

Supporting Information

Synthesis of isochromanones via laccase-mediated oxidative [4+2] cyclization of pyrocatechuic acid with styrenes

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1. General Information

Chemicals and solvents were purchased from commercial suppliers and used as received unless noted. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker spectrometers. Chemical shifts of ^1H were reported in part per million relatives to the CDCl_3 residual peak (δ 7.26). Chemical shifts of ^{13}C NMR were reported relative to CDCl_3 (δ 77.16). The used abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), m (multiplet), br (broad). Multiplets which arise from accidental equality of coupling constants of magnetically non-equivalent protons are marked as virtual (*virt.*) All products were purified by flash chromatography on silica gel. Reactions were monitored by TLC analysis using silica gel 60 Å F-254 thin layer plates and compounds were visualized with a UV light at 254 nm or 365 nm. Flash column chromatography was performed on silica gel 60Å, 10-40 μm . Melting points were measured on a SGW® X-4B. High resolution mass spectra (HRMS) data were measured on a ESI-microTOFII. The protein concentration was quantified by the Thermo eliasa. The protein of circular dichroism spectra was measured by Jasco J-810-CD.

2. Expression and Purification of Multicopper Oxidases (MnxEFG)

mnxEFG Gene Cloning:

The sequence of *mnxE* to *mnxG* (NCBI accession EF158106) from *Bacillus* sp. PL-12 (Taxonomy ID: 161537) were synthesized by Genewiz (Wuhan, China). Gibson cloning primers were designed to recess DNA fragments¹, *mnxEFG* sequence with single-stranded DNA overhangs were amplified by the following primers:

Forward primer:

5'-CTTTAAGAAGGAGATATACAAATGATGCATGACTCGCCATTAAAATC-3', and Reverse primer:

5'-GGGTGGCTCCAAGCGCTCCCTGCCTTTTCTTCATTGTCCCACC-3'.

Linear vector pASG-IBA103 was amplified by the following primers:

Forward primer: 5'-TGTATATCTCCTTCTTAAAG-3', and Reverse primer: 5'-GGGAGCGCTTGGAGCCACCC-3'.

The two adjacent DNA fragments sharing terminal sequence overlaps were joined into a covalently sealed molecule in a one-step isothermal reaction. T5 exonuclease removed nucleotides from the 5' ends of double-stranded DNA molecules, complementary single-stranded DNA overhangs annealed, Phusion DNA polymerase filled the gaps and Taq DNA ligase sealed the nicks. The *mnxEFG* gene was then cloned into the Twin--Strep-tag affinity purification pASG-IBA103 expression vector. In place of the *mnxG* stop codon the Twin--Strep-tag (underlined) was engineered to a linker (*italicized*) at the C-terminus (*GSAWSHPQFEKGGGSGGSAWSHPQFEK*). The sequencing primers were as follows:

Forward primer: 5'- GAGTTATTTTACCACTCCCT -3'

Reverse primer: 5'- CGCAGTAGCGGTAAACG -3'

Gel electrophoresis analysis was performed in an DYY-6C electrophoresis apparatus (Liuyi Biotechnology Co.,Ltd, Beijing). The resulting construct was transformed into *E. coli* BL21 (DE3).

Protein expression and purification:

Protein MnxEFG was induced by methods described previously². The harvested cells were

suspended into equilibration buffer (100 mM Tris-HCl pH 8.0, 1.5 M NaCl) supplemented with 10 mM CaCl₂, 1 mM CuSO₄, and EDTA-free protease inhibitor (Sigma) and lysed using JY92-IIID (Ningbo Dongnan instrument co., ltd., China) for 1 min/ml cell lysate at 60% amplitude with 10 s on/off pulses on ice. The crude extract was clarified by 20 min of incubation at 70 °C. The debris was pelleted by centrifugation 15,000 × g 4 °C 30 min and the supernatant was filtered through a 0.4 μm pore PVDF filter. The clarified lysate was then added to 5 ml column volume (CV) of gravity flow Strep-Tactin@XT superflow® (IBA, Germany). Washed column 5 × with 1 CV of Buffer W (100 mM Tris/HCl, pH 8.0; 150 mM NaCl; 1 mM EDTA), collected the wash fractions and saved 10 μl of wash fraction for application on an analytical SDS-PAGE. Added 6 × 0.5 CV of Buffer BXT (100 mM Tris/HCl, pH 8.0; 150 mM NaCl; 1 mM EDTA; 50 mM biotin), to get high protein concentrations in one fraction add 0.6 CV as elution fraction 1 (E1), then 1.6 CV (E2) and finally 0.8 CV (E3). Main protein content should be in E2. 10 μl sample of E2 can be used for SDS-PAGE analysis. All buffers up to this point are supplemented with 50 μM CuSO₄ to avoid copper leaching by Tris. This as-isolated oxidized protein complex (denoted as MnxEFG) was then flash frozen in liquid nitrogen and stored at -80 °C until use. The protein was quantified by the Thermo Scientific Pierce bicinchoninic acid (BCA) protein assay.

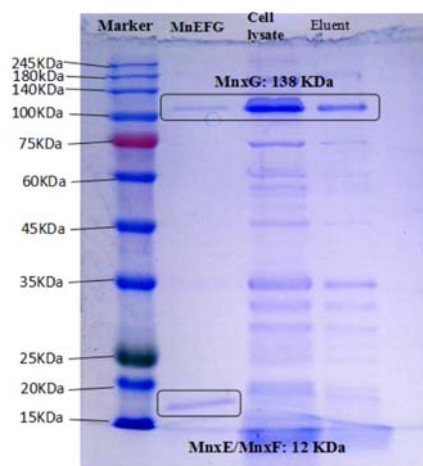


Figure S1. SDS-PAGE of purified protein.

3. General Procedure for the Synthesis of Isochromanones

In a dry 5 ml round bottom flask, 2,3-dihydroxybenzoic acid (2.0 eq, 0.3 mmol), styrene derivatives (1.0 eq, 0.15 mmol), multicopper oxidase in PBS (0.01 mol%), 30% H₂O₂ (5.0 eq), hydrochloric acid (2.0 eq) and deionized water (0.25 mL), acetonitrile (0.25 mL) was then injected into the flask. The reaction mixture was stirred at room temperature for 48 h. After the completion of reaction, the reaction system was diluted with 1.0 mL water and extracted with ethyl acetate. The extract was dried over Na₂SO₄ and concentrated on a rotary evaporator. The crude was purified by silica-gel column chromatography using ethyl acetate/hexane (10/1 to 7/3).

