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FULL PAPER

A concise approach to oxo-dehydrorotenoid by direct lactonization and the total syntheses of stemonone, rotenonone, 6-oxo-dehydroelliptone, and 6-oxo-6a,12a,-dehydrodeguelin

Jutatip Boonsombat,[a,*] Sanit Thongnest,[a] and Somsak Ruchirawat[a,b,c]

Abstract: An approach to construct the oxo-dehydrorotenoids via direct lactonization of isoflavone-2-carboxylic acids is reported. The present reaction proceeds smoothly with good substrate scope and an operationally simple protocol. The application of this method for the total syntheses of the natural products, stemonone, 6-oxo-dehydroelliptone, rotenonone, and 6-oxo-6a,12a,-dehydrodeguelin, are demonstrated.

Introduction

Rotenoids are a group of naturally occurring compounds in the isoflavone class found in a fairly diverse range of medicinal plants in tropical countries, especially plants from Leguminosae and Nyctaginaceae families.[1] This group of compounds was originally known for its wide use as insecticides and pesticides with its best known component called rotenone.[2] In recent years, several rotenoids have received considerable attention because of their attractive biological properties,[3-6] especially their anticancer properties.[7] Many members in this group, such as deguelin[8] and boeravinone G and H,[9] exhibit impressive antitumor activity in human cancer cell lines. Because of their biological interests, syntheses of rotenoids have been investigated by several research groups.[10] However, when considering oxo-dehydrorotenoid natural products which is a small family in rotenoid group (**Figure 1**), the studies of these natural products are underexplored. Consequently, the development of a concise and efficient synthetic method for oxo-dehydrorotenoid natural products is desirable and worthwhile from the viewpoint of medicinal/pharmaceutical chemistry.

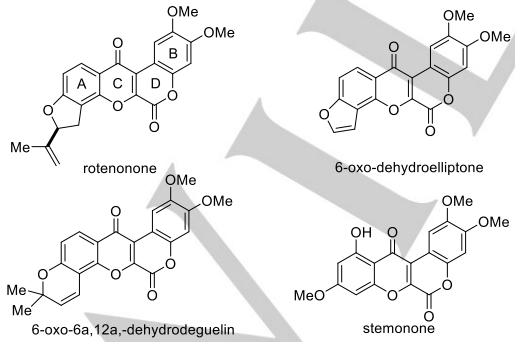

Figure 1. Naturally occurring oxo-dehydrorotenoids

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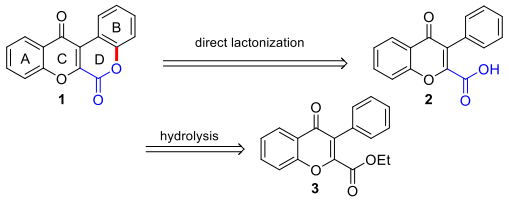
Recently, the synthetic strategy of direct coupling of oxygen with an unfunctionalized aryl Csp^2–H carbon has gained prominence due to its high atom economy and its access to the more complex oxygen heterocycles from relatively simple precursors. The direct lactonization between the aryl Csp^2–H carbon and the carboxylic group is of great synthetic interest since lactone represents structural subunits found in many biologically interesting molecules. Consequently, several research groups have been reported efficient synthetic conditions for this protocol.[11]

In 2013, palladium(II)-catalyzed direct lactonization of 2-phenylacetic acids through a C−H activation/C−O formation sequence was described for benzofuranone synthesis.[11d] In the same year, Wang reported an enantioselective Pd(II) approach with the use of an amino acid ligand to achieve chiral benzofuranones[11h] and he also applied this method for the directed lactonization of biphenyl-2-carboxylic acid.[11g] A radical based reaction has also been used in the highly efficient direct lactonization of carboxylic acid with unfunctionalized aryl Csp^2–H carbon. One of the earlier works was described by Davies and Waring in 1967 using $Pb(OAc)_4$ in refluxing benzene to give biaryl lactones.[11a] This radical oxidative cyclization was also achieved by *N*-iodosuccinimide (NIS) under visible light [11j] or through iodine (III) reagent generated in situ.[11k] Furthermore, a silver- and copper- catalyzed procedure has also gained attention for this radical process. Gallardo-Donaire and Martin disclosed the protocol using a Cu-catalyst in 2013.[11f] Soon after, Gevorgyan independently reported the similar Cu-catalyzed transformation, and in this same paper, he also reported another complimentary procedure by the $K_2S_2O_8$-mediated reaction.[11e] In 2015, a similar synthetic design was achieved at room temperature by using $AgNO_3$ with $(NH_4)_2S_2O_8$ and KOAc.[11i] An electrochemical method where the carboxylate radical was generated by anodic oxidation was also developed for this transformation.[11l,11m]

Guided by previous reports, we were interested in developing synthetic access to the lactone moiety of oxo-dehydrorotenoid core via a direct lactonization to the aryl Csp^2–H carbon. Based on the premise that rotenoids are indeed isoflavones with an additional six-membered oxygen heterocycle, the strategy for oxo-dehydrorotenoid **1** was an elaboration of the isoflavone structure (Scheme 1). In our retrosynthetic approach, the target oxo-dehydrorotenoid **1** was disconnected by the cleavage of the aromatic sp^2 C−O bond to give isoflavone-2-carboxylic acid **2**. We envisioned that the formation of this lactone D-ring could be realized via direct

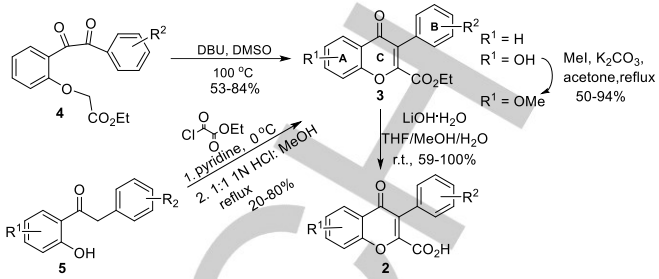
lactonization. The isoflavone-2-carboxylic acid **2** could be obtained by hydrolysis of the corresponding isoflavone-2-ethyl ester **3** which could be prepared using the previously described methods.[12]



Scheme 1. A retrosynthetic analysis to oxo-dehydrorotenoid

Results and Discussion

The synthesis started with the preparation of isoflavone-2-carboxylic acid **2**, as depicted in **Scheme 2**. Isoflavone-2-ethyl ester **3** was prepared through the base-induced cyclization of aryl diketone phenoxy ether **4** using DBU in DMSO at 100 °C.[12a] Alternatively, isoflavone-2-ethyl ester **2** with a mono- or dihydroxy group on ring A was obtained by cyclization of the corresponding deoxybenzoin **5** with ethyl chlorooxoacetate.[12b] The respective methoxy derivatives were then synthesized by a methylation reaction. Hydrolysis of the C-2 ethyl ester moiety with LiOH·H_2O gave the isoflavone-2-carboxylic acid **2** (see the Supporting Information for detailed experiments).



Scheme 2. Preparation of the isoflavone-2-carboxylic acids

Next, was an exploration of the direct lactonization using a simple isoflavone carboxylic acid as a model substrate. Several reagent systems and conditions, following literature reports, were screened and the results are reported in **Table 1**. The use of a Pd-catalyzed reaction showed only trace to small amounts of product **1a** (entries 3−5 and 7−10), but under the conditions using $Pd(OAc)_2$ and $PhI(OAc)_2$ with the Boc-L-valine ligand, the product **1a** could be isolated in modest yield (21%, entry 6). The reaction with lead tetra-acetate ($Pb(OAc)_4$) gave oxo-dehydrorotenoid **1a** in 31% yield with the majority of starting material remaining (entry 1). However, an increase in the amount of $Pb(OAc)_4$ with a longer reaction time did not improve the yield (entry 2). The copper-catalyzed reaction gave only trace amounts of product along with unreacted starting material (entries 11 and 12). When $K_2S_2O_8$ was used as an oxidant, the desired lactone D-ring was generated in good yield (57%, entry 13). However, using oxone as an oxidant gave only a 7% yield of oxo-dehydrorotenoid **1a** (entry 14).

Table 1. Screening reaction conditions for oxo-dehydrorotenoid D-ring formation

Entry	Reagents and Conditions	Yield%[d]	Refs
1	$Pb(OAc)_4$ (1.7 equiv), EtOAc, reflux, 4h	31[a]	[11a]
2	$Pb(OAc)_4$ (3.5 equiv), EtOAc, reflux, 15 h	24[a]	[11a]
3	$Pd(OAc)_2$ (5 mol%), Ag_2O (2.0 equiv), AcOH, 120 °C, 15 h	trace[a]	[13]
4	$Pd(OAc)_2$ (5 mol%), PIFA (2.0 equiv), DCE, 80 °C, Ar, 5 h	trace[c]	[14]
5	$Pd(OAc)_2$ (5 mol%), PIFA (2.0 equiv), DCE, r.t., 7 d	8[c]	-
6	$Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (1.5 equiv), Boc-L-valine (30 mol%), KOAc (2.0 equiv), *t*-BuOH, 100 °C, 18 h	21[a]	[11g]
7	$Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (1.5 equiv), Ac-Gly-OH (30 mol%), KOAc (2.0 equiv), *t*-BuOH, 100 °C, 18 h	3[a]	[11g]
8	$Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2.0 equiv), AgOAc (30 mol%), CsOAc (30 mol%), NaOAc (30 mol%), *t*-BuOH, Ar, 100 °C, 18 h	trace[a]	[11d]
9	$Pd(OAc)_2$ (5 mol%), selectflour (2.0 equiv), TFA/TFAA, 100 °C, 4 h	8[c]	[15]
10	$Pd(OAc)_2$ (5 mol%), selectflour (2.0 equiv), TFA/TFAA, r.t., 20 h	trace[c]	-
11	$Cu(OAc)_2$ (5 mol%), $(PhCO_2)_2$ (1.25 equiv), HFIP, 75 °C, 18 h	trace[a]	[11f]
12	$Cu(OAc)_2 H_2O$ (10 mol%), $(PhCO_2)_2$ (4.0 equiv), DCE, 85 °C, 15 h%	trace[a]	[11e]
13	$K_2S_2O_8$ (3.0 equiv), 1:1 MeCN:H_2O, 60 °C, 15 h	57[c]	[11e]
14	Oxone (3.0 equiv), 1:1 MeCN:H_2O, 60 °C, 24 h	7[a]	-
15	$K_2S_2O_8$ (3.0 equiv), $AgNO_3$ (10 mol%), 1:1 MeCN:H_2O, 60 °C, 15 h	67	[11e]
16	$K_2S_2O_8$ (1.5 equiv), $AgNO_3$ (10 mol%), 1:1 MeCN:H_2O, 60 °C, 15 h	45	-
17	$K_2S_2O_8$ (1.5 equiv), $AgNO_3$ (10 mol%), 1:1 MeCN:H_2O, 60 °C, 24 h	50	-
18	$K_2S_2O_8$ (3.0 equiv), $AgNO_3$ (10 mol%), 1:1 MeCN:H_2O, 100 °C, 1 h	14	-
19	$K_2S_2O_8$ (3.0 equiv), $AgNO_3$ (10 mol%), 1:1 MeCN:H_2O, r.t., 24 h	13	
20	$(NH_4)_2S_2O_8$ (3.0 equiv), $AgNO_3$ (10 mol%), 1:1 MeCN:H_2O, 60 °C, 15 h	24[c]	-
21	$K_2S_2O_8$ (3.0 equiv), $AgNO_3$ (10 mol%), MeCN, 60 °C, 15 h	18	-

