Synthesis of Chroman Derivatives by the Ring Expansion Reaction of Spirodienones, and an Assessment of their Plant Growth Inhibition

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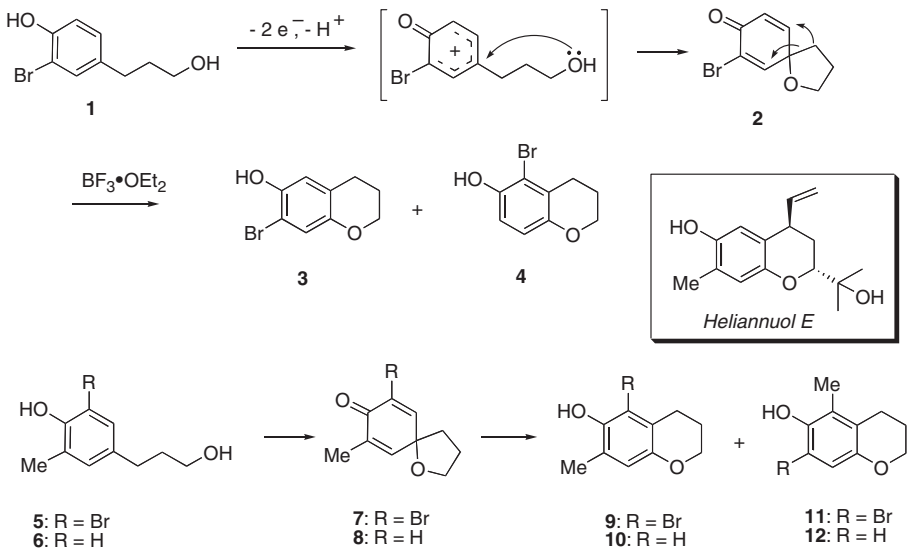
Lewis acid-promoted 1,2-shift rearrangement reactions of the spirodienones, generated by the anodic oxidation of phenol derivatives, provided corresponding chromans. In addition to steric repulsion, electron-donating or withdrawing characteristics of the arylic substituents controlled the direction of the rearrangements. The plant growth inhibitory activity of several chroman derivatives was evaluated. In contrast to apparent inhibitions of **21c** and **22c** against both cress and oat, the selective activity against coleoptile and root of oat was observed in **21a**, **21b**, and **22d**. Interestingly, the regioisomer **22b** of **21b** showed no activity.

During our extensive electrochemical approach towards the synthesis of a wide range of biologically active substances,[1] it was observed that the spirodienone derivative **2**, generated by anodic oxidation of the corresponding monobromophenol **1**, was converted under $BF_3 \cdot OEt_2$ conditions into chromans **3** and **4** (Scheme 1).[2] To apply this series of anodic oxidation and the following 1,2-rearrangement reactions to the synthesis of heliannuol E, an allelochemical of sunflower, *Helianthus annuus* L. cv.,[3] the bromomethyl and methyl derivatives, **5** and **6**, were submitted to anodic oxidation. Whereas **6** provided the spiro compound **8** in 20% yield, the bromo-spiro derivative **7** was produced in 50% yield, and the following rearrangement gave a mixture of **9** and **11** in 33 and 6% yields, respectively.[4a] Based on a preferential production of **9** carrying the same methyl substitution as that of heliannuol E, the phenol derivatives carrying a bromine substituent (type-**5**), which was considered to regulate the oxidation potential as well as the reaction-mode,[1] was employed for the synthesis of natural products.[4] In addition, despite its low yield, treatment of **8** with $BF_3 \cdot OEt_2$ underwent high rearrangement selectivity to give the corresponding chromans **10** in 62% yield,[5] as well as a trace amount of **12**.[6]

At the outset, the direction of this rearrangement reaction (ex. **2** → **3**, **4**) was considered to be the opposite side of such bulky substituents as methyl and bromo groups to avoid steric repulsion.[2b] However, as mentioned above, the ratio of the chroman-isomers produced, depended on the substituents at the *ortho* positions of the phenol groups; the methyl derivative



Scheme 1. Synthesis of the spirodienones, and its conversion into the chroman derivatives.

