Concise Total Synthesis of Biologically Interesting Pyranochalcone Natural Products: Citrunobin, Boesenbergin A, Boesenbergin B, Xanthohumol C, and Glabrachromene

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Abstract: New and efficient synthetic approaches to the biologically interesting natural products citrunobin, boesenbergins A and B, xanthohumol C, and glabrachromene are described. The key strategies involve ethylenediamine diacetate catalyzed benzopyran formation reactions and base-catalyzed aldol reactions.

Key words: pyranochalcone, citrunobin, boesenbergins A and B, xanthohumol C, glabrachromene

Pyranochalcones are an abundant subclass of the flavonoids and are widely distributed in nature.[1] Members of the pyranochalcones have been associated with a wide variety of biological activities, such as antimutagenic, antimicrobial, antiulcer, and antitumor activities, and some plants containing pyranochalcones are used in traditional medicines in China and in Europe.[2] This wide range of biological properties has stimulated interest in the synthesis of naturally occurring pyranochalcones (Figure 1). Among these, citrunobin (**1**) with the pyranochalcone moiety has been isolated from *Citrus sinensi*,[3] while boesenbergins A (**2**) and B (**3**) have been isolated from *Boesenbergia pandurata*.[4] Xanthohumol C (**4**) has been isolated from *Humulus lupulus*, the hop plant, which is widely cultivated throughout the temperate zones of the world.[5] This plant is extensively used in the brewing industry to add bitterness and aroma to beer. Xanthohumol C (**4**) has also been shown to have potent antifungal, antiproliferative, cancer chemopreventive, antimutagenic, and antioxidative activities.[2b,6] Xanthohumol C (**4**) is known by another name, dehydrocycloxanthohumol.[2b] Glabrachromene (**5**) has been isolated from *Pongamia glabra*.[7] Although a few partial synthetic approaches to boesenbergins A (**2**) and B (**3**), and glabrachromene (**5**) have been reported,[5,8] there is still a demand for a more general and efficient method that can efficiently provide these biologically interesting pyranochalcone natural products. In particular, no synthetic approaches to citrunobin (**1**) and xanthohumol C (**4**) have been reported.

We have reported convergent synthetic routes to the naturally occurring pyranochalcones, lonchocarpin (**8**) and 4-hydroxylonchocarpin (**9**), via a key intermediate benzopyran **7**, as shown in Scheme 1.[9] Although the overall yield from dione **6** to benzopyran **7** is satisfactory (5 steps, 45%), simpler and more concise synthetic routes are still needed.

Several syntheses of benzopyran nuclei using the Claisen rearrangement of propargyl ethers[10] and Lewis acid catalyzed condensation of phenols with acetals or ketals have been reported.[11] These reactions have been limited due to harsh reaction conditions, long reaction steps, unsatisfactory yields, and the use of stoichiometric amounts of catalysts. Another useful strategy for the synthesis of

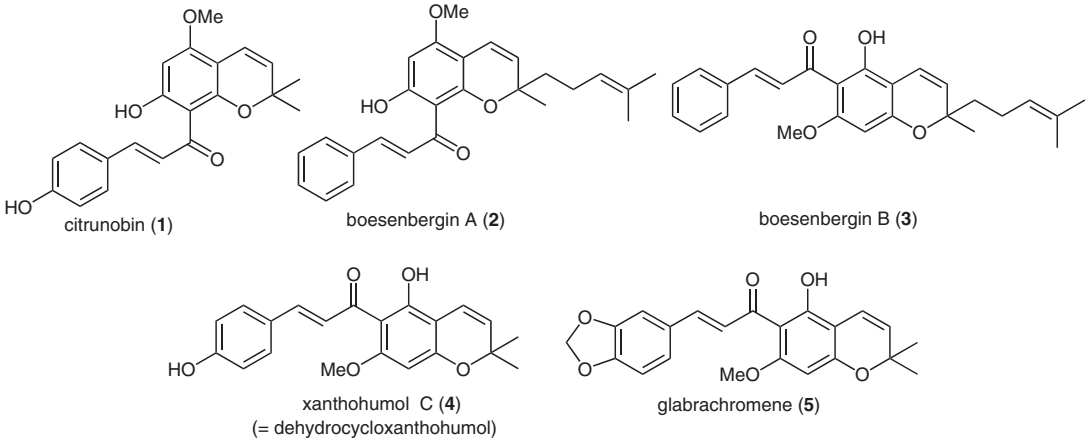

Figure 1 Naturally occurring pyranochalcones

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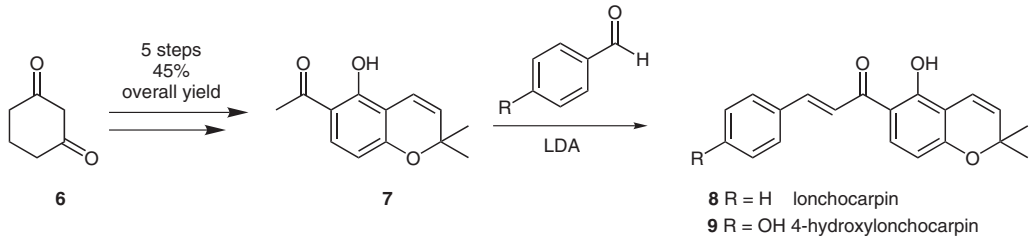
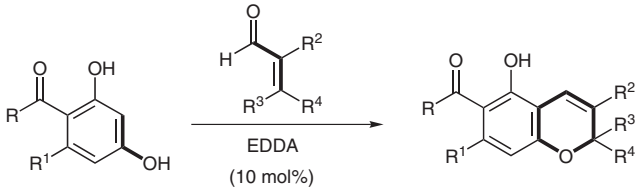