4. The HRMS of intermediate and byproducts

In a dry 5 ml round bottom flask, 2,3-dihydroxybenzoic acid, multicopper oxidase in PBS (0.01 mol%), 30% H₂O₂ (5 eq), and deionized water (0.25 mL), acetonitrile (0.25 mL) was then injected

into the flask. The reaction mixture was stirred at room temperature for 5 min. A high resolution mass spectrometry was obtained by the reaction solution.

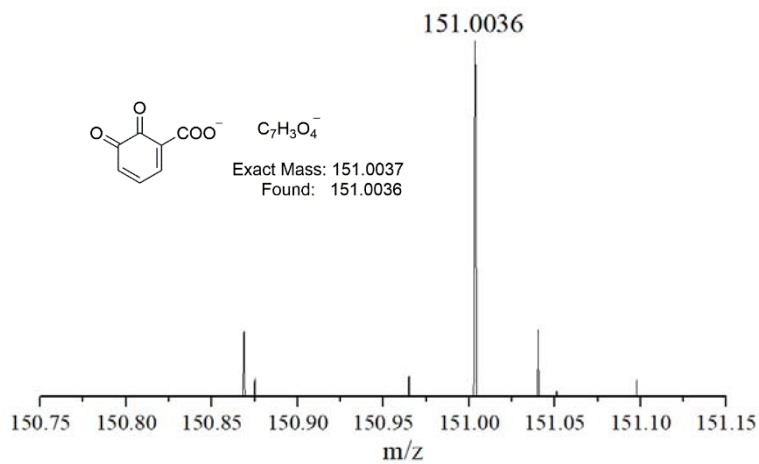
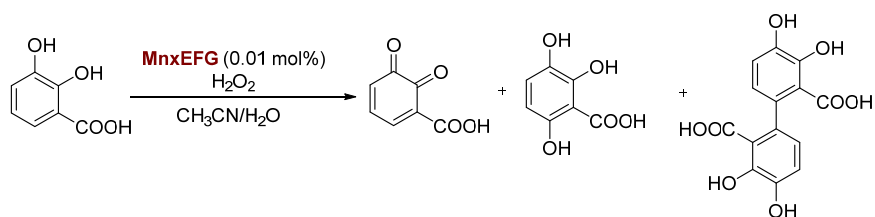


Figure S2. The HRMS spectrum of intermediate.

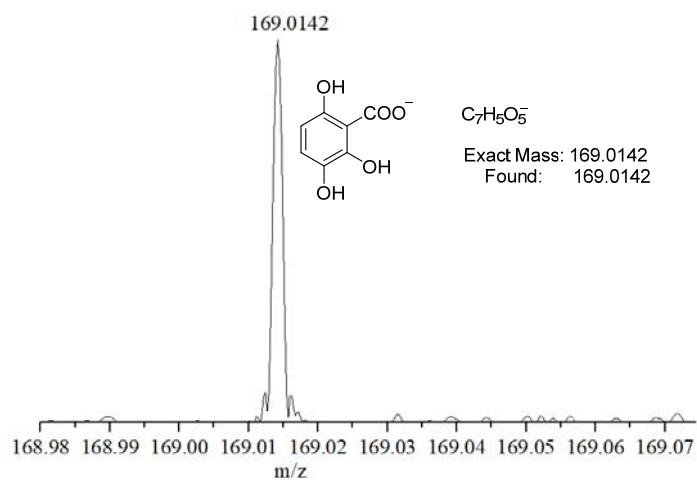


Figure S3. The HRMS spectrum of byproduct.

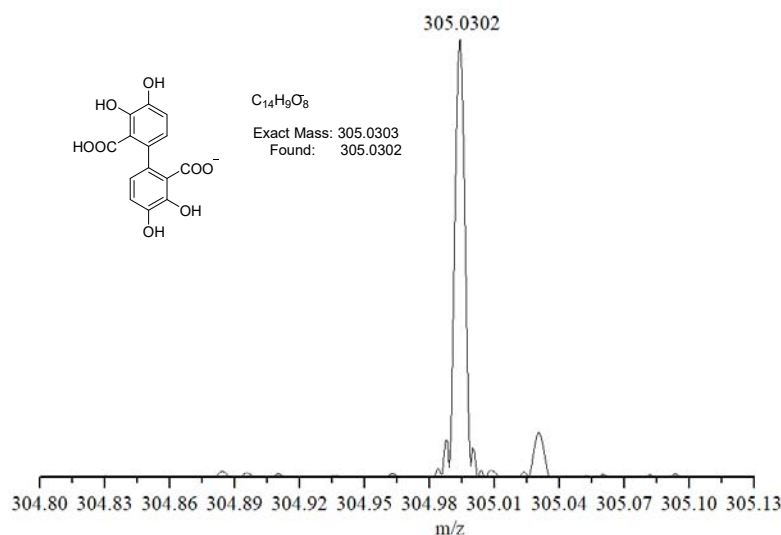


Figure S4. The HRMS spectrum of dimerized byproduct.

5. Enzymatic Assays

The Mnx, CueO, CotA of kinetic parameters was performed in standard conditions at 25 °C with different concentration of pyrocatechuic acid substrate (1-30 mM) by measuring the initial rate of product formation (at 320 nm maximum ultraviolet absorption wavelength). Kinetic constants (km and kcat) were fitted directly to the Michaelis–Menten equation (OriginLab software, North-ampton, MS, USA). All enzymatic assays were performed at least in triplicate. The protein concentration was quantified by the Thermo Scientific Pierce bicinchoninic acid (BCA) protein assay. The reaction profile was following by monitoring the characteristic absorption peak at 317 nm (λ_{max}), see the UV-Vis spectra (Figure S5). Reaction profiles of formation of product **3a** at 25 °C and 60 °C are shown in Figure S6. The rate of product formation at 60 °C was higher than that exhibited at 25 °C but the final yields were almost the same.