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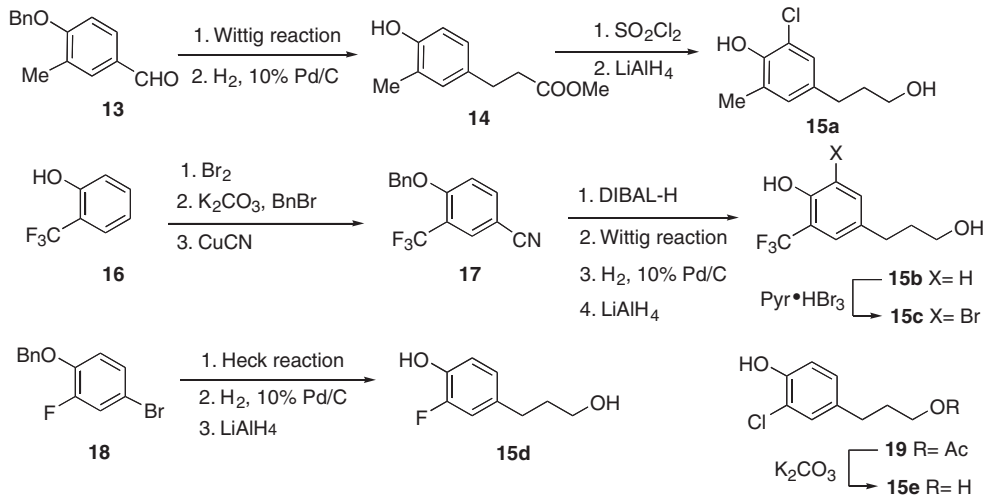
8 provided **10** with high selectivity, while a nearly equal product distribution (**3**/**4** = 3:2 at 0 °C, ca. 1:1 at room temperature) was observed in the case of the bromophenol **1**.[2b] To understand the perspective of the rearrangement to the chroman derivatives under the $BF_3 \cdot OEt_2$ conditions, the effect of substituents should be inspected by utilizing several spirodienones synthesized from the *p*-(3-hydroxypropyl)phenol derivatives. In a previous paper,[5] we assessed the plant growth inhibitory activity of heliannuol congeners possessing chroman or benzooxepin skeletons. Among them, **9**–**11** carrying relatively simple or bromine-containing structures, exhibited activities in 10^{-3}–10^{-4} M (1 M = 1 mol dm^{-3}) concentrations against hypocotyl and the root of cress, as well as coleoptile and the root of oat. Against such a background, several chromans synthesized in this investigation were submitted to biological assessments to acquire further structure–activity relationships of the growth-inhibitory activity of the chroman derivatives against cress and oat. We describe herein the investigation process.

Results and Discussion

Spirodienones **20a**–**e**, substrates for the rearrangement examination, were synthesized by the anodic oxidation of the corresponding phenols, **15a**–**e**. The phenol derivative carrying a methyl substituent **15a** was produced from the known aldehyde **13**[7] by a carbon-chain elongation reaction, and concomitant hydrogenolysis (**14**[8]) and halogenation at an appropriate step (Scheme 2). Trifluoromethyl and fluoro derivatives (**15b**, **15c**, and **15d**) were prepared by essentially the same procedure as in the case of **15a**, starting from **16** through its benzaldehyde derivative, obtained by reduction of **17**,[9] and from **18**.[10] The chlorine derivative **15e** was produced from **19**.[11]

When **15a** was submitted to constant current electrolysis conditions (30 mA, 3.0 F/mol in $MeNO_2$), the spirodienone **20a** was produced in 51% yield (Table 1). Although the oxidation of **15a** and **15e** gave the corresponding spirodienones in moderate yields, **15b**, **15c**, and **15d** provided **20b**, **20c**, and



Scheme 2. Synthesis of **15a**–**15e**.

Table 1. Synthesis of the Spirodienones **20a**–**20e**

Entry	Compound	R	X	Condition[a)]	Yield/%	
1	**5**	Me	Br	CCE	**7**	78[b)]
2	**6**	Me	H	CCE	**8**	36[b)]
3	**15a**	Me	Cl	CCE	**20a**	51
4	**15b**	CF_3	H	CCE	**20b**	4
5				PIFA		47
6	**15c**	CF_3	Br	CCE	**20c**	38
7				PIFA		65
8	**15d**	H	F	CCE	**20d**	35
9				PIFA		61
10	**15e**[c)]	H	Cl	CCE	**20e**	68

a) In CCE conditions, $MeNO_2$ (solvent) and *n*-Bu_4NClO_4 as supporting salts were used. b) Upon using dioxane–60% aq $HClO_4$ for **5** and acetone for **6** as solvents, **7** and **8** were obtained in 50 (Ref. 4a) and 20% (Ref. 5) yields, respectively. c) Ref. 11.