Scheme 1 Reported synthetic route to lonchocarpin (**8**) and 4-hydroxylonchocarpin (**9**)



Scheme 2 Benzopyran formation by a [3+3]-cycloaddition reaction

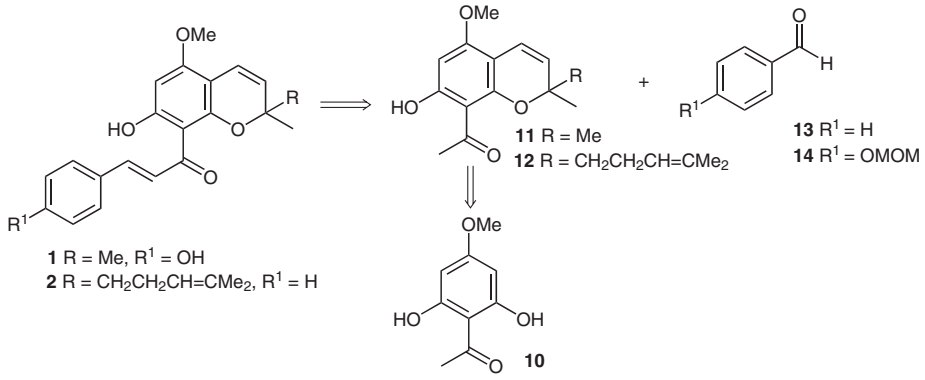
benzopyrans, the cycloaddition of phenols to α,β-unsaturated aldehydes in refluxing pyridine, has been reported.[12] These reactions have limitations such as low yields and difficulty of isolation of the products. Accordingly, there has been considerable research on improved synthetic approaches to pyranochalcone derivatives. In order to overcome limitations of this process, metal-catalyzed reactions have been developed by several groups.[13]

Recently, we developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate (EDDA) catalyzed reactions of resorcinols with α,β-unsaturated aldehydes.[14] This methodology provides a rapid route for the synthesis of benzopyran derivatives with a variety of substituents on the pyranyl ring (Scheme 2).[15]

Our efforts in developing these methodologies led to the synthesis of pyranochalcone natural products with the benzopyran skeleton. This paper reports a concise total synthesis of the biologically interesting citrunobin (**1**), boesenbergins A (**2**) and B (**3**), xanthohumol C (**4**), and glabrachromene (**5**).

The retrosynthetic strategy for citrunobin (**1**) and boesenbergin A (**2**) is shown in Scheme 3. Citrunobin (**1**) and boesenbergin A (**2**) could be prepared from base-catalyzed aldol reactions of benzopyrans **11** and **12** with the corresponding benzaldehydes **14** and **13**, respectively. The crucial intermediates **11** and **12** could be generated from the readily available 2,6-dihydroxy-4-methoxyacetophenone (**10**) using ethylenediamine diacetate catalyzed benzopyran formation reactions.

The total synthesis of citrunobin (**1**) and boesenbergin A (**2**) was carried out by the formation of the benzopyrans, followed by an aldol reaction, starting from 2,6-dihydroxy-4-methoxyacetophenone (**10**), as shown in Scheme 4. Reaction of **10** with 3-methyl-2-butenal in the presence of 10 mol% of ethylenediamine diacetate in refluxing xylene for 10 hours gave alloevodionol (**11**), in a yield of 95%, which has been isolated from *Melicope ptelefolia*[16] and *Evodia lunuankenda*.[17] The spectroscopic data of the synthetic material **11** agreed well with that reported in the literature.[16] To complete the total synthesis of natural citrunobin (**1**), an aldol reaction was next attempted. As a model study, reaction of compound **11** with benzaldehyde (**13**) using potassium hydroxide in ethanol at room temperature for 48 hours provided compound **15** in 96% yield. Attempts to condense compound **11** with 4-hydroxybenzaldehyde using potassium hydroxide in ethanol were unsuccessful. However, treatment of compound **11** with protected benzaldehyde **14**, followed by cleavage of the MOM ether with 3 N HCl in ethanol at 50 °C for 1 hour, gave compound **1** in 86% yield (2 steps). The spectroscopic data of the synthetic material **1** are in good agreement with that of the natural product as reported in the literature.[3] On the other hand, reaction of compound **10** with citral in the presence of 10 mol% of ethylenediamine diacetate in refluxing xylene for 10 hours afforded