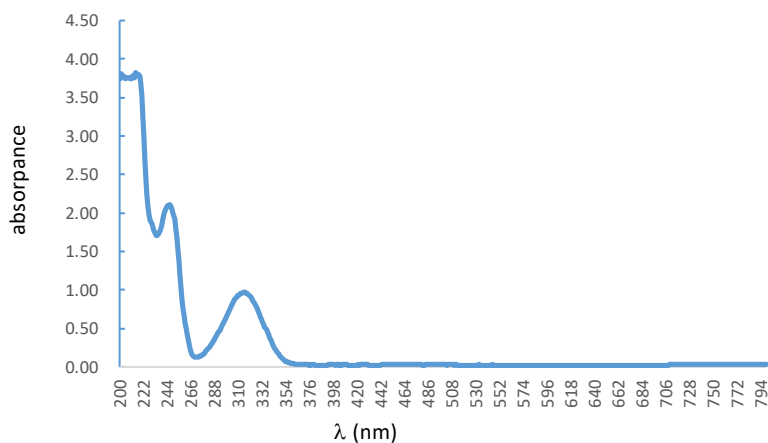


Figure S5 UV-Vis absorption of **3a** in CH₃CN

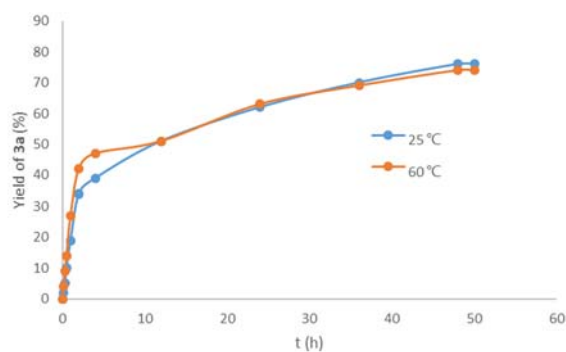


Figure S6 The reaction profile at 25 °C and 60 °C

6. Green chemistry metrics

Atom economy, Reaction mass efficiency, E-factor, and EcoScale were calculated for the synthesis of **3e** by the present method and compared to the current state of the art protocols. These green chemistry metrics are measured by following the well-recognized definitions:

Atom economy (AE)³ was calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation and expressed as a percentage. AE is a theoretical number which assumes the use of exact stoichiometric quantities of starting materials and a theoretical chemical yield and disregards substances, such as solvents and auxiliary chemicals which do not appear in the stoichiometric equation.

Reaction mass efficiency (RME)⁴ was calculated by dividing the mass of desired product by the total mass of reactants and expressed as a percentage. RME is a refinement of AE taking yield and use of excess reagents into account. Notably, Neither AE nor RME takes into account the solvents or all auxiliary components that are not reflected in the stoichiometric equation.

E factor⁵ is the actual amount of waste produced in the process and takes waste from all auxiliary components, for example, solvent losses and chemicals used in workup, into account. The total mass of waste is calculated by the deduction of mass of the desired product from the total mass of input reactants/reagents/catalyst(s)/solvent.

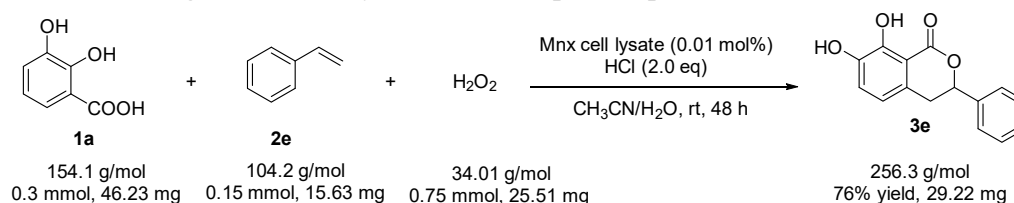
The EcoScale⁶ value of the reactions based on six parameters (yield, price of the reaction component, safety, technical setting, temperature/time, and treatment and purification).

$$\text{Atom Economy (AE)} = \frac{\text{mol wt of product}}{\text{sum of mol wts of reactants}} \times 100\%$$

$$\text{Reaction mass efficiency (RME)} = \frac{\text{Mass of product}}{\text{total mass of reactants}} \times 100\%$$

$$\text{E factor} = \frac{\text{total mass of waste}}{\text{mass of desired product}}$$

Assessment of the green chemistry metrics of the present protocol.



$$\text{Atom Economy (AE)} = \frac{\text{mol wt of product}}{\text{sum of mol wts of reactants}} \times 100\% \pm$$

$$= \frac{256.3 \text{ (3e)}}{154.1 \text{ (1a)} + 104.2 \text{ (2e)} + 34.0 \text{ (H}_2\text{O}_2)} \times 100\% = 87.7 \%$$

$$\text{Reaction mass efficiency (RME)} = \frac{\text{Mass of product}}{\text{total mass of reactants}} \times 100\%$$

$$= \frac{29.22 \text{ mg (3e)}}{46.23 \text{ mg (1a)} + 15.63 \text{ g (2e)} + 25.51 \text{ mg (H}_2\text{O}_2)} \times 100\% = 33.4\%$$

$$\text{E factor} = \frac{\text{total mass of waste}}{\text{mass of desired product}}$$

$$= \frac{(46.23 \text{ mg (1a)} + 15.63 \text{ mg (2e)} + 3.2 \text{ mg (Mnx)} + 85.0 \text{ mg (H}_2\text{O}_2 \text{ solution)} + 29.59 \text{ mg (HCl solution)} + 250 \text{ mg (H}_2\text{O)} + 197 \text{ mg (MeCN)}) - 29.22 \text{ mg (3e)}}{29.22 \text{ mg (3e)}}$$

$$= 20.45 \text{ Kg waste per 1 Kg product}$$

Table. S1. EcoScale calculation for the synthesis of **3a**

	parameters	Penalty points
1 Yield	(100-%yield)/2=(100-76)/2=12	12
2 Price of reaction components (per 10 mmol of end products)	a. Alkene and 3-hydroxysalicylicacid = \$8 b. enzyme 0.0001 mmol = \$1 c. ACN 20 mL = \$0.5 Total \$9.5 inexpensive	0
3 Safety		0
4 Technical setup	Common setup	0
5 Temperature and time	Room temperature and 48 hours	1
6 Workup and purification	Liquid-liquid extraction Classical chromatography purification	13
Total Penalty points		26
EcoScale		74

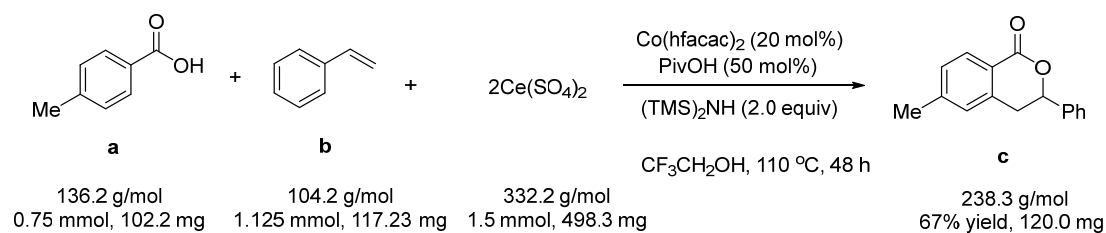
EcoScale = 100 - Sum of individual penalties

Scores on EcoScale: >75, Excellent; >50, Acceptable; <50, inadequate

The Ecoscale value of the present synthesis is 74, which is an acceptable protocol and is very close to an excellent point.

