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Total Synthesis of Naturally Occurring 5,7,8-Trioxygenated Homoisoflavonoids

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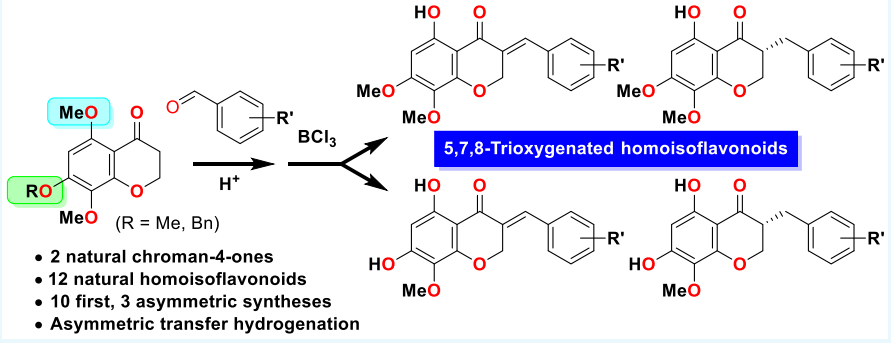

ABSTRACT: Homoisoflavonoids are in the subclass of the larger family of flavonoids but have one more alkyl carbon than flavonoids. Among them, 5,7,8-trioxygenated homoisoflavonoids have not been extensively studied for synthesis and biological evaluation. Our current objective is to synthesize 2 5,7,8-trioxygenated chroman-4-ones and 12 5,7,8-trioxygenated homoisoflavonoids that have been isolated from the plants *Bellevalia eigii*, *Drimiopsis maculata*, *Ledebouria graminifolia*, *Eucomis autumnalis*, *Eucomis punctata*, *Eucomis pallidiflora*, *Chionodoxa luciliae*, *Muscari comosum*, and *Dracaena cochinchinensis*. For this purpose, 1,3,4,5-tetramethoxybenzene and 4′-benzyloxy-2′,3′-dimethoxy-6′-hydroxyacetophenone were used as starting materials. Asymmetric transfer hydrogenation using Noyori's Ru catalyst provided 5,7,8-trioxygenated-3-benzylchroman-4-ones with R-configuration in high yield and enantiomeric excess. By selective deprotection of homoisoflavonoids using BCl_3, the total synthesis of natural products including 10 first syntheses and three asymmetric syntheses has been completed, and three isomers of the reported dracaeconolide B could be provided. Our research on 5,7,8-trioxygenated homoisoflavonoids would be useful for the synthesis of related natural products and pharmacological applications.

INTRODUCTION

Homoisoflavonoids are a subclass of the larger family of flavonoids, with a 16-carbon skeleton that has 1 more carbon (C9 position) than flavonoids and isoflavonoids (Figure 1). They have a structure including two aromatic rings and a heterocycle containing oxygen. As some review articles dealt with the natural origins and structures of homoisoflavonoids, they are mainly found in Asparagaceae and Fabaceae families and are rarely seen in Polygonaceae, Portulacaceae, Orchidaceae, and Gentianaceae families.[1,2] Homoisoflavonoids have been reported to have various biological activities, including antiangiogenic, antibacterial, antimutagenic, antioxidant, and anti-inflammatory effects.[3] Initially, the structural types of homoisoflavonoids were categorized into four scaffolds—3-benzylchroman-4-one, 3-benzylidenechroman-4-one, 3-benzyl-3-hydroxychroman-4-one, and scillascillins—by du Toit's group.[4] As some isolated natural products were not included in such a category of homoisoflavonoids, the newly classified

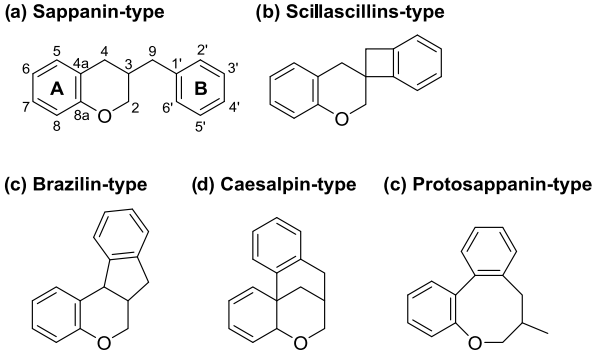

Figure 1. Categories of homoisoflavonoids.

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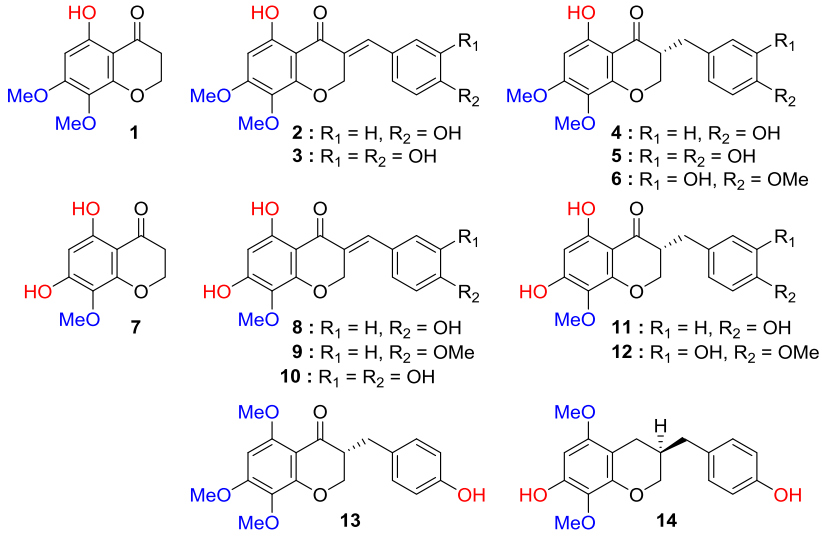

Figure 2. Naturally occurring 5,7,8-trioxygenated chromanones and homoisoflavonoids.

five types of homoisoflavonoids are as follows: sappanin-type, scillascillin-type, brazilin-type, caesalpin-type, and protosappanin-type (Figure 1).[1]

Among them, sappanin-type natural products are the most isolated and studied. The methoxy and hydroxy groups are mainly substituted in the A ring and the B ring, respectively. In the A ring, naturally occurring homoisoflavonoids having mono- to tetra-substituents have been reported so far. In particular, we have been interested in the total synthesis and biological activities of 5,6,7-trisubstituted homoisoflavonoids. Naturally occurring homoisoflavonoids that contain either 5,7-dihydroxy-6-methoxy or 7-hydroxy-5,6-dimethoxy groups in the A ring have been synthesized by us.[5,6] Cremastranone and its synthetic analogs having the 5,6,7-trimethoxy group in the A ring were biologically evaluated against retinal and choroidal neovascularization as a promising drug candidate for wet age-related macular degeneration and other neovascular eye diseases.[7−12] Moreover, we developed an enantioselective synthesis of 5,6,7-trisubstituted homoisoflavonoids such as cremastranone having the C3-stereogenic center, which was confirmed to have an R-configuration, and the antiangiogenic activity of the unnatural S-isomer was found to be more potent than the R-isomer.[13] While synthetic and medicinal chemistry on 5,6,7-trisubstituted homoisoflavonoids were established by us, 5,7,8-trisubstituted homoisoflavonoids have not been well studied yet, although isolated natural products have been reported.

Naturally occurring 5,7,8-trioxygenated homoisoflavonoids have been isolated from the plants *Bellevalia eigii*, *Drimiopsis maculata*, *Ledebouria graminifolia*, *Eucomis autumnalis*, *Eucomis punctata*, *Eucomis pallidiflora*, *Chionodoxa luciliae*, *Muscari comosum*, and *Dracaena cochinchinensis* (Figure 2).[14−23] Punctatin is known as the representative natural product for 5,7,8-trioxygenated homoisoflavonoids, and its congeners can be given a chemical name based on punctatin. *B. eigii* is a perennial plant belonging to the family Asparagaceae, subfamily Scilloideae. The Alali group reported the cytotoxic activity of the natural products isolated from the bulb of this plant.[14] Among them, 5-hydroxy-7,8-dimethoxychroman-4-one (**1**), 7-*O*-methylpunctatin (**2**), 7-*O*-methyl-3′-hydroxypunctatin (**3**), 7-methyl-3,9-dihydropunctatin (**4**), 7-*O*-methyl-3′-hydroxy-3,9-dihydropunctatin (**5**), and 7,4′-di-*O*-methyl-3′-hydroxy-3,9-dihydropunctatin (**6**) were isolated. *D. maculata* is distributed mainly in South Africa and belongs to the family Asparagaceae, subfamily Scilloideae. The Mulholland group isolated 7-methyl-3,9-dihydropunctatin (**4**) from *D. maculata*, which has traditionally been used as a medicine for stomach ailments in children.[15,1615,16] *Eucomis* genus is a perennial bulb of the plant belonging to the family Asparagaceae, subfamily Scilloideae. The plants are widely distributed mainly in South Africa. The bulbs are toxic but have been used in South Africa as traditional medicines for urologic diseases, abdominal pain, and as an antipyretic. The Tamm group isolated 4′-*O*-methylpunctatin (**9**) from the bulb of *E. autumnalis*.[17] Punctatin (**8**) and 3,9-dihydropunctatin (**11**) were isolated from the bulbs of *E. punctata*, *Eucomis comosa*, and *E. pallidiflora*.[18,19] *C. luciliae* and *M. comosum* are perennial plants distributed in Southeast Europe belonging to the family Asparagaceae and subfamily Scilloideae. The Parrilli group isolated punctatin (**8**), 3′-hydroxypunctatin (**10**), 3,9-dihydropunctatin (**11**), and 4′-*O*-methyl-3,9-dihydropunctatin (**12**) from bulbs of plants.[20,21] *D. cochinchinensis* belongs to the family Asparagaceae and subfamily Nolinoideae in the APG IV system. *L. graminifolia* is one of the 16 species comprising the *Ledebouria* genus in Botswana. *Ledebouria* belongs to the family Asparagaceae, subfamily Scilloideae. The Abegza group isolated 5,7-*O*-dimethyl-3,9-dihydropunctatin (**13**) by separating the organic extract from the bulb of this plant, which has traditionally been widely used mainly for skin irritations, wound dressing, sores, coughs, backaches, gastroenteritis, and as a sedative during pregnancy.[22] The Jiang group isolated dracaeconolide B (**14**) from the resin of this plant, which is called dragon's blood, and it has traditionally been used to treat traumatic injury, fractures, diarrhea, and dysmenorrhea.[23]

Although various synthetic studies of the homoisoflavonoids have been introduced, there have been few reports toward 5,7,8-trioxygenated homoisoflavonoids except Strelisky's synthesis in 1971.[24] Facile synthesis of 5,7,8-trioxygenated homoisoflavonoids has the potential to provide a general and expedient entry into a plethora of analogues for interesting biological activities. Herein, we report the first synthesis of naturally occurring and synthetic 5,7,8-trioxygenated homoisoflavonoids from the proper acetophenones, moreover, in an

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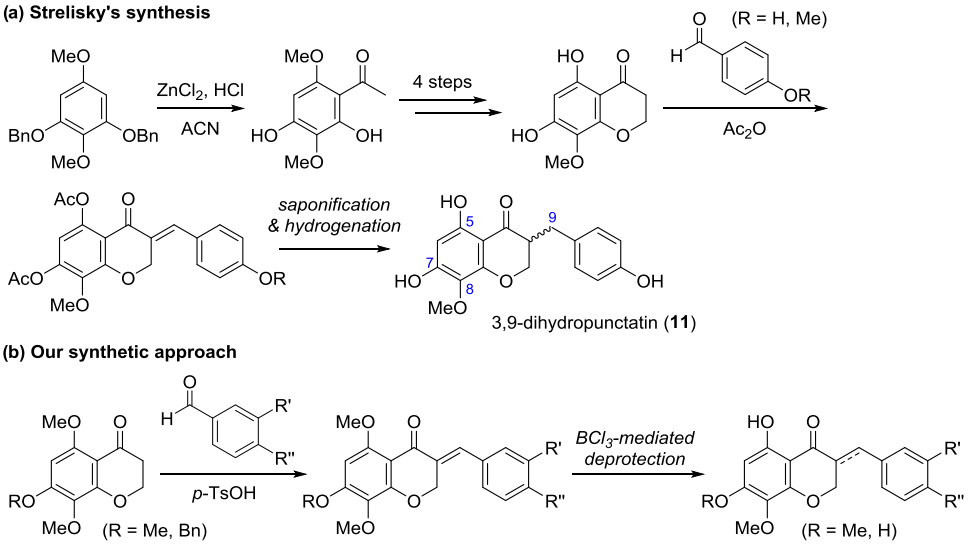
Scheme 1. Strelisky's and Our Synthetic Approaches of 5,7,8-Trioxygenated Homoisoflavonoids