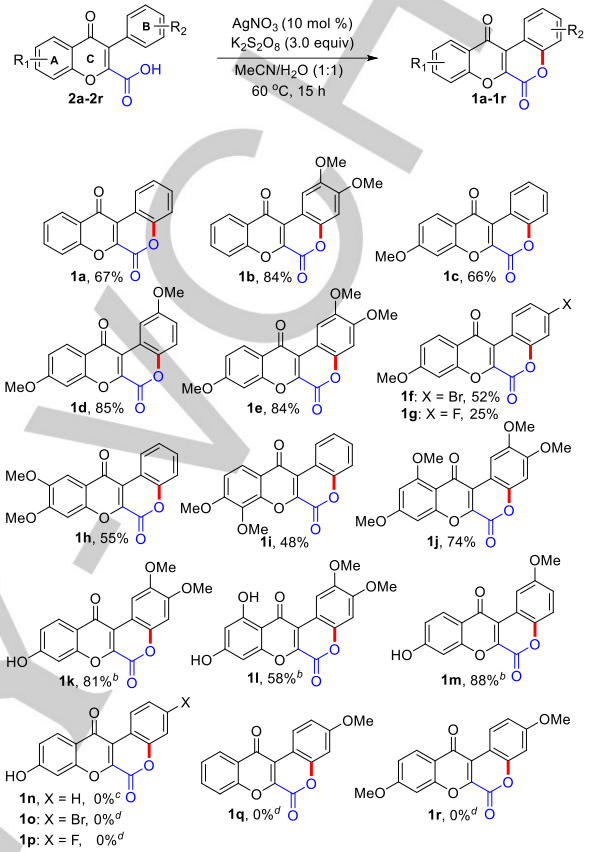
[a] Reaction was not completed along with recovered starting material. [b] complex mixture. [c] Starting material was consumed. [d] isolated yield.

The combination of $K_2S_2O_8$ and $AgNO_3$ gave the best yield for product **1a** (57% and 67%, entries 13 and 15) which was in agreement with the results reported by Gevorgyan.[11e] After receiving the desired product in good yield with the $K_2S_2O_8$/$AgNO_3$ system (entry 15), further optimization conditions were attempted for the substrate, but all attempts (entires16-21) gave inferior results. Reducing the amount of $K_2S_2O_8$ from 3.0 equiv to 1.5 equiv resulted in a lower yield (entries 16−17). The longer reaction time was unable to drive the reaction to completion and only a slight improvement in the product yield was observed (45% to 50%, entries 16 and 17). Raising the temperature to 100 °C caused the starting material to be very rapidly consumed, but drastically decreased the product yield (entries 15 and 18). Given the fact that a loss of CO_2 from a carboxylate radical could be taken place at high temperatures under a similar set of conditions,[16] it was speculated that decarboxylation followed by other pathways could lead to the decomposition of the material. Conversely, decreasing the temperature negatively affected the reaction, with only 13% of **1a** was retrieved after 24 h (entry 19). When changing $K_2S_2O_8$ to another persulfate source $(NH_4)_2S_2O_8$, the yield of 1a was diminished (entry 20). When MeCN was used as the solvent alone without water as a co-solvent, the reaction provided only 18% of the product **1a** (entry 21). Low conversion even with a prolong reaction time suggested indispensability of H_2O in this reaction. After reaction screening, conditions using $K_2S_2O_8$ (3.0 equiv), $AgNO_3$ (10 mol%) in 1:1 MeCN:H_2O at 60 ºC for 15 h (entry 15) were chosen for further synthetic exploration.

The scope of the reaction was evaluated next. A variety of substituted isoflavone-2-carboxylic acids **2a–2u** were submitted to the optimized conditions and the results are outlined in **Table 2**. It was found that the reaction proceeded smoothly to the oxo-dehydrorotenoids in moderate to good yield (**1a**–**1m**). The substrates containing halogens (**2f** and **2g**) could be used under the reaction conditions. This reaction could also tolerate some of unprotected OH substrates (**2k**–**2m**) and delivered the oxo-dehydrorotenoids **1k**–**1m** in good yield. The electronic factor of the substituents on the arene B-ring seemed to play an important role toward the directed lactonization. When the electron withdrawing groups were placed on the arene B-ring, the product yields were lower. The Br substrate **2f** gave product **1f** in 55% yield, while the more electron withdrawing F substrate **2g** gave much lower yield for **1g** (25%).

When electron donating OMe groups were placed on the arene B-ring, a mixture of results was obtained depending on the position of the OMe group. When the *m*-OMe substituent **2d** was used, the reaction became more efficient as the product yield increased from 66% (**1c**) to 85% (**2d**). This result could be due to the contribution of the resonance effect from the OMe group toward the reacting position. However, when *p*-OMe group was presented on the arene B-ring (**1q** and **1r**), the reaction gave a complex mixture with the starting material being a major component, and decomposition occurred with prolonged reaction time. The low efficiency of the *p*-OMe cyclization was presumably due to inactivation of *p*-OMe toward the reacting position, and other reaction pathways might come into play, leading to a complex mixture. Remarkably, the cyclization was indeed overpowered by the influence of the *m*-OMe position. As can be seen in substrate **2e**, where the *m*-, *p*-$(OMe)_2$ arene B-ring were used, the oxo-dehydrorotenoid **1e** was generated in 84% yield, which is comparable to that of the *m*-OMe substrate **1d**.

Table 2. Synthesis of dehydrorotenoid derivatives[a]

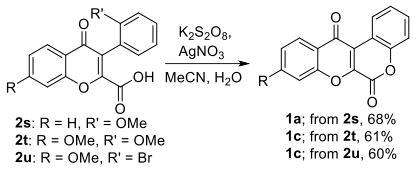


[a] Isolated yield. [b] Product was collected by filtration. [c] Starting material as major [d] Complex mixture

Placement of the OMe at *m*-position on ring A did not affect the cyclization process since the yield was comparable between with and without *m*-OMe on ring A (**1a** and **1c**, **1b** and **1e**). However, when an additional OMe group was placed on ring A, the yield was a slightly lower (**1h–i**) for **1a** compared to **1c**. This could be a result of the instability of the carboxylic acid substrates **2h–i**. For the placement of the OH on ring A, the results were mixed depending on substituents on B ring. With the acids containing *m*- *p*-$(OMe)_2$ or *m*-OMe in B-ring **2k**-**2m**, the reaction can proceed smoothly, but with acids **2n-2p**, the reactions were unable to deliver the product. Closely monitored the reaction progress of **1d** and **1m**, we found that the reaction was actually finished within 4h. This may imply that the high reactivity of B-ring was crucial for the success of the process of the substrate with unprotected OH.

When the *o*-OMe substrates **2s** and **2t** were subjected to the optimized conditions, the oxo-dehydrorotenoids **1a** and **1c** were produced in 68% and 61% yield, respectively (**Scheme 3**). It was speculated that due to the steric hindrance between OMe and the keto carbonyl, the addition of the carboxylate radical at the *ipso*-position was then preferred, leading to the final products **1a** and **1c** after the loss of the methoxide radical.[17] This

speculation was confirmed by the use of the steric *o*-Br substrate **2u**, in which the oxo-dehydrorotenoid **1c** was also the sole product.



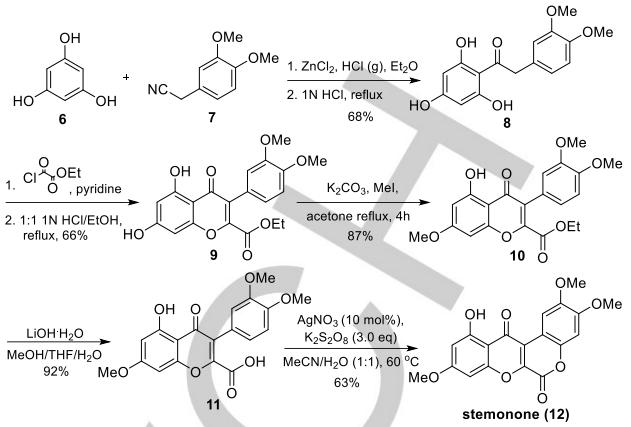
Scheme 3. Lactone formation of *ortho*-subsitiuted analogs

Note that this present reaction serves as a good extension to the current knowledge of the aryl Csp^2–H activation type lactonization. As the difference between the substrates causes the different reactivity and scope, it can be seen that not all the reported conditions of direct lactonization of biphenyl-2-carboxylic acids could be applied to the isoflavone-2-carboxylic acid **1a**, but the current radical persulfate conditions provided a good yield of the product **2a** (**Table 1**). Additionally, under similar set of $K_2S_2O_8$ conditions reported by Gevorgyan[11e] and Xu[11i], the overall results of the direct lactonization of the isoflavone-2-carboxylic acids gave a slightly lower yield compared to those of biphenyl-2-carboxylic acid counterparts. These results might be attributed to an extra electron withdrawing pyrone unit that could destabilize the generating carboxylate radical.

To demonstrate the applicability of the present method, the first total syntheses of four oxo-dehydrorotenoid natural products, including stemonone, 6-oxo-dehydroelliptone, and 6-oxo-6a, 12a,-dehydrodeguelin, and rotenonone, were synthesized, and the procedures are described in the following section.

Total synthesis of stemonone (12)

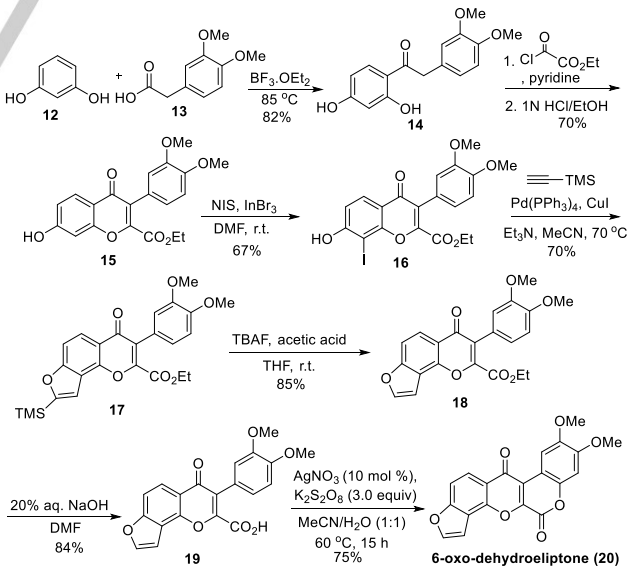
The synthesis of stemonone[18] began with the condensation of phloroglucinol **6** with 2-(3,4-dimethoxyphenyl)acetonitrile **7** using the Houben-Hoesh reaction to give deoxybenzoin **8**,[19] which was then cyclized with ethyl chlorooxoacetate in pyridine to generate isoflavone-2-ethyl ester **9**.[12b] Next, mono-methylation of the alcohol preceded using MeI and K_2CO_3 in refluxed acetone by close TLC monitoring of the reaction progress to give the product **10** with 87% yield. After hydrolysis of the ester moiety to the carboxylic group, direct lactonization was carried out to give stemonone (**12**) in 63% yield. This work also provided the first completed ^1H and ^{13}C NMR spectroscopic data of this natural product (**Scheme 4**).