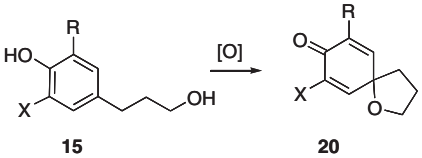
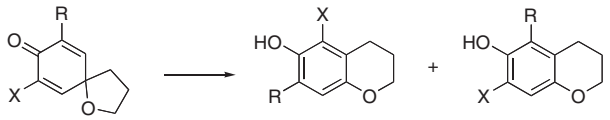


Table 2. Synthesis of the Chromans

Entry[a)]	Compound	R	X	Temperature	Time	Yield/%	(Product ratio)
1	**20a**	Me	Cl	rt	1.5 h	**21a**/**22a**	42 (2:1)
2	**20b**	CF_3	H	rt	1 h	**21b**/**22b**	quant (1:2.3)
3	**20c**	CF_3	Br	reflux	3 h	**21c**/**22c**	65 (1:2.6)
4				rt	2 d		74 (1:1.5)
5	**20d**	H	F	rt	20 min	**21d**/**22d**	63 (0:1)
6	**20e**	H	Cl	rt	25 min	**21e**/**22e**	59 (1:9)
7	**7**	Me	Br	rt	3 h	**9**/**11**	39 (5:1)[c)]
8	**8**	Me	H	rt	20 min	**10**/**12**	62 (1:trace)[d)]

a) CH_2Cl_2 was used as a reaction solvent. b) The ratios were determined by comparison of integrations of the ^{1}H NMR spectra. c) Ref. 4a. d) Ref. 5.



20a-e **21a-e** **22a-e**

Table 3. Inhibitory Activity of the Chroman Derivatives on the Growth of Cress and Oat Seedlings

	EC_{50}[a)]/M			
	Cress		Oat	
Compounds	Hypocotyl	Root	Coleoptile	Root
21a	1.0×10^{-3}	7.0×10^{-4}	$>10^{-2}$	6.8×10^{-3}
21b	7.5×10^{-4}	1.0×10^{-3}	8.0×10^{-3}	—
21c	9.9×10^{-4}	2.9×10^{-3}	2.6×10^{-3}	1.5×10^{-3}
22b	—	—	$>10^{-2}$	—
22c	9.0×10^{-4}	1.8×10^{-3}	1.0×10^{-3}	2.9×10^{-3}
22d	1.2×10^{-3}	9.0×10^{-4}	—	1.3×10^{-3}
(±)-Heliannuol E	8.4×10^{-4}	1.5×10^{-3}	8.2×10^{-4}	$>10^{-2}$

a) EC_{50} represents the concentration of samples, which cause 50% inhibition of the shoot and root growth of cress or oat seedlings, respectively. — No activity.

20d in 4, 38, and 35% yields, respectively. On the other hand, the bis(trifluoroacetoxy)iodobenzene (PIFA) oxidation of **15b–d** provided **20b–d** in acceptable yields, while a sufficient yield was not obtained under anodic oxidation conditions.

Transformation of **20a–e** into chromans **21a–e** and **22a–e** under $BF_3 \cdot OEt_2$ conditions was carried out (Table 2). In the case of the trifluoromethyl derivatives, **20b** and **20c** were preferentially rearranged to the trifluoromethyl-side (**22b**, **22c**), which was sterically more hindered moiety. This observation indicated that the reaction was modulated by an apparent electron-withdrawing effect of the trifluoromethyl group, rather than its steric hindrance. In contrast, **20d** carrying a fluorine-substituent, was predominantly converted into **22d**. The fluorine-substituent might not play an electron-withdrawing part, but an electron-donating part by the resonance effect.