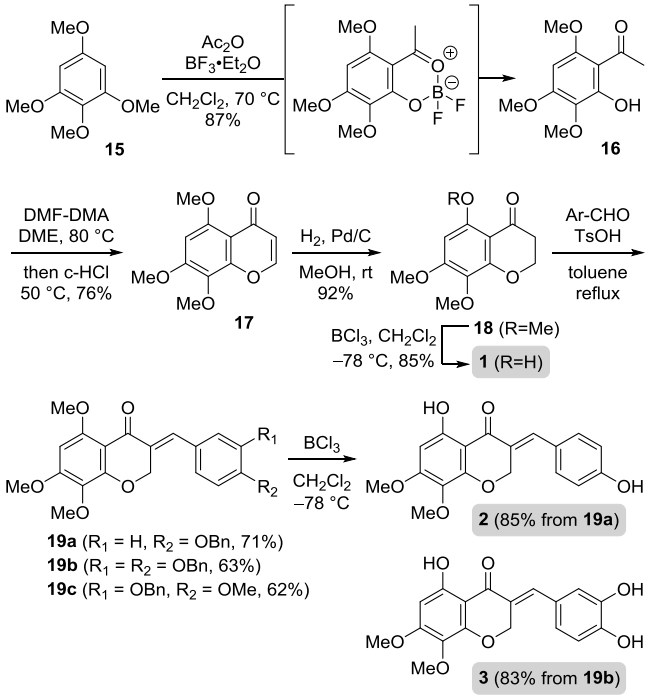
enantioselective fashion by asymmetric transfer hydrogenation and subsequent alcohol oxidation.[13,25]

RESULTS AND DISCUSSION

The syntheses of 5,7-dihydroxy-8-methoxychroman-4-one (**7**) and three homoisoflavonoids (**8**, **9**, and **11**) were studied by Strelisky et al.[24] (Scheme 1). Using the Hoesch reaction, 1,3-bis(benzyloxy)-2,5-dimethoxybenzene was converted into the corresponding acetophenone, and a four-step synthesis was carried out to synthesize **7**. The acetate of 3-benzylidenechroman-4-one was obtained by a condensation reaction using Ac_2O, and finally natural products **8**, **9**, and **11** were synthesized via saponification and hydrogenation. To obtain 5,7,8-trioxygenated homoisoflavonoids with improved chemical yield and reproducibility, we contemplated aldol condensation with methoxy- and benzyl-protected chroman-4-ones. Instead, mild and facile deprotection by BCl_3 was carried out to synthesize various 5,7-dihydroxy-8-methoxy or 5-hydroxy-7,8-dimethoxy homoisoflavonoids. Referring to enantioselective total synthesis of cremastranone by asymmetric transfer hydrogenation, we planned to synthesize 5,7,8-trioxygenated homoisoflavonoids with an R-configuration (Scheme 1).

Our synthesis of 5,7,8-trioxygenated homoisoflavonoids commenced with the synthesis of 3-benzylidenechroman-4-ones having 5-hydroxy-7,8-dimethoxy groups, which were prepared from 1,2,3,5-tetramethoxybenzene **15** via 5,7,8-trimethoxychroman-4-one **18** as shown in Scheme 2. The acetylation of **15** provided by methylation of 3,4,5-trimethoxyphenol was conducted using Ac_2O and $BF_3{\cdot}OEt_2$, and 3 equiv of $BF_3{\cdot}OEt_2$ affected simultaneous demethylation in 87% yield. On the other hand, when 1 equiv of $BF_3{\cdot}OEt_2$ was used, only the acetyl group was introduced without demethylation. During the removal of the methyl group, the sterically hindered methoxy group was more easily removed among the four methoxy groups to obtain only the desired acetophenone **16**. With the acetophenone **16** in hand, the 4*H*-chromen-4-one **17** was provided by treatment with dimethylformamide-dimethyl acetal (DMF-DMA) and subsequent c-HCl solution in good yield. Catalytic hydrogenation of **17** converted it to the chroman-4-one **18**. BCl_3-mediated demethylation afforded the naturally occurring chroman-4-one

Scheme 2. Synthesis of 3-Benzylidenechroman-4-ones Having the 5-Hydroxy-7,8-dimethoxy Group[a]



[a]The gray box is the reported natural product and in all other schemes.

1 in 85% yield, and the NMR spectral data of **1** were identical to those reported.[14] Three benzaldehydes, 4-benzyloxybenzaldehyde, 3-benzyloxy-4-methoxybenzaldehyde, and 3,4-bis(benzyloxy)benzaldehyde, were used for the condensation with chroman-4-one **18** to provide the three benzylidene compounds (**19a–c**) in 62–71% yield, respectively. Unfortunately, general aldol condensation did not proceed with chroman-4-one **1** having a free phenol group instead of **18**. Finally, the benzyl and methyl groups of the benzylidenechroman-4-ones **19a** and **19b** under BCl_3-mediated conditions were removed to provide the desired natural products **2** and **3**, respectively.

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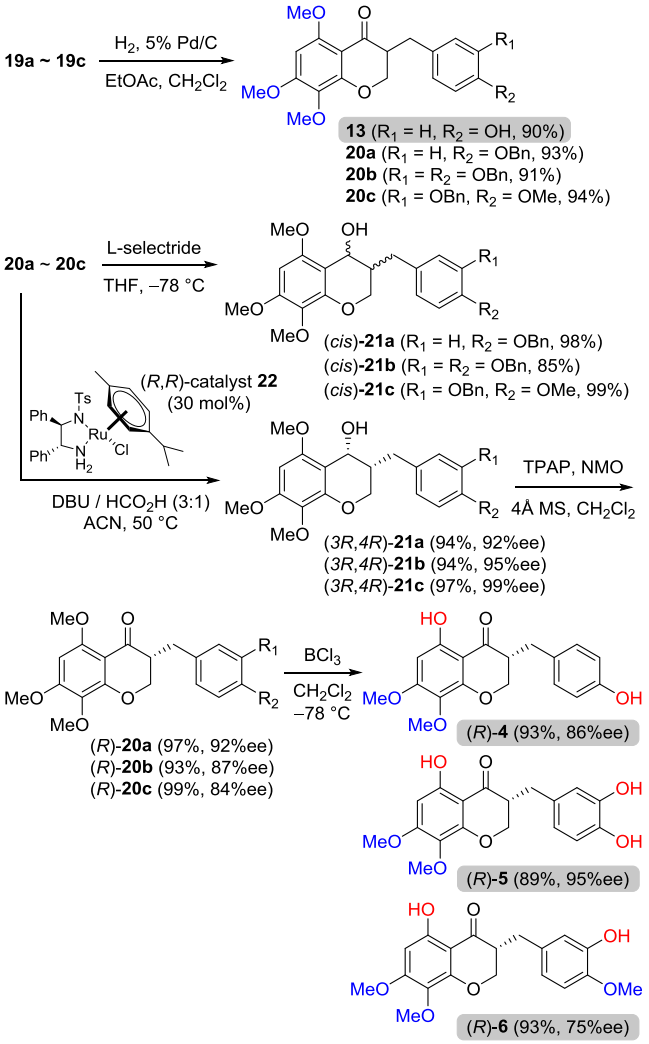
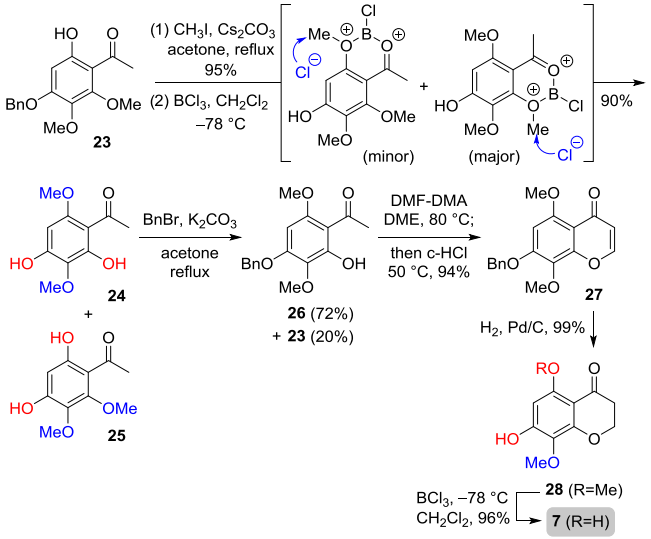
With 3-benzylidenechroman-4-ones (**19a−c**) in hand, four benzylchroman-4-ones, including naturally occurring homoisoflavonoid **13**, were prepared by catalytic hydrogenation as shown in Scheme 3. The double bond of 3-benzylidenechroman-4-ones (**19a−c**) could be hydrogenated to afford 3-benzylchroman-4-ones (**20a−c**) without the removal of benzyl groups by controlling the catalyst loading and reaction time. As in our recent report on asymmetric transfer hydrogenation by Noyori's Ru catalyst,[26] the 3-benzylchroman-4-one (**20a−c**) was treated with 30 mol % of the (*R*,*R*)-catalyst, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and formic acid to afford (3*R*,4*R*)-3-benzylchroman-4-ols (**21a−c**) in excellent yields (94−97%) and enantioselectivity (92−99% enantiomeric excess (ee)) along with the preparation of racemic *cis*-3-benzylchroman-4-ols by L-selectride reduction. Ley's oxidation of a secondary alcohol with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) was chosen as a suitable alcohol oxidation of (3*R*,4*R*)-3-benzylchroman-4-ols (**21a−c**) to afford three kinds of the corresponding (*R*)-3-benzylchroman-4-ones ((*R*)-**20a−c**).[27] Finally, BCl_3-mediated deprotection was carried out to provide naturally occurring **4−6** through the cleavage of the C5-methyl in the A ring and benzyl group(s) in the B ring.[28]

Scheme 3. Synthesis of 3-Benzylchroman-4-ones Having 5-Hydroxy-7,8-dimethoxy Groups



Based on the successful synthesis of 5-hydroxy-7,8-dimethoxychroman-4-one **1**, we turned to consider the desired acetophenone for the synthesis of 5,7-dihydroxy-8-methoxychroman-4-one **7**. Thus, the known acetophenone **23** was used as a starting material as shown in Scheme 4, and the hydroxy group of **23** was converted into methoxy by CH_3I and Cs_2CO_3, followed by selective demethylation under BCl_3-mediated conditions in which it was reported to occur selectively at a hindered methyl ether in polymethoxyarenes.[29] Two isomers **24** and **25** were generated by BCl_3-mediated demethylation, followed by the introduction of a benzyl group on C4 to afford the desired acetophenones **26** and **23** with 72 and 20% yields, respectively. With **26** in hand, the chromen-4-one **27** was afforded by the treatment of DMF−DMA and subsequent c-HCl. Finally, the conversion of **27** to the debenzylated chroman-4-one **28** by general catalytic hydrogenation, followed by BCl_3-mediated demethylation on the C5 position, provided the naturally occurring chroman-4-one **7** in 96% yield.[30]

Scheme 4. Synthesis of 5,7-Dihydroxy-8-methoxychroman-4-one



For the synthesis of 5,7-dihydroxy-8-methoxy homoisoflavonoids, the protection of the phenol group was necessary; otherwise, the yield of condensation was quite low. Thus, **28** was benzylated on the C7 position and condensed with four benzaldehydes to afford the corresponding 5,7,8-trioxygenated-3-benzylidenechroman-4-ones (**29a−d**) as shown in Scheme 5. BCl_3-mediated deprotection was carried out to provide naturally occurring 5,7-dihydroxy-8-methoxy homoisoflavonoids (**8−10**) in moderate yield (42−60%). Also, 3-benzylchroman-4-ones (**30** and **31**) were obtained by catalytic hydrogenation of **29a** and **29d**, and both the methyl on C5 and the benzyl on the B ring were smoothly removed by BCl_3-mediated reactions to afford two naturally occurring 3-benzylchroman-4-ones (**11** and **12**).