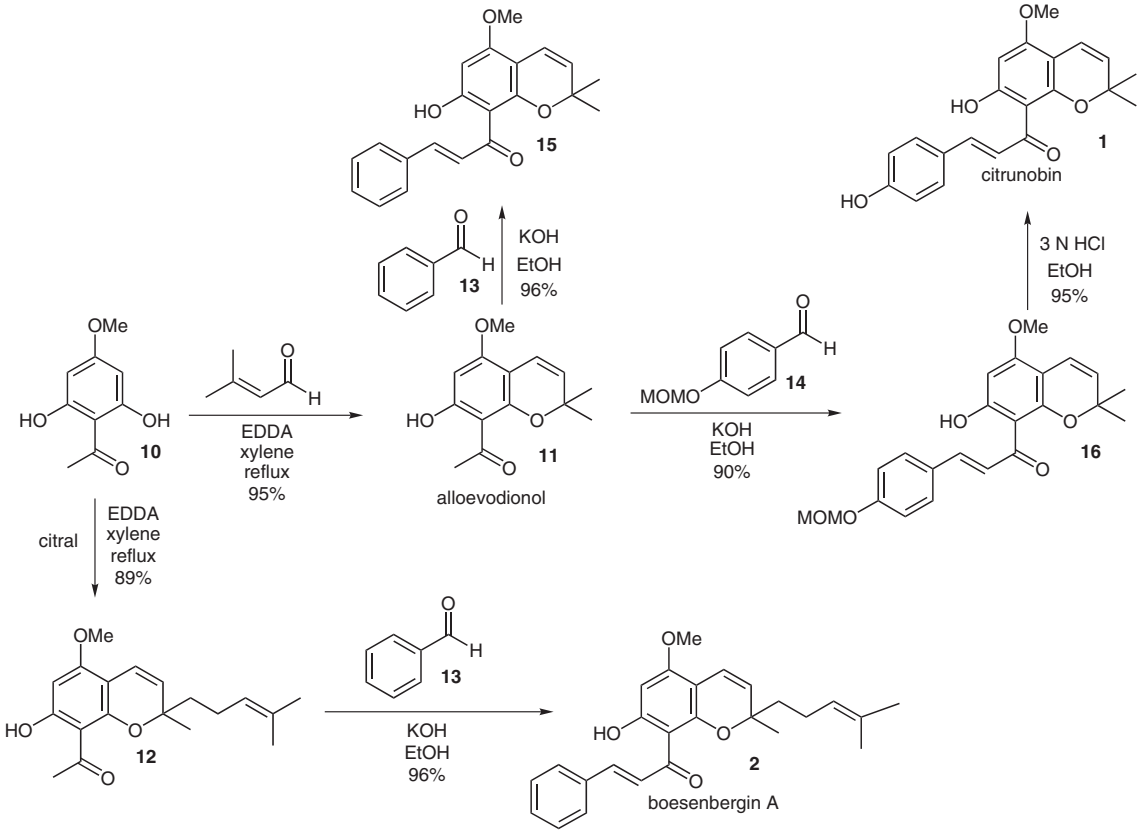


Scheme 3 Retrosynthetic analysis of citrunobin (**1**) and boesenbergin A (**2**)

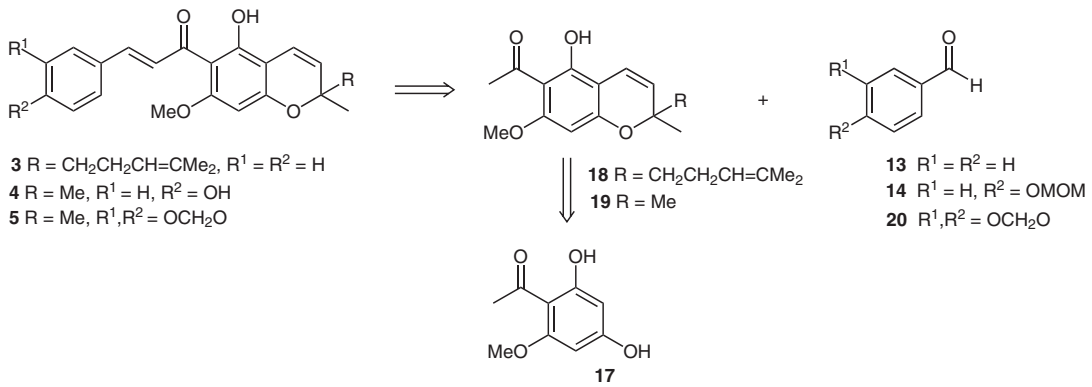
the adduct **12** in 89% yield; then, treatment of compound **12** with benzaldehyde (**13**) in an ethanolic potassium hydroxide solution gave boesenbergin A (**2**) in 96% yield. The spectroscopic data of the synthetic material **2** agreed with that reported in the literature.[4a]

Scheme 5 shows the retrosynthetic approaches to natural boesenbergin B (**3**), xanthohumol C (**4**), and glabrachromene (**5**). Compounds **3**–**5** could be prepared by base-catalyzed aldol reactions of benzopyrans **18** and **19** with the corresponding benzaldehydes **13**, **14**, and **20**. The crucial intermediates **18** and **19** could be generated from the readily available 2,4-dihydroxy-6-methoxyacetophenone (**17**) using ethylenediamine diacetate catalyzed benzopyran formation reactions.