As observed in the case of **7** and **8**,[4a,5] rearrangement of **20a** was conducted to avoid bulky methyl groups, leading to **21a**. Chloro- and bromo-substituents of the methyl phenols interfered with the predominant production of **21a** and **9** by the electron-donating effect, which caused longer reaction times (entries 1 and 7) than in the case of **10** (entry 8). The fluorine-substituent of **20d** exhibited strong electron donation to provide **22d** as a sole product, whereas **2** having a bromine atom (rt, 15 min),[2b] and **20e** possessing a chlorine, provided 1:1 (**3**/**4**)[2b] and 1:9 (**21e**/**22e**) mixtures (entry 6). Accordingly, the effectiveness of the electron-donation was in the order of the electron negativity, F > Cl > Br. The electron-withdrawing property of a trifluoromethyl group gave **22b** and **22c** as major products, although the rearrangement rate slowed down upon having a bromine substituent (**20c**).

Biological Assessment of Chroman Derivatives. A biological assay of the chroman derivatives synthesized in this investigation was performed (Table 3). Owing to good inhibitory activity of the brominated chroman derivatives against both cress and oat in a precedent investigation,[5] other related derivatives, particularly fluorine-containing derivatives, were expected to have effective activity for its similar atomic size to that of hydrogen atom and strong electron negativity. As can be seen in Table 3, while **22b** showed no activity, compounds **21a–c**, **22c**, and **22d** exhibited inhibitory activity against hypocotyls and root of cress at 10^{-3}–10^{-4} M concentration (EC_{50}), which was similar to that of (±)-heliannuol E.[5] Comparing **21b** with **22b**, the position of the trifluoromethyl group might contribute to the inhibitory effect; **22b** carrying the trifluoromethyl group at C5, showed no activity, whereas substitution at C7 (**21b**) provided inhibitory activity against cress, as well as coleoptile of oat. Although **21b** and **22d** inhibited both hypocotyl and root of cress, **21b** exhibited no activity against root

of oat, and no inhibition against coleoptile was detected in the case of **22d**. However, **21c**, possessing a brominated structure of **21b**, recovered inhibition against root of oat. A direct comparison of the inhibitory activity between trifluoromethyl and methyl derivatives has not been performed. However, upon referring to previous data,[5] brominated derivatives **21c** and **22c** inhibited all parts of cress and oat, similar to the case of **9** and **11**, whereas the inactivity of **10** against coleoptile showed different selectivity from that of **21b**.

In conclusion, we identified that a dienone–phenol rearrangement was conducted, not only by the steric hindrance, but also by both electron-donating and withdrawing effects. In addition, a biological assay of several chroman derivatives indicated that trifluoro compounds **21c** and **22c** evenly inhibited both cress and oat; however no activity of **21b** against root of oat, and low inhibition of **21a** against coleoptile were observed. Despite of a structural similarity to **21b**, **22b** showed no activity. Further investigation is in progress.

Experimental

General. All of the melting points were obtained on a Yanaco MP-S3 melting-point apparatus and were uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JNM EX-270 and JEOL JNM GX-400 spectrometers in deuteriochloroform ($CDCl_3$) using tetramethylsilane as an internal standard, unless otherwise stated. High-resolution mass spectra were obtained on a Hitachi M-80 B GC–MS spectrometer operating at the ionization energy of 70 eV. Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merck A. G., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto silica-gel 60N (spherical. neutral, 63–210 μm) was used for column chromatography. Elemental analyses were obtained on an ELEMENTAR Vario EL CHNS apparatus. All anodic oxidation was conducted using a glassy carbon beaker as an anode, a platinum wire as a cathode, and a standard calomel electrode as a reference electrode.

Synthesis of 6-Chloro-4-(3-hydroxypropyl)-2-methylphenol (15a): A mixture of **14** (252 mg, 1.4 mmol) and SO_2Cl_2 (0.5 mL, 6.3 mmol) in $CHCl_3$ (5 mL) was stirred at room temperature for 6 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ at 0 °C, and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A solution of the residue in THF (4 mL) was slowly added to a solution of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (4 mL) at 0 °C; the mixture was stirred for 15 min. The reaction mixture was diluted with EtOAc, and the organic layer was washed with 6 M HCl, sat. aq. $NaHCO_3$ and brine, then dried (Na_2SO_4). After evaporation, the residue was chromatographed on a silica-gel column (hexane–EtOAc 4/1) to afford **15a** (251.1 mg, 89%) as an oil: IR (NaCl) 3365, 2943, 1487, 1327, 1120, 1051 cm^{-1}; ^{1}H NMR δ 1.83 (2H, tt, $J = 6.6$, 7.8 Hz), 2.25 (3H, s), 2.58 (2H, t, $J = 7.8$ Hz), 3.66 (2H, t, $J = 6.6$ Hz), 6.86 (1H, d, $J = 1.2$ Hz), 6.99 (1H, d, $J = 1.2$ Hz); ^{13}C NMR δ 16.4, 31.0, 34.2, 62.0, 119.2, 125.6, 125.8, 129.6, 134.0, 147.5; HRMS found m/z 200.0622, calcd for $C_{10}H_{13}{}^{35}ClO_2$: M, 200.0604. Found: C, 59.70; H, 6.48%. Calcd for $C_{10}H_{13}ClO_2$: C, 59.86; H, 6.53%.