To obtain homoisoflavonoids containing either 5-hydroxy-7,8-dimethoxy or 5,7-dihydroxy-8-methoxy groups, it was important to study deprotection conditions to properly remove methyl and benzyl groups from the advanced intermediates of 5,7,8-trioxygenated homoisoflavonoids such as (*R*)-**20a−c**, **29a**, and **29b**, as shown in Scheme 6. BCl_3 was considered an excellent reagent for deprotection owing to its mild and site-

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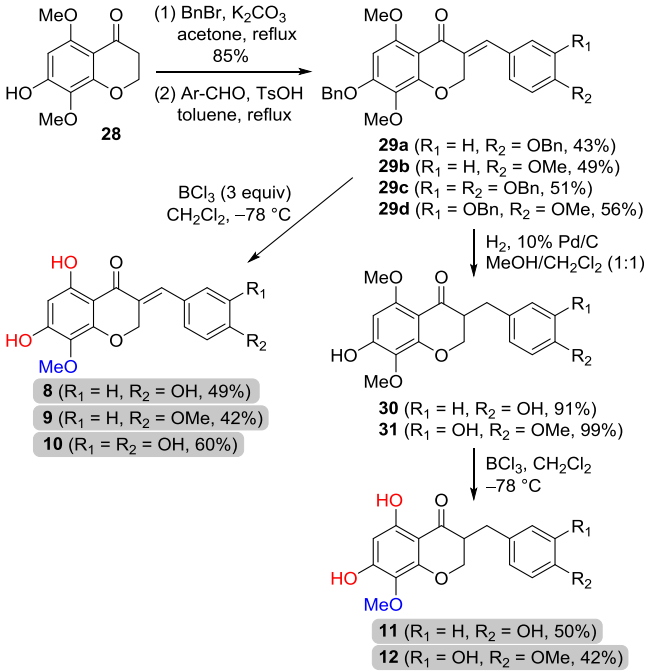
Scheme 5. Synthesis of Homoisoflavonoids Having 5,7-Dihydroxy-8-methoxy Groups



selective conditions. Interestingly, the order and process by which benzyl and methyl are removed could be understood through the structural confirmation of isolated intermediates (**32a–c**). In the case of phenol-deprotection of 3-benzylidenechroman-4-one (**19a**, **29a**, and **29b**), which was a highly conjugated system, the benzyl group(s) was removed first followed by methyl on the C5 position. However, slightly lower yields resulted in the overreaction of demethylation and instability of benzylidene derivatives. In 3-benzylchroman-4-ones ((*R*)-**20a** and (*R*)-**20b**), on the other hand, a methyl group neighboring the carbonyl group was first removed using BCl_3 to yield the resulting intermediates (**33a** and **33b**) having a hydroxy group on the C5 position, followed by the removal of benzyl group(s) on the B ring finally to afford **4** and **5**, respectively. During BCl_3-mediated deprotection of (*R*)-**20c**, the product **6** was provided via a mixture of **33c** and **33d**, and so it was concluded that the reactivity to removal of methyl and benzyl groups was similar.

Dracaeconolide B (**14**), 3-(4-hydroxybenzyl)-7-hydroxy-5,8-dimethoxychromane, is unique in having the combination of a hydroxy at the C7 position and two methoxys on C5 and C8 positions of the homoisoflavonoid and a natural chromane skeleton, deoxygenated chroman-4-one, compared to other 5,7,8-trioxygenated homoisoflavonoids. We undertook catalytic hydrogenation of the previous intermediate **29a** to reduce the double bond and cleave two benzyl groups as shown in Scheme 7. Unfortunately, the spectral data of our synthetic compound **14** were not identical to the reported ones of ^1H and ^{13}C NMR spectroscopies.[23] We attempted to synthesize other regioisomers of dracaeconolide B to determine whether its structure would be corrected. 3-Benzylidenechroman-4-one **19a** was converted to 5-hydroxy-7,8-dimethoxy isomer **34** by BCl_3 reaction and catalytic hydrogenation of **2**. In contrast, **19a** was reduced to 3-(4-hydroxybenzyl)-5,7,8-trimethoxychromane **35** in which the sterically hindered C8-methoxy group could be cleaved predominantly under the BCl_3-mediated condition to provide the 8-hydroxy-5,7-dimethoxy isomer **36**. The structural elucidation of three different regioisomers (**14**, **34**, and **36**) was confirmed by comparison of the ^1H and ^{13}C NMR data (Table S14) and two-dimensional (2D) NMR spectroscopy (Figures S1–S3). The position and combination of one hydroxy and two methoxy groups on the C5, C7, and C8 positions of the A ring were assigned by heteronuclear multiple bond correlation (HMBC) correlations from H-6 to C-4a, C-5, C-7, and C-8; H_2-4 to C-4a, C-5, C-6, C-8a, and C-8; and H_2-2 to C-2 and C-8a.

CONCLUSIONS

We have developed total syntheses of 2 naturally occurring 5,7,8-trioxygenated chroman-4-ones and 12 5,7,8-trioxygenated homoisoflavonoids, including 10 synthesized for the first time. 1,3,4,5-Tetramethoxybenzene and 4′-benzyloxy-2′,3′-dimethoxy-6′-hydroxyacetophenone were used as starting materials. Asymmetric transfer hydrogenation using Noyori's Ru catalyst provided three 5,7,8-trioxygenated homoisoflavanones having an R-configuration in >94% yield and >92% ee. During BCl_3-mediated deprotection, we observed that the order in which the protecting groups are removed differs depending on the substrate. To synthesize the 5,7,8-trioxygenated benzylchromane dracaeconolide B, the synthesis and structural analysis of three regioisomers were executed. Our research on 5,7,8-trioxygenated homoisoflavonoids will be useful for the synthesis of related natural products and drug discovery.

EXPERIMENTAL SECTION

All starting materials and reagents were obtained from commercial sources and used without further purification. Air- and moisture-sensitive reactions were performed under nitrogen. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (Merck). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker 600 MHz spectrometer as solutions in deuterochloroform ($CDCl_3$) or methanol-d_4 (CD_3OD). ^1H NMR data were reported on the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiplet resonances), number of protons, and coupling constant (*J* value) in hertz (Hz). Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) on an Agilent 1100 using one chiral column (CHIRALPAK IA, IB, IC, ID, IG). High-resolution mass spectra (HRMS) were recorded on an Agilent 6530 quadrupole time-of-flight (Q-TOF) liquid chromatography (LC)/tandem mass spectrometry (MS/MS) system (electrospray ionization (ESI)).

1,2,3,5-Tetramethoxybenzene (15). To an *N*,*N*-dimethylformamide (20 mL) solution of 3,4,5-trimethoxy-phenol (3.0 g, 16 mmol), dimethyl sulfate (4.6 mL, 49 mmol) and Cs_2CO_3 (10 g, 33 mmol) were added. The reaction mixture was refluxed for 4 h. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and the organic phase was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:5) to afford 1,2,3,5-tetramethoxybenzene (**15**) (3.2 g, 98%). ^1H NMR (600 MHz, $CDCl_3$) δ 6.15 (s, 2H), 3.84 (s, 6H), 3.78 (s, 3H), 3.78 (s, 3H). $^{13}C\{^1H\}$ NMR

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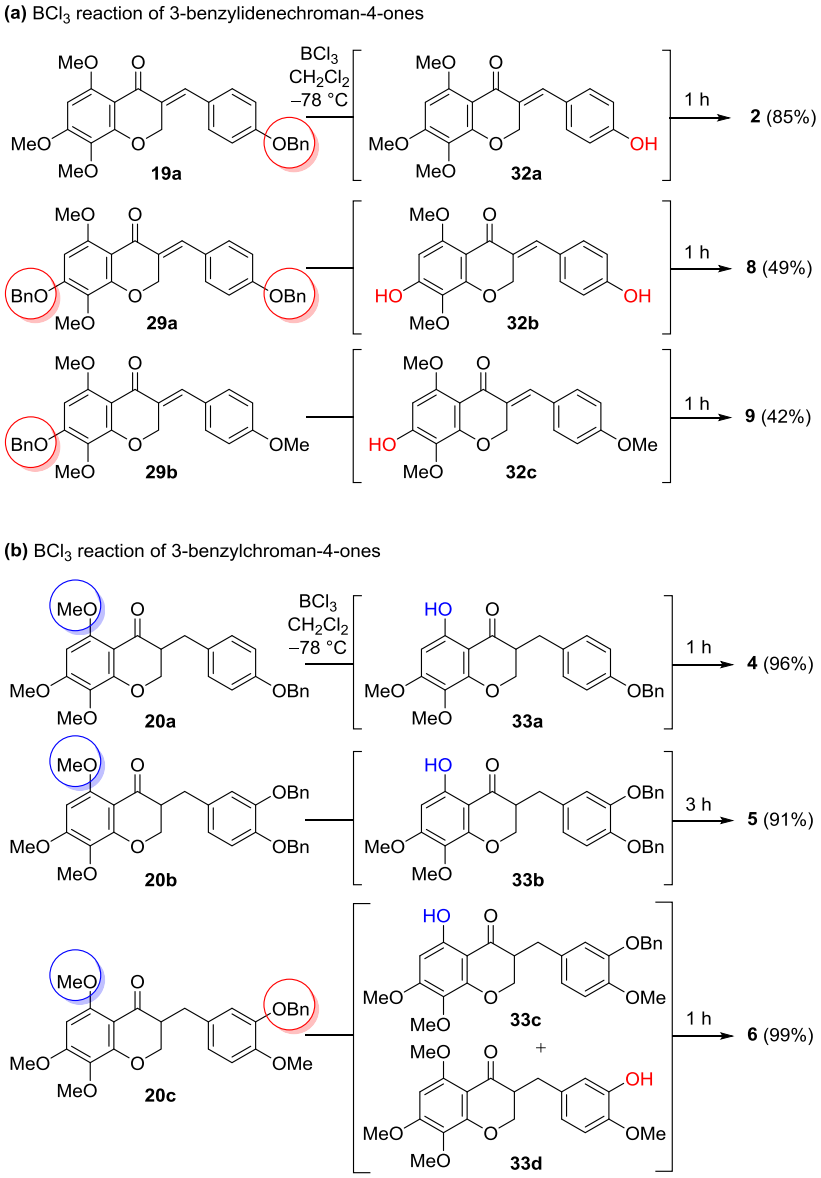
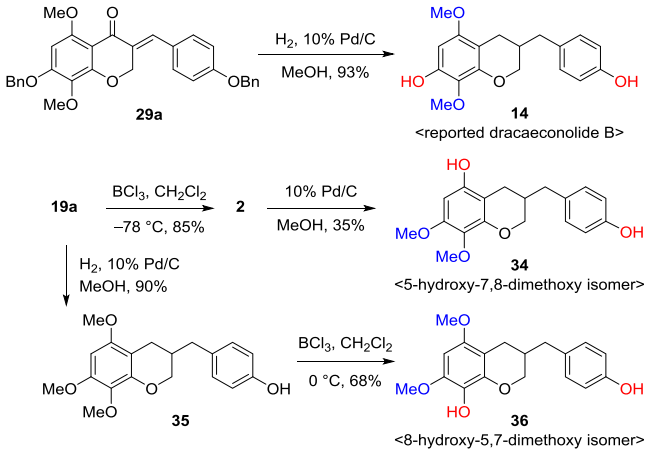
Scheme 6. Sequential BCl_3-Mediated Deprotection of (a) 3-Benzylidenechroman-4-one and (b) 3-Benzylchroman-4-one



Scheme 7. Synthesis of Suggested Dracaeconolide B and Its Two Isomers



(150 MHz, $CDCl_3$) δ 156.4, 153.8, 132.4, 91.7, 61.1, 56.2, 55.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_{14}O_4$ 199.0970; found, 199.0966.

1-(2-Hydroxy-3,4,6-trimethoxyphenyl)ethan-1-one (16). To a chloroform (15 mL) solution of 1,2,3,5-tetramethoxybenzene (**15**) (3.2 g, 16 mmol), acetic anhydride (1.7 mL, 18 mmol) and $BF_3{\cdot}OEt_2$ (6.9 mL, 56 mmol) were added at 0 °C. After stirring at 70 °C for 4 h, the reaction mixture was cooled, and ice-cold water and 5% NaOH (5 mL) were poured into the mixture. The reaction mixture was diluted with ethyl acetate, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/*n*-hexane = 1:3) to afford 1-(2-hydroxy-3,4,6-trimethoxyphenyl)ethan-1-one (**16**) (3.1 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.80 (s, 1H), 5.95 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 2.61 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 203.9, 159.2, 158.9, 158.5, 130.6, 106.4, 86.5, 60.8, 56.1, 55.7, 33.3.

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HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}O_5$ 227.0919; found, 227.0914.

5,7,8-Trimethoxy-4*H*-chromen-4-one (17). To a solution of 1-(2-hydroxy-3,4,6-trimethoxyphenyl)ethan-1-one (**16**) (2.7 g, 12 mmol) in dimethoxyethane (DME) (30 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (4.8 mL, 36 mmol). After stirring for 24 h at 80 °C, the reaction mixture was cooled to 0 °C and c-HCl (6 mL) was added. After stirring for 1 h at 50 °C, the reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford 5,7,8-trimethoxy-4*H*-chromen-4-one (**17**) (2.2 g, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 5.9 Hz), 6.43 (s, 1H), 6.18 (d, 1H, J = 5.9 Hz), 3.99 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 176.9, 156.7, 156.6, 152.9, 152.4, 130.7, 114.2, 110.2, 92.7, 61.8, 56.7, 56.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}O_5$ 237.0763; found, 237.0760.