Scheme 4. The total synthesis of stemonone (**12**)

Total synthesis of 6-oxo-dehydroelliptone (20)

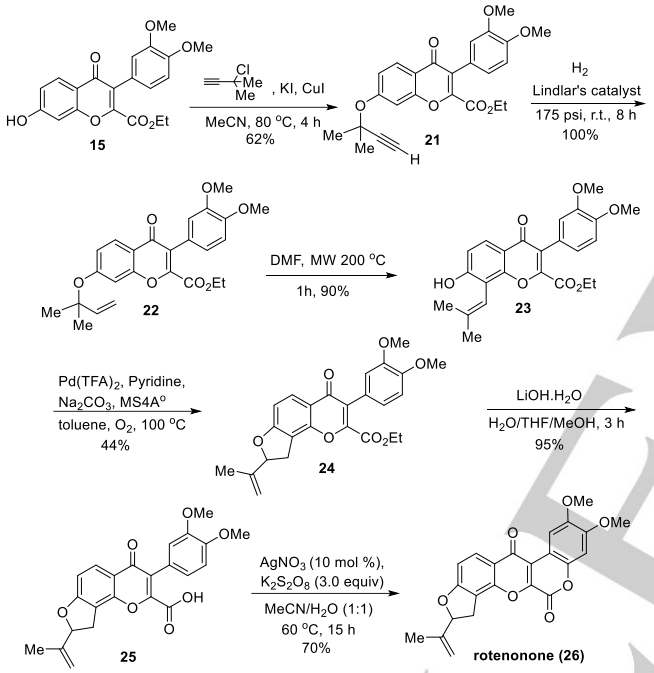
The 6-oxo-dehydroelliptone[20] is the oxo-dehydrorotenoid featuring the furan on the E-ring. In this synthesis, construction of the furan was planned to employ the tandem Sonogashira coupling annulation reaction. Therefore, the synthesis started by preparing the isoflavone-2-ethyl ester **15** from the Friedel-Craft acylation of resorcinol **12** and homoveratric acid **13** followed by base induced cyclization of the resulting deoxybenzoin **14**.[21] Then, the iodination of isoflavone-2-ethyl ester **15** using NIS and $InBr_3$ was regioselectively produced the iodinated product **16** in 67% yield.[22] The tandem Sonogashira coupling annulation reaction with ethynyltrimethylsilane gave the furan **17** in 70% yield, and subsequent removal of the TMS moiety by treatment with TBAF led to the unsubstituted furan **18** in 85% yield.[23] Hydrolysis of ester **18** using 20% NaOH in DMF gave the acid **19** in 84% yield.[24] Finally, the direct lactonization under standard conditions completed the total synthesis of 6-oxo-dehydroelliptone (**20**) in 75% yield (**Scheme 5**).



Scheme 5. Total synthesis of 6-oxo-dehydroelliptone (**20**)

Total synthesis of rotenonone (26)

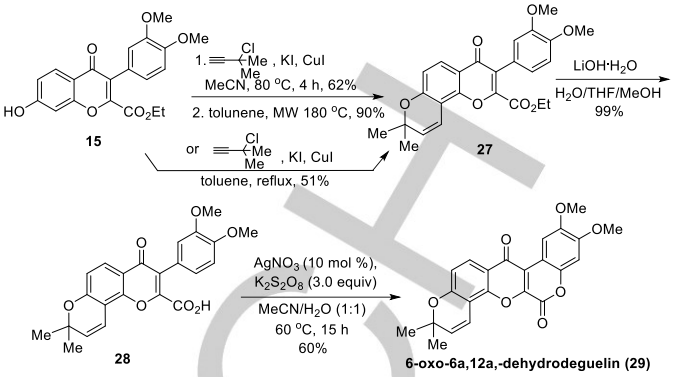
The third target compound, rotenonone (**26**)[25] was synthesized next. In this synthesis, the dihydrofuran E ring was synthesized using a protocol similar to the previously reported palladium-catalyzed oxidative cyclization reaction.[26] The synthesis began with the copper-catalyzed etherification of the isoflavone-2-ethyl ester **15** with chloro-3-methylbut-1-yne, giving the corresponding alkyne **21** in 60% yield.[27] Then, alkyne reduction using Lindlar's catalyst was followed by the Claisen reaction in which the rearrangement occurred with highly regioselective manner to give C-prenyl compound **23** in excellent yield. Next, the palladium-catalyzed oxidative cyclization was performed to give the dihydrofuran **24** in 44% yield, along with a minor amount of chromene isomer (compound **27**) in 19% yield. After careful separation by column chromatography, the compound **24** was hydrolyzed to give the acid **25** in 95% yield. Subsequently, the directed lactonization completed the total synthesis of rotenonone (**26**) in 70% yield (**Scheme 6**).



Scheme 6. Total synthesis of rotenonone (**26**)

Total synthesis of 6-oxo-6a,12a,-dehydrodeguelin (29)

The synthesis of 6-oxo-6a,12a,-dehydrodeguelin[28] (**29**) started with the formation of a chromene ring which could be completed in consecutive manner by formation of the alkyne **21**[27] following the thermal cyclization reaction under microwave conditions at 180 °C, which gave rise to the desired chromene **27** in 90% yield with highly regioselective manner. Alternatively, chromene **27** could be synthesized in one step by subjecting the isoflavone-2-ethyl ester **15** to the copper-catalyzed conditions under refluxing toluene to give the chromene product **27** in 51% yield. After hydrolysis of the ester moiety, the key directed lactonization was proceeded smoothly to provide the natural product 6-oxo-6a,12a,-dehydrodeguelin (**29**) in 60% yield (**Scheme 7**).



Scheme 7. Total synthesis of 6-oxo-6a,12a,-dehydrodeguelin (**29**)

Biological activities of the oxo-dehydrorotenoids 1a-1m, 12, 20, 26, and 29

The oxo-dehydrorotenoids **1a–1m**, **12**, **20**, **26** and **29** were evaluated for cytotoxic activity against a panel of four human cancer cell lines; hepatoblastoma HepG2, T-lymphoblast (acute lymphoblastic leukemia) MOLT-3, lung carcinoma A549, and cholangiocarcinoma HUCCA-1 by using MTT and XTT assays depending on the cell-line types. Most of the compounds were inactive towards cancer cytotoxicity. Only compounds **1a**, **1c**, **1d**, and **29** displayed moderate cytotoxic activity against HepG2 with IC_{50} values of 88.94±11.20, 67.08±5.23, 34.85±1.45, and 20.17±1.25 μM respectively, and compound **1k** showed moderate cytotoxic activity against MOLT-3 with IC_{50} of 27.24±2.79 μM (see **Table 1**, Supporting information). Interestingly, the structure of 6-oxo-6a,12a,-dehydrodeguelin (**29**) is very similar to the promising anticancer agent, degelin;[8] however, even though compound **29** gave the best cytotoxic activity among all tested compounds, the cytotoxic activity was only mild. Therefore, the extra carbonyl group and double-bond ring junction in 6-oxo-6a,12a,-dehydrodeguelin (**29**) should play an important role in weakening the anticancer activity of the deguelin framework. The oxo-dehydrorotenoids **1a–1m**, **12**, **20**, **26** and **29** were also evaluated for their cancer chemoprevention activities including radical scavenging, antioxidant, anti-inflammatory, and aromatase inhibitory activities (see **Table 2**, Supporting information) as well as antimalarial property (**Table 3**, Supporting information). The results showed that these compounds were all inactive.

Conclusions

An efficient method to oxo-dehydrorotenoids by means of direct lactonization between the aryl Csp^2–H carbon and the carboxylic group of isoflavone-2-carboxylic acids has been established. This reaction proceeded smoothly with good substrate scope to construct a rotenoid framework. The applicability of the present method to the first total syntheses of four oxo-dehydrorotenoid natural products, including stemonone, 6-oxo-dehydroelliptone, rotenonone, and 6-oxo-6a,12a,-dehydrodeguelin, was also demonstrated. The series of oxo-dehydrorotenoids was evaluated for their biological activities including cancer cytotoxicity, cancer chemoprevention, and antimalarial property; however, most of them showed poor

biological activity. Nevertheless, in view of the broad range of impressive biological activities possessed by some representative rotenoids, this present method shows potential applications in exploring biologically potent compounds of other derivatives that possess a rotenoid framework.

Experimental Section

General Information Commercial grade reagents and solvents were used as received from the supplier except where indicated otherwise. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates. Silica gel 60 (Silicycle, 230–400 mesh) was used for flash column chromatography and Silica gel 60 PF254 (Merck) was used for preparative thin layer chromatography. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$, Acetone-*d6*, or DMSO-*d6* using a Bruker AVANCE 300 NMR or a Bruker AVANCE 600 NMR spectrometer. ^{1}H-NMR and ^{13}C-NMR chemical shifts (δ) were reported in units of part per million (ppm). Coupling constants (*J*) were reported in Hertz (Hz) and refer to apparent peak multiplicities. IR spectra were recorded on a PerkinElmer Spectrum One Spectrophotometer using the universal attenuated total reflectance (ATR) technique and were reported in cm^{-1}. High resolution mass spectra (HRMS) were performed using an ESI ionization technique on a Bruker MicroTOF$_{LC}$ spectrometer.

Typical procedure for the synthesis of oxo-dehydrorotenoids 1a-1m. Chromeno[3,4-b]chromene-6,12-dione (1a). To a solution containing 25 mg (0.09 mmol) of the isoflavone-2-carboxylic acid (**2a**) in 1.0 mL of a 1:1 mixture of MeCN and H_2O at r.t., were added 76 mg (0.28 mmol) of $K_2S_2O_8$ and 1.6 mg (0.009 mmol) of $AgNO_3$. The mixture was stirred at 60 °C for 15 h, and then a saturated aqueous $NaHCO_3$ solution was added and stirred for an additional 15 min. After that, the resulting mixture was extracted with a 1:3 *i*-PrOH:CH_2Cl_2 solution (4x). The combined organic phase was washed with a saturated NaCl solution, dried over Na_2SO_4 (s), and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using CH_2Cl_2 and 1% MeOH/CH_2Cl_2 as an eluent to give 17 mg (67% yield) of the title compound **1a** as a white solid. mp 233-234 °C; IR (neat) 2924, 2847, 1739, 1648, 1615, 1464, 1305, and 1213 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.42 (m , 2H), 7.43-7.54 (m, 2H), 7.67 (dd, 1H, *J* = 8.5 and 0.7 Hz), 7.77 (ddd, 1H, *J* = 8.5, 7.0, and 1.6 Hz), 8.28 (dd, 1H, *J* = 8.0 and 1.5 Hz), and 9.34 (dd, 1H, *J* = 8.0 and 1.5 Hz); ^{13} C-NMR (75 MHz, $CDCl_3$) δ 177.0, 155.6, 155.1, 149.5, 143.9, 135.5, 130.6, 127.7, 126.4, 126.2, 125.7, 124.1, 121.1, 118.8, 116.6, and 115.5; HRMS Calcd for $[(C_{16}H_8O_4)+H]^+$: 265.0495. Found: 265.0499. This compound was also obtained by following the procedure B using 25 mg (0.08 mmol) of the acid **2n** to give 15 mg (68% yield) of the oxo-dehydrorotenoid **1a**.