Comparison of the green chemistry metrics of the present protocol with the current state of the art protocol.

The cobalt-catalyzed intermolecular coupling of benzoic acid with styrene is taken for comparison (T. Nguyen, L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.*, 2018, 57, 1688–1691). This reaction represents the most current state of the art protocol towards the synthesis of isochromanones. According to the synthetic procedure given in its supporting information, the reaction equation and their stoichiometry are shown below.



$$\text{Atom Economy (AE)} = \frac{\text{mol wt of product}}{\text{sum of mol wts of reactants}} \times 100\%$$

$$= \frac{238.3\text{ (c)}}{136.2\text{ (a)} + 104.2\text{ (b)} + 2 * 332.2\text{ (c)}} \times 100\% = 26.3\%$$

$$\text{Reaction mass efficiency (RME)} = \frac{\text{Mass of product}}{\text{total mass of reactants}} \times 100\%$$

$$= \frac{120.0\text{ mg (c)}}{102.2\text{ mg (a)} + 117.23\text{ mg (b)} + 498.3\text{ mg [Ce(SO}_4)_2]} \times 100\% = 16.7\%$$

$$\text{E factor} = \frac{\text{total mass of waste}}{\text{mass of desired product}}$$

$$= \frac{102.2\text{ mg (a)} + 117.23\text{ (b)} + 498.3\text{ mg [Ce(SO}_4)_2] + 71\text{ mg [Co(hfacac)}_2] + 38\text{ mg (PivOH)} + 242\text{ mg (TMS)}_2\text{NH} + 10425\text{ mg [CF}_3\text{CH}_2\text{OH]} - 120\text{ mg [c]}}{120\text{ mg (c)}}$$

$$= 94.8\text{ Kg waste per 1 Kg product}$$

Table. S2. EcoScale calculation for the synthesis of **c**

	parameters	Penalty points
1 Yield	$(100\text{-}\% \text{yield})/2 = (100-67)/2 = 16.5$	16.5
2 Price of reaction components (per 10 mmol of end products)	a. Alkene and <i>p</i> -Toluic acid = \$9 b. Co(hfacac) ₂ , PivOH, (TMS) ₂ NH, Ce(SO ₄) ₂ = \$6 c. CF ₃ CH ₂ OH 100 mL = \$2	3
3 Safety	CF ₃ CH ₂ OH (Toxic) Flammable	5 5
4 Technical setup	gas atmosphere	1
5 Temperature and time	110 °C and 48 hours	3
6 Workup and purification	Liquid-liquid extraction Classical chromatography purification	13
Total Penalty points		46.5
EcoScale		53.5

EcoScale = 100 - Sum of individual penalties

Scores on EcoScale: >75, Excellent; >50, Acceptable; <50, inadequate

The Ecoscale value is 53.5, which is much lower than the protocol developed in this study.

7. Other unsuccessful alkene substrate

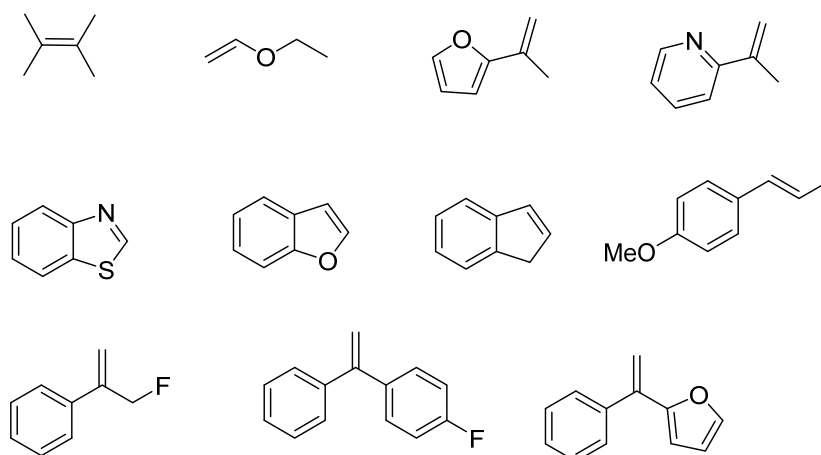
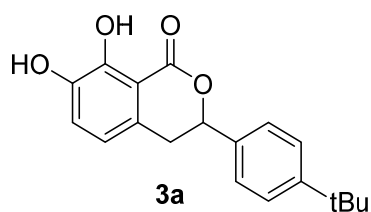


Figure S7. Some typical olefins which cannot react with pyrocatechuic acid.

8. Analytical Data of Synthetic Products

3-(4-(*tert*-Butyl)phenyl)-7,8-dihydroisochroman-1-one (3a)



A pale yellow oil. 24.9 mg, 77% yield.

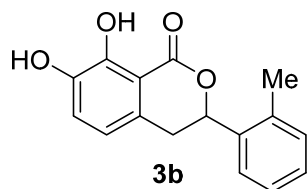
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 11.06 (s, 1H), 7.47 – 7.45 (m, 2H), 7.41 – 7.37 (m, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 5.63 – 5.58 (m, 2H), 3.31 (dd, $J = 15.9$ Hz, 3.6 Hz, 1H), 3.09 (dd, $J = 15.9$ Hz, 3.6 Hz, 1H), 1.35 (s, 9H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 170.0, 152.0, 150.9, 149.1, 148.2, 143.9, 142.3, 134.8, 134.3, 129.7, 126.0, 125.7, 123.6, 120.7, 117.7, 81.7, 34.6, 34.3, 31.2.

HRMS (ESI): calculated for $\text{C}_{19}\text{H}_{21}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 313.1434, found: 313.1437.

7, 8-Dihydroxy-3-(*o*-tolyl) isochroman-1-one (3b)



A pale yellow oil. 30.8 mg, 72% yield.