5,7,8-Trimethoxychroman-4-one (18). 5,7,8-Trimethoxy-4*H*-chromen-4-one (**17**) (2.8 g, 12 mmol) and 10% Pd/C (0.38 g, 3.5 mmol) in methanol (40 mL) were placed under an atmosphere of hydrogen. After stirring for 1 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) afforded 5,7,8-trimethoxychroman-4-one (**18**) (2.6 g, 92.%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.09 (s, 1H), 4.50 (t, 2H, J = 6.4 Hz), 3.93 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H), 2.72 (t, 2H, J = 6.4 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 189.5, 158.6, 158.1, 156.7, 130.8, 106.7, 89.3, 67.3, 61.3, 56.3, 56.1, 39.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{14}O_5$ 239.0919; found, 239.0912.

5-Hydroxy-7,8-dimethoxychroman-4-one (1). To a solution of 5,7,8-trimethoxychroman-4-one (**18**) (50 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was added boron trichloride (0.62 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 and washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to afford 5-hydroxy-7,8-dimethoxychroman-4-one (**1**) (40 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.98 (s, 1H), 6.08 (s, 1H), 4.52 (t, 2H, J = 6.3 Hz), 3.88 (s, 2H), 3.77 (s, 2H), 2.79 (t, 2H, J = 6.3 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 196.2, 161.5, 160.3, 154.0, 129.6, 103.3, 93.1, 67.1, 61.5, 56.4, 36.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{12}O_5$ 225.0763; found, 225.0760.

(*E*)-3-(4′-(Benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (19a). To a solution of 5,7,8-trimethoxychroman-4-one (**18**) (0.50 g, 2.1 mmol) in toluene (20 mL) were added 4-benzyloxybenzaldehyde (0.67 g, 3.1 mmol) and *p*-toluenesulfonic acid (36 mg, 0.21 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:2:0.1) to afford (*E*)-3-(4′-(benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (**19a**) (0.64 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.43 (d, J = 7.4 Hz, 2H), 7.37 (t, 2H, J = 7.6 Hz), 7.30 (t, 1H, J = 7.3 Hz), 6.92 (d, 1H, J = 8.4 Hz), 6.88 (dd, 1H, J = 8.4, 1.7 Hz), 6.78 (d, 1H, J = 1.7 Hz), 6.15 (s, 1H), 5.17 (s, 2H), 5.13 (d, 2H, J = 1.5 Hz), 3.93 (s, 3H), 3.92 (s, 3H), 3.92 (s, 3H), 3.78 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 179.8, 159.6, 158.4, 158.3, 155.9, 136.5, 135.9, 131.8, 130.9, 130.1, 128.7, 128.1, 127.6, 127.5, 115.0, 107.6, 90.1, 70.1, 67.9, 61.3, 56.3, 56.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{24}O_6$ 433.1651; found, 433.1650.

(*E*)-3-(3′,4′-Bis(benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (19b). To a solution of 5,7,8-trimethoxychroman-4-one (**18**) (0.50 g, 2.1 mmol) in toluene (20 mL) were added 3,4-bis(benzyloxy)benzaldehyde (1.0 g, 3.2 mmol) and *p*-toluenesulfonic acid (36 mg, 0.21 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/CH_2Cl_2 = 1:5) to afford (*E*)-3-(3′,4′-bis(benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (**19b**) (0.71 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.47−7.43 (m, 4H), 7.38 (td, 4H, J = 7.5, 2.1 Hz), 7.34−7.30 (m, 2H), 6.97−6.94 (m, 1H), 6.84 (dd, 2H, J = 5.4, 1.9 Hz), 6.17 (s, 1H), 5.22 (s, 2H), 5.19 (s, 2H), 5.15 (d, 2H, J = 1.7 Hz), 3.94 (s, 3H), 3.94 (s, 3H), 3.79 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 179.9, 158.5, 158.5, 156.0, 150.1, 148.6, 137.0, 136.9, 136.1, 131.1, 130.4, 128.8, 128.7, 128.2, 128.1, 127.4, 127.4, 124.3, 116.9, 114.4, 107.8, 90.2, 71.6, 71.2, 67.9, 61.5, 56.5, 56.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{33}H_{30}O_7$ 539.2070; found, 539.2067.

(*E*)-3-(3′-(Benzyloxy)-4′-methoxybenzylidene)-5,7,8-trimethoxychroman-4-one (19c). To a solution of 5,7,8-trimethoxychroman-4-one (**18**) (0.50 g, 2.1 mmol) in toluene (20 mL) were added 3-(benzyloxy)-4-methoxybenzaldehyde (0.77 g, 3.2 mmol) and *p*-toluenesulfonic acid (36 mg, 0.21 mmol) at 0 °C. The reaction mixture was refluxed for 13 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:2:0.1) to afford (*E*)-3-(3′-(benzyloxy)-4′-methoxybenzylidene)-5,7,8-trimethoxychroman-4-one (**19c**) (0.60 g, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.41 (d, 2H, J = 7.3 Hz), 7.37 (t, 2H, J = 7.3 Hz), 7.32 (d, 1H, J = 7.3 Hz), 7.23 (d, 2H, J = 8.7 Hz), 7.00 (d, 2H, J = 8.7 Hz), 6.16 (s, 1H), 5.28 (d, 2H, J = 1.6 Hz), 5.08 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.77 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 179.8, 158.4, 158.4, 155.9, 150.8, 147.9, 136.8, 136.1, 131.0, 130.2, 128.8, 128.1, 127.5, 127.3, 124.2, 115.9, 111.6, 107.7, 90.2, 71.2, 67.9, 61.4, 56.4, 56.1, 56.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{26}O_7$ 463.1757; found, 463.1754.

7-*O*-Methoxypunctatin (2). To a solution of (*E*)-3-(4′-(benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (**19a**) (31 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.21 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford 7-*O*-methoxypunctatin (**2**) (20 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.66 (s, 1H), 7.79 (s, 1H), 7.20 (d, 2H, J = 8.6 Hz), 6.91 (d, 2H, J = 8.6 Hz), 6.11 (s, 1H), 5.55 (s, 1H), 5.34 (d, 2H, J = 1.7 Hz), 3.88 (s, 3H), 3.76 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 185.8, 161.5, 161.1, 157.5, 153.0, 137.7, 132.5, 129.5, 127.6, 127.0, 116.1, 103.2, 93.4, 67.8, 61.6, 56.4. HRMS

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(ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}O_6$ 329.1025; found, 329.1023.

7-*O*-Methyl-3′-hydroxypunctatin (3). To a solution of (*E*)-3-(3′,4′-bis(benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (**19b**) (31 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.17 mL, 1.0 M solution in CH_2Cl_2) at 0 °C. After stirring for 30 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford (*E*)-3-(3,4-dihydroxybenzylidene)-5-hydroxy-7,8-dimethoxychroman-4-one (**3**) (16 mg, 83%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.72 (s, 1H), 6.89 (d, 1H, J = 8.2 Hz), 6.85 (s, 1H), 6.81 (d, 1H, J = 8.2 Hz), 6.19 (s, 1H), 5.40 (s, 1H), 3.89 (s, 1H), 3.72 (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 187.1, 162.9, 162.2, 154.5, 149.4, 146.8, 139.3, 130.7, 128.0, 127.5, 125.1, 118.6, 116.8, 104.1, 94.2, 69.1, 61.7, 56.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}O_7$ 345.0974; found, 345.0978.

5,7,8-Trimethoxy-3-(4′-hydroxybenzyl)-4-chromanone (13). (*E*)-3-(4′-(Benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (**19a**) (30 mg, 0.07 mmol) and 10% Pd/C (3.7 mg, 0.03 mmol) in methanol (3 mL) were placed under an atmosphere of hydrogen. After stirring for 2 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:2:0.1) afforded 5,7,8-trimethoxy-3-(4′-hydroxybenzyl)-4-chromanone (**13**) (22 mg, 90%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.08 (d, 2H, J = 8.1 Hz), 6.76 (d, 2H, J = 8.1 Hz), 6.32 (s, 1H), 4.34 (dd, 1H, J = 11.3, 3.8 Hz), 4.18 (dd, 1H, J = 11.3, 7.1 Hz), 3.96 (s, 3H), 3.90 (s, 3H), 3.73 (s, 3H), 3.06 (dd, J = 13.8, 4.6 Hz, 1H), 2.76−2.70 (m, 1H), 2.66 (dd, 1H, J = 13.6, 10.4 Hz). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 193.9, 160.4, 159.6, 157.4, 156.9, 131.4, 131.0, 130.2, 116.2, 106.1, 90.5, 70.1, 61.2, 56.5, 56.2, 49.7, 33.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}O_6$ 345.1338; found, 345.1332.

3-(4′-Benzyloxy)-5,7,8-trimethoxychroman-4-one (20a). An ethyl acetate (3 mL) and CH_2Cl_2 (1 mL) solution of (*E*)-3-(4-(benzyloxy)-benzylidene)-5,7,8-trimethoxychroman-4-one (**19a**) (27 mg, 0.06 mmol) as well as 5% wet Pd/C (3.5 mg, 0.03 mmol) was placed under an atmosphere of hydrogen. After stirring for 1 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:3:0.1) afforded 3-(4′-(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one (**20a**) (25 mg, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, 2H, J = 7.3 Hz), 7.38 (t, 2H, J = 7.5 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.15 (d, 2H, J = 8.6 Hz), 6.92 (d, 2H, J = 8.6 Hz), 6.12 (s, 1H), 5.04 (s, 2H), 4.35 (dd, 1H, J = 11.3, 4.1 Hz), 4.18 (dd, 1H, J = 11.3, 7.5 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.19 (dd, 1H, J = 14.0, 4.4 Hz), 2.77 (m, 1H), 2.64 (dd, 1H, J = 14.0, 10.6 Hz). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 191.7, 158.6, 158.3, 157.6, 156.4, 137.2, 130.9, 130.7, 130.3, 128.7, 128.0, 127.6, 115.1, 105.8, 89.3, 70.1, 69.3, 61.3, 56.3, 56.1, 48.7, 32.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{26}O_6$ 435.1810; found, 435.1803.

3-(3′,4′-Bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one (20b). An ethyl acetate (9 mL) and CH_2Cl_2 (3 mL) solution of (*E*)-3-(3′,4′-bis(benzyloxy)-benzylidene)-5,7,8-trimethoxychroman-4-one (**19b**) (82 mg, 0.15 mmol) as well as 5% wet Pd/C (8.0 mg, 0.07 mmol) was placed under an atmosphere of hydrogen. After stirring for 1 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:3:0.1) afforded 3-(3′,4′-bis-(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one (**20b**) (75 mg, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47−7.43 (m, 4H), 7.38−7.34 (m, 4H), 7.33−7.28 (m, 2H), 6.87 (d, 1H, J = 8.1 Hz), 6.82 (d, 1H, J = 2.0 Hz), 6.74 (dd, 1H, J = 8.1, 2.0 Hz), 6.12 (s, 1H), 5.15 (d, 4H, J = 6.2 Hz), 4.28 (dd, 1H, J = 11.3, 4.2 Hz), 4.09 (dd, 1H, J = 11.3, 7.5 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H), 3.15 (dd, 1H, J = 14.0, 4.3 Hz), 2.72 (m, 1H), 2.59 (dd, 1H, J = 14.0, 10.6 Hz). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 191.7, 158.6, 158.3, 156.5, 149.0, 147.8, 137.5, 137.34, 132.0, 130.7, 128.6, 127.9, 127.9, 127.6, 127.4, 122.3, 116.3, 115.5, 105.9, 89.4, 71.6, 71.5, 69.3, 61.3, 56.3, 56.2, 48.6, 32.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{33}H_{32}O_7$ 541.2226; found, 541.2224.

3-(3′-(Benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-one (20c). An ethyl acetate (9 mL) and CH_2Cl_2 (3 mL) solution of (*E*)-3-(3-(benzyloxy)-4-methoxybenzylidene)-5,7,8-trimethoxychroman-4-one (**19c**) (0.16 g, 0.35 mmol) as well as 5% wet Pd/C (18 mg, 0.17 mmol) was placed under an atmosphere of hydrogen. After stirring for 1 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:3:0.1) afforded 3-(3′-(benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-one (**20c**) (0.15 g, 94%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 7.6 Hz), 7.35 (t, 2H, J = 7.6 Hz), 7.28 (t, 1H, J = 7.4 Hz), 6.83 (d, 1H, J = 8.1 Hz), 6.79−6.76 (m, 2H), 6.12 (s, 1H), 5.14 (s, 2H), 4.26 (dd, 1H, J = 11.3, 4.1 Hz), 4.07 (dd, 1H, J = 11.3, 7.5 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.14 (dd, 1H, J = 13.9, 4.2 Hz), 2.70 (ddd, 1H, J = 11.6, 8.3, 4.2 Hz), 2.59 (dd, 1H, J = 13.9, 10.6 Hz). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 191.7, 158.6, 158.3, 156.5, 148.6, 148.2, 137.2, 131.1, 130.6, 128.7, 128.0, 127.6, 122.1, 115.4, 112.1, 105.9, 89.4, 71.2, 69.3, 61.3, 56.3, 56.2, 56.2, 48.7, 32.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{28}O_7$ 465.1913; found, 465.1909.