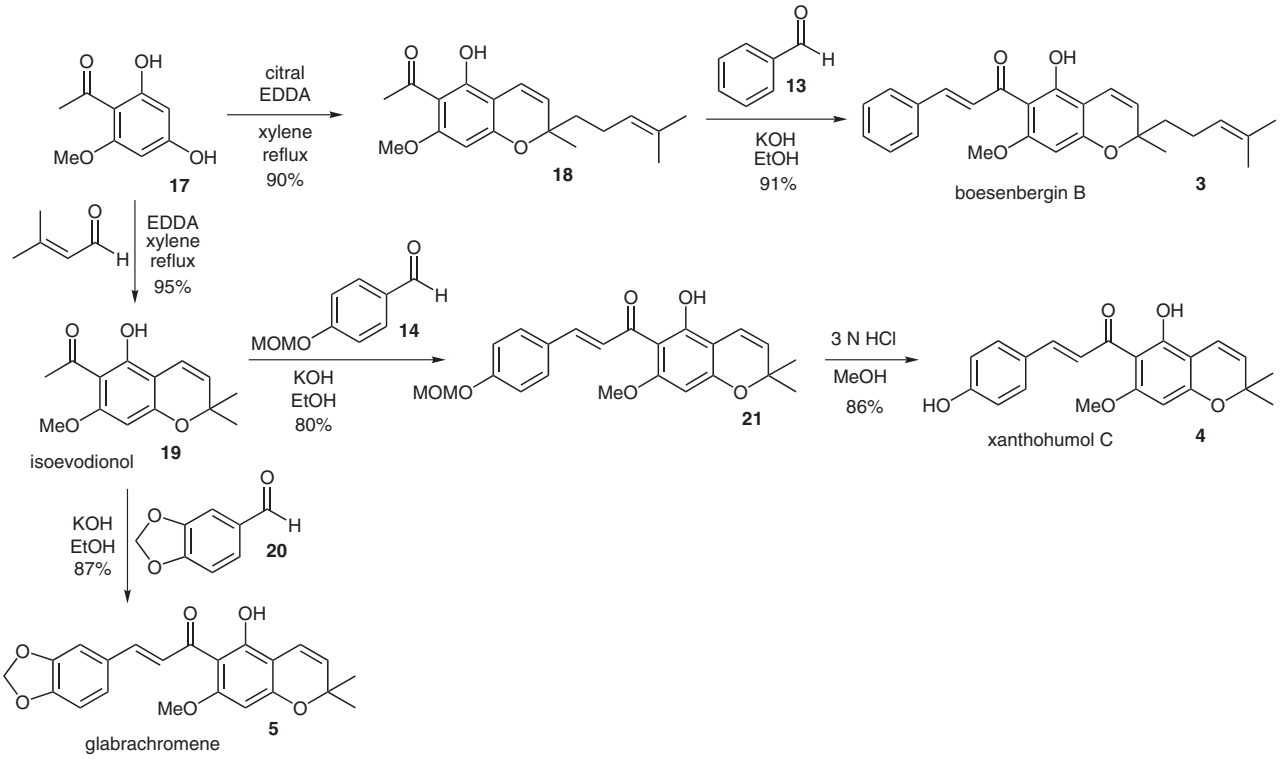
The synthesis of boesenbergin B (**3**), xanthohumol C (**4**), and glabrachromene (**5**) was undertaken starting from 2,4-dihydroxy-6-methoxyacetophenone (**17**), as shown in Scheme 6. Treatment of compound **17** with citral in the presence of 10 mol% of ethylenediamine diacetate in refluxing xylene for 10 hours provided compound **18** in 90% yield. In this reaction, no regioisomers were found. The adduct **18** was further reacted with benzaldehyde (**13**) in an ethanolic potassium hydroxide solution at room temperature for 48 hours to give boesenbergin B (**3**) in 91% yield. The spectroscopic data of this synthetic material **3** was in agreement with that reported in the literature.[4b] Reaction of compound **17** with 3-methyl-2-butenal in the presence of 10 mol% of ethylenediamine diacetate in refluxing xylene for 10 hours afforded isoevodionol (**19**),



Scheme 4 Synthesis of citrunobin (**1**) and boesenbergin A (**2**)



Scheme 5 Retrosynthetic analysis of boesenbergin B (**3**), xanthohumol C (**4**), and glabrachromene (**5**)