Synthesis of 4-Phenylmethoxy-3-(trifluoromethyl)benzonitrile (17): A mixture of **16** (3.12 g, 19 mmol) and Br_2 (0.99 mL, 19 mmol) in $CHCl_3$ (50 mL) at room temperature was stirred for 2.5 h. The resultant mixture was washed with H_2O, sat. aq. $Na_2S_2O_3$, and brine. The organic layer was dried (Na_2SO_4), and evaporated. A mixture of the residue, K_2CO_3 (5.3 g, 38 mmol) and BnBr (2.28 mL, 19 mmol) in DMF (30 mL) was stirred at room temperature for 21 h. The mixture was diluted with H_2O at 0 °C, and extracted with EtOAc–hexane (1/1). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude oil was chromatographed on a silica-gel short column (hexane–EtOAc 60/1), and the product was immediately submitted to the next reaction.

To a solution of the benzyl ether in DMF (65 mL) was added CuCN (6.02 g, 67 mmol); the mixture was stirred at 130 °C for 26 h. After the addition of H_2O (75 mL), aqueous NH_3 (70 mL), Et_2O (70 mL), and EDTA (2.86 g, 7.7 mmol) at 0 °C, the mixture was stirred at room temperature for 20 h. The resultant mixture was diluted with H_2O, and washed with hexane–EtOAc (1/1). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was chromatographed on a silica-gel column (hexane–EtOAc 12/1 to 8/1) to afford **17** (26.5 g, 62%, 3 steps): mp 114.5–115 °C (needles, EtOAc–hexane); IR (KBr) 3080, 2227, 1618, 1508, 1335, 1288, 1130, 1059, 1022 cm^{-1}; ^{1}H NMR δ 5.27 (2H, s), 7.11 (1H, d, $J = 8.3$ Hz), 7.34–7.75 (5H, complex), 7.76 (1H, broad d, $J = 8.3$ Hz), 7.89 (1H, broad s); ^{13}C NMR δ 70.8, 104.0, 113.9, 117.7, 120.4 (q, $J = 31.5$ Hz), 122.3 (q, $J = 271.6$ Hz), 126.7, 128.4, 128.7, 131.3 (q, $J = 5$ Hz), 134.7, 137.4, 159.4; HRMS found m/z 277.0707, calcd for $C_{15}H_{10}NF_3O$: M, 277.0713.

Synthesis of 4-(3-Hydroxypropyl)-2-(trifluoromethyl)phenol (15b): To a solution of **17** (2.47 g, 11 mmol) in PhMe (70 mL) was added DIBAL-H (1.01 M in PhMe, 20 mL) at −78 °C under an argon atmosphere; the mixture was stirred at −78 °C for 15 min. The reaction was quenched by the addition of 6 M HCl, and warmed up to 0 °C. After 15 min, the mixture was extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and then evaporated. The crude oil was chromatographed on a silica-gel column (hexane–EtOAc 8/1 to 3/1) to afford an aldehyde (2.05 g, 82%): mp 81.5–82.5 °C (needles, EtOAc–hexane): IR (NaCl) 3066, 2806, 1687, 1614, 1500, 1441, 1277, 1196, 1134 cm^{-1}; ^{1}H NMR δ 5.29 (2H, s), 7.16 (1H, d, $J = 8.8$ Hz), 7.32–7.44 (5H, complex), 8.00 (1H, dd, $J = 1.2$, 8.8 Hz), 8.13 (1H, d, $J = 1.2$ Hz), 9.91 (1H, s); ^{13}C NMR δ 70.7, 113.3, 119.9 (q, $J = 31.4$ Hz), 122.9 (q, $J = 271.7$ Hz), 126.7, 128.3, 128.7, 129.0, 129.2 (q, $J = 4.9$ Hz), 134.9, 135.0, 160.8, 189.5; HRMS found m/z 280.0684, calcd for $C_{15}H_{11}F_3O_2$: M, 280.0709.