2,3-Dimethoxychromeno[3,4-b]chromene-6,12-dione (1b). Following procedure for the synthesis of **1a** using 25 mg (0.08 mmol) of the acid **2b** to give 21 mg (84% yield) of the oxo-dehydrorotenoid **1b** as a white solid; mp 322-323 °C; IR (neat) 2924, 1737, 1638, 1613, 1504, 1460, 1406, 1293, 1248, 1225, 1159, and 1021 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.98 (s, 3H), 4.05 (s, 3H), 6.92 (s, 1H), 7.53 (ddd, 1H, *J* = 8.0, 7.1, and 1.0 Hz), 7.73 (dd, 1H, *J* = 8.5 and 1.0 Hz), 7.83 (ddd, 1H, *J* = 8.0, 7.1, and 1.6 Hz), 8.33 (dd, 1H, *J* = 8.0 and 1.6 MHz), and 8.97 (s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 177.4, 156.1, 155.3, 151.5, 147.1, 145.2, 142.6, 135.4, 126.2, 126.0, 123.9, 121.5, 118.9, 108.2, 107.7, 99.7, 56.4, and 56.2; HRMS Calcd for $[(C_{18}H_{12}O_6)+H]^+$: 325.0707. Found: 325.0705.

2,9-Methoxychromeno[3,4-b]chromene-6,12-dione (1c). Following procedure for the synthesis of **1a** using 25 mg (0.08 mmol) of the acid **2c** to give 16 mg (66% yield) of the oxo-dehydrorotenoid **1c**, or using 25 mg (0.08 mmol) of the acid **2t** to give 14 mg (61% yield) of the oxo-dehydrorotenoid **1c**, or using 25 mg (0.07 mmol) of the acid **2u** to give 12 mg (60% yield) of the oxo-dehydrorotenoid **1c** as a white solid; mp 244-245 °C IR (neat) 2924, 2853, 1744, 1644, 1621, 1446, 1295, 1260, 1210, 1183, 1117, and 1026 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.50 (s, 3H), 7.05-7.12 (m, 2H), 7.37 (d, 1H, *J* = 7.8 Hz), 7.44 (d, 1H, *J* = 7.8 Hz), 7.55 (t, 1H, *J* = 7.5 Hz), 8.23 (d, 1H, *J* = 8.7 Hz), and 9.44 (d, 1H, *J* = 7.5 Hz); ^{13} C-NMR (75 MHz, $CDCl_3$) δ 176.0, 165.5, 157.1, 156.8, 149.6, 143.7, 130.5, 127.9, 127.8, 125.6, 121.3, 118.2, 116.5, 115.8, 100.3, and 56.1; HRMS Calcd for $[(C_{17}H_{10}O_5)+H]^+$: 295.0601. Found: 295.0601.

2,9-Dimethoxychromeno[3,4-b]chromene-6,12-dione (1d). Following procedure for the synthesis of **1a** using 25 mg (0.08 mmol) of the acid **2**d to give 21 mg (85% yield) of the oxo-dehydrorotenoid **1d** as a yellow solid; mp 252-253 °C; IR (neat) 2924, 2851, 1740, 1621, 1442, 1284, 1247, and 1030 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.96 (s, 3H), 7.03-7.15 (m, 3H), 7.26-7.35 (m, 1H), 8.21 (d, 1H, = 8.6 Hz), and 9.01 (d, 1H, J = 2.3 Hz); ^{13} C-NMR (75 MHz, $CDCl_3$) δ 176.2, 165.6, 157.1, 157.0, 144.0, 127.7, 125.4, 119.1, 118.7, 118.1, 117.4, 116.4, 116.3, 116.2, 109.6, 100.3, 56.1, and 55.9; HRMS Calcd for $[(C_{18}H_{12}O_6)+H]^+$: 325.0707. Found: 325.0710.

2,3,9-Trimethoxychromeno[3,4-b]chromene-6,12-dione (1e). Following procedure for the synthesis of **1a** using 25 mg (0.07 mmol) of the acid **2e** to give 21 mg (84% yield) of the oxo-dehydrorotenoid **1e** as a white solid; mp 291-292 °C; IR (neat) 3461, 2957, 2923, 2853, 1744, 1625, 1438, 1260, 1219, 1099, and 1017 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 6.90 (s, 1H), 7.07 (dd, 1H, *J* = 8.8 and 2.4 Hz), 7.10 (d, 1H, *J* = 2.4 Hz), 8.21 (d, 1H, *J* = 8.8 Hz), and 8.99 (s, 1H); ^{13} C-NMR (75 MHz, $CDCl_3$) δ 176.4, 165.5, 157.3, 156.1, 151.4, 147.0, 145.2, 142.3, 127.6, 121.7, 118.0, 116.2, 108.3, 108.0, 100.3, 99.7, 56.3, 56.2, and 56.1; HRMS Calcd for $[(C_{19}H_{14}O_7)+H]^+$: 355.0812. Found: 355.0817.

3-Bromo-9-methoxychromeno[3,4-b]chromene-6,12-dione (1f). Following procedure for the synthesis of **1a** using 25 mg (0.07 mmol) of the acid **2f** to give 13 mg (52% yield) of the oxo-dehydrorotenoid **1f** as a white solid; mp 280-282 °C; IR (neat) 3079, 1746, 1651, 1623, 1594, 1576, 1484, 1438, 1389, 1280, 1247, 1208, 1180, 1130, and 1075 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.07-7.11 (m, 2H), 7.57 (dd, 1H, *J* = 8.7 and 1.9 Hz), 7.59 (d, 1H, *J* = 1.9 Hz), 8.25 (d, 1H, *J* = 8.7 Hz), and 9.35 (d, 1H, *J* = 8.7 Hz); ^{13} C-NMR (75 MHz, $CDCl_3$) δ 175.6, 165.7, 157.1, 155.1, 149.8, 143.6, 19.0(x2), 127.8, 124.2, 10.9, 119.7, 118.1, 116.5, 114.7, 100.4, and 56.1; HRMS Calcd for $[(C_{17}H_9BrO_5)+H]^+$: 372.9706. Found: 372.9711.

3-Fluoro-9-methoxychromeno[3,4-b]chromene-6,12-dione (1g). Following procedure for the synthesis of **1a** using 25 mg (0.08 mmol) of the acid **2g** to give 6 mg (25% yield) of the oxo-dehydrorotenoid **1g** as a white solid; mp 242-244 °C; IR (neat) 2924, 2851, 1750, 1649, 1622, 1504, 1440, 1278, 1209, 1179, and 1117 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.05 (m, 4H), 8.22 (d, 1H, *J* = 9.3 Hz), and 9.46 (dd, 1H, *J* = 9.1 and 6.3 Hz); ^{13} C-NMR (75 MHz, $CDCl_3$) δ 175.7, 165.6, 163.3 (d, *J* = 253 Hz), 157.1, 155.5, 150.6 (d, *J* = 12 Hz), 129.7 (d, *J* = 9 Hz), 127.8, 121.1, 118.1, 116.5, 113.6 (d, *J* = 22 Hz), 112.3 (d, *J* = 3 Hz), 104.2 (d, *J* = 26 Hz), 100.3, 56.1; ; HRMS Calcd for $[(C_{19}H_{14}O_7)+H]^+$: 313.0507. Found: 313.0497.

9,10-Dimethoxychromeno[3,4-b]chromene-6,12-dione (1h). Following procedure for the synthesis of **1a** using 25 mg (0.08 mmol) of the acid **2h** to give 14 mg (55% yield) of the oxo-dehydrorotenoid **1h** as a white solid; mp 280-281 °C; IR (neat) 2924, 2853, 1738, 1618, 1511, 1435, 1296, 1210, and 992 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3H), 4.04 (s, 3H), 7.13 (s, 1H), 7.37-7.49 (m, 2H), 7.55 (dd, 1H, *J* = 8.0 and 1.6 Hz), 7.58 (dd, 1H, *J* = 8.0 and 1.6 Hz), 7.62 (s, 1H), and 9.46 (dd, 1H, *J* = 8.0 and 1.4 Hz); ^{13} C-NMR (75 MHz, $CDCl_3$) δ 175.5, 156.1, 155.8, 151.5, 149.6, 148.7, 143.3, 130.4, 127.8, 125.6, 120.6, 118.0, 116.5, 115.9, 104.4, 100.0, 56.8, and 56.4; HRMS Calcd for $[(C_{18}H_{12}O_6)+H]^+$: 325.0707. Found: 325.070

8,9-Dimethoxychromeno[3,4-b]chromene-6,12-dione (1i). Following procedure for the synthesis of **1a** using 25 mg (0.08 mmol) of the acid **2i** to give 12 mg (48% yield) of the oxo-dehydrorotenoid **1i** as a pale yellow solid; mp 233-234 °C; IR (neat) 2917, 1766, 1647, 1613, 1456, 1292, 1205, 1123, and 1092 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 3H), 4.16 (s, 3H), 7.15 (d, 1H, *J* = 9.1 Hz), 7.39-7.48 (m, 2H), 7.56 (ddd, 1H, *J* = 8.1, 7.6, 1.6 Hz), 8.06 (d, 1H, *J* = 9.1 Hz), and 9.41 (dd, 1H, *J* = 8.0 and 1.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.4, 157,7, 155.4, 149.6, 149.4, 143.8, 137.1, 130.4, 127.8, 125.5, 121.6, 120.5, 118.9, 116.5, 115.7, 111.1, 61.9, and 56.6; HRMS Calcd for $[(C_{18}H_{12}O_6)+H]^+$: 325.0707. Found: 325.0716.

2,3,9,11-Tetramethoxychromeno[3,4-b]chromene-6,12-dione (1j). Following procedure for the synthesis of **1a** using 25 mg (0.07 mmol) of the acid **2j** to give 19 mg (74% yield) of the oxo-dehydrorotenoid **1j** as a bright yellow solid, mp 297-298 °C;IR (neat) 2921, 2846, 1732, 1651, 1627, 1607, 1511, 1416, 1278, 1160, and 1035 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.94 (s, 3H), 4.00 (s, 6H), 6.41 (d, 1H, J = 1.8 Hz), 6.68 (d, 1H, *J* = 1.8 Hz), 6.86 (s, 1H), and 8.99 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.6, 165.3, 161.5, 158.9, 156.2, 151.1, 146.8, 145.3, 140.9, 122.5, 109.6, 108.2, 108.0, 99.5, 97.0, 92.9, 56.6, 56.4, 56.2, and 56.0; HRMS Calcd for $[(C_{20}H_{16}O_8)+H]^+$: 385.0918. Found: 385.0932.