Scheme 6 Synthesis of boesenbergin B (**3**), xanthohumol C (**4**), and glabrachromene (**5**)

which has been isolated from *Evodia lepta*.[18,19] Treatment of **19** with the MOM ether protected benzaldehyde **14** in an ethanolic potassium hydroxide solution at room temperature for 48 hours afforded compound **21** (80%), which was followed by cleavage of the MOM ether with 3 N HCl in methanol to give xanthohumol C (**4**) in 86% yield. On the other hand, reaction of compound **19** with piperonal (**20**) in an ethanolic potassium hydroxide solution at room temperature for 48 hours gave glabrachromene (**5**) in 87% yield. Interestingly, no doublets were observed for the H-α and H-β protons of the chalcone moiety of compound **4**. The H-α and H-β protons of the chalcone moiety of synthetic compounds **4**, **5**, and **21** gave rise to a singlet at ca. δ 7.7, integrating for two protons, due to the same chemical shifts. The spectroscopic data of the synthetic materials **4** and **5** were in agreement with those reported in the literature.[5b,8]

In conclusion, a new and concise synthetic route for biologically interesting pyranochalcones was developed starting from 2,6-dihydroxy-4-methoxyacetophenone (**10**) and 2,4-dihydroxy-6-methoxyacetophenone (**17**). These synthetic routes provide the biologically interesting natural products citrunobin (**1**), boesenbergins A (**2**) and B (**3**), xanthohumol C (**4**), and glabrachromene (**5**). The key strategies involve benzopyran formation via ethylenediamine diacetate catalyzed reactions, and base-catalyzed aldol reactions. This synthetic route is expected to be used for the synthesis of over 10 grams of natural products.

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Model ARX spectrometer (at 300 and 75 MHz, respectively) in $CDCl_3$ using δ = 77.0 ppm as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS and MS spectra were recorded on a Jeol JMS 700 spectrometer at 70 eV and were carried out at the Korea Basic Science Institute.

Alloevodionol (11)

To a soln of 2,6-dihydroxy-4-methoxyacetophenone (**10**) (182 mg, 1.0 mmol) and 3-methyl-2-butenal (168 mg, 2.0 mmol) in xylene (20 mL) was added ethylenediamine diacetate (18 mg, 0.1 mmol) at r.t. The reaction mixture was refluxed for 10 h and then cooled to r.t. H_2O (30 mL) was added and the soln was extracted with EtOAc (3 × 30 mL). Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 7:1) gave **11** (236 mg, 95%) as a solid; mp 81–82 °C.

IR (KBr): 2924, 2855, 1642, 1613, 1588, 1447, 1366, 1287, 1265, 1207, 1161, 1125, 1076, 962, 880, 818, 773, 729 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.8 (s, 1 H), 6.53 (d, *J* = 9.9 Hz, 1 H), 5.98 (s, 1 H), 5.39 (d, *J* = 9.9 Hz, 1 H), 3.81 (s, 3 H), 2.57 (s, 3 H), 1.42 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.3, 166.3, 161.1, 156.1, 124.5, 116.4, 106.1, 102.8, 92.4, 77.8, 55.6, 33.2, 27.8, 27.7.

MS (EI): *m*/*z* (%) = 248 (50) [M$^+$], 234 (30), 233 (100), 215 (34), 202 (10).

HRMS: *m*/*z* [M$^+$] calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1050.

1-(7-Hydroxy-5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-phenyl-2-propen-1-one (15)

To a soln of **11** (100 mg, 0.4 mmol) in EtOH (10 mL) was added KOH (112 mg, 2.0 mmol) and benzaldehyde (**13**) (53 mg, 0.5 mmol) at r.t. The reaction mixture was stirred for 48 h at r.t. Evap-

oration of EtOH and extraction with EtOAc (3 × 50 mL), then washing with 2 N HCl (30 mL) and brine (30 mL), drying ($MgSO_4$), and removal of the solvent followed by flash column chromatography on silica gel (hexane–EtOAc, 10:1) gave **15** (129 mg, 96%) as a solid; mp 92–93 °C.

IR (KBr): 2975, 1636, 1603, 1555, 1447, 1256, 1225, 1154, 1121, 1040, 990, 878, 818, 766 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.29 (s, 1 H), 8.11 (d, *J* = 15.7 Hz, 1 H), 7.76 (d, *J* = 15.7 Hz, 1 H), 7.61–7.58 (m, 2 H), 7.41–7.24 (m, 3 H), 6.57 (d, *J* = 9.9 Hz, 1 H), 6.05 (s, 1 H), 5.45 (d, *J* = 9.9 Hz, 1 H), 3.81 (s, 3 H), 1.53 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.3, 172.6, 168.8, 161.7, 156.1, 142.7, 136.0, 134.2, 130.6, 129.7, 129.4, 128.9, 128.7, 127.8, 125.1, 117.1, 93.1, 78.4, 56.2, 28.3.

MS (EI): *m*/*z* (%) = 336 (35) [M^+], 322 (16), 321 (74), 218 (13), 217 (100), 160 (9), 103 (7).

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{20}O_4$: 336.1362; found: 336.1365.