To a solution of the aldehyde (1.61 g, 7.1 mmol) in dry THF (16 mL) was added $Ph_3P{=}CHCOOMe$ (4.8 g, 14 mmol) at room temperature; the mixture was stirred for 6 h. The mixture was warmed up to 55 °C and stirred for an additional 12 h. After evaporation, the residue was purified by silica-gel column chromatography (hexane–EtOAc 4/1) to afford an ester (1.94 g, 81%): mp 104.5–105 °C (needles, hexane–EtOAc); IR (KBr) 3041, 2952, 1709, 1637, 1614, 1508, 1438, 1385, 1340, 1282 cm^{-1}; ^{1}H NMR δ 3.80 (3H, s), 5.24 (2H, s), 6.36 (1H, d, $J = 16.4$ Hz), 7.04 (1H, d, $J = 8.4$ Hz), 7.33–7.44 (5H, complex), 7.61 (1H, dd, $J = 2$, 8.4 Hz), 7.64 (1H, d, $J = 16.4$ Hz), 7.77 (1H, d, $J = 2$ Hz); ^{13}C NMR δ 51.8, 70.4, 113.5, 117.1, 119.7 (q, $J = 30.5$ Hz), 123.2 (q, $J = 270.6$ Hz), 126.7, 126.8 (q, $J = 5$ Hz), 128.1, 128.6, 132.9, 135.6, 142.9, 157.6 (q, $J = 1.6$ Hz), 167.1; HRMS found m/z 336.0960, calcd for $C_{18}H_{15}F_3O_3$: M, 336.0972.

A mixture of the ester (1.78 g, 5.3 mmol) and a catalytic amount of 10% Pd/C in MeOH (30 mL) was stirred at room temperature for 5 h under a hydrogen atmosphere. After filtration, the

filtrate was evaporated, and the residue was chromatographed on a silica-gel column (hexane–EtOAc 3/1 to 2/1) to afford a phenol (1.66 g, 92%, 2 steps): mp 91.5–92 °C (needles, hexane–EtOAc); IR (KBr) 3376, 2958, 1709, 1624, 1525, 1444, 1333, 1211, 1182 cm^{-1}; ^1H NMR δ 2.62 (2H, t, $J = 7.8$ Hz), 2.91 (2H, t, $J = 7.8$ Hz), 3.68 (3H, s), 5.77 (1H, broad s), 6.85 (1H, d, $J = 2$ Hz), 7.25 (1H, dd, $J = 2$, 8.3 Hz), 7.33 (1H, d, $J = 2$ Hz); ^{13}C NMR δ 29.9, 35.7, 51.9, 116.4 (q, $J = 30.6$ Hz), 117.6, 123.9 (q, $J = 271.7$ Hz), 126.2 (q, $J = 4.9$ Hz), 132.0, 133.2, 152.4 (q, $J = 1.6$ Hz), 173.8; HRMS found m/z 248.0705, calcd for $C_{11}H_{11}F_3O_3$: M, 248.0751.

A mixture of the phenol (1.08 g, 4.4 mmol) and $LiAlH_4$ (0.5 g, 13 mmol) in THF (40 mL) was stirred at room temperature for 25 min. The mixture was diluted with EtOAc (150 mL), washed with 6 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica-gel column (hexane–EtOAc 1/1) to afford **15b** (0.91 g, 95%): mp 119.5–121 °C (needles, hexane–EtOAc); IR (NaCl) 3464, 2956, 1624, 1520, 1448, 1325, 1205, 1117 cm^{-1}; ^1H NMR (CD_3OD) δ 1.78 (2H, tt, $J = 6.4$, 7.6 Hz), 2.62 (2H, t, $J = 7.6$ Hz), 3.54 (2H, t, $J = 6.4$ Hz), 4.90 (1H, broad s), 6.84 (1H, d, $J = 8.4$ Hz), 7.21 (1H, dd, $J = 2$, 8.4 Hz), 7.30 (1H, d, $J = 2$ Hz); ^{13}C NMR (CD_3OD) δ 32.0, 35.5, 62.0, 117.6, 117.6 (q, $J = 29.8$ Hz), 125.5 (q, $J = 270$ Hz), 127.2 (q, $J = 5$ Hz), 133.8, 134.1, 155.0 (q, $J = 1.6$ Hz); HRMS found m/z 220.0712, calcd for $C_{10}H_{11}F_3O_2$: M, 220.0710.