9-Hydroxy-2,3-dimethoxychromeno[3,4-b]chromene-6,12-dione (1k). Following procedure for the synthesis of **1a** using 25 mg (0.07 mmol) of the acid **2k** but the work up procedure was modified as followed. After stirring at 60 °C for 15 h, the resulting mixture was then filtered through filtered paper. The yellow solid residue was thoroughly washed with H_2O followed by EtOAc, and dried under vacuum to give 20 mg (82%) of the oxo-dehydrorotenoid **1k** as a bright yellow solid; decomp 369-371 °C; IR (neat) 3368, 2926, 1717, 1646, 1619, 1513, 1464, 1289, 1231, 1023, and 994 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 3.84 (s, 3H), 3.86 (s, 3H), 6.92 (d, 1H, *J* = 2.2 Hz), 7.02 (dd, 1H, *J* = 8.8 and 2.2 Hz), 7.14 (s, 1H), 8.05 (d, 1H, *J* = 8.8 Hz), 8.86 (s, 1H), and 11.22 (s, 1H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 175.7, 164.1, 156.6, 155.5, 150.7, 146.1, 144.7, 142.6, 127.6, 120.1, 116.4, 116.1, 107.9, 107.7, 102.1, 100.2, 56.0, and 55.8; HRMS Calcd for $[(C_{18}H_{12}O_7)+H]^+$: 341.0656. Found: 341.0650.

9,11-Dihydroxy-2,3-dimethoxychromeno[3,4-b]chromene-6,12-dione (1l). Following procedure for the synthesis of **1a** using 25 mg (0.07 mmol) of the acid **2l** but the work up procedure was modified as followed. After stirring at 60 °C for 15 h, the resulting mixture was then filtered through filtered paper. The yellow solid residue was thoroughly washed with H_2O followed by EtOAc, and dried under vacuum to give 14.4 mg (58%) of the oxo-dehydrorotenoid **1l** as a yellow solid; decomp. 369-370 °C; IR (neat) 3352, 1725, 1654, 1515, 1306, 1271, 1254, 1223, 1194, 1171, 1044, and 1030 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 3.83 (s, 3H), 3.85 (s, 3H), 6.30 (d, 1H, *J* = 1.9 Hz), 6.49 (d, 1H, *J* = 1.9 Hz), 7.13 (s, 1H), 8.65 (s, 1H), 11.33 (s, 1H), and 12.43 (s, 1H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 180.6, 165.9, 162.0,156.5, 154.8, 150.9, 146.1, 144.7, 142.7, 119.3, 107.7, 107.0, 105.1, 100.3, 99.6, 94.1, 56.0, and 55.9; HRMS Calcd for $[(C_{18}H_{12}O_8+H)^+]$: 357.0605. Found: 357.0605.

9-Hydroxy-2-methoxychromeno[3,4-b]chromene-6,12-dione (1m). Following procedure for the synthesis of **1a** using 25 mg (0.07 mmol) of the acid **2m** but the work up procedure was modified as followed. After stirring at 60 °C for 15 h, the resulting mixture was then filtered through filtered paper. The yellow solid residue was thoroughly washed with H_2O followed by EtOAc, and dried under vacuum to give 21.8 mg (88%) of the oxo-dehydrorotenoid **1m** as a yellow solid; decomp. 278-280 °C; IR (neat) 3273, 2931, 1705, 1621, 1499, 1424, 1287, 1206, 1126, and 1035 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 3.31 (s, 3H), 6.96 (d, 1H, *J* = 2.0 Hz), 7.01 (dd, 1H, *J* = 8.8 and 2.0 Hz), 7.14 (dd, 1H, *J* = 9.0 and 3.0 Hz), 7.37 (d, 1H, *J* = 9.0 Hz), 8.2 (d, 1H, *J* = 8.8 Hz), 8.83 (d, 1H, *J* = 3.0 Hz), and 11.20 (s, 1H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 175.5, 164.1, 156.4, 156.0, 154.9, 144.5, 143.4, 127.5, 119.1, 117.1, 116.7, 116.4, 116.2, 109.9, 102.1, and 55.5; HRMS Calcd for $[(C_{17}H_{10}O_6)-H]^-$: 309.0405. Found: 309.0396.

2-(3,4-Dimethoxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethanone (8).[13] To a solution containing 3.00 g (23.79 mmol) of phloroglucinol (**6**) and 4.64 g (26.17 mmol) of 2-(3,4-dimethoxyphenyl)acetonitrile (**7**) in 95 mL of Et_2O at r.t. was added 649 mg (4.76 mmol) of $ZnCl_2$. Then the solution was cooled to 0 °C and HCl (gas), which was generated by dropwise addition of a concentrated H_2SO_4 solution to a concentrated HCl solution, was flowed to the reaction mixture for 10 min. The resulting mixture was warmed to r.t. and stirred for additional 19 h. After which time, 23.8 mL (23.79 mmol) of 1N HCl solution was added and the mixture was refluxed for another 19 h. Then the mixture was extracted wit Et_2O, dried over Na_2SO_4 (s) and the solvent was concentrated under reduced pressure. The crude residue was then purified by flash silica gel column chromatography using a solution of 4:1:5 of EtOAc:Acetone:Hexane as an eluent to provide 4.92 g (68% yield) of the compound **8** as a pale yellow solid; mp 158-160 °C; IR (neat) 3356, 1630, 1606, 1516, 1464, 1263, 1217, 1157, 1075, and 1024 cm^{-1}; ^{1}H-NMR (300 MHz, acetone-d_6) δ 3.76 (s, 3H), 3.76 (s, 3H), 4.34 (s, 3H), 5.94 (s, 2H), 6.79 (dd, 1H, *J* = 8.2, 1.7 Hz), 6.84 (d, 1H, *J* = 8.2 Hz), and 6.91 (d, 1H, *J* = 1.7 Hz); ^{13}C-NMR (75 MHz, acetone-d_6) δ 203.9, 165.5, 165.5, 150.1, 149.1, 129.5, 122.8, 115.0, 112.8, 105.1, 95.9, 56.2, 56.1, and 49.7; HRMS Calcd for $[(C_{16}H_{16}O_6)+H]^+$: 305.1020. Found: 305.1009.

Ethyl 3-(3,4-dimethoxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromene-2-carboxylate (9). To the solution of 1.00 g (3.29 mmol) of the deoxybenzoin **8** in 13 mL of pyridine was added 1.84 mL (13.15 mmol) of ethyl chlorooxoacetate. The mixture was stirred at r.t. for 2 h, and then cooled to 0 °C overnight. The resulting mixture was acidified to pH 3 by a rapid addition of a cold 6N HCl solution and extracted with 1:4 of Acetone/EtOAc solution (4x). The combined organic layer was then dried with an anhydrous Na_2SO_4(s) and the solvent was removed under reduced pressure. The crude residue was taken up to 13 mL of a 1:1 of a 1N HCl/EtOH solution and the resulting solution was refluxed for 4 h. After which time, the solvent was removed under reduced pressure. The crude residue was then pre-absorbed on silica gel and purified by flash silica gel column chromatography using 3:1:6 of EtOAc:Acetone:Hexane as an eluent to provide 833 mg (66% yield) of the title compound **9** as a pale yellow solid; mp 175-176 °C; IR (neat) 3372, 2925, 2853, 1736, 1649, 1617, 1586, 1515, 1453, 1251, 1199, 1170, and 1022 cm^{-1}; ^{1}H-NMR (300 MHz, acetone-d_6) δ 1.03 (t, 3H, *J* = 7.1 Hz), 3.81 (s, 3H), 3.84 (s, 3H), 4.15 (q, 2H, *J* = 7.1 Hz), 6.30 (d, 1H, *J* = 2.1 Hz), 6.44 (d, 1H, *J* = 2.1 Hz), 6.84 (dd, 1H, *J* = 8.2, 2.1 Hz), 6.96 (d, 1H, *J* = 2.0 Hz), 9.87 (br s, 1H), and 12.63 (s, 1H); ^{13}C-NMR (75 MHz, acetone-d_6) δ 182.1, 165.7, 163.5, 161.8, 158.1, 152.1, 150.7, 149.9, 124.6, 123.7, 123.5, 115.0, 112.2, 105.8, 100.2, 94.6, 63.0, 56.2, 56.1, and 13.9; HRMS Calcd for $[(C_{20}H_{18}O_8)+H]^+$: 387.1074. Found: 387.1093.

Ethyl 3-(3,4-dimethoxyphenyl)-5-hydroxy-7-methoxy-4-oxo-4H-chromene-2-carboxylate (10). To a stirred solution containing 400 mg (1.04 mmol) of the alcohol **9** and 157 mg (1.14 mmol) of K_2CO_3 in 4.0 mL of acetone at r.t. was added 322 µL (5.18 mmol) of MeI. The reaction mixture was refluxed for 4h, then cooled to r.t., filtered through a pad of celite, and washed thoroughly with EtOAc. After that the filtrate was concentrated under reduce pressure, and the crude residue was pre-absorbed on silica gel and purified by flash silica gel column chromatography using a solution of 2:1:7 of EtOAc/Acetone/Hexane as an eluent to provide 361 mg (87% yield) of the compound **10** as a yellow solid; mp 139-140 °C; IR (neat) 2939, 1736, 1655, 1616, 1603, 1516, 1445, 1259, 1212, 1159, and 1027 cm^{-1}; ^{1}H-NMR (300 MHz, acetone-d_6) δ 1.05 (t, 3H, J = 7.1 Hz), 3.80 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 4.16 (q, 2H, *J* = 7.1 Hz), 6.36 (d, 1H, *J* = 2.2 Hz), 6.56 (d, 1H, *J* = 2.2 Hz), 6.85 (dd, 1H, *J* = 8.2, 2.2 Hz), 6.96 (d, 1H, *J* = 2.0 Hz), 7.01 (d, 1H, *J* = 8.2 Hz), and 12.57 (s, 1H); ^{13}C-NMR (75 MHz, acetone-d_6) δ 182.2, 167.3, 163.1, 161.7, 158.0, 152.2, 150.7, 149.9, 124.8, 123.6, 123.5, 115.0, 112.2, 106.4, 99.3, 93.1, 63.0, 56.6, 56.2, 56.1, and 13.9; HRMS Calcd for $[(C_{21}H_{21}O_8)+H]^+$: 401.1231. Found: 401.1243.