3-(4′-(Benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((*cis*)-21a). To a solution of 3-(4′-(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one (**20a**) (30 mg, 0.069 mmol) in anhydrous tetrahydrofuran (THF) (2 mL), L-selectride (0.10 mL, 1.0 M in THF) was added dropwise at −78 °C. After 1 h, the reaction was completed and quenched with NH_4Cl, extracted with ethyl ether, and dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to afford 3-(4′-(benzyloxy)-benzyl)-5,7,8-trimethoxychroman-4-ol (*cis*-**21a**) (30 mg, 98%).

(3*R*,4*R*)-3-(4′-(Benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((3*R*,4*R*)-21a). DBU and formic acid (3:1 (v/v)) were dissolved in acetonitrile. The solution was sparged with nitrogen for 15 min. Separately, 3-(4′-(benzyloxy)-benzyl)-5,7,8-trimethoxychroman-4-one (**20a**) (53 mg, 0.12 mmol) and RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (**22**) (23 mg, 0.036 mmol) were dissolved in acetonitrile and then added to the mixture of DBU and formic acid. The mixture was stirred for 24 h at 50 °C and then quenched by adding saturated NH_4Cl solution at ambient temperature. After extraction with diethyl ether, the organic layer was washed with an additional

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portion of saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford (3*R*,4*R*)-3-(4′-(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((3*R*,4*R*)-**21a**) (50 mg, 94%) $[\alpha]_D^{24}$ = +100 (*c* 0.10, CH_3OH). ee % = 92% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 7.3 Hz), 7.39 (t, 2H, *J* = 7.5 Hz), 7.33 (t, 1H, *J* = 7.3 Hz), 7.20 (d, 2H, *J* = 8.6 Hz), 6.94 (d, 2H, *J* = 8.6 Hz), 6.09 (s, 1H), 5.06 (s, 2H), 4.73 (d, 1H, *J* = 2.5 Hz), 4.19−4.13 (m, 1H), 4.07−4.01 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 2.90 (dd, 1H, *J* = 13.8, 8.4 Hz), 2.63 (dd, 1H, *J* = 13.8, 7.3 Hz), 2.17 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 157.4, 154.2, 153.3, 149.0, 137.3, 131.9, 131.5, 130.2, 128.7, 128.1, 127.6, 115.0, 107.9, 88.6, 70.2, 65.5, 61.2, 59.9, 56.4, 55.67, 40.1, 32.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{28}O_6$ 541.2226; found, 541.2224. T_R = 10 min (chiral IC, *n*-hexane/EtOH = 60:40).

3-(3′,4′-Bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((*cis*)-21b). To a solution of 3-(3′,4′-bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one (**20b**) (30 mg, 0.056 mmol) in anhydrous THF (2 mL), L-selectride (0.08 mL, 1.0 M in THF) was added dropwise at −78 °C. After 1 h, the reaction was completed, quenched with saturated NH_4Cl solution, extracted with ethyl ether, and dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to afford 3-(3′,4′-bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol (*cis*-**21b**) (26 mg, 85%).

(3*R*,4*R*)-3-(3′,4′-Bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((3*R*,4*R*)-21b). DBU and formic acid (3:1 (v/v)) were dissolved in acetonitrile. The solution was sparged with nitrogen for 15 min. Separately, 3-(3′,4′-bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one (**20b**) (30 mg, 0.06 mmol) and RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (**22**) (11 mg, 0.02 mmol) were dissolved in acetonitrile and then added to the mixture of DBU and formic acid. The mixture was stirred for 24 h at 50 °C and then quenched by adding saturated NH_4Cl solution at ambient temperature. After extraction with diethyl ether, the organic layer was washed with an additional portion of saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford (3*R*,4*R*)-3-(3′,4′-bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((3*R*,4*R*)-**21b**) (28 mg, 94%) $[\alpha]_D^{24}$ = +103 (*c* 0.096, CH_3OH). ee % = 95% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 7.45 (dd, 4H, *J* = 7.2, 1.9 Hz), 7.36 (dt, 4H, *J* = 15.2, 7.6 Hz), 7.30 (dd, 2H, *J* = 14.6, 7.3 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 6.87 (d, 1H, *J* = 2.0 Hz), 6.78 (dd, 1H, *J* = 8.2, 2.0 Hz), 6.09 (s, 1H), 5.14 (dd, 4H, *J* = 10.7, 2.7 Hz), 4.65 (s, 1H), 4.10 (ddd, 1H, *J* = 10.4, 3.5, 1.0 Hz), 4.03−3.98 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 2.83 (dd, 1H, *J* = 13.8, 8.5 Hz), 2.59 (dd, 1H, *J* = 13.8, 7.2 Hz), 2.16−2.09 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 154.2, 153.3, 149.0, 147.6, 137.6, 137.5, 133.0, 131.5, 128.6, 128.6, 127.9, 127.6, 127.5, 122.2, 116.6, 115.5, 107.9, 88.6, 71.6, 71.6, 65.5, 61.2, 59.8, 56.4, 55.7, 40.0, 32.4. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{33}H_{34}O_7$ 565.2202; found, 565.2204. T_R = 30 min (chiral ID, *n*-hexane/IPA/EtOH = 60:20:20).

3-(3′-(Benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-ol ((*cis*)-21c). To a solution of 3-(3′-(benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-one (**20c**) (30 mg, 0.065 mmol) in anhydrous THF (2 mL), L-selectride (0.10 mL, 1.0 M in THF) was added dropwise at −78 °C. After 1 h, the reaction was completed and quenched with NH_4Cl, extracted with ethyl ether, and dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to afford 3-(3′-(benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-ol (*cis*-**21c**) (30 mg, 99%).

(3*R*,4*R*)-3-(3′-(Benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-ol ((3*R*,4*R*)-21c). DBU and formic acid (3:1 (v/v)) were dissolved in acetonitrile. The solution was sparged with nitrogen for 15 min. Separately, 3-(3′-(benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-one (**20c**) (86 mg, 0.19 mmol) and RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (**22**) (35 mg, 0.06 mmol) were dissolved in acetonitrile and then added to the mixture of DBU and formic acid. The mixture was stirred for 24 h at 50 °C and then quenched by adding saturated NH_4Cl solution at ambient temperature. After extraction with diethyl ether, the organic layer was washed with an additional portion of saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford (3*R*,4*R*)-3-(3′-(benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxy-chroman-4-ol ((3*R*,4*R*)-**21c**) (84 mg, 97%) $[\alpha]_D^{24}$ = +92 (*c* 0.098, CH_3OH). ee % = 99% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 7.3 Hz), 7.35 (t, 2H, *J* = 7.6 Hz), 7.29−7.25 (m, 1H), 6.86−6.81 (m, 3H), 6.08 (s, 1H), 5.14 (s, 2H), 4.63 (d, 1H, *J* = 2.8 Hz), 4.11−4.07 (m, 1H), 4.02−3.97 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 2.81 (dd, 1H, *J* = 13.8, 8.6 Hz), 2.58 (dd, 1H, *J* = 13.8, 7.2 Hz), 2.15−2.08 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 154.2, 153.3, 148.91, 148.3, 148.1, 137.4, 132.0, 131.5, 128.6, 127.9, 127.5, 121.9, 115.6, 112.1, 107.8, 88.5, 71.2, 65.5, 61.1, 59.8, 56.4, 56.2, 55.6, 40.0, 32.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{30}O_7$ 497.2070; found, 467.2063. T_R = 26 min (chiral ID, *n*-hexane/IPA/EtOH = 60:20:20).

(*R*)-3-(4′-(Benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-20a). A solution of (3*R*,4*R*)-3-(4′-(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((3*R*,4*R*)-**21a**) (0.11 g, 0.24 mmol) in CH_2Cl_2 (5 mL) was treated with molecular sieves (4 Å, 0.10 g) and *N*-methylmorpholine *N*-oxide (0.1 g, 0.84 mmol), and the mixture was stirred for 15 min. Then, tetrapropylammonium perruthenate (85 mg, 0.24 mmol) was added, and stirring was continued at ambient temperature for 30 min. The reaction mixture was diluted with diethyl ether, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to afford (*R*)-3-(4′-(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-**20a**) (0.10 g, 97%) $[\alpha]_D^{24}$ = −83 (*c* 0.072, CH_3OH). ee % = 92% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 7.3 Hz), 7.38 (t, 2H, *J* = 7.5 Hz), 7.32 (t, 1H, *J* = 7.3 Hz), 7.15 (d, 2H, *J* = 8.6 Hz), 6.92 (d, 2H, *J* = 8.6 Hz), 6.12 (s, 1H), 5.05 (s, 2H), 4.35 (dd, 1H, *J* = 11.3, 4.1 Hz), 4.18 (dd, 1H, *J* = 11.3, 7.5 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.19 (dd, 1H, *J* = 14.0, 4.3 Hz), 2.77 (m, 1H), 2.64 (dd, 1H, *J* = 14.0, 10.6 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 191.7, 158.6, 158.3, 157.6, 156.4, 137.2, 130.9, 130.7, 130.3, 128.7, 128.1, 127.6, 115.1, 105.8, 89.4, 70.2, 69.3, 61.3, 56.3, 56.2, 48.7, 32.0.

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HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{26}O_6$ 435.1808; found, 435.1803. T_R = 21 min (chiral ID, *n*-hexane/EtOH = 70:30).

(*R*)-3-(3′,4′-Bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-20b). A solution of (3*R*,4*R*)-3-(3′,4′-bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-ol ((3*R*,4*R*)-**21b**) (17 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) was treated with molecular sieves (4 Å, 13 mg) and *N*-methylmorpholine *N*-oxide (13 mg, 0.11 mmol), and the mixture was stirred for 15 min. Then, tetrapropylammonium perruthenate (11 mg, 0.03 mmol) was added, and stirring was continued at ambient temperature for 30 min. The reaction mixture was diluted with diethyl ether, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to afford (*R*)-3-(3′,4′-bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-**20b**) (69 mg, 93%) $[\alpha]_D^{24}$ = −87 (*c* 0.058, CH_3OH). ee % = 87% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 7.44 (dd, 4H, *J* = 7.1, 4.1 Hz), 7.35 (td, 4H, *J* = 7.5, 2.5 Hz), 7.30 (td, 2H, *J* = 7.2, 5.5 Hz), 6.86 (d, 1H, *J* = 8.2 Hz), 6.82 (d, 1H, *J* = 1.9 Hz), 6.74 (dd, 1H, *J* = 8.2, 1.9 Hz), 6.12 (s, 1H), 5.15 (s, 2H), 5.13 (s, 2H), 4.27 (dd, 1H, *J* = 11.3, 4.1 Hz), 4.08 (dd, 1H, *J* = 11.3, 7.5 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.14 (dd, 1H, *J* = 14.0, 4.3 Hz), 2.71 (m, 1H), 2.59 (dd, 1H, *J* = 14.0, 10.6 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 191.7, 158.6, 158.3, 156.4, 149.0, 147.8, 137.5, 137.3, 132.0, 130.7, 128.6, 127.9, 127.9, 127.6, 127.4, 122.3, 116.3, 115.5, 105.9, 89.3, 71.6, 71.5, 69.3, 61.3, 56.3, 56.2, 48.6, 32.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{33}H_{32}O_7$ 541.2226; found, 541.2222. T_R = 27 min (chiral ID, *n*-hexane/EtOH = 70:40).