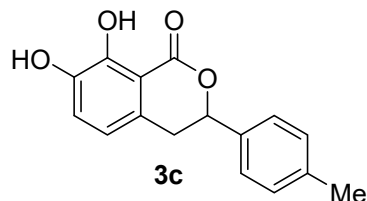
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 11.07 (s, 1H), 7.57 – 7.54 (m, 1H), 7.32 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 5.83 (dd, $J = 12.4, 3.1$ Hz, 1H), 5.64 (s, 1H), 3.29 (dd, $J = 16.5, 3.0$ Hz, 1H), 3.03 (dd, $J = 16.5, 3.0$ Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] (101 MHz, CDCl_3) 170.2, 149.1, 144.0, 135.8, 134.9, 130.7, 129.8, 128.7, 126.5, 125.9, 120.7, 117.6, 108.3, 79.1, 33.5, 19.1.

HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{15}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 271.0965, found: 271.0967.

7, 8-Dihydroxy-3-(*p*-tolyl) isochroman-1-one (3c)



A pale yellow oil. 32.7 mg, 74% yield.

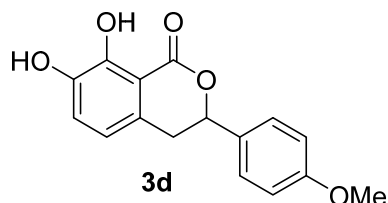
TLC: R_f = 0.6 (PE: EA = 7:3).

^1H NMR (400 MHz, CDCl_3): δ [ppm] 11.06 (s, 1H), 7.37 – 7.34 (m, 2H), 7.26 – 7.23 (m, 2H), 7.14 (d, J = 5.6 Hz, 1H), 6.70 (d, J = 5.6 Hz, 1H), 5.65 (s, 1H), 5.59 (d, J = 8.0 Hz, 1H), 3.29 (t, J = 16.3 Hz, 1H), 3.09 (d, J = 16.3 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] 170.0, 149.1, 143.9, 138.8, 134.9, 129.7, 129.4, 126.1, 120.7, 117.7, 108.3, 81.8, 34.5, 21.2.

HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{15}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 271.0965, found: 271.0967.

7, 8-Dihydroxy-3-(4-methoxyphenyl) isochroman-1-one (3d)



A pale yellow oil. 28.6 mg, 67% yield.

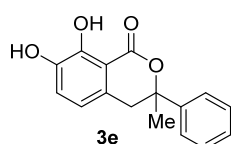
TLC: R_f = 0.6 (PE: EA = 7:3).

^1H NMR (400 MHz, CDCl_3): δ [ppm] 11.06 (s, 1H), 7.44 – 7.36 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.69 (d, J = 8.0 Hz, 1H), 5.63 (s, 1H), 5.57 (dd, J = 12.2 Hz, 3.2 Hz, 1H), 3.85 (s, 3H), 3.36 – 3.25 (m, 1H), 3.07 (dd, J = 16.4 Hz, 3.2 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] 170.0, 160.0, 149.1, 143.9, 129.9, 129.7, 127.7, 120.6, 117.6, 114.1, 108.3, 81.7, 55.3, 34.3.

HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{15}\text{O}_5$ $[\text{M} + \text{H}]^+$ m/z 287.0914, found: 287.0916.

7, 8-Dihydroxy-3-methyl-3-phenylisochroman-1-one (3e)



A pale yellow oil. 35.6 mg, 76% yield.

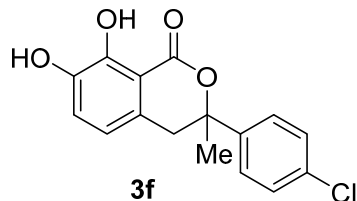
TLC: R_f = 0.6 (PE: EA = 7:3).

^1H NMR (400 MHz, CDCl_3): δ [ppm] 11.03 (s, 1H), 7.44 – 7.43 (m, 2H), 7.36 – 7.33 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 5.50 (s, 1H), 3.47 (d, J = 16.2 Hz, 1H), 3.33 (d, J = 16.2 Hz, 1H), 1.79 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] 169.7, 148.9, 143.7, 143.0, 128.6, 127.7, 125.3, 124.6, 124.1, 120.6, 117.9, 113.5, 108.4, 85.8, 38.1, 29.7.

HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{15}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 271.0965, found: 271.0967.

3-(4-Chlorophenyl)-7,8-dihydroxy-3-methylisochroman-1-one (3f)



A pale yellow oil. 39.4 mg, 71% yield.

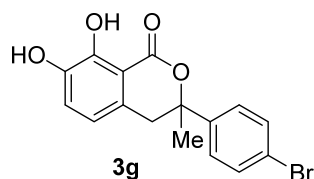
TLC: $R_f = 0.6$ (PE: EA = 7:3).

^1H NMR (400 MHz, CDCl_3): δ [ppm] 10.97 (s, 1H), 7.39 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.06 (d, $J = 8.0$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 5.55 (s, 1H), 3.43 (d, $J = 16.3$ Hz, 1H), 3.32 (d, $J = 16.3$ Hz, 1H), 1.77 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] 169.4, 149.0, 143.8, 141.6, 133.7, 128.8, 128.2, 126.1, 120.7, 118.0, 108.1, 85.3, 38.0, 29.7.

HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{14}\text{ClO}_4$ $[\text{M} + \text{H}]^+$ m/z 305.0575, found: 305.0577.

3-(4-Bromophenyl)-7,8-dihydroxy-3-methylisochroman-1-one (3g)



A pale yellow oil. 27.2 mg, 60% yield.

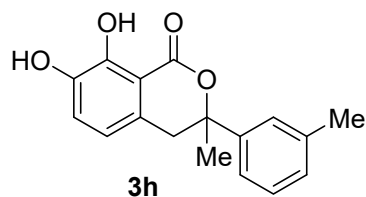
TLC: $R_f = 0.6$ (PE: EA = 7:3).

^1H NMR (400 MHz, CDCl_3): δ [ppm] 10.96 (s, 1H), 7.48 – 7.46 (m, 2H), 7.32 – 7.30 (m, 2H), 7.06 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.57 (s, 1H), 3.42 (d, $J = 16.3$ Hz, 1H), 3.32 (d, $J = 16.3$ Hz, 1H), 1.77 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] 169.4, 149.0, 143.8, 142.1, 131.8, 128.2, 126.4, 121.9, 120.7, 118.0, 108.0, 85.3, 38.0, 29.7.

HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{14}\text{BrO}_4$ $[\text{M} + \text{H}]^+$ m/z 349.0070, found: 349.0073.

7, 8-Dihydroxy-3-methyl-3-(*m*-tolyl) isochroman-1-one (3h)



A pale yellow oil. 29.3 mg, 62% yield.

TLC: $R_f = 0.6$ (PE: EA = 7:3).