3-(3,4-Dimethoxyphenyl)-5-hydroxy-7-methoxy-4-oxo-4H-chromene-2-carboxylic acid (11). To a solution containing 171 mg (0.43 mmol) of the ester **10** in 1.8 mL of 3:2:1 of THF/MeOH/H_2O at r.t. was added 76 mg (4.2 mmol) of LiOH·H_2O. The resulting mixture was stirred for 4 h and organic solvent was removed under reduced pressure. The crude residue was then diluted with H_2O and partitioned with EtOAc. The aqueous layer was acidified with a 1N HCl solution to pH3 and extracted with EtOAc (4x). The combined organic layer was then washed with a saturated NaCl solution, dried with Na_2SO_4 (s), and concentrated under reduced pressure to give 147 mg (92% yield) of the acid **11** as a yellow solid; mp 126-136 °C IR (neat) 3482, 3235, 1737, 1654, 1618, 1516, 1445, 1321, 1262, 1212, 1170, 1059, and 1023 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 3.73 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 6.39 (d, 1H, *J* = 2.2 Hz), 6.65 (d, 1H, *J* = 2.2 Hz), 6.83 (dd, 1H, *J* = 8.2 and 1.9 Hz), 6.92 (d, 1H, *J* = 1.9 Hz), 6.98 (d, 1H, *J* = 8.2 Hz), and 12.54 (s, 1H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 181.1 165.9, 162.0, 161.4, 156.6, 152.5, 148.9, 148.2, 122.6, 122.5, 122.3, 113.9, 111.3, 105.0, 98.4, 92.5, 56.2, 55.6, and 55.5; HRMS Calcd for $[(C_{19}H_{17}O_8)+H]^+$: 373.0918. Found: 373.0923.

Stemonone (12).[23] To solution containing 25 mg (0.07 mmol) of the isoflavone -2-carboxylic acid 11 in 0.7 mL of 1:1 MeCN/H_2O solution, were added 54 mg (0.20 mmol) of $K_2S_2O_8$ and 1.1 mg (0.007 mmol) of $AgNO_3$. The solution mixture was heated at 60 °C for 15 h, cooled to r.t., and quenched with a saturated aqueous $NaHCO_3$ solution. After stirring additional 15 min, the mixture was extracted with aa 1:3 *i*-PrOH:CH_2Cl_2 solution (4x). The combined organic layer was then washed with a saturated aqueous NaCl solution, dried with Na_2SO_4 (s), and concentrated under reduced pressure. The crude residue was pre-absorbed on silica gel and purified by flash silica gel column chromatography using CH_2Cl_2 and 1% MeOH/CH_2Cl_2 as an eluent to give 16 mg (63%) of stemonone **12** as a bright yellow solid; mp 303-304 °C; IR (neat) 2920, 2851, 1738, 1651, 1514, 1275, 1222, 1168, 1045, and 1023 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 6.45 (d, 1H, *J* = 2.3 Hz), 6.65 (d, 1H, *J* = 2.3 Hz), 8.86 (s, 1H), and 12.44 (s, 1H); ^{13} C-NMR (150 MHz, $CDCl_3$) δ 181.1, 167.2, 162.8, 157.0, 155.5, 151.5, 147.1, 145.3, 142.3, 120.9, 108.1, 107.3, 106.7, 99.8, 99.4, 93.0, 56.4, 56.2, and 56.0; HRMS Calcd for $[(C_{19}H_{14}O_8)+H]^+$: 371.0761. Found: 371.0767.

1-(2,4-dihydroxyphenyl)-2-(3,4-dimethoxyphenyl)ethanone (14).[Ref] The solution of 3.00 g (27.25 mmol) of resorcinol **12** and 5.35 g (27.25 mmol) of 2-(3,4-dimethoxyphenyl)acetic acid **13** in 20.5 mL (163.50 mmol) of BF_3·OEt_2 was heated at 85 °C for 3 h. After that, the resulting mixture was cooled to 0 °C, quenched with a saturated aqueous NaOAc solution, extracted with EtOAc. The organic layer was washed with H_2O and brine, dried with Na_2SO_4(s), and concentrated under reduced pressure. The crude residue was then pre-absorbed on silica gel and purified by flash silica gel column chromatography using a mixture of 2.0:0.5:7.5 of EtOAc:acetone:hexane as an eluent to give 6.47 g (82% yield) of the tittle compound **14** as an orange-brown solid; mp 158-159 °C; IR(neat) 3375, 2935, 1627, 1593, 1514, 1449, 1261, 1231, 1139, and 1024 cm^{-1}; ^{1}H-NMR (300 MHz, acetone-D) δ 3.77 (s, 6H), 4.20 (s, 2H), 6.32 (s,1H), 6.43 (d, 1H, *J* = 8.3 Hz), 6.86 (brs, 2H), 6.96 (s, 1H), 7.98 (d, 1H, *J* = 8.7 Hz), 9.55 (brs, 1H), and 12.74 (s, 1H); ^{13}C-NMR (75 MHz, acetone-D) δ 203.6, 166.7, 165.6, 150.4, 149.4, 134.3, 128.5, 122.4, 114.4, 113.5, 112.9, 108.8, 103.6, 56.1(x2), and 44.7; HRMS Calcd for $[(C_{16}H_{16}O_5)+Na]^+$: 311.0890. Found: 311.0880.

Ethyl 3-(3,4-dimethoxyphenyl)-7-hydroxy-4-oxo-4H-chromene-2-carboxylate (15).[2] To a solution containing 1.50 g (5.20 mmol) of 1-(2,4-dihydroxyphenyl)-2-(3,4-dimethoxyphenyl)ethanone **14** in 21 mL of pyridine was added 1.75 mL (5.20 mmol) of ethyl chlorooxoacetate. The mixture was stirred at rt for 2 h, then cooled to 0 °C overnight. The resulting mixture was then acidified to pH3 by a rapid addition of a cold 6N HCl solution and extracted with a 4:1 EtOAc/Acetone solution. The combined organic layer was then dried with an anhydrous Na_2SO_4(s) and the solvent was removed under reduced pressure. The crude residue was taken up to 21 mL of a 1:1 of 1N HCl/EtOH solution and the resulting solution was refluxed for 4 h. After which time, the solvent was removed under reduced pressure. The crude residue was then pre-absorbed on silica gel and purified by flash silica gel column chromatography using a mixture of 3:1:6 of EtOAc/Acetone/Hexane as an eluent to provide 1.28 g (67% yield) of the title compound **15** as a yellow solid; mp 205-206 °C; IR(neat) 3198, 2938, 2839, 1736, 1623, 1515, 1457, 1411, 1290, 1265, 1229, 1197, 1172, 1141, 1113, and 1023 cm^{-1}; ^{1}H-NMR (300 MHz, acetone-D) δ 1.05 (t, 3H, *J* = 7.1 Hz), 3.82 (s, 3H), 3.85 (s, 3H), 4.16 (q, 2H, *J* = 7.1 Hz), 6.83 (dd, 1H, *J* = 2.0 Hz), 6.94-7.00 (m, 3H), 7.05 (dd, 1H, *J* = 2.3 Hz), and 8.03 (d, 1H, *J* = 8.8 Hz); ^{13}C-NMR (75 MHz, acetone-D) δ 176.3, 164.0, 162.4, 158.1, 151.7, 150.6, 149.8, 128.5, 125.5, 123.5, 117.8, 116.3, 115.1, 112.2, 103.2, 62.8, 56.2, 56.1, and 13.9 cm^{-1}; HRMS Calcd for $[(C_{20}H_{18}O_7)+Na]^+$: 393.0938. Found: 393.0945.

Ethyl 3-(3,4-dimethoxyphenyl)-7-hydroxy-8-iodo-4-oxo-4H-chromene-2-carboxylate (16). The mixture of 50 mg (0.14 mmol) of compound **15**, 30 mg (0.14 mmol) of *N*-Iodosuccinimide and 4.8 mg (0.0135 mmol) of $InBr_3$ in 3 mL of DMF under Ar atmosphere was stirred at r.t. for 8 h. After that, the solvent was then removed under reduce pressure and the crude residue was purified by flash silica gel column chromatography using a solution of 1:3 and 1:1 EtOAc:Hexane as an eluent to give 45 mg (67%) of the compound **16** as a yellow solid; mp 168-169 °C; IR (neat) 3503, 3428, 3212, 1733, 1646, 1609, 1580, 1519, 1417, 1290, 1250, 1209, 1171, 1143, and 1019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (t, s, 3H, *J* = 7.1 Hz), 3.88 (s, 3H), 3.91 (s, 3H), 4.22 (q, 2H, *J* = 7.1 Hz), 6.60 (brs, 1H), 6.82-6.85 (m, 2H), 6.91 (d, 1H, *J* = 8.1 Hz), 7.07 (d, 1H, *J* = 8.8 Hz), and 8.13 (d, 1H, *J* = 8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.6, 161.3, 161.1, 155.7, 150.8, 149.4, 148.7, 128.2, 125.7, 123.1, 122.3, 118.3, 114.2, 112.9, 110.8, 74.5, 62.5, 55.9(x2), and 13.7; HRMS Calcd for $[(C_{20}H_{17}O_7)+Na]^+$: 518.9911. Found: 518.9902.

Ethyl 3-(3,4-dimethoxyphenyl)-4-oxo-8-(trimethylsilyl)-4H-furo[2,3-h]chromene-2-carboxylate (17). To a mixture containing 20 mg (0.04 mmol) of the compound **16**, 2.3 mg (0.002 mmol) of $Pd(PPh_3)_4$, and 0.8 mg (0.004 mmol) of CuI in 1 mL of 1:1 MeCN /Et_3N solution was added 6 µL (0.044 mmol) of trimethylsilane. The reaction was stirred at 70 °C for 3 h, the solvent was removed under reduce pressure. The crude residue was then pre-absorbed on silica gel and purified by flash silica gel column chromatography using a solution of 1:3 and 1:1 EtOAc:Hexane as an eluent to give 10.2 mg (70%) of the compound **17** as a yellow solid; mp 128-129 °C; IR (neat) 2957, 2932, 2835, 1736, 1652, 1628, 1583, 1516, 1462, 1407, 1312, 1264, 1205, 1171, 1143, 1087, and 1027 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.40 (s, 9H), 1.07 (t, 3H, *J* = 7.1 Hz), 3.89 (s, 3H), 3.91 (s, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 6.80-6.95 (m, 3H), 7.36 (d, 1H, *J* = 0.9 Hz), 7.57 (dd, 1H, *J* = 8.8 and 0.9 Hz), and 8.15 (d, 1H, *J* = 8.8 Hz);^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.2, 165.7, 162.0(x2), 150.4, 150.0, 149.3, 148.7, 125.8, 123.9, 122.4, 122.2, 118.9, 117.8, 113.3, 110.9, 110.8, 62.4, 55.9(x2), 13.7, and -1.9(x3); HRMS Calcd for $[(C_{25}H_{26}O_7Si)+Na]^+$: 489.1340. Found: 489.1329.