(*R*)-3-(3′-(Benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-20c). A solution of (3*R*,4*R*)-3-(3′-(benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxy-chroman-4-ol ((3*R*,4*R*)-**21c**) (70 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was treated with molecular sieves (4 Å, 60 mg) and *N*-methylmorpholine *N*-oxide (60 mg, 0.51 mmol), and the mixture was stirred for 15 min. Then, tetrapropylammonium perruthenate (54 mg, 0.15 mmol) was added, and stirring was continued at ambient temperature for 20 min. The reaction mixture was diluted with diethyl ether, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to afford (*R*)-3-(3′-(benzyloxy)-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-**20c**) (69 mg, 99%) $[\alpha]_D^{24}$ = −57 (*c* 0.088, CH_3OH). ee % = 84% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 7.5 Hz), 7.34 (t, 2H, *J* = 7.5 Hz), 7.29−7.25 (m, 1H), 6.82 (d, 1H, *J* = 7.9 Hz), 6.77 (m, 2H), 6.11 (s, 1H), 5.12 (s, 2H), 4.25 (dd, 1H, *J* = 11.2, 3.7 Hz), 4.06 (dd, 1H, *J* = 11.2, 7.7 Hz), 3.93 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 3.76−3.76 (m, 1H), 3.12 (dd, 1H, *J* = 13.6, 3.8 Hz), 2.69 (m, 1H), 2.58 (dd, 1H, *J* = 13.6 10.9 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 191.6, 158.6, 158.3, 156.4, 148.5, 148.1, 137.1, 131.0, 130.6, 128.6, 127.9, 12 127.5, 122.0, 115.3, 112.0, 105.8, 89.3, 71.1, 69.2, 61.3, 56.3, 56.2, 56.1, 48.6, 32.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{28}O_7$ 465.1913; found, 465.1908. T_R = 24 min (chiral ID, *n*-hexane/EtOH = 70:40).

(*R*)-7-Methyl-3,9-dihydropunctatin ((*R*)-4). To a solution of (*R*)-3-(4-(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-**20a**) (32 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.23 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 40 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford (*R*)-7-methyl-3,9-dihydropunctation ((*R*)-**4**) (23 mg, 93%). $[\alpha]_D^{24}$ = −74 (*c* 0.068, CH_3OH). ee % = 86% ee. ^1H NMR (600 MHz, CD_3OD) δ 7.03 (d, 2H, *J* = 8.5 Hz), 6.70 (d, 2H, *J* = 8.5 Hz), 6.13 (s, 1H), 4.29 (dd, 1H, *J* = 11.4, 4.3 Hz), 4.14 (dd, 1H, *J* = 11.4, 7.3 Hz), 3.84 (s, 3H), 3.66 (s, 3H), 3.08 (dd, 1H, *J* = 14.0, 4.7 Hz), 2.83 (m, 1H), 2.64 (dd, 1H, *J* = 14.0, 10.1 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, CD_3OD) δ 199.8, 162.5, 161.3, 157.1, 154.9, 131.0, 130.2, 129.8, 116.2, 103.1, 93.6, 70.4, 61.3, 56.5, 48.0, 32.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}O_6$ 331.1181; found, 331.1181. T_R = 7.7 min (chiral IB, 0.1% diethanolamine (DEA) in *n*-hexane/EtOH = 70:30).

(*R*)-7-*O*-Methyl-3′-hydroxy-3,9-dihydropunctatin ((*R*)-5). To a solution of (*R*)-3-(3,4-bis(benzyloxy)benzyl)-5,7,8-trimethoxychroman-4-one ((*R*)-**20b**) (30 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) was added boron trichloride (0.16 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 90 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford (*R*)-7-*O*-methyl-3′-hydroxy-3,9-dihydropunctatin ((*R*)-**5**) (17 mg, 89%). $[\alpha]_D^{24}$ = −75 (*c* 0.066, CH_3OH). ee % = 95% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 12.02 (s, 1H), 6.78 (d, 1H, *J* = 8.0 Hz), 6.73 (d, 1H, *J* = 2.0 Hz), 6.63 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.08 (s, 1H), 5.54 (br s, 1H), 5.43 (br s, 1H), 4.32 (dd, 1H, *J* = 11.4, 4.2 Hz), 4.17 (dd, 1H, *J* = 11.5, 6.9 Hz), 3.87 (s, 3H), 3.76 (s, 3H), 3.08 (dd, 1H, *J* = 14.0, 4.6 Hz), 2.79 (m, 1H), 2.65 (dd, 1H, *J* = 14.0, 10.3 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 198.4, 161.5, 160.5, 153.8, 144.0, 142.6, 130.8, 129.4, 121.8, 116.3, 115.7, 102.5, 93.2, 69.5, 61.6, 56.4, 47.0, 32.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}O_7$ 347.1131; found, 347.1125. T_R = 26 min (chiral IG, 0.1% trifluoroacetic acid (TFA) in *n*-hexane/EtOH = 70:30).

(*R*)-7,4′-Di-*O*-methyl-3′-hydroxy-3,9-dihydropunctatin ((*R*)-6). To a solution of (*R*)-3-(3-(benzyloxy)-4-methoxybenzyl)-5,7,8-trimethoxy-chroman-4-one ((*R*)-**20c**) (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.16 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:1:0.1) to afford (*R*)-7,4′-di-*O*-methyl-3′-hydroxy-3,9-dihydropunctatin ((*R*)-**6**) (18 mg, 93%). $[\alpha]_D^{24}$ = −48 (*c* 0.10, CH_3OH). ee % = 75% ee. ^1H NMR (600 MHz, $CDCl_3$) δ 12.04 (s, 1H), 6.80 (d, 1H, *J* = 2.1 Hz), 6.78 (d, 1H, *J* = 8.2 Hz), 6.69 (dd, 1H, *J* = 8.2, 2.1 Hz), 6.09 (s, 1H), 5.62 (s, 1H), 4.34 (dd, 1H, *J* = 11.4, 4.3 Hz), 4.19 (dd, 1H, *J* = 11.4, 7.3 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 3.15 (dd, 1H, *J* = 14.0, 4.6 Hz), 2.87−2.82 (m, 1H), 2.67 (dd, 1H, *J* = 14.0, 10.4 Hz). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 198.3, 161.5, 160.4, 153.9, 145.9, 145.6, 131.1, 129.5, 120.8, 115.3, 110.9, 102.5, 93.2, 69.5, 61.5, 56.4, 56.2, 47.0, 32.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}O_7$ 361.1287; found, 361.1283. T_R = 12 min (chiral IB, 0.1% diethanolamine (DEA) in *n*-hexane/EtOH = 70:30).

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1-(4-(Benzyloxy)-2-hydroxy-3,6-dimethoxyphenyl)-ethan-1-one (26). First step: To an acetone (20 mL) solution of 1-(4-(benzyloxy)-6-hydroxy-2,3-dimethoxyphenyl)-ethan-1-one (**23**) (2.0 g, 6.6 mmol), 2.0 M in *t*-butyl methyl ether of solution iodomethane (3.6 mL, 7.3 mmol) and Cs_2CO_3 (4.3 g, 13 mmol) were added. The reaction mixture was refluxed for 12 h. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and saturated NH_4Cl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to afford 1-(4-(benzyloxy)-2,3,6-trimethoxyphenyl)-ethan-1-one (2.0 g, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.34 (d, J = 7.1 Hz, 1H), 6.29 (s, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 201.4, 154.0, 152.5, 151.4, 136.9, 136.7, 128.8, 128.3, 127.4, 119.1, 94.7, 71.4, 62.2, 61.3, 56.2, 32.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}O_5$ 317.1389; found, 317.1384. Second step: To a solution of 1-(4-(benzyloxy)-2,3,6-trimethoxyphenyl)ethan-1-one (1.1 g, 5.4 mmol) in CH_2Cl_2 (20 mL) was added boron trichloride (16 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/methanol = 1:5) to afford intermediates (**24** and **25**) (1.0 g, 90%). Third step: To an acetone (20 mL) solution of intermediates (**24** and **25**) (1.0 g, 4.8 mmol), benzyl bromide (0.6 mL, 5.3 mmol) and K_2CO_3 (1.3 g, 9.6 mmol) were added. The reaction mixture was refluxed for 2 h. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and saturated NH_4Cl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:2) to afford 1-(4-(benzyloxy)-2-hydroxy-3,6-dimethoxyphenyl)ethan-1-one (**26**) (1.0 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.82 (s, 1H), 7.43 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 5.97 (s, 1H), 5.22 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 203.9, 159.2, 158.8, 157.6, 136.4, 131.2, 128.8, 128.3, 127.3, 106.6, 88.6, 70.9, 60.9, 55.6, 33.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{18}O_5$ 303.1232; found, 303.1227.

7-(Benzyloxy)-5,8-dimethoxy-4*H*-chromen-4-one (27). To a solution of 1-(4-(benzyloxy)-2-hydroxy-3,6-dimethoxyphenyl)ethan-1-one (**26**) (1.0 g, 3.3 mmol) in DME (20 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (1.3 mL, 9.9 mmol). After stirring for 24 h at 80 °C, the mixture was cooled to 0 °C and c-HCl (5 mL) was added. After stirring for 1 h at 50 °C, the reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (ethyl acetate/CH_2Cl_2 = 1:3) to afford 7-(benzyloxy)-5,8-dimethoxy-4*H*-chromen-4-one (**27**) (0.97 g, 94%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 5.9 Hz), 7.45 (d, 2H, J = 7.4 Hz), 7.40 (t, 2H, J = 7.4 Hz), 7.35 (t, 1H, J = 7.3 Hz), 6.45 (s, 1H), 6.17 (d, 1H, J = 5.9 Hz), 5.26 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 176.9, 156.3, 155.6, 152.9, 152.5, 136.1, 131.2, 128.9, 128.6, 127.4, 114.2, 110.5, 94.7, 71.4, 61.8, 56.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{16}O_5$ 313.1076; found, 313.1071.

7-Hydroxy-5,8-dimethoxychroman-4-one (28). 7-(Benzyloxy)-5,8-dimethoxy-4*H*-chromen-4-one (**27**) (0.30 g, 0.96 mmol) and 10% Pd/C (0.01 g, 0.10 mmol) in anhydrous methanol (15 mL) were placed under an atmosphere of hydrogen. After stirring for 4 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/CH_2Cl_2 = 1:3) afforded 7-hydroxy-5,8-dimethoxychroman-4-one (**28**) (0.22 g, 99%). ^{1}H NMR (600 MHz, CD_3OD) δ 6.13 (s, 1H), 4.48 (t, 2H, J = 6.4 Hz), 3.78 (s, 3H), 3.74 (s, 3H), 2.69 (t, 2H, J = 6.4 Hz). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 191.9, 159.6, 159.3, 158.6, 130.6, 106.4, 94.0, 68.1, 61.3, 56.1, 39.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{12}O_5$ 225.0763; found, 225.0759.

5,7-Dihydroxy-8-methoxychroman-4-one (7). To a solution of 7-hydroxy-5,8-dimethoxy-chroman-4-one (**28**) (30 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added boron trichloride (0.4 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to afford 5,7-dihydroxy-8-methoxychroman-4-one (**7**) (27 mg, 96%). ^{1}H NMR (600 MHz, dimethyl sulfoxide (DMSO)-d_6) δ 11.95 (s, 1H), 10.64 (s, 1H), 5.93 (s, 1H), 4.49 (t, 2H, J = 6.4 Hz), 3.62 (s, 3H), 2.77 (t, 2H, J = 6.4 Hz). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 196.4, 159.8, 158.7, 154.6, 128.3, 102.1, 95.7, 66.7, 60.4, 35.9. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_{10}O_5$ 211.0606; found, 211.0601.

7-(Benzyloxy)-5,8-dimethoxychroman-4-one. To an acetone (10 mL) solution of 7-hydroxy-5,8-dimethoxychroman-4-one (**28**) (0.21 g, 0.94 mmol), benzyl bromide (0.1 mL, 1.0 mmol) and K_2CO_3 (0.39 g, 2.8 mmol) were added. The reaction mixture was refluxed for 48 h. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and saturated NH_4Cl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to afford 7-(benzyloxy)-5,8-dimethoxychroman-4-one (0.25 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 7.3 Hz), 7.38 (m, 2H), 7.32 (m, 1H), 6.12 (s, 1H), 5.20 (s, 2H), 4.50 (t, 2H, J = 6.4 Hz), 3.81 (s, 3H), 3.79 (s, 3H), 2.71 (t, 2H, J = 6.4 Hz). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 189.4, 157.8, 157.7, 156.8, 136.2, 131.3, 128.8, 128.4, 127.3, 106.9, 91.2, 70.9, 67.2, 61.3, 56.2, 38.9. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{18}O_5$ 315.1232; found, 315.1230.