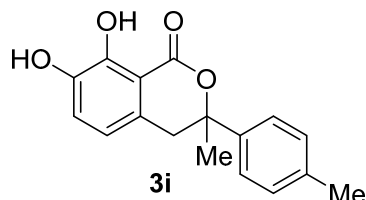
^1H NMR (400 MHz, CDCl_3): δ [ppm] 7.27 – 7.19 (m, 3H), 7.09 – 7.02 (m, 2H), 6.65 (d, $J = 8.0$

Hz, 1H), 3.46 (d, $J = 16.3$ Hz, 2H), 3.30 (d, $J = 16.3$ Hz, 2H), 2.35 (s, 3H), 1.77 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.7, 148.9, 143.6, 143.0, 138.3, 128.7, 128.5, 128.4, 125.3, 121.6, 120.6, 117.9, 108.2, 85.8, 38.1, 29.7, 21.5.

HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 285.1121, found: 285.1123.

7, 8-Dihydroxy-3-methyl-3-(*p*-tolyl) isochroman-1-one (3i)



A pale yellow oil. 37.6 mg, 81% yield.

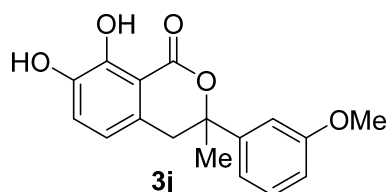
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 11.04 (s, 1H), 7.31 – 7.30 (m, 2H), 7.14 – 7.12 (m, 2H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 5.72 (s, 1H), 3.46 (d, $J = 16.4$ Hz, 1H), 3.31 (d, $J = 16.4$ Hz, 1H), 2.31 (s, 3H), 1.77 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.8, 148.9, 143.6, 140.0, 137.5, 129.3, 128.7, 124.5, 120.5, 117.9, 108.3, 85.9, 38.1, 29.9, 20.9.

HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 285.1121, found: 285.1123.

7, 8-Dihydroxy-3-(3-methoxyphenyl)-3-methylisochroman-1-one (3j)



A pale yellow oil. 30.2 mg, 64% yield.

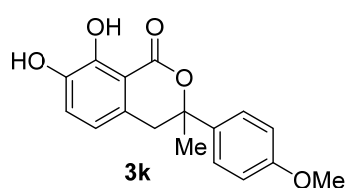
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ [ppm] 11.02 (s, 1H), 7.25 (t, $J = 8.1$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 7.4$ Hz, 2H), 6.80 (d, $J = 7.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.53 (s, 1H), 3.81 (s, 3H), 3.45 (d, $J = 16.2$ Hz, 1H), 3.32 (d, $J = 16.2$ Hz, 1H), 1.78 (s, 3H).

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ [ppm] 169.7, 159.7, 148.9, 144.7, 143.7, 129.7, 128.6, 120.6, 117.9, 116.9, 112.7, 111.0, 108.2, 85.7, 55.2, 38.1, 29.8.

HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{17}\text{O}_5$ $[\text{M} + \text{H}]^+$ m/z 301.1071, found: 301.1072.

7, 8-Dihydroxy-3-(4-methoxyphenyl)-3-methylisochroman-1-one (3k)



A pale yellow oil. 34.2 mg, 73% yield.

TLC: $R_f = 0.6$ (PE: EA = 7:3).

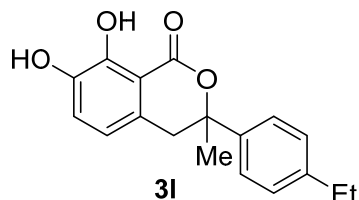
$^1\text{H NMR}$ (600 MHz, CDCl_3): δ [ppm] 11.05 (s, 1H), 7.35 – 7.33 (m, 2H), 7.05 (d, $J = 8.0$ Hz, 1H),

6.86 – 6.84 (m, 2H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.54 (s, 1H), 3.79 (s, 3H), 3.46 (d, $J = 16.3$ Hz, 1H), 3.31 (d, $J = 16.3$ Hz, 1H), 1.77 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3): δ [ppm] 169.8, 159.0, 158.6, 149.0, 143.6, 135.0, 128.8, 126.0, 120.5, 117.9, 113.9, 108.3, 100.0, 85.7, 55.2, 38.1, 30.0.

HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{17}\text{O}_5$ $[\text{M} + \text{H}]^+$ m/z 301.1071, found: 301.1072.

3-(4-Ethylphenyl)-7, 8-dihydroxy-3-methylisochroman-1-one (3l)



A pale yellow oil. 28.6 mg, 74% yield.

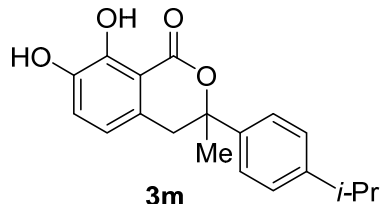
TLC: $R_f = 0.6$ (PE: EA = 7:3).

^1H NMR (400 MHz, CDCl_3): δ [ppm] 11.05 (s, 1H), 8.06 (s, 1H), 7.34 – 7.32 (m, 2H), 7.17 – 7.15 (m, 2H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.53 (s, 1H), 3.47 (d, $J = 16.0$ Hz, 1H), 3.31 (d, $J = 16.0$ Hz, 1H), 2.62 (q, $J = 15.2, 7.6$ Hz, 2H), 1.77 (s, 3H), 1.22 (t, $J = 7.6$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] 169.8, 149.1, 143.7, 143.6, 140.2, 128.8, 128.0, 124.6, 120.5, 117.9, 108.1, 85.9, 37.9, 29.9, 28.3, 15.2.

HRMS (ESI): calculated for $\text{C}_{18}\text{H}_{19}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 299.1278, found: 299.1280.

7, 8-Dihydroxy-3-(4-isopropylphenyl)-3-methylisochroman-1-one (3m)



A pale yellow oil. 28.8 mg, 71% yield.

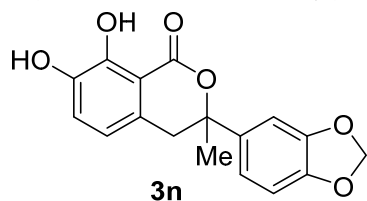
TLC: $R_f = 0.6$ (PE: EA = 7:3).

^1H NMR (400 MHz, CDCl_3): δ [ppm] 11.07 (s, 1H), 7.36 – 7.32 (m, 2H), 7.19 – 7.17 (m, 2H), 7.06 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 2H), 5.53 (s, 1H), 3.47 (d, $J = 16.3$ Hz, 1H), 3.31 (d, $J = 16.3$ Hz, 1H), 2.88 (dt, $J = 13.8, 6.9$ Hz, 1H), 1.77 (s, 3H), 1.23 (d, $J = 6.9$ Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3): δ [ppm] 169.8, 149.0, 148.3, 143.6, 140.3, 128.8, 126.6, 124.6, 120.5, 117.9, 108.3, 85.8, 38.1, 33.6, 29.8, 23.8.