1-(7-Hydroxy-5-methoxy-2,2-dimethyl-2*H*-chromen-8-yl)-3-[4-(methoxymethoxy)phenyl]-2-propen-1-one (16)

To a soln of **11** (124 mg, 0.5 mmol) in EtOH (10 mL) was added KOH (140 mg, 2.5 mmol) and aldehyde **14** (100 mg, 0.6 mmol) at r.t. The reaction mixture was stirred for 48 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), then washing with 2 N HCl (30 mL) and brine (30 mL), drying ($MgSO_4$), and removal of the solvent followed by flash column chromatography on silica gel (hexane–EtOAc, 10:1) gave **16** (178 mg, 90%) as an oil.

IR (neat): 2922, 2851, 1604, 1551, 1510, 1346, 1225, 1152, 1121, 1082, 992, 831, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.34 (s, 1 H), 8.03 (d, *J* = 15.7 Hz, 1 H), 7.73 (d, *J* = 15.7 Hz, 1 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 6.56 (d, *J* = 9.9 Hz, 1 H), 6.04 (s, 1 H), 5.44 (d, *J* = 9.9 Hz, 1 H), 5.21 (s, 2 H), 3.84 (s, 3 H), 3.48 (s, 3 H), 1.53 (s, 6 H).

HRMS: *m*/*z* [M^+] calcd for $C_{23}H_{24}O_6$: 396.1573; found: 396.1571.

Citrunobin (1)

To a soln of **16** (158 mg, 0.4 mmol) in EtOH (10 mL) was added 3 N HCl (5 drops) and the reaction mixture was heated at 50 °C for 1 h. The mixture was cooled, diluted with H_2O (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with sat. $NaHCO_3$ soln (30 mL) and H_2O (30 mL), and dried ($MgSO_4$). Removal of the solvent under reduced pressure left an oily residue, which was then purified by column chromatography on silica gel (hexane–EtOAc, 4:1) to give **1** (134 mg, 95%) as a solid; mp 183–184 °C.

IR (KBr): 3343, 2926, 1630, 1605, 1547, 1514, 1445, 1348, 1221, 1155, 1121, 1042, 986, 833, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.34 (s, 1 H), 8.01 (d, *J* = 15.6 Hz, 1 H), 7.74 (d, *J* = 15.6 Hz, 1 H), 7.50 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 6.57 (d, *J* = 10.0 Hz, 1 H), 6.06 (s, 1 H), 5.45 (d, *J* = 10.0 Hz, 1 H), 3.84 (s, 3 H), 1.52 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.2, 167.3, 161.2, 158.2, 155.7, 142.6, 130.3, 128.4, 125.0, 124.5, 116.7, 116.2, 104.5, 103.3, 92.7, 78.3, 55.7, 28.1.

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{20}O_5$: 352.1311; found: 352.1310.

1-[7-Hydroxy-5-methoxy-2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromen-8-yl]ethanone (12)

To a soln of 2,6-dihydroxy-4-methoxyacetophenone (**10**) (182 mg, 1.0 mmol) and citral (304 mg, 2.0 mmol) in xylene (20 mL) was added ethylenediamine diacetate (18 mg, 0.1 mmol) at r.t. The reaction mixture was refluxed for 10 h and then cooled to r.t. H_2O (30 mL) was added and the soln was extracted with EtOAc (3 × 30 mL). Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 7:1) gave **12** (282 mg, 89%) as an oil.

IR (neat): 2926, 2855, 1613, 1588, 1447, 1366, 1285, 1208, 1165, 1119, 1076, 962, 816, 775 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 13.8 (s, 1 H), 6.56 (d, *J* = 10.0 Hz, 1 H), 6.00 (s, 1 H), 5.35 (d, *J* = 10.0 Hz, 1 H), 5.09–5.04 (m, 1 H), 3.80 (s, 3 H), 2.63 (s, 3 H), 2.12–2.05 (m, 2 H), 1.85–1.77 (m, 2 H), 1.63 (s, 3 H), 1.54 (s, 3 H), 1.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.1, 166.3, 160.9, 156.3, 132.0, 123.6, 123.1, 117.0, 105.7, 102.4, 92.0, 80.6, 55.7, 41.4, 33.1, 26.5, 25.6, 23.0, 17.6.

MS (EI): *m*/*z* (%) = 316 (10) [M^+], 234 (14), 233 (100), 215 (8), 109 (5), 97 (6), 95 (7), 81 (6).

HRMS: *m*/*z* [M^+] calcd for $C_{19}H_{24}O_4$: 316.1675; found: 316.1674.

Boesenbergin A (2)

To a soln of **12** (158 mg, 0.5 mmol) in EtOH (10 mL) was added KOH (140 mg, 2.5 mmol) and benzaldehyde (**13**) (64 mg, 0.6 mmol) at r.t. The reaction mixture was stirred for 48 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), then washing with 2 N HCl (30 mL) and brine (30 mL), drying ($MgSO_4$), and removal of the solvent followed by flash column chromatography on silica gel (hexane–EtOAc, 10:1) gave **2** (194 mg, 96%) as a solid; mp 89–90 °C.