Ethyl 3-(3,4-dimethoxyphenyl)-4-oxo-4H-furo[2,3-h]chromene-2-carboxylate (18). To a solution of 20 mg (0.043mmol) of compound **17** in 1 mL of THF was added 3 µL (0.043 mmol) of acetic acid followed by 15 mg (0.047 mmol) of TBAF. The resulting mixture was stirred at r.t. under Ar atmosphere for 30 min. After that, the solvent was removed under reduce pressure and the crude residue was purified by flash silica gel column chromatography using a solution of 1:3 and 1:1 EtOAc:Hexane as an eluent to give 13.3 mg (85%) of the compound **18** as a yellow solid; mp 143-145 °C; IR (neat) 2937, 2835, 1737, 1651, 1516, 1464, 1408, 1341, 1291, 1251, 1214, 1193, 1171, 1143, and 1026 cm^{-1}; ^{1} H-NMR (300 MHz, $CDCl_3$) δ 1.07 (t, 3H, *J* = 7.1 Hz), 3.89 (s, 3H), 3.92 (s, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 6.80-6.95 (m, 3H), 7.20 (dd, 1H, *J* = 2.2 and 0.8 Hz), 7.58 (dd, 1H, *J* = 8.8 and 0.8 Hz), 7.77 (d, 1H, *J* = 2.2 Hz), and 8.18 (1H, *J* = 8.8 Hz);^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.1, 161.9, 158.6, 150.4, 150.2, 149.4, 148.7, 145.9, 125.8, 123.7, 122.4, 122.3, 119.3, 117.1, 113.2, 110.9, 110.8, 104.5, 62.4, 55.9(x2), and 13.6; HRMS Calcd for $[(C_{22}H_{18}O_7)+Na]^+$: 417.0945. Found: 417.0931.

3-(3,4-dimethoxyphenyl)-4-oxo-4H-furo[2,3-h]chromene-2-carboxylic acid (19). To a solution of 9.0 mg (0.023 mmol) of compound **18** in 0.5 mL of DMF was added 0.2 mL of a 20% aqueous NaOH solution, and the reaction mixture was stirred at r.t. for 10 min. The resulting mixture was then partitioned between H_2O and EtOAc. The aqueous layer was acidified with a 1N HCl solution to pH3 and extracted with EtOAc. The organic phase was dried with Na_2SO_4 (s), and concentrated under reduced pressure to give 7.1 mg (84% yield) of the acid **19** as a yellow solid; mp 146-148 ºC; IR (neat) 2926, 2853, 1703, 1618, 1516, 1463, 1258, 1141, and 1027 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.73 (s, 3H), 3.79 (s, 3H), 6.85 (dd, 1H, *J* = 8.3 and 1.6 Hz), 6.93 (d, 1H, *J* = 1.6 Hz), 6.98 (d, 1H, *J* = 8.3 Hz), 7.39 (d, 1H, *J* = 1.7 Hz), 7.80 (d, 1H, *J* = 8.8 Hz), 8.01 (d, 1H, *J* = 8.8 H), and 8.27 (brs, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 176.2, 162.6, 157.9, 152.4, 149.4, 148.8, 148.1, 147.8, 123.7, 123.4, 122.5, 121.6 118.7, 116.8, 113.9, 111.2, 111.0, 104.3, 55.53, and 55.50; HRMS Calcd for $[(C_{20}H_{15}O_7)+H]^+$: 367.0812. Found: 367.0819.

6-oxo-dehydroelliptone (20). To solution containing 8.5 mg (0.023 mmol) of the acid **19** in 0.2 mL of 1:1 MeCN/H_2O solution, were added 18 mg (0.070 mmol) of $K_2S_2O_8$ and 0.7 mg (0.002 mmol) of $AgNO_3$. The solution mixture was heated at 60 ºC for 15 h, cooled to r.t., and quenched with a saturated aqueous $NaHCO_3$ solution. After stirring additional 15 min, the mixture was extracted with aa 1:3 *i*-PrOH:CH_2Cl_2 solution (4x). The combined organic layer was then washed with a saturated aqueous NaCl solution, dried with Na_2SO_4 (s), and concentrated under reduced pressure to give 6.2 mg (75% yield) of the title compound **20** as a bright yellow solid; bright yellow solid, mp decomp. 321-323 ºC; IR (neat) 3146, 1741, 1648, 1625, 1513, 1449, 1292, 1271, 1223, 1165, and 1051 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.06 (s, 3H), 6.94 (s, 1H), 7.38 (dd, 1H, *J* = 2.2 and 0.8 Hz), 7.66 (dd, 1H, *J* = 8.9 and 0.8 Hz), 7.82 (d, 1H, *J* = 2.2 Hz), 8.26 (d, 1H, *J* = 8.9 Hz), and 9.04 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.1, 159.0, 156.0, 151.4, 150.1, 146.9, 146.4, 145.4, 142.1, 122.1, 122.0, 119.6, 117.5, 111.4, 108.1, 107.9, 104.9, 99.6, 56.34, 56.27; HRMS Calcd for $[(C_{20}H_{12}O_7)+H]^+$: 365.0656. Found: 365.0663.

Ethyl 3-(3,4-dimethoxyphenyl)-7-((2-methylbut-3-yn-2-yl)oxy)-4-oxo-4H-chromene-2-carboxylate (21). To a solution containing 200 mg (0.54 mmol) of the alcohol **15** in 5.4 mL of acetone at r.t. under Ar atmosphere was added 82 µL (0.81 mmol) of 3-chloro-3-methylbut-1-yne, 373 mg (2.7 mmol) of K_2CO_3, 21 mg (0.108 mmol), and 99 mg (0.59 mmol) of KI. The mixture was then stirred at 60 °C for 1.5 h. After that, the resulting solution was cooled to r.t., filtered through a pad of celite and washed thoroughly with EtOAc. The filtrate was evaporated under reduced pressure and the crude residue was purified by flash silica gel column chromatography eluted with 15% and 40% acetone/hexane solution to give 145 mg (62% yield) of the alkyne **21** as the pale yellow solid; IR (neat) 3245, 2990, 2837, 1736, 1648, 1620, 1515, 1440, 1263, 1248, 1195, 1137, and 1025 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* = 7.1 Hz), 1.75 (3, 6H), 2.71 (s, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 4.14 (q, 2H, *J* = 7.1 Hz), 6.81 (dd, 1H, *J* = 8.2 and 2.0 Hz), 6.86 (d, 1H, *J* = 2.2 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 7.15 (dd, 1H, *J* = 8.9 and 2.3 Hz), 7.43 (d, 1H, *J* = 2.3 Hz), and 8.12 (d, 1H, *J* = 8.9 Hz); ^{13}C-NMR (100 MHz, CDCl3) 176.7, 162.1, 160.9, 156.5, 150.8, 149.1, 148.6, 127.1, 125.1, 123.7, 122.3, 118.9, 118.1, 113.0, 110.7, 106.0, 84.3, 75.5, 72.8, 62.3, 55.83, 55.82, 29.4(x2), and 13.6; HRMS Calcd for $[(C_{25}H_{24}O_7)+Na]^+$: 459.1414. Found: 459.1414.

Ethyl 3-(3,4-dimethoxyphenyl)-7-((2-methylbut-3-en-2-yl)oxy)-4-oxo-4H-chromene-2-carboxylate (22). The solution of 400 mg (0.92 mmol) of the alkyne **21** and 194 mg (0.092 mmol of Pd) of Lindlar catalyst (5% Pd) in 9.2 mL of CH_2Cl_2 was stirred under 175 psi of H_2 atmosphere for 8 h. After the reaction completed, the solution was filtered to a pad of celite and washed thoroughly with CH_2Cl_2. The filtrated was evaporated under reduced pressure and the crude residue was purified by flash silica gel column chromatography eluted with 20% acetone/hexane solution to give 402 mg (100% yield) of the alkene **22** as a pale yellow solid; IR (neat) 2979, 2936, 1837, 1736, 1647, 1619, 1607, 1515, 1439, 1261, 1205, 1171, 1139, and 1025 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, *J* = 7.1 Hz), 1.55 (3, 6H), 3.85 (s, 3H), 3.87 (s, 3H), 4.11 (q, 2H, *J* = 7.1 Hz), 5.23 (d, 1H, *J* = 10.9 Hz), 5.27 (d, 1H, *J* = 17.7 Hz), 6.12 (dd, 1H, *J* = 17.7 and 10.9 Hz), 6.76-6.90 (m, 3H), 6.99 (dd, 1H, *J* = 8.9 and 2.2 Hz), 7.05 (d, 1H, *J* = 8.9 and 2.2 Hz), 8.05 (d, 1H, *J* = 8.9 Hz); ^{13}C-NMR (100 MHz, CDCl3) 176.7, 162.0, 161.8, 156.5, 150.7, 149.0, 148.5, 142.9, 126.9, 125.0, 123.7, 122.2, 119.2, 117.5, 114.7, 112.9, 110.7, 105.8, 81.1, 62.2, 55.75, 55.74, 27.0(x2), and 13.5; HRMS Calcd for $[(C_{25}H_{26}O_7)+Na]^+$: 4611.1571. Found: 461.1572.

Ethyl 3-(3,4-dimethoxyphenyl)-7-hydroxy-8-(2-methylprop-1-en-1-yl)-4-oxo-4H-chromene-2-carboxylate (23). The solution of 20 mg (0.049 mmol) of the alkene **22** in 0.5 mL of DMF was heated using microwave reactor at 200 °C for 30 min. After that, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography eluted with 20% acetone/hexane solution to give 18 mg (90% yield) of the alkene **23** as the pale yellow solid; IR (neat) 3221, 2934, 1739, 1619, 1560, 1515, 1438, 1267, 1212, 1171, and 1025 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, *J* = 7.1 Hz), 1.71 (s, 3H), 1.82 (s, 3H), 3.59 (d, 2H, *J* = 7.3 Hz), 3.85 (s, 3H), 3.87 (s, 3H), 4.18 (q, 2H, *J* = 7.1 Hz), 5.31 (brt, 1H, *J* = 7.3 Hz), 6.82 (dd, 1H, *J* = 8.1 and 1.9 Hz), 6.86-6.92 (m, 3H), and 7.93 (brd, 1H, *J* = 8.8 Hz; ^{13}C-NMR (100 MHz, CDCl3) 178.0, 161.8, 160.5, 155.0, 150.9, 149.1, 148.6, 134.1, 133.9, 124.8, 124.7, 123.6, 122.3, 120.7, 117.0, 115.5, 115.2, 113.0, 110.7, 62.4, 55.8(x2), 25.8, 22.1, 17.8, and 13.7; HRMS Calcd for $[(C_{25}H_{26}O_7)+Na]^+$: 461.1571. Found: 461.1568.