HRMS (ESI): calculated for $\text{C}_{19}\text{H}_{21}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 313.1434, found: 313.1438.

3-(Benzo[d][1,3]dioxol-5-yl)-7,8-dihydroxy-3-methylisochroman-1-one (3n)



A pale white solid. 26.9 mg, 75% yield.

Melting point: 160-162 °C

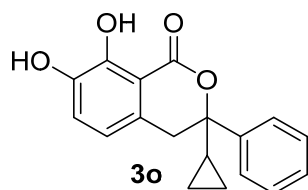
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 11.01 (s, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 6.92 (d, $J = 1.9$ Hz, 1H), 6.89 – 6.85 (m, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 5.95 (s, 2H), 5.54 (s, 1H), 3.42 (d, $J = 16.0$ Hz, 1H), 3.29 (d, $J = 16.0$ Hz, 1H), 1.75 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.6, 149.0, 147.9, 147.0, 143.7, 136.9, 128.6, 120.6, 118.1, 117.9, 108.2, 108.1, 105.7, 101.2, 85.7, 38.1, 30.1.

HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{15}\text{O}_6$ $[\text{M} + \text{H}]^+$ m/z 315.0863, found: 315.0865.

3-Cyclopropyl-7, 8-dihydroxy-3-phenylisochroman-1-one (3o)



A pale yellow oil. 26.1 mg, 68% yield.

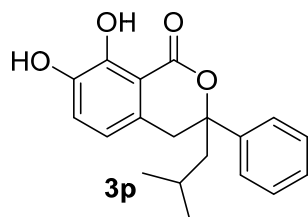
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ [ppm] 10.95 (s, 1H), 7.37 – 7.34 (m, 2H), 7.31 – 7.27 (m, 3H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 5.47 (s, 1H), 3.50 (dd, $J = 16.0$ Hz, 3.4 Hz, 2H), 1.45 – 1.40 (m, 1H), 0.62 – 0.49 (m, 4H).

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ [ppm] 169.8, 148.8, 143.5, 140.3, 128.7, 128.3, 128.2, 127.8, 126.8, 125.7, 125.6, 120.5, 117.9, 108.6, 87.7, 36.6, 22.2, 2.1, 1.4.

HRMS (ESI): calculated for $\text{C}_{18}\text{H}_{17}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 297.1121, found: 297.1123.

7, 8-Dihydroxy-3-isobutyl-3-phenylisochroman-1-one (3p)



A pale yellow oil. 26.2 mg, 65% yield.

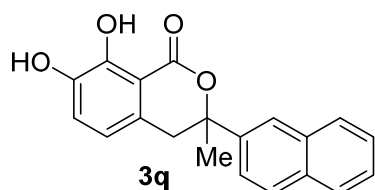
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 11.05 (s, 1H), 7.39 – 7.31 (m, 5H), 7.02 (d, $J = 8.0$ Hz, 1H), 6.61 (d, $J = 8.0$ Hz, 1H), 5.50 (s, 1H), 3.37 (dd, $J = 16.0$ Hz, 3.0 Hz, 2H), 2.02 (dd, $J = 14.6, 5.4$ Hz, 1H), 1.93 (dd, $J = 14.6, 5.4$ Hz, 1H), 1.70 - 1.64 (m, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.7, 148.8, 143.5, 141.9, 130.8, 128.6, 128.5, 127.5, 125.1, 120.5, 117.9, 108.4, 99.9, 88.7, 50.5, 37.7, 29.7, 24.1, 24.0.

HRMS (ESI): calculated for $\text{C}_{19}\text{H}_{21}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 313.1434, found: 313.1438.

7, 8-Dihydroxy-3-methyl-3-(naphthalen-2-yl) isochroman-1-one (3q)



A brown yellow oil. 29.1 mg, 70% yield.

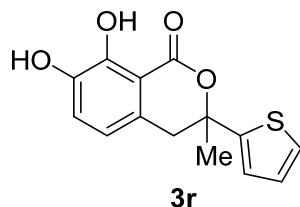
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 11.02 (s, 1H), 7.89 - 7.80 (m, 4H), 7.55 - 7.48 (m, 3H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 5.55 (s, 1H), 3.59 (d, $J = 16.4$ Hz, 1H), 3.42 (d, $J = 16.4$ Hz, 1H), 1.87 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.7, 149.0, 143.7, 140.3, 132.9, 132.5, 128.6, 128.5, 128.2, 127.4, 126.5, 126.4, 123.7, 122.6, 120.6, 118.0, 108.2, 85.9, 38.1, 29.7.

HRMS (ESI): calculated for $\text{C}_{20}\text{H}_{17}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 321.1121, found: 321.1125.

7, 8-Dihydroxy-3-methyl-3-(thiophen-2-yl) isochroman-1-one (3r)



A pale yellow solid. 26.9 mg, 75% yield.

Melting point: 149-151 °C

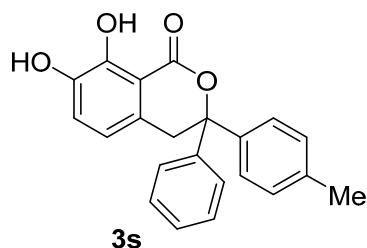
TLC: $R_f = 0.6$ (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 11.02 (s, 1H), 7.23 (dd, $J = 5.1, 1.0$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.00 (dd, $J = 3.6, 1.1$ Hz, 1H), 6.91 (dd, $J = 5.0, 3.7$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 5.60 (s, 1H), 3.49 (d, $J = 16.3$ Hz, 1H), 3.37 (d, $J = 16.3$ Hz, 1H), 1.91 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.2, 149.1, 146.6, 143.8, 128.4, 126.7, 125.2, 124.4, 120.7, 118.1, 83.9, 39.2, 30.4.

HRMS (ESI): calculated for $\text{C}_{14}\text{H}_{13}\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ m/z 277.0529, found: 277.0531.

7,8-Dihydroxy-3-phenyl-3-(*p*-tolyl) isochroman-1-one (3s)



A pale yellow oil. 28.1 mg, 59% yield.

TLC: $R_f = 0.6$ (PE: EA = 7:3).