IR (KBr): 2924, 2855, 1634, 1603, 1555, 1449, 1345, 1231, 1208, 990, 897, 818, 768, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.25 (s, 1 H), 8.11 (d, *J* = 15.6 Hz, 1 H), 7.76 (d, *J* = 15.6 Hz, 1 H), 7.60–7.57 (m, 2 H), 7.39–7.34 (m, 3 H), 6.62 (d, *J* = 10.0 Hz, 1 H), 6.04 (s, 1 H), 5.41 (d, *J* = 10.0 Hz, 1 H), 5.09–5.05 (m, 1 H), 3.81 (m, 3 H), 2.20–2.08 (m, 2 H), 1.90–1.71 (m, 2 H), 1.62 (s, 3 H), 1.48 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.2, 167.6, 161.5, 156.2, 142.3, 135.9, 132.5, 130.2, 129.1, 128.5, 127.9, 123.7, 123.5, 117.3, 106.3, 103.1, 92.5, 80.0, 55.7, 41.5, 26.6, 25.6, 23.1, 17.6.

HRMS: *m*/*z* [M^+] calcd for $C_{26}H_{28}O_4$: 404.1988; found: 404.1990.

1-[5-Hydroxy-7-methoxy-2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromen-6-yl]ethanone (18)

To a soln of 2,4-dihydroxy-6-methoxyacetophenone (**17**) (182 mg, 1.0 mmol) and citral (304 mg, 2.0 mmol) in xylene (20 mL) was added ethylenediamine diacetate (18 mg, 0.1 mmol) at r.t. The reaction mixture was refluxed for 10 h and then cooled to r.t. H_2O (30 mL) was added and the soln was extracted with EtOAc (2 × 30 mL). Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 7:1) gave **18** (285 mg, 90%) as an oil.

IR (neat): 2924, 2855, 1622, 1591, 1377, 1267, 1165, 1142, 1123, 883, 835, 812, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.29 (s, 1 H), 6.68 (d, *J* = 10.0 Hz, 1 H), 5.85 (s, 1 H), 5.37 (d, *J* = 10.0 Hz, 1 H), 5.10–5.06 (m, 1 H), 3.82 (s, 3 H), 2.57 (s, 3 H), 2.21–2.04 (m, 2 H), 1.79–1.64 (m, 2 H), 1.61 (s, 3 H), 1.56 (s, 3 H), 1.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.0, 163.0, 161.8, 160.5, 131.8, 124.0, 123.8, 116.4, 105.5, 102.4, 80.6, 55.5, 41.7, 33.0, 29.7, 27.2, 22.6, 17.6, 14.1.

MS (EI): *m*/*z* (%) = 316 (8) [M^+], 234 (14), 233 (100), 215 (12), 109 (5), 97 (8), 95 (7), 85 (5), 83 (7), 81 (6).

HRMS: *m*/*z* [M^+] calcd for $C_{19}H_{24}O_4$: 316.1675; found: 316.1677.

Boesenbergin B (3)

To a soln of **18** (126 mg, 0.4 mmol) in EtOH (10 mL) was added KOH (112 mg, 2.0 mmol) and benzaldehyde (**13**) (53 mg, 0.5 mmol) at r.t. The reaction mixture was stirred for 48 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), then washing with 2 N HCl (30 mL) and brine (30 mL), drying ($MgSO_4$), and removal of the solvent followed by flash column chromatography on silica gel (hexane–EtOAc, 10:1) gave **3** (147 mg, 91%) as a solid; mp 95–96 °C.

IR (KBr): 2971, 2926, 1616, 1580, 1451, 1424, 1339, 1204, 1155, 1119, 1063, 810, 766 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.51 (s, 1 H), 7.87 (d, *J* = 15.6 Hz, 1 H), 7.75 (d, *J* = 15.6 Hz, 1 H), 7.60–7.57 (m, 2 H), 7.41–7.34 (m, 3 H), 6.71 (d, *J* = 10.0 Hz, 1 H), 5.90 (s, 1 H), 5.40 (d, *J* = 10.0 Hz, 1 H), 5.09–5.06 (m, 1 H), 3.90 (s, 3 H), 2.16–2.03 (m, 2 H), 1.85–1.68 (m, 2 H), 1.65 (s, 3 H), 1.56 (s, 3 H), 1.40 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.5, 167.5, 160.7, 142.2, 142.1, 135.5, 131.7, 129.8, 128.7, 128.3, 127.6, 124.0, 123.8, 116.5, 105.8, 102.7, 91.4, 79.3, 55.8, 41.7, 27.4, 25.6, 22.6, 17.7.

HRMS: *m*/*z* [M^+] calcd for $C_{26}H_{28}O_4$: 404.1988; found: 404.1987.

Isoevodionol (19)

To a soln of 2,4-dihydroxy-6-methoxyacetophenone (**17**) (182 mg, 1.0 mmol) and 3-methyl-2-butenal (168 mg, 2.0 mmol) in xylene (20 mL) was added ethylenediamine diacetate (18 mg, 0.1 mmol) at r.t. The reaction mixture was refluxed for 10 h and then cooled to r.t. H_2O (30 mL) was added and the soln was extracted with EtOAc (3 × 30 mL). Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 7:1) gave **19** (236 mg, 95%) as a solid; mp 128–129 °C.

IR (KBr): 2924, 2855, 1620, 1464, 1362, 1269, 1206, 1159, 1124, 891, 831, 731 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.28 (s, 1 H), 6.62 (d, *J* = 10.0 Hz, 1 H), 5.85 (s, 1 H), 5.38 (d, *J* = 10.0 Hz, 1 H), 3.81 (s, 3 H), 2.56 (s, 3 H), 1.41 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.0, 162.8, 161.7, 160.0, 125.2, 115.9, 105.5, 102.5, 90.5, 78.0, 55.4, 32.9, 28.2.

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1047.

1-(5-Hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-[4-(methoxymethoxy)phenyl]-2-propen-1-one (21)

To a soln of **19** (124 mg, 0.5 mmol) in EtOH (10 mL) was added KOH (140 mg, 2.5 mmol) and aldehyde **14** (100 mg, 0.6 mmol) at r.t. The reaction mixture was stirred for 48 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), then washing with 2 N HCl (30 mL) and brine (30 mL), drying ($MgSO_4$), and removal of the solvent followed by flash column chromatography on silica gel (hexane–EtOAc, 10:1) gave **21** (159 mg, 80%) as an oil.

IR (neat): 2969, 1605, 1510, 1424, 1339, 1235, 1198, 1150, 1080, 995, 922, 831, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.60 (s, 1 H), 7.76 (s, 2 H), 7.73 (d, *J* = 8.2 Hz, 2 H), 7.04 (d, *J* = 8.2 Hz, 2 H), 6.66 (d, *J* = 10.0 Hz, 1 H), 5.90 (s, 1 H), 5.39 (d, *J* = 10.0 Hz, 1 H), 5.20 (s, 2 H), 3.89 (s, 3 H), 3.47 (s, 3 H), 1.43 (s, 6 H).

HRMS: *m*/*z* [M^+] calcd for $C_{23}H_{24}O_6$: 396.1573; found: 396.1571.

Xanthohumol C (4)

To a soln of **21** (79 mg, 0.2 mmol) in MeOH (10 mL) was added 3 N HCl (5 drops) and the reaction mixture was heated at 50 °C for 30 min. The mixture was cooled, diluted with H_2O (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with sat. $NaHCO_3$ soln (30 mL) and H_2O (30 mL), and dried ($MgSO_4$). Removal of the solvent under reduced pressure left an oily residue, which was then purified by column chromatography on silica gel (hexane–EtOAc, 4:1) to give **4** (61 mg, 86%) as a solid; mp 192–193 °C.

IR (KBr): 3368, 2973, 1616, 1512, 1440, 1341, 1281, 1198, 1148, 980, 832, 725 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.6 (s, 1 H), 7.73 (s, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 6.82 (d, *J* = 8.2 Hz, 2 H), 6.64 (d, *J* = 10.0 Hz, 1 H), 5.89 (s, 1 H), 5.43 (d, *J* = 10.0 Hz, 1 H), 3.88 (s, 3 H), 1.42 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.7, 163.3, 162.1, 161.1, 160.5, 144.3, 131.6, 126.7, 126.6, 124.2, 116.9, 116.1, 106.3, 102.9, 92.8, 79.1, 57.2, 28.9.

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{20}O_5$: 352.1311; found: 352.1313.

Glabrachromene (5)

To a soln of **19** (124 mg, 0.5 mmol) in EtOH (10 mL) was added KOH (140 mg, 2.5 mmol) and aldehyde **20** (90 mg, 0.6 mmol) at r.t. The reaction mixture was stirred for 48 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), then washing with 2 N HCl (30 mL) and brine (30 mL), drying ($MgSO_4$), and removal of the solvent followed by flash column chromatography on silica gel (hexane–EtOAc, 10:1) gave **5** (165 mg, 87%) as a solid; mp 124–125 °C.

IR (KBr): 2920, 1615, 1489, 1447, 1360, 1250, 1198, 1150, 1040, 910, 860, 812, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.20 (s, 1 H), 7.70 (s, 2 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 7.08 (s, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.66 (d, *J* = 10.0 Hz, 1 H), 6.00 (s, 2 H), 5.88 (s, 1 H), 5.44 (d, *J* = 10.0 Hz, 1 H), 3.89 (s, 3 H), 1.43 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.4, 162.5, 160.1, 150.9, 149.0, 142.5, 128.5, 125.3, 122.6, 116.0, 111.1, 110.3, 108.8, 106.0, 103.0, 91.5, 78.2, 55.8, 28.3.

HRMS: *m*/*z* [M^+] calcd for $C_{22}H_{20}O_6$: 380.1260; found: 380.1263.

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