(*E*)-7-(Benzyloxy)-3-(4′-(benzyloxy)benzylidene)-5,8-dimethoxychroman-4-one (29a). To a solution of 7-(benzyloxy)-5,8-dimethoxychroman-4-one (0.10 g, 0.32 mmol) in toluene (8 mL) were added 4-benzyloxybenzaldehyde (0.11 g, 0.49 mmol) and *p*-toluenesulfonic acid (5.5 mg, 0.03 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/

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CH_2Cl_2 = 1:3) to afford (*E*)-7-(benzyloxy)-3-(4′-(benzyloxy)-benzylidene)-5,8-dimethoxychroman-4-one (**29a**) (69 mg, 43%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.44 (d, 4H, J = 7.8 Hz), 7.40−7.39 (m, 4H), 7.34−7.33 (m, 2H), 7.25 (d, 2H, J = 8.7 Hz), 7.02 (d, 2H, J = 8.7 Hz), 6.20 (s, 1H), 5.31 (d, 2H, J = 1.6 Hz), 5.23 (s, 2H), 5.11 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 180.0, 159.7, 158.2, 157.6, 156.2, 136.6, 136.3, 136.1, 131.9, 131.6, 130.2, 128.9, 128.8, 128.4, 128.3, 127.7, 127.6, 127.4, 115.2, 108.1, 92.2, 71.1, 70.2, 68.1, 61.5, 56.4. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{32}H_{28}O_6$ 509.1964; found, 509.1961.

(*E*)-7-(Benzyloxy)-5,8-dimethoxy-3-(4′-methoxybenzylidene)chroman-4-one (29b). To a solution of 7-(benzyloxy)-5,8-dimethoxychroman-4-one (50 mg, 0.16 mmol) in toluene (5 mL) were added 4-methoxybenzaldehyde (0.03 mL, 0.24 mmol) and *p*-toluenesulfonic acid (2.8 mg, 0.02 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/CH_2Cl_2 = 1:5) to afford (*E*)-7-(benzyloxy)-5,8-dimethoxy-3-(4′-methoxybenzylidene)chroman-4-one (**29b**) (34 mg, 49%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.44 (d, 2H, J = 7.3 Hz), 7.41−7.39 (m, 2H), 7.35−7.33 (m, 1H), 7.26−7.25 (m, 2H), 6.95 (d, 2H, J = 8.7 Hz), 6.20 (s, 1H), 5.31 (d, 1H, J = 1.7 Hz), 5.23 (s, 1H), 3.85 (s, 1H), 3.85 (s, 1H), 3.81 (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 180.1, 160.6, 158.2, 157.5, 156.2, 136.3, 136.2, 131.9, 131.6, 130.1, 128.9, 128.4, 127.5, 127.4, 114.3, 108.1, 92.3, 71.1, 68.1, 61.5, 56.4, 55.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{26}H_{24}O_6$ 433.1651; found, 433.1649.

(*E*)-7-(Benzyloxy)-3-(3′,4′-bis(benzyloxy)-benzylidene)-5,8-dimethoxychroman-4-one (29c). To a solution of 7-(benzyloxy)-5,8-dimethoxychroman-4-one (0.10 g, 0.32 mmol) in toluene (8 mL) were added 3,4-bis(benzyloxy)benzaldehyde (0.15 g, 0.48 mmol) and *p*-toluenesulfonic acid (6.2 mg, 0.04 mmol) at 0 °C. The reaction mixture was refluxed for 13 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/CH_2Cl_2 = 1:3:0.1) to afford (*E*)-7-(benzyloxy)-3-(3′,4′-bis(benzyloxy)-benzylidene)-5,8-dimethoxychroman-4-one (**29c**) (0.10 g, 51%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.46−7.43 (m, 6H), 7.42−7.37 (m, 6H), 7.34−7.30 (m, 3H), 6.95 (d, 1H, J = 8.8 Hz), 6.84−6.82 (m, 2H), 6.19 (s, 1H), 5.22 (s, 2H), 5.21 (s, 2H) 5.18 (s, 2H), 5.15 (d, 2H, J = 1.6 Hz), 3.83 (s, 3H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 179.8, 158.1, 157.5, 156.1, 150.1, 148.6, 137.0, 136.8, 136.3, 136.1, 131.5, 130.4, 128.8, 128.7, 128.7, 128.4, 128.1, 128.1, 127.3, 127.3, 124.2, 116.9, 114.3, 107.9, 92.2, 71.5, 71.1, 71.0, 67.9, 61.4, 56.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{39}H_{34}O_7$ 615.2383; found, 615.2379.

(*E*)-7-(Benzyloxy)-3-(3′-(benzyloxy)-4′-methoxybenzylidene)-5,8-dimethoxychroman-4-one (29d). To a solution of 7-(benzyloxy)-5,8-dimethoxychroman-4-one (0.27 g, 0.87 mmol) in toluene (15 mL) were added 3-(benzyloxy)-4-methoxybenzaldehyde (0.32 mg, 1.3 mmol) and *p*-toluenesulfonic acid (14 mg, 0.09 mmol) at 0 °C. The reaction mixture was refluxed for 13 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane/CH_2Cl_2 = 1:1:0.1) to afford (*E*)-7-(benzyloxy)-3-(3′-(benzyloxy)-4′-methoxybenzylidene)-5,8-dimethoxychroman-4-one (**29d**) (0.26 g, 56%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.46−7.43 (m, 4H), 7.41−7.38 (m, 4H), 7.36−7.30 (m, 2H), 6.93 (d, 1H, J = 8.4 Hz), 6.89 (dd, 1H, J = 8.4, 1.8 Hz), 6.79 (d, 1H, J = 1.8 Hz), 6.19 (s, 1H), 5.23 (s, 2H), 5.18 (s, 2H), 5.14 (d, 2H, J = 1.7 Hz), 3.94 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 179.9, 158.2, 157.5, 156.2, 150.9, 148.0, 136.9, 136.3, 136.3, 131.6, 130.3, 128.9, 128.8, 128.4, 128.2, 127.6, 127.4, 127.3, 124.2, 115.9, 111.6, 108.0, 92.2, 71.3, 71.1, 67.9, 61.5, 56.4, 56.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{33}H_{30}O_7$ 539.2070; found, 539.2071.

Punctatin (8). To a solution of (*E*)-7-(benzyloxy)-3-(4′-(benzyloxy)benzylidene)-5,8-dimethoxychroman-4-one (**29a**) (30 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.18 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/CH_2Cl_2 = 1:3) to afford punctatin (**8**) (9.1 mg, 49%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.62 (s, 1H), 10.74 (br s, 1H), 10.17 (br s, 1H), 7.69 (s, 1H), 7.35 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.6 Hz), 5.99 (s, 1H), 5.41 (d, 3H, J = 1.4 Hz), 3.63 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 184.6, 160.1, 159.5, 159.5, 153.4, 136.9, 132.9, 128.3, 126.1, 124.7, 115.8, 101.8, 96.2, 67.4, 60.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{14}O_6$ 315.0869; found, 315.0865.

4′-*O*-Methylpunctatin (9). To a solution of (*E*)-7-(benzyloxy)-5,8-dimethoxy-3-(4-methoxybenzylidene)-chroman-4-one (**29b**) (34 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.25 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/CH_2Cl_2 = 1:3) to afford 4′-*O*-methylpunctatin (**9**) (11 mg, 42%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.58 (s, 1H), 10.77 (br s, 1H), 7.73 (s, 1H), 7.45 (d, 2H, J = 8.7 Hz), 7.06 (d, 2H, J = 8.8 Hz), 5.99 (s, 1H), 5.41 (d, 2H, J = 1.8 Hz), 3.83 (s, 3H), 3.63 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 184.6, 160.7, 160.2, 159.6, 153.4, 136.4, 132.6, 128.4, 127.1, 126.2, 114.4, 101.9, 96.2, 67.4, 60.5, 55.4. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{16}O_6$ 329.1025; found, 329.1025.

3-(3′,4′-Dihydroxybenzylidene)-5,7-dihydroxy-8-methoxychroman-4-one (10). To a solution of (*E*)-7-(benzyloxy)-3-(3,4-bis(benzyloxy)benzylidene)-5,8-dimethoxy-chroman-4-one (**29c**) (45 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.37 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 3 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/CH_2Cl_2 = 1:3) to afford 3-(3′,4′-dihydroxybenzylidene)-5,7-dihydroxy-8-methoxychroman-4-one (**10**) (14 mg, 60%). ^{1}H NMR (600 MHz, CD_3OD) δ 12.58 (s, 1H), 7.69 (s, 1H), 6.87 (d, 1H, J = 8.2 Hz), 6.84 (d, 1H, J = 2.0 Hz), 6.78 (dd, 1H, J = 8.2, 2.0 Hz), 5.96 (s, 1H), 5.39 (d, 2H, J = 1.7 Hz), 3.74 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 186.6, 161.6, 161.2, 154.9, 149.1, 146.7, 138.8, 129.7, 128.0, 127.5, 124.8, 118.4, 116.6, 103.6, 97.3,

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69.0, 61.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}O_7$ 331.0818; found, 331.0813.

7-Hydroxy-3-(4′-hydroxybenzyl)-5,8-dimethoxychroman-4-one (30). (*E*)-7-(Benzyloxy)-3-(4-(benzyloxy)-benzylidene)-5,8-dimethoxychroman-4-one (**29a**) (21 mg, 0.04 mmol) and 10% Pd/C (1.5 mg, 0.01 mmol) in methanol/dichloromethane (1 mL, 1 mL) were placed under an atmosphere of hydrogen. After stirring for 3 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) afforded 7-hydroxy-3-(4′-hydroxybenzyl)-5,8-dimethoxychroman-4-one (**30**) (12 mg, 91%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.05 (d, 2H, J = 8.4 Hz), 6.73 (d, 2H, J = 8.4 Hz), 6.14 (s, 1H), 4.31 (dd, 1H, J = 11.3, 3.9 Hz), 4.16 (dd, 1H, J = 11.3, 6.6 Hz), 3.79 (s, 3H), 3.74 (s, 3H), 3.03 (dd, 1H, J = 13.3, 4.2 Hz), 2.70−2.66 (m, 1H), 2.63 (dd, 1H, J = 13.3, 10.2 Hz). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 194.0, 159.7, 159.0, 158.1, 157.1, 131.2, 130.4, 116.4, 105.6, 94.1, 70.2, 61.4, 56.2, 49.8, 33.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}O_6$ 331.1181; found, 331.1181.

7-Hydroxy-3-(3′-hydroxy-4′-methoxybenzyl)-5,8-dimethoxychroman-4-one (31). (*E*)-7-(Benzyloxy)-3-(3-(benzyloxy)-4-methoxybenzylidene)-5,8-dimethoxychroman-4-one (**29d**) (0.10 mg, 0.19 mmol) and 10% Pd/C (6.0 mg, 0.06 mmol) in methanol/dichloromethane (3 mL, 3 mL) were placed under an atmosphere of hydrogen. After stirring for 1 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) afforded 7-hydroxy-3-(3′-hydroxy-4′-methoxybenzyl)-5,8-dimethoxychroman-4-one (**31**) (67 mg, 98%). ^{1}H NMR (600 MHz, CD_3OD) δ 6.85 (d, 1H, J = 8.2 Hz), 6.71 (d, 1H, J = 2.0 Hz), 6.67 (dd, 1H, J = 8.2, 2.0 Hz), 6.14 (s, 1H), 4.31 (dd, 1H, J = 11.3, 4.0 Hz), 4.16 (dd, 1H, J = 11.3, 6.8 Hz), 3.82 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.01 (dd, 1H, J = 13.7, 4.6 Hz), 2.71−2.67 (m, 1H), 2.60 (dd, 1H, J = 13.7, 10.3 Hz). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 193.9, 159.7, 159.1, 158.1, 147.8, 147.7, 132.6, 130.4, 121.4, 117.1, 112.9, 105.6, 94.1, 70.2, 61.4, 56.4, 56.2, 49.7, 33.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}O_7$ 361.1287; found, 361.1284.

(*E*)-3-(4′-Hydroxybenzylidene)-5,7,8-trimethoxychroman-4-one (32a). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.19 (d, 2H, J = 8.3 Hz), 6.94 (d, 2H, J = 8.3 Hz), 6.45 (s, 1H), 6.17 (s, 1H), 5.30 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 180.4, 158.7, 158.7, 157.5, 156.1, 136.8, 132.1, 131.0, 129.7, 127.1, 116.0, 107.6, 90.1, 68.0, 61.5, 56.4, 56.2.

(*E*)-7-Hydroxy-3-(4′-hydroxybenzylidene)-5,8-dimethoxychroman-4-one (32b). ^{1}H NMR (600 MHz, CD_3OD) δ 7.71 (s, 1H), 7.24 (d, 2H, J = 8.5 Hz), 6.88 (d, 2H, J = 8.5 Hz), 6.20 (s, 1H), 5.30 (d, 2H, J = 1.7 Hz), 3.82 (s, 3H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 180.4, 159.0, 158.5, 157.6, 156.3, 136.3, 131.9, 129.4, 129.2, 125.8, 115.3, 106.0, 93.4, 67.5, 60.2, 54.8.