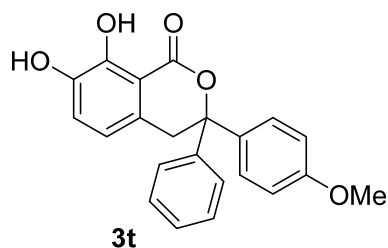
$^1\text{H NMR}$ (600 MHz, CDCl_3): δ [ppm] 10.94 (s, 1H), 7.42 - 7.40 (m, 2H), 7.34 - 7.30 (m, 3H), 7.26 - 7.25 (m, 1H), 7.13 - 7.11 (m, 2H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 5.50 (s, 1H),

3.75 – 3.68 (m, 2H), 2.31 (s, 3H).

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ [ppm] 169.3, 149.0, 143.6, 142.8, 141.4, 139.4, 137.7, 129.2, 129.1, 128.4, 127.8, 126.1, 126.0, 120.7, 117.7, 111.3, 108.8, 88.6, 38.3, 21.0.

HRMS (ESI): calculated for $\text{C}_{22}\text{H}_{19}\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 347.1278, found: 347.1280.

7, 8-Dihydroxy-3-(4-methoxyphenyl)-3-phenylisochroman-1-one (3t)



A brown yellow oil. 36.2 mg, 77% yield.

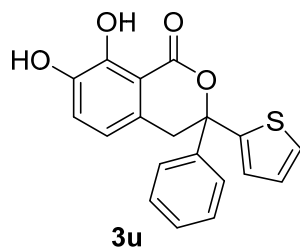
TLC: R_f = 0.6 (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 10.95 (s, 1H), 7.41 - 7.39 (m, 2H), 7.34 – 7.27 (m, 5H), 7.07 (d, J = 8.0 Hz, 1H), 6.88 – 6.78 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.75 – 3.64 (m, 2H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.8, 159.1, 149.0, 143.6, 142.9, 134.4, 129.2, 128.4, 127.8, 127.7, 126.0, 120.8, 117.7, 116.0, 114.8, 113.8, 108.8, 88.6, 55.2, 38.4.

HRMS (ESI): calculated for $\text{C}_{22}\text{H}_{19}\text{O}_5$ $[\text{M} + \text{H}]^+$ m/z 363.1227, found: 363.1229.

7,8-Dihydroxy-3-phenyl-3-(thiophen-2-yl) isochroman-1-one (3u)



A brown yellow oil. 32.0 mg, 63% yield.

TLC: R_f = 0.6 (PE: EA = 7:3).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 10.92 (s, 1H), 7.52 – 7.47 (m, 2H), 7.39 – 7.31 (m, 3H), 7.28 – 7.25 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.91 – 6.89 (m, 2H), 6.72 (d, J = 8.0 Hz, 1H), 5.57 (s, 1H), 3.78 (dd, J = 16.6 Hz, 3.6 Hz, 2H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ [ppm] 169.2, 149.1, 146.3, 143.8, 142.2, 128.6, 128.5, 128.3, 126.5, 126.5, 126.4, 125.5, 120.9, 117.9, 108.4, 86.7, 39.6, 29.7.

HRMS (ESI): calculated for $\text{C}_{19}\text{H}_{14}\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ m/z 339.0686, found: 339.0688.

9. Determination of the enantiomeric composition of isochromanones

Taking the synthesis of compound **3a** as an illustration, the racemic product was prepared via the oxidative [4+2] cyclization of **1a** and **2a** using Ag_2O (5.0 eq) and HCOOH (2 eq) in 10% yield (Vincent 's protocol).⁷ The enantiomeric composition of product **3a** was found to be 0% *ee*.

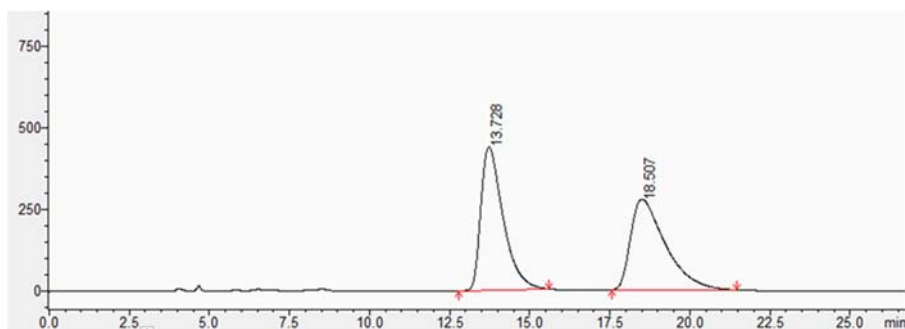
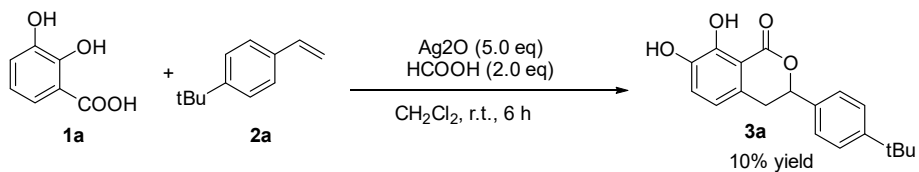
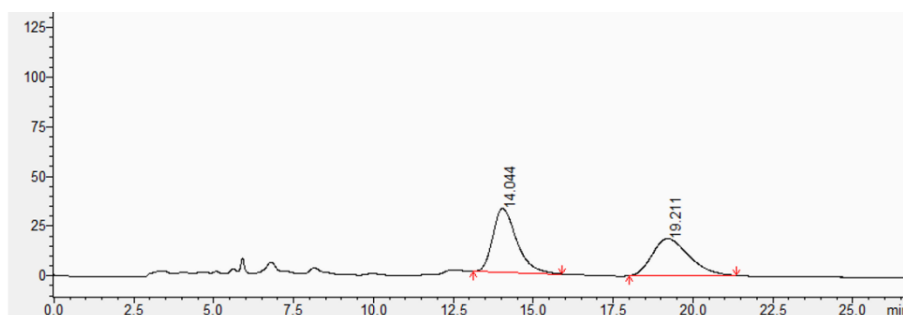


Figure S8 HPLC trace of Racemic **3a**

	Retention Time (min)	Area (%)
Peak 1	13.728	50.188
Peak 2	18.507	49.812

HPLC trace of **3a** produced by the present method.



	Retention Time (min)	Area (%)
Peak 1	14.044	50.364
Peak 2	19.211	49.636

Figure S9 HPLC trace of **3a** produced by the present protocol

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10. NMR Spectra of Synthetic Products