Synthesis of 2-Bromo-4-(3-hydroxypropyl)-6-(trifluoromethyl)phenol (15c): To a solution of **15b** (133 mg, 0.6 mmol) in $CHCl_3$ (4 mL) was added a solution of Pyr·HBr_3 (193 mg, 0.6 mmol) at room temperature; the mixture was stirred for 1.5 h. The reaction mixture was diluted with $CHCl_3$, and washed with H_2O, sat. aq. $Na_2S_2O_3$, and brine. The organic layer was dried (Na_2SO_4), and evaporated. The crude oil was chromatographed on a silica-gel column (hexane–EtOAc 7/2) to afford **15c** (174 mg, 96%) as an oil: IR (NaCl) 3336, 2944, 1617, 1483, 1319, 1132 cm^{-1}; ^1H NMR δ 1.86 (2H, tt, $J = 6.6$, 7.8 Hz), 2.68 (2H, t, $J = 7.8$ Hz), 3.68 (2H, t, $J = 6.6$ Hz), 7.34 (1H, s), 7.50 (1H, s); ^{13}C NMR δ 30.8, 33.9, 61.7, 111.7, 117.7 (q, $J = 31.4$ Hz), 122.9 (q, $J = 271.5$ Hz), 126.4 (q, $J = 5$ Hz), 135.0, 135.2, 148.2 (q, $J = 1.6$ Hz); HRMS found m/z 279.9717, calcd for $C_{10}H_8F_3{}^{79}BrO$: M − H_2O, 279.9711.

Synthesis of 2-Fluoro-4-(3-hydroxypropyl)phenol (15d): To a solution of **18** (1.96 g, 6.6 mmol) in DMF (15 mL) were added Et_3N (15 mL), methyl acrylate (2.98 mL, 33 mmol), and $Pd(dppf)_2Cl_2$ (269 mg, 0.33 mmol); the mixture was stirred at 90 °C for 12 h. After evaporation, the remaining mixture was diluted with H_2O (100 mL), and washed with EtOAc–hexane (1/1). The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica-gel column (hexane–EtOAc 10/1 to 4/1) to afford an ester (1.55 g, 82%): mp 91.5–93 °C (needles, EtOAc–hexane): IR (KBr) 2952, 1706, 1637, 1152, 1273, 1173 cm^{-1}; ^1H NMR δ 3.79 (3H, s), 5.17 (2H, s), 6.29 (1H, d, $J = 16.1$ Hz), 6.98 (1H, t, $J = 8.8$ Hz), 7.19 (1H, broad d, $J = 8.8$ Hz), 7.29 (1H, dd, $J = 12.2$, 2.2 Hz), 7.32–7.45 (5H, complex), 7.58 (1H, d, $J = 16.1$ Hz); ^{13}C NMR δ; HRMS found m/z 286.1023, calcd for $C_{17}H_{15}FO_3$: M, 286.1005.

A solution of the benzyl ether (0.93 g, 3.3 mmol) in EtOAc (40 mL) in the presence of a catalytic amount of 10% Pd/C was stirred for 2 h under a hydrogen atmosphere. After filtration, the filtrate was evaporated, and the residue was chromatographed on a silica-gel column (hexane–EtOAc 9/1) to afford a phenol (0.63 g, 98%), as an oil: ^1H NMR δ 2.60 (2H, t, $J = 6.8$ Hz), 2.87 (2H, t, $J = 6.8$ Hz), 3.67 (3H, s), 6.85–6.94 (3H, complex); ^{13}C NMR δ 30.0, 35.7, 51.8, 115.3 (d, $J = 17.3$ Hz), 117.1, 124.3 (d, $J = 3.3$ Hz), 133.2, 141.8 (d, $J = 14$ Hz), 150.7 (d, $J = 236.0$ Hz), 173.3.

A mixture of the phenol and $LiAlH_4$ (273.2 mg, 7.2 mmol) in THF (40 mL) was stirred at room temