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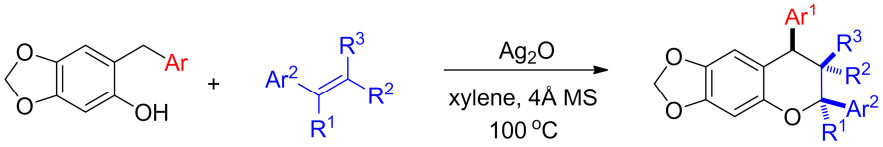
Department of Chemistry, the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China; Shenzhen Research Institute of Population and Family Planning, Shenzhen, China



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A One-Pot Oxidation/Cycloaddition Cascade Synthesis of 2,4-Diaryl Chromans via *ortho*-Qunione Methides

Yuk Fai Wong,[a] Zhaobin Wang,[a] Wen-Xu Hong,[b] and Jianwei Sun [a,]*

[a]*Department of Chemistry, the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China*
[b] *Shenzhen Research Institute of Population and Family Planning, Shenzhen, China*

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ABSTRACT

A one-pot oxidation/cycloaddition cascade for the synthesis of 2,4-diaryl chromans is developed. The reaction involves in situ oxidative generation of the unstable *o*-quinone methides followed by *endo* selective [4+2] cycloaddition with styrenes.

* Corresponding author. Tel.: +852-2358-7351; fax: +842-2358-1594; e-mail: sunjw@ust.hk

1. Introduction

Chroman is an important structural framework present in a wide range of natural products and biologically active unnatural molecules.[1] For example, myristinin B and their analogues, a family of 2,4-dirayl chromans, exhibit selective inhibitory activities against various enzymes including cyclooxygenase-2, DNA polymerase β, etc.[2] Diinsininol is a biflavonoid natural product with anti-inflammatory activity (Fig. 1).[3] As a result of their wide occurrence and important utility, various strategies for the synthesis of the chroman skeleton have been developed.[4] Among them, the [4+2] cycloaddition of *ortho*-quinone methides (*o*-QMs) and alkenes represents a facile and convergent strategy that allows flexible substitution of the chroman products.[5,6]

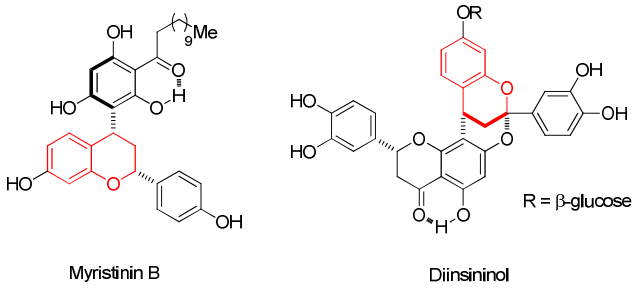
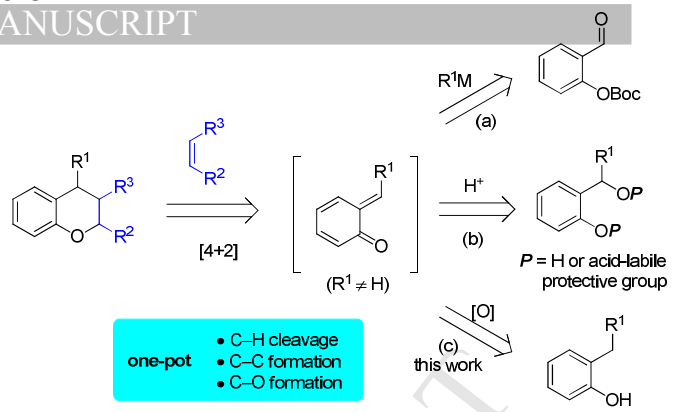


Fig. 1. Useful chroman-containing molecules

Although *o*-QMs have been recognized as useful synthetic intermediates for more than a century, their high reactivity and instability have impeded their characterization and application organic synthesis.[6] To date, only very few *o*-QMs stabilized with electron-donating groups have been synthesized and purified.[7] Nevertheless, even with these few pure *o*-QMs, various useful reactions have been developed. However, the scope of these reactions have been extremely narrow due to the lack of pure *o*-QMs that can be used.[7] In this context, in situ generation of *o*-QMs for one-pot reactions has been a pursuit of organic chemists to expand their utility. Thus, the compatibility of the *o*-QM generation and subsequent reaction is the key issue to address. In the past few decades, significant progress has been achieved.[5,6] However, there remain great challenges and high demand in effective utilization of the in situ generated *o*-QMs. In continuation of our interest in the studies of *o*-QMs,[8] here we report a one-pot stereoselective synthesis of 2,4-diaryl chromans by an oxidation/cycloaddition cascade via *o*-QMs.

It has been previously demonstrated that in situ generation of *o*-QMs either by addition of an organometallic reagent (such as alkyl/aryl lithium or Grignard reagents) to a salicylaldehyde derivative (path a, Scheme 1) or by acid-promoted elimination of an *o*-hydroxybenzyl alcohol derivative is compatible with the subsequent [4+2] cycloaddition with an alkene to form substituted chromans.[5] However, these acidic and strong basic conditions may have compatibility issues with certain labile functional groups. Therefore, the generation of *o*-QMs by oxidation of the non-functionalized benzylic position provides a complementary one-pot approach to chroman synthesis (path c).[7,9-10] In addition to the previously explored cases with β-unsubstituted *o*-QMs (R^1 = H),[9] here we describe the synthesis of 2,4-diaryl chromans from β-substituted *o*-QMs with regio- and stereoselectivity.

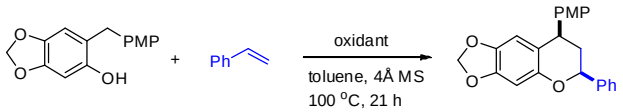


Scheme 1. One-pot synthesis of chromans via *o*-QMs

2. Results and discussion

We employed substituted phenol **1a** as the *o*-QM precursor and styrene **2a** as the cycloaddition partner. Initial preliminary condition evaluation indicated that the reaction at room temperature did not proceed. After substantial effort, we were delighted to find that certain oxidants can promote the formation of the desired chroman product **3a** at 100 °C in toluene with 4Å molecular sieves as additive. As shown in Table 1, among all the examined oxidants, MnO_2, Ag_2CO_3, and Ag_2O behave similarly well. Ag_2O provided the best reaction efficiency. Evaluation of different solvents indicated that xylene can slight improve the results.[11]

Table 1. Evaluation of oxidants



1a **2a** **3a**

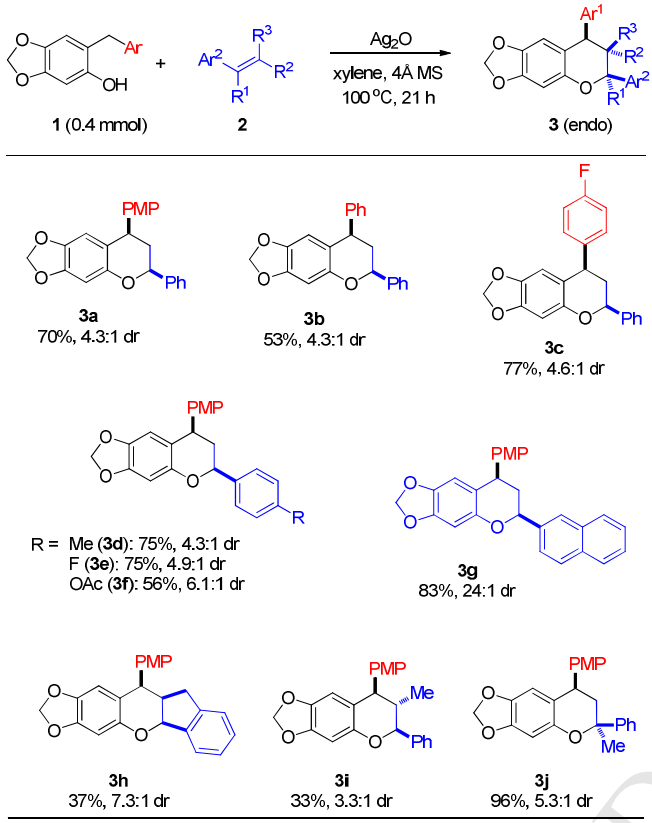
entry	oxidant	yield[b]	dr[b]
1	^{t}BuOOH	<10%	–
2	H_2O_2	<10%	–
3	PCC	<10%	–
4	Oxone	<10%	–
5	$K_2S_2O_8$	<10%	–
6	MnO_2	70%	4.6:1
7	Ag_2CO_3	63%	4.3:1
8	Ag_2O	78%	4.3:1
9[c]	Ag_2O	79%	4.6:1

[a] Reaction scale: phenol (0.1 mmol), styrene (1.0 mmol), oxidant (0.15 mmol), solvent (1.0 mL). [b] Yield and dr value were determined by ^{1}H NMR with CH_2Br_2 as internal standard. [c] Run with xylene as solvent.

With the standard conditions established in entry 9 of Table 1, we then examined the reaction scope. As shown in Table 2, a range of 2,4-diaryl chromans can be synthesized with moderate to high efficiency and diastereoselectivity. Substrates with electron-withdrawing and electron-donating groups are all suitable. The reaction is not limited to mono-substituted styrenes. 1,2-Disubstituted olefins with *Z* and *E* configuration can both give the desired products (**3h** and **3i**). 1,1-Disbustitutend olefins also reacted smoothly with high efficiency. Notably, in view of

the multiple bond cleavage/formation events, including C−H bond cleavage as well as C−C and C−O bond formation, our one-pot protocol is an expedient and efficient strategy for multi-substituted chroman synthesis. It is probably worth noting that although we chose Ag_2O as the oxidant in view of overall reaction efficiency, MnO_2 is also a good choice if price is taken into consideration.

Table 2. Reaction scope[a]



[a] Isolated yield. The dr value was determined by NMR analysis of the crude mixture.

The major products from the one-pot reaction generally have *cis* relative stereochemistry for the 2,4-diaryl substituents. To rationalize the observation, we proposed two possible transition states **TS1** and **TS2**, corresponding to *endo* and *exo* selectivity, respectively. We believe that in **TS1** there is secondary orbital overlap between the aryl group of the styrene and the π system of the *o*-QM intermediate, which provides stabilization of this transition state and thus results in a lower barrier than that with **TS2**. This analysis is consistent with the observation of *endo* product (via **TS1**) as the major diastereomer.

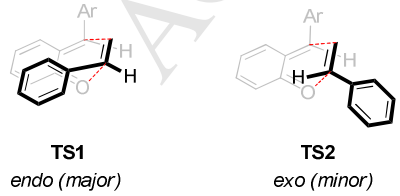


Fig. 2. *Endo* and *exo* transition states

3. Conclusions

In summary, we have developed a one-pot oxidation/cycloaddition cascade for the synthesis of 2,4-diaryl chromans, a family of useful molecules of broad utility in medicinal chemistry. Our approach involves an in situ oxidative generation of unstable *o*-QMs, which is complementary not only to those strategies requiring pre-synthesis of *o*-QMs, but also to the previously reported acidic and organometallic conditions for one-pot synthesis of chromans. Further investigations to extend this cascade strategy to catalytic asymmetric synthesis of 2,4-diaryl chromans are underway.

4. Experimental section

4.1. General

All air moisture sensitive reactions were conducted in oven-dried glassware under nitrogen atmosphere using dry solvents. Flash column chromatography was performed over silica gel (230-400 mesh) purchased from Qindao Puke Co., China. Anhydrous tetrahydrofuran, diethyl ether, acetonitrile, and toluene were purified by the Innovative® solvent purification system. Cyclopentyl methyl ether (CPME) and xylene were purchased from Sigma-Aldrich and Riedel-de Haën, respectively, and used as received. ^1H and ^{13}C NMR were collected on a Bruker AV 400 MHz NMR spectrometer using residue solvent peaks as an internal standard (^1H NMR: $CDCl_3$ at 7.26 ppm, ^{13}C NMR: $CDCl_3$ at 77.2 ppm).

4.2. Procedures

*4.2.1. General procedure for the one-pot preparation of 2,4-diaryl chromans (**3a-3j**).*At room temperature, a 4-mL vial was charged with a mixture of phenol (0.4 mmol), styrene (4 mmol), Ag_2O (0.6 mmol), 4Å MS (40 mg), and xylene (2.0 mL). The reaction mixture was heated to 100 °C and stirred at the same temperature for 21 h. After cooling, the mixture was purified by silica gel column chromatography to afford the desired product.

*4.2.1.1. cis-8-(4-Methoxyphenyl)-6-phenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3a**)* was synthesized as white solid according to the General Procedure (100.7 mg, 70% yield, 4.3:1 dr, purified by column chromatography, eluent: hexane/Et_2O = 8:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.37 – 7.33 (m, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.53 (s, 1H), 6.27 (s, 1H), 5.86 (d, *J* = 6.0 Hz, 2H), 5.15 (d, *J* = 11.2 Hz, 1H), 4.24 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.82 (s, 3H), 2.41 – 2.37 (m, 1H), 2.26 – 2.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.4, 146.8, 141.7, 141.3, 136.9, 129.5, 128.7, 128.2, 126.2, 117.9, 114.2, 109.2, 101.0, 98.7, 78.4, 55.4, 42.8, 41.0.

*4.2.1.2 cis-6,8-Diphenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3b**)* was synthesized as yellow oil according to the General Procedure (70.4 mg, 53% yield, 4.3:1 dr, purified by column chromatography, eluent: hexanes/Et_2O = 8:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.34 – 7.30 (m, 3H), 7.24 – 7.21 (m, 3H), 6.51 (s, 1H), 6.22 (s, 1H), 5.84 (d, *J* = 6.4 Hz, 2H), 5.13 (d, *J* = 11.6 Hz, 1H), 4.27 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.41 – 3.36 (m, 1H), 2.26 – 2.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.4, 144.9, 141.8, 141.3, 128.9, 128.7, 128.6, 128.2, 127.0, 126.3, 117.5, 108.6, 101.1, 98.8, 78.4, 43.7, 40.9. IR (neat, cm^{-1}) 2879, 1630, 1479, 1148. HRMS (EI+) calculated for $C_{22}H_{18}O_3$ [M^+]: 330.1256, found: 330.1256.

*4.2.1.3 cis-8-(4-Fluorophenyl)-6-phenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3c**)* was synthesized as yellow oil

according to the General Procedure (107.6 mg, 77% yield, 4.6:1 dr, purified by column chromatography, eluent: hexanes/Et_2O = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.33 (m, 5H), 7.21 – 7.18 (m, 2H), 7.03 (t, *J* = 8.4 Hz, 2H), 6.53 (s, 1H), 6.22 (s, 1H), 5.87 (d, *J* = 7.2 Hz, 2H), 5.14 (d, *J* = 11.2 Hz, 1H), 4.28 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.41 – 2.37 (m, 1H), 2.23 – 2.14 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 243 Hz), 150.5, 147.0, 141.9, 141.2, 140.6 (d, J_{C-F} = 3 Hz), 130.0 (d, J_{C-F} = 8 Hz), 128.7, 128.3, 126.2, 117.2, 115.7 (d, J_{C-F} = 21 Hz), 108.4, 101.1, 98.9, 78.3, 42.9, 41.1. IR (neat, cm^{-1}) 2879, 1634, 1479, 1226, 1151. HRMS (EI+) calculated for $C_{22}H_{17}FO_3$ [M^+]: 348.1162, found: 348.1168.

*4.2.1.4. cis-8-(4-Methoxyphenyl)-6-(p-tolyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3d**)* was synthesized as pale yellow solid according to the General Procedure (111.9 mg, 75% yield, 4.3:1 dr, purified by column chromatography, eluent: hexane/Et_2O = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d. *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.55 (s, 1H), 6.30 (s, 1H), 5.88 (d, *J* = 5.6 Hz, 2H), 5.14 (d, *J* = 11.2 Hz, 1H), 4.26 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.85 (s, 3H), 2.42 – 2.40 (m, 4H), 2.30 – 2.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.5, 146.8, 141.7, 138.6, 137.9, 137.0, 129.5, 129.4, 126.3, 117.9, 114.2, 108.5, 101.0, 98.7, 78.3, 55.4, 42.9, 40.8, 21.3. IR (neat, cm^{-1}) 2879, 1610, 1474, 1146. HRMS (EI+) calculated for $C_{24}H_{22}O_4$ [M^+]: 374.1518, found: 374.1513.

*4.2.1.5. cis-6-(4-Fluorophenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3e**)* was synthesized as yellow solid according to the General Procedure (106.8 mg, 71% yield, 4.9:1 dr, purified by column chromatography, eluent: hexanes/Et_2O = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.15 – 7.03 (m, 4H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.49 (s, 1H), 6.25 (s, 1H), 5.85 (d, *J* = 5.2 Hz, 2H), 5.11 (d, *J* = 11.2 Hz, 1H), 4.22 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H), 3.81 (s, 3H), 2.37 – 2.32 (m, 1H), 2.21 – 2.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J_{C-F} = 245 Hz), 158.6, 150.3, 146.9, 151.9, 137.2 (d, J_{C-F} = 3 Hz), 136.8, 129.5, 128.0 (d, J_{C-F} = 8 Hz), 117.8, 155.6 (d, J_{C-F} = 22 Hz), 114.3, 108.5, 101.1, 98.7, 77.7, 55.4, 42.8, 41.0.

*4.2.1.6. 4-(cis-8-(4-Methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-yl)phenyl acetate (**3f**)* was synthesized as yellow solid according to the General Procedure (93.2 mg, 56% yield, 6.1:1 dr, purified by column chromatography, eluent: hexanes/Et_2O = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 21 Hz, 2H), 7.14 – 7.11 (m, 4H), 6.87 (d, *J* = 21 Hz, 2H), 6.49 (s, 1H), 6.24 (s, 1H), 5.84 (d, *J* = 6.0 Hz, 2H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.21 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.81 (s, 3H), 2.38 – 2.33 (m, 1H), 2.31 (s, 3H), 2.21 – 2.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 158.6, 150.4, 150.2, 146.8, 141.8, 138.9, 136.7, 129.5, 127.3, 121.8, 117.8, 141.2, 108.5, 101.0, 98.7, 77.8, 55.4, 42.7, 40.9, 21.3. IR (neat, cm^{-1}) 2881, 1634, 1508, 1478, 1184. HRMS (EI+) calculated for $C_{25}H_{22}O_6$ [M^+]: 418.1416, found: 418.1409.

*4.2.1.7. cis-8-(4-Methoxyphenyl)-6-(naphthalen-2-yl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3g**)* was synthesized as yellow solid according to the General Procedure (135.7 mg, 83% yield, 24:1 dr, purified by column chromatography, eluent: hexanes/Et_2O = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.91 – 7.86 (m, 3H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.60 (s, 1H), 6.31 (s, 1H), 5.88 (d, *J* = 5.2 Hz, 2H), 5.31 (d, *J* = 10.8 Hz, 1H), 4.28 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.82 (s, 3H), 2.50 – 2.45 (m, 1H), 2.36 – 2.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.4, 146.9, 141.8, 138.7, 136.9, 133.5, 133.3, 129.5, 128.5, 128.2, 127.9, 126.3, 126.2, 125.1, 124.3, 117.9, 114.3, 108.6, 101.0, 98.8, 78.5, 55.4, 42.9, 40.9. IR (neat, cm^{-1}) 2880, 1630, 1477, 1247, 1149. HRMS (EI+) calculated for $C_{27}H_{22}O_4$ [M^+]: 410.1518, found: 410.1517.

*4.2.1.8. cis-11-(4-Methoxyphenyl)-5a,10,10a,11-tetrahydro-[1,3]dioxolo[4,5-g]indeno[1,2-b]chromene (**3h**)* was synthesized as yellow solid according to the General Procedure (54.5 mg, 37% yield, 7.3:1 dr, purified by column chromatography, eluent: hexanes/Et_2O = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 1H), 7.31 – 7.26 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.21 – 7.18 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.43 (d, *J* = 4.4 Hz, 2H), 5.86 (d, *J* = 3.6 Hz, 2H), 5.46 (d, *J* = 4.8 Hz, 1H), 4.54 (d, *J* = 6.0 Hz, 1H), 3.87 (s, 3H), 3.08 – 3.03 (m, 1H), 2.99 – 2.92 (m, 1H), 2.56 – 2.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.9, 146.5, 144.6, 142.5, 141.7, 134.2, 130.4, 129.3, 126.9, 125.4, 125.2, 116.7, 114.1, 108.2, 101.0, 99.2, 81.8, 55.5, 45.9, 42.6, 33.8. IR (neat, cm^{-1}) 2897, 1506, 1474, 1243, 1145. HRMS (EI+) calculated for $C_{24}H_{20}O_4$ [M^+]: 372.1362, found: 372.1365.

*4.2.1.9. cis-8-(4-Methoxyphenyl)-7-methyl-6-phenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3i**)* was synthesized as yellow solid according to the General Procedure (49.9 mg, 33% yield, 3.3:1 dr, purified by column chromatography: hexanes/Et_2O = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 3H), 7.39 – 7.31 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.45 (s, 1H), 6.14 (s, 1H), 5.83 (d, *J* = 5.2 Hz, 2H), 4.68 (d, *J* = 10.0 Hz, 1H), 3.82 (s, 3H), 2.26 – 2.15 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 1H), 0.59 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 150.3, 146.6, 141.8, 140.1, 136.2, 131.6, 128.7, 128.6, 128.4, 127.7, 114.2, 108.9, 101.0, 98.4, 84.7, 55.4, 50.5, 41.4, 15.8. IR (neat, cm^{-1}) 2897, 1507, 1476, 1245, 1151. HRMS (EI+) calculated for $C_{24}H_{22}O_4$ [M^+]: 374.1518, found: 374.1525.

*4.2.1.10. cis-8-(4-Methoxyphenyl)-6-methyl-6-phenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene (**3j**)* was synthesized as yellow oil yellow oil according to the General Procedure (144.0 mg, 96% yield, 5.3:1 dr, purified by column chromatography, eluent: hexanes/Et_2O = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.42 – 7.34 (m, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.60 (s, 1H), 6.30 (s, 1H), 5.87 (d, *J* = 7.2 Hz, 2H), 4.13 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.81 (s, 3H), 2.39 – 2.34 (m, 1H), 2.16 (t, *J* = 12.4 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 148.6, 147.1, 147.0, 141.5, 136.8, 129.7, 128.4, 127.1, 124.5, 116.7, 114.1, 108.5, 100.9, 99.2, 77.8, 55.4, 44.6, 39.5, 24.7. IR (neat, cm^{-1}) 2976, 1611, 1508, 1378, 1274, 1153. HRMS (EI+) calculated for $C_{24}H_{22}O_4$ [M^+]: 374.1518, found: 374.1512.

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Supplementary data

The procedures for the synthesis of substrates together with ^{1}H and ^{13}C NMR spectra for compounds the new compounds. Supplementary data associated with this article can be found in the online version.

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