(*E*)-7-Hydroxy-5,8-dimethoxy-3-(4′-methoxybenzylidene)chroman-4-one (32c). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.39 (s, 1H), 7.55 (s, 1H), 7.38 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 6.20 (s, 1H), 5.27 (d, 2H, J = 1.6 Hz), 3.82 (s, 3H), 3.73 (s, 3H), 3.63 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 177.9, 160.1, 157.5, 156.8, 155.9, 134.1, 132.0, 130.3, 129.3, 126.7, 114.3, 106.1, 94.2, 67.5, 60.6, 55.7, 55.3.

3-(4′-(Benzyloxy)benzyl)-5-hydroxy-7,8-dimethoxychroman-4-one (33a). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.06 (s, 1H), 7.44 (d, 2H, J = 7.5 Hz), 7.39 (t, 2H, J = 7.5 Hz), 7.33 (t, 1H, J = 7.3 Hz), 7.16 (d, 2H, J = 8.6 Hz), 6.94 (d, 2H, J = 8.6 Hz), 6.11 (s, 1H), 5.06 (s, 2H), 4.36 (dd, 1H, J = 11.5, 4.2 Hz), 4.21 (dd, 1H, J = 11.5, 7.1 Hz), 3.89 (s, 3H), 3.78 (s, 3H), 3.18 (dd, 1H, J = 14.0, 4.5 Hz), 2.85 (m, 1H), 2.74 (dd, 1H, J = 14.0, 10.3 Hz). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 198.3, 161.4, 160.4, 157.8, 153.8, 137.1, 130.3, 130.1, 129.5, 128.7, 128.1, 127.6, 115.2, 102.5, 93.1, 70.2, 69.5, 61.5, 56.4, 47.1, 32.1.

3-(3′,4′-Bis(benzyloxy)benzyl)-5-hydroxy-7,8-dimethoxychroman-4-one (33b). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.04 (s, 1H), 7.44 (d, 4H, J = 7.7 Hz), 7.36 (td, 4H, J = 7.4, 4.1 Hz), 7.30 (dd, 2H, J = 14.3, 7.1 Hz), 6.88 (d, 1H, J = 8.2 Hz), 6.80 (d, 1H, J = 2.0 Hz), 6.74 (dd, 1H, J = 8.2, 2.0 Hz), 6.10 (s, 1H), 5.15 (d, 4H, J = 4.9 Hz), 4.27 (dd, 1H, J = 11.5, 4.2 Hz), 4.09 (dd, 1H, J = 11.5, 7.3 Hz), 3.89 (s, 3H), 3.77 (s, 3H), 3.12 (dd, 1H, J = 14.0, 4.4 Hz), 2.79 (m, 1H), 2.68 (dd, 1H, J = 14.0, 10.2 Hz).

3-(3′-(Benzyloxy)-4′-methoxybenzyl)-5-hydroxy-7,8-dimethoxychroman-4-one (33c). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.04 (s, 1H), 7.43 (d, 2H, J = 7.5 Hz), 7.36 (t, 2H, J = 7.6 Hz), 7.29 (t, 1H, J = 7.4 Hz), 6.84 (d, 1H, J = 8.1 Hz), 6.78 (dd, 1H, J = 8.1, 1.9 Hz), 6.75 (d, 1H, J = 1.9 Hz), 6.10 (s, 1H), 5.14 (s, 2H), 4.27 (dd, 1H, J = 11.5, 4.2 Hz), 4.09 (dd, 1H, J = 11.5, 7.3 Hz), 3.89 (s, 3H), 3.88 (s, 3H), 3.78 (s, 3H), 3.11 (dd, 1H, J = 13.9, 4.4 Hz), 2.78 (m, 1H), 2.69 (dd, 1H, J = 13.9, 10.1 Hz). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 198.2, 161.5, 160.4, 153.8, 148.8, 148.2, 137.1, 130.2, 129.5, 128.7, 128.0, 127.5, 122.1, 115.4, 112.1, 102.5, 93.1, 71.2, 69.4, 61.5, 56.4, 56.2, 46.9, 32.4.

3-(3′-Hydroxy-4′-methoxybenzyl)-5,7,8-trimethoxychroman-4-one (33d). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.78 (d, 1H, J = 8.1 Hz), 6.71 (d, 1H, J = 8.1 Hz), 6.12 (s, 1H), 5.59 (s, 1H), 4.35 (dd, 1H, J = 11.2, 3.6 Hz), 4.18 (dd, 1H, J = 10.8, 8.0 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.18 (dd, J = 14.0, 4.0 Hz, 1H), 2.78 (m, 1H), 2.58 (dd, J = 14.0, 10.5 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 191.6, 158.5, 158.2, 156.3, 145.6, 145.3, 131.8, 130.6, 120.6, 115.2, 110.8, 105.7, 89.2, 69.3, 61.2, 56.2, 56.1, 56.0, 48.5, 32.1.

3,9-Dihydropunctatin (11). To a solution of 7-hydroxy-3-(4′-hydroxybenzyl)-5,8-dimethoxy-chroman-4-one (**30**) (17 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.15 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to afford 3,9-dihydropunctatin (**11**) (8.0 mg, 50%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.96 (s, 1H), 10.68 (s, 1H), 9.26 (s, 1H), 7.03 (d, 2H, J = 8.4 Hz), 6.69 (d, 2H, J = 8.4 Hz), 5.94 (s, 1H), 4.31 (dd, 1H, J = 11.3, 4.4 Hz), 4.13 (dd, 1H, J = 11.4, 7.9 Hz), 3.60 (s, 3H), 3.00 (dd, 1H, J = 13.7, 5.0 Hz), 2.98−2.93 (m, 1H), 2.61 (dd, 1H, J = 13.7, 9.3 Hz). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 198.0, 159.8, 158.8, 155.9, 154.3, 130.0, 128.2, 128.0, 115.2, 101.3, 95.9, 69.1, 60.4, 45.6, 31.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}O_6$ 317.1025; found, 317.1019.

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5,6-Dihydroxy-3-(3′-hydroxy-4′-methoxybenzyl)-8-methoxychroman-4-one (12). To a solution of 7-hydroxy-3-(3′-hydroxy-4′-methoxybenzyl)-5,8-dimethoxy-chroman-4-one (**31**) (20 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added boron trichloride (0.16 mL, 1.0 M solution in CH_2Cl_2) at −78 °C. After stirring for 3 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to afford 5,6-dihydroxy-3-(3′-hydroxy-4′-methoxybenzyl)-8-methoxychroman-4-one (**12**) (8.1 mg, 42%). ^{1}H NMR (600 MHz, CD_3OD) δ 6.86 (d, 1H, J = 8.2 Hz), 6.72 (d, 1H, J = 2.1 Hz), 6.68 (dd, 1H, J = 8.2, 2.1 Hz), 5.94 (s, 1H), 4.33 (dd, 1H, J = 11.4, 4.3 Hz), 4.17 (dd, 1H, J = 11.4, 7.2 Hz), 3.83 (s, 3H), 3.73 (s, 3H), 3.08 (dd, 1H, J = 13.9, 4.7 Hz), 2.86−2.82 (m, 1H), 2.65 (dd, 1H, J = 13.9, 10.2 Hz). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 199.5, 161.1, 161.1, 155.7, 147.9, 147.7, 132.2, 129.6, 121.4, 117.1, 112.9, 102.9, 97.0, 70.6, 61.5, 56.4, 47.9, 33.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{18}O_7$ 347.1131; found, 347.1125.

3-(4-Hydroxybenzyl)-5,8-dimethoxychroman-7-ol (14). (*E*)-7-(Benzyloxy)-3-(4-(benzyloxy)benzylidene)-5,8-dimethoxychroman-4-one (**29a**) (30 mg, 0.06 mmol), and 10% Pd/C (1.8 mg, 0.006 mmol) in methanol (2 mL) were placed under an atmosphere of hydrogen. After stirring for 3 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) afforded 3-(4-hydroxybenzyl)-5,8-dimethoxychroman-7-ol (**14**) (17 mg, 93%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.01 (d, 2H, J = 8.5 Hz), 6.72 (d, 2H, J = 8.5 Hz), 6.03 (s, 1H), 4.11 (ddd, 1H, J = 10.5, 3.0, 1.5 Hz), 3.71−3.69 (m, 4H), 3.68 (s, 3H), 2.61 (ddd, 1H, J = 16.3, 5.4, 1.5 Hz), 2.58−2.49 (m, 2H), 2.18 (dd, 1H, J = 16.3, 8.5 Hz), 2.14−2.07 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 156.8, 155.1, 149.6, 149.4, 131.7, 131.0, 130.8, 116.2, 103.8, 92.4, 70.78, 61.2, 55.8, 38.2, 35.2, 26.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}O_5$ 317.1389; found, 317.1386.

3-(4-Hydroxybenzyl)-7,8-dimethoxychroman-5-ol (34). 7-*O*-Methoxypunctatin (**2**) (10 mg, 0.03 mmol) and 10% Pd/C (1.4 mg, 0.01 mmol) in methanol (2 mL) were placed under an atmosphere of hydrogen. After stirring for 24 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) afforded 3-(4-hydroxybenzyl)-7,8-dimethoxychroman-5-ol (**34**) (3.4 mg, 35%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.03 (d, 2H, J = 8.4 Hz), 6.73 (d, 2H, J = 8.4 Hz), 6.06 (s, 1H), 4.13 (ddd, 1H, J = 10.4, 2.7, 1.2 Hz), 3.75 (s, 3H), 3.76−3.71 (m, 1H), 3.67 (s, 3H), 2.67 (ddd, 1H, J = 16.3, 5.4, 1.1 Hz), 2.56 (m, 2H), 2.24 (dd, 1H, J = 16.3, 8.5 Hz), 2.16−2.09 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 156.6, 152.3, 152.2, 149.6, 131.5, 131.1, 130.8, 115.9, 103.8, 92.9, 70.6, 61.1, 56.1, 38.0, 35.0, 26.2.

3-(4-Hydroxybenzyl)-5,7-dimethoxychroman-8-ol (36). First step: (*E*)-3-(4-(benzyloxy)benzylidene)-5,7,8-trimethoxychroman-4-one (**19a**) (0.15 g, 0.35 mmol) and 10% Pd/C (14 mg, 0.13 mmol) in methanol (6 mL) were placed under an atmosphere of hydrogen. After stirring for 24 h, the mixture was filtered through a Celite pad. After the filtrate was concentrated under reduced pressure, purification of the residue via flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) afforded 4-((5,7,8-trimethoxychroman-3-yl)methyl)phenol (**35**) (0.10 g, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, 2H, J = 8.2 Hz), 6.77 (d, 2H, J = 8.5 Hz), 6.09 (s, 1H), 5.07 (br s, 1H), 4.21 (ddd, 1H, J = 10.5, 3.0, 1.6 Hz), 3.86 (s, 3H), 3.79 (s, 3H), 3.79−3.74 (m, 4H), 2.72 (ddd, 1H, J = 16.3, 5.3, 1.6 Hz), 2.59 (d, 2H, J = 7.2 Hz), 2.26 (dd 1H, J = 16.3, 8.6 Hz,), 2.23−2.16 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.2, 153.6, 151.4, 148.9, 131.6, 130.2, 115.4, 104.4, 88.9, 70.0, 61.2, 56.5, 55.7, 37.5, 33.7, 25.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{22}O_5$ 331.1545; found, 331.1540. Second step: To a solution of 4-((5,7,8-trimethoxychroman-3-yl)methyl)phenol (**35**) (0.10 g, 0.31 mmol) in CH_2Cl_2 (3 mL) was added boron trichloride (1.0 mL, 1.0 M solution in CH_2Cl_2) at 0 °C. After stirring for 3 h at ambient temperature, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to afford 3-(4-hydroxybenzyl)-5,7-dimethoxychroman-8-ol (**36**) (67 mg, 68%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.02 (d, 2H, J = 8.4 Hz), 6.72 (d, 2H, J = 8.4 Hz), 6.20 (s, 1H), 4.15 (ddd, 1H, J = 10.5, 2.9, 1.5 Hz), 3.82 (s, 3H), 3.73 (s, 3H), 3.75−3.70 (m, 1H), 2.66 (ddd, 1H, J = 16.5, 5.4, 1.3 Hz), 2.58−2.52 (m, 2H), 2.22 (dd, 1H, J = 16.5, 8.7 Hz), 2.12 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 156.8, 151.7, 147.2, 144.9, 131.7, 131.0, 129.6, 116.2, 105.4, 90.6, 70.9, 57.0, 56.2, 38.3, 35.3, 26.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00932.

^{1}H and ^{13}C{^{1}H} NMR spectral data and HPLC analysis for synthesized chiral compounds; 2D NMR (HMBC) of **14**, **34**, and **36** (PDF)

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Notes

The authors declare no competing financial interest.

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