Ethyl 3-(3,4-dimethoxyphenyl)-4-oxo-8-(prop-1-en-2-yl)-8,9-dihydro-4H-furo[2,3-h]chromene-2-carboxylate (24). To a solution containing 25 mg (0.057 mmol) of the alkyne **23** in 0.6 mL of toluene under Ar atmosphere at rt was added 7 mg (125 mg/mmol by wt) of 4Aº molecular sieve powder, 12 mg (0.11 mmol) of Na_2CO_3, 1 µL (0.012 mmol) of pyridine, and 7.4 mg (0.023 mmol) of $Pd(TFA)_2$. The solution flask was then flushed with O_2 and kept under O_2 balloon. The reaction mixture was stirred at 100 °C for 15 h, then filtered to a pad of celite and washed thoroughly with CH_2Cl_2. The filtrated was evaporated under reduced pressure and the crude residue was purified by preparative TLC eluted with 30% acetone/hexane solution to give 10.8 mg (44% yield) of the title compound **24** as a pale yellow solid, along with 4.8 mg (19% yield) of compound **27** as a pale yellow solid; Compound **24**; IR (neat) 2959, 2935, 2835, 1734, 1647, 1627, 1606, 1515, 1452, 1404, 1263, 1244, 1192, 1170, 1142, and 1024 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02 (t, 3H, *J* = 7.1 Hz), 1.79 (s, 3H), 3.23 (dd, 1H, *J* = 16.8 and 7.8 Hz) , 3.57 (dd, 1H, *J* = 16.0 and 9.9 Hz), 3.86 (s, 3H), 3.89 (s, 3H), 4.13 (q, 2H, *J* = 7.1 Hz), 4.96 (s, 1H), 5.11 (s, 1H), 5.42 (brt, 1H, *J* = 9.0 Hz), 6.81 (dd, 1H, *J* = 8.3 and 1.9 Hz), 6.86 (d, 1H, *J* = 1.9 Hz), 6.88 (d, 1H, *J* = 8.3 Hz), 6.91 (d, 1H, *J* = 8.6 Hz), and 8.07 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, CDCl3) 176.5, 165.5, 162.0, 152.8, 150.2, 149.1, 148.5, 142.7, 128.0, 124.9, 123.7, 122.3, 117.9, 113.1, 113.0, 112.9, 110.7, 109.1, 87.9, 62.3, 55.80, 55.79, 31.3, 17.0, and 13.5; HRMS Calcd for $[(C_{25}H_{24}O_7)+Na]^+$: 459.1414. Found: 459.1412.

3-(3,4-dimethoxyphenyl)-4-oxo-8-(prop-1-en-2-yl)-8,9-dihydro-4H-furo[2,3-h]chromene-2-carboxylic acid (25). To a solution containing 18 mg (0.04 mmol) of the ester **24** in 0.5 mL of a 3:2:1 of THF/MeOH/H_2O solution at r.t. was added 4 mg (0.08 mmol) of LiOH·H_2O. The resulting mixture was stirred for 4 h and organic solvent was removed under reduced pressure. The crude residue was then diluted with H_2O and partitioned with EtOAc. The aqueous layer was acidified with a 1N HCl solution to pH3 and extracted with EtOAc (4x). The combined organic layer was then washed with a saturated aqueous NaCl solution, dried with Na_2SO_4(s), and concentrated under reduced pressure to give 16 mg (95%) of the title compound **25** as a pale yellow solid; IR (neat) 2926, 2858, 1737, 1619, 1575, 1516, 1453, 1295, 1263, 1241, 1212, 1198, 1171, and 1028 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.77 (s, 3H), 3.19 (dd, 1H, *J* = 15.9 and 7.8 Hz), 3.62 (dd, 1H, *J* = 15.9 and 9.9 Hz), 3.72 (s, 3H), 3.79 (s, 3H), 4.97 (s, 1H), 5.12 (s, 1H), 5.54 (brt, 1H, *J* = 8.1 Hz), 6.80 (dd, 1H, *J* = 8.3 and 1.9 Hz), 6.88 (d, 1H, *J* = 1.9 Hz), 6.97 (d, 1H, *J* = 8.3 Hz), 7.06 (d, 1H, *J* = 8.6 Hz), and 7.92 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR (75 MHz, CDCl3) δ 175.4, 164.9 162.5, 152.1, 151.8, 148.7, 148.0, 143.0, 127.2, 123.7, 122.7,

122.4, 117.4, 113.9, 113.4, 112.5, 111.2, 108.9, 87.5, 55.5, 55.4, 30.5, and 16.8; HRMS Calcd for $[(C_{23}H_{20}O_7)+H]^+$: 409.1282. Found: 409.1274.

Rotenonone (26). To solution containing 60 mg (0.15 mmol) of the acid **25** in 1.5 mL of 1:1 MeCN/H_2O solution, were added 119 mg (0.44 mmol) of $K_2S_2O_8$ and 2.5 mg (0.015 mmol) of $AgNO_3$. The solution mixture was heated at 60 ºC for 15 h, cooled to r.t., and quenched with a saturated aqueous $NaHCO_3$ solution. After stirring for additional 15 min, the mixture was extracted with a 1:3 *i*-PrOH:CH_2Cl_2 solution (4x). The combined organic layer was then washed with a saturated aqueous NaCl solution, dried with Na_2SO_4 (s), and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography eluted with 80% CH_2Cl_2/hexane solution and CH_2Cl_2 to give 41.6 mg (70 %) of the title compound **26** as a bright yellow solid; IR (neat) 2956, 2923, 2853, 1748, 1628, 1455, 1370, 1299, 1260, 1219, 1058, and 1037 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 3.34 (dd, 1H, *J* = 16.0 and 7.9 Hz), 3.68 (dd, 1H, *J* = 16.0 an 9.9 Hz), 3.94 (s, 3H), 4.01 (s, 3H), 5.00 (s, 1H), 5.15 (s, 1H), 5.47 (brt, 1H, *J* = 8.9 Hz), 6.85 (s, 1H), 6.97 (d, 1H, *J* = 8.7 Hz), 8.14 (d, 1H, *J* = 8.7 Hz), and 8.95 (s, 1H); ^{13}C-NMR (100 MHz, CDCl3) δ 176.4, 166.5, 156.0, 152.6, 151.1, 146.8, 145.2, 142.5, 141.9, 128.2, 121.4, 118.3, 113.7, 113.1, 109.7, 107.9, 99.5, 88.4, 56.3, 56.2, 31.3, 29.7, and 17.1; HRMS Calcd for $[(C_{23}H_{18}O_7)+H]^+$: 407.1125. Found: 407.1129.

Ethyl 3-(3,4-dimethoxyphenyl)-8,8-dimethyl-4-oxo-4,8-dihydropyranol[2,3-f]chromene-2-carboxylate (27). The procedure was modified from literature as followed.[1,2] The solution containing 50 mg (0.14 mmol) of the alcohol **15**, 38 µL (0.34 mmol) of 3-chloro-3-methyl-1-butyne, 51 µL (0.34 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 2.57 mg (0.34 mmol) of copper (I) iodide, and 56 mg (0.34 mmol) of potassium iodide in 1.4 mL of dry toluene was refluxed for 24 h under Ar atmosphere. Afterward the mixture was diluted with CH_2Cl_2, then a saturated NH_4Cl solution was added, and the mixture was extracted with CH_2Cl_2. The combined organic phase was washed with a saturated NaCl solution, dried over $MgSO_4$(s), and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a mixture of 2.0:0.5:7.5 of EtOAc:Acetone:Hexane as an eluent to give 24 mg (41% yield) of the title compound **27** as a pale yellow solid; m.p. 165-166 ºC; IR (neat) 2978, 2936, 1736, 1646, 1636, 1515, 1441, 1287, 1266, 1201, 1171, 1114, 1026; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (t, 3H), 1.51 (3, 6H), 3.87 (s, 3H), 3.90 (s, 3H), 4.16 (q, 2H, *J* = 7.1 Hz), 5.73 (d, 1H, *J* = 10.1 Hz), 6.80-6.92 (m, 4H), and 8.00 (d, 1H, *J* = 8.8 Hz); ^{13}C-NMR (75 MHz, CDCl3) 176.7, 161.9, 158.0, 151.7, 150.2, 149.3, 148.7, 130.3, 126.6, 125.3, 123.8, 122.4, 117.6, 115.8, 114.9, 113.2, 110.9, 109.3, 78.0, 62.3, 55.9(x2), 28.2(x2), and 13.7; HRMS Calcd for $[(C_{25}H_{24}O_7)+H]^+$: 437.1595. Found: 437.1594.

3-(3,4-dimethoxyphenyl)-8,8-dimethyl-4-oxo-4,8-dihydropyrano[2,3-f]chromene-2-carboxylic acid (28). To a solution containing 80 mg (0.18 mmol) of the ester **27** in 1.6 mL of a 3:2:1 of THF/MeOH/H_2O solution at r.t. was added 16 mg (0.38 mmol) of LiOH·H_2O. The resulting mixture was stirred for 4 h and organic solvent was removed under reduced pressure. The crude residue was then diluted with H_2O and partitioned with EtOAc. The aqueous layer was acidified with a 1N HCl solution to pH3 and extracted with EtOAc (4x). The combined organic layer was then washed with a saturated aqueous NaCl solution, dried with Na_2SO_4(s), and concentrated under reduced pressure to give 74 mg (99%) of the title compound **28** as a pale yellow solid; m.p. 248-250 ºC; IR(neat); 2933, 1740, 1600, 1517, 1443, 1266, 1198, 1170, 1145, 1117, and 1029 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-D) *δ* 1.47 (s, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 5.97 (d, 1H, *J* = 10.1Hz), 6.78 (d, 1H, *J* = 10.1 Hz), 6.80 (dd, 1H, *J* = 8.2 and 1.9 Hz) 6.88 (d, 1H, *J* = 1.9 Hz), 6.96 (d, 1H, *J* = 8.8 Hz), 6.97 (d, 1H, *J* = 8.2 Hz), and 7.85 (d, 1H, *J* = 8.8 Hz); ^{13}C-NMR (75 MHz, DMSO-D) *δ* 175.9, 162.6, 157.4, 151.9, 151.0, 148.8, 148.1, 131.7, 126.2, 123.9, 123.4, 122.6, 117.1, 115.6, 114.1, 114.0, 111.3, 109.2, 78.3, 55.64, 55.61, 48.8, and 27.8; HRMS Calcd for $[(C_{23}H_{20}O_7)+H]^+$: 409.1282. Found: 409.1290.

6-Oxo-6a,12a,-dehydrodeguelin (29). To a solution containing 50 mg (0.12 mmol) of the acid **28** in 0.6 mL of a 1:1 mixture of MeCN and H_2O at r.t., were added 99 mg (0.36 mmol) of $K_2S_2O_8$ and 2 mg (0.012 mmol) of $AgNO_3$. The mixture was stirred at 60 ºC for 15 h, and then a saturated aqueous $NaHCO_3$ solution was added and stirred for an additional 15 min. After that, the resulting mixture was extracted with a 1:3 *i*-PrOH:CH_2Cl_2 solution. The combined organic phase was washed with a saturated NaCl solution, dried over Na_2SO_4(s), and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using CH_2Cl_2 and 1% MeOH/CH_2Cl_2 as an eluent to give 30 mg (60 % yield) of the title compound **29** as a pale yellow solid. m.p. 267-269 ºC; IR (neat) 2924, 1734, 1619, 1513, 1441, 1375, 1288, 1162, 1112, and 1065 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 6H), 3.96 (s, 3H), 4.02 (s, 3H), 5.77 (d, 1H, *J* = 10.1 Hz), 6.90 (s, 1H), 6.92 (d, 1H, *J* = 8.9 Hz), 7.02 (d, 1H, *J* = 10.1 Hz), and 8.05 (d, 1H, *J* = 8.9 Hz), 8.97 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.5, 158.9, 156.0, 151.4, 151.1, 146.8, 145.2, 142.1, 130.5, 126.5, 121.3, 117.8, 116.3, 114.8, 109.5, 108.0, 107.9, 99.5, 78.6, 56.3, 56.2, and 28.3(x2); HRMS Calcd for $[(C_{23}H_{18}O_7)+H]^+$: 407. 1125. Found: 407.1128.

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