8, 127.8, 122.4, 122.0, 115.7, 110.3, 108.5, 105.5, 102.9, 94.4, 94.0, 94.0, 93.3, 89.5, 56.4, 56.3, 56.1, 36.2, 25.8, 25.8, 21.2, 18.0, 17.8. IR (neat): v 3361, 2919, 2850, 1732, 1635, 1572, 1448, 1219, 1077, 947, 816, 777 cm^{-1}. HRMS (ESI) calcd for $C_{31}H_{39}O_{10}$ $[M+H]^+$ 571.2538, found 571.2532.

4.16. The synthesis of 20 and 18

To a Schlenk flask dried and degassed by argon was added **16** (20 mg, 0.046 mmol) and Cs_2CO_3 (59.9 mg, 0.184 mmol), followed by dry THF (2 mL). To the solution was added *tert*-buty-2-methylbut-3-en-2-yl carbonate (0.093 mL, 1.38 mmol) via syringe, followed by $Pd(PPh_3)_4$ (2.6 mg, 0.0023 mmol). The reaction vessel was stirred at room temperature under argon for 12 h and then water (1 mL) was added, extracted with EtOAc (3 × 5 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The resultant oil was dissolved in 5 mL toluene and heated to 110 °C with stirring for 9 h. The solvent was removed on the rotary evaporator and the residue was then purified by silica gel column chromatography (6% EtOAc/PE) to afford **20** (17 mg, 65% for two steps) and **18** (7.4 mg, 32% for two steps) as yellow oils.

4.17. The synthesis of (±)-sanggenol F (1)

To a round-bottomed flask, **20** (10 mg, 0.017 mmol) and HCl(g)/*i*-PrOH (0.6 mL, 2.4 M) was added at 0°C. After stirring for 4 h, the reaction mixture was adjusted to neutral with aq. $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). The combined extracts was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was then purified by silica gel column chromatography (15% EtOAc/PE) to afford **1** (5.3 mg, 69%) as a yellow oil. ^{1}H NMR (400 MHz, acetone-d_6): δ 11.93 (s, 1H, Ar-OH)，9.95 (s, 1H, Ar-OH)，8.79 (s, 1H, Ar-OH)，7.36 (d, J = 8.0 Hz, 1H, Ar-H), 7.13 (s, 1H, R-OH), 6.52 (br d, J = 8.0 Hz, 1H, Ar-H)，6.40 (br s, 1H，Ar-H), 5.92 (s, 1H, Ar-H), 5.24 (t, J = 7.0 Hz, 1H, -CH_2CH=), 5.19 (t, J = 7.0 Hz, 1H, -CH_2CH=), 3.22 (d, J = 7.0 Hz, 2H, -CH_2CH=), 3.13 (dd, J = 14.5, 8.8 Hz, 1H, -CH_2CH=), 2.77 (dd, J = 14.5, 6.5 Hz, 1H, -CH_2CH=), 1.73 (s, 3H, CH_3), 1.62 (s, 6H, 2×CH_3), 1.51 (s, 3H, CH_3). ^{13}C NMR (150 MHz, acetone-d_6): δ 188.3, 166.6, 162.6, 161.5, 161.3, 161.2, 136.5, 131.5, 125.7, 123.3, 121.4, 118.7, 109.7, 109.1, 102.6, 100.2, 99.5, 95.3, 91.8, 32.1, 25.9, 25.8, 21.5, 18.1, 17.8. IR (neat): v 3447, 2969, 2359, 2329, 1633, 1337, 960, 827 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{27}O_7$ $[M+H]^+$ 439.1751, found 439.1747.

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Supplementary data

These data include ^{1}H, ^{13}C NMR data for the key compounds described in this article. Supplementary data related to this article can be found online at XXXX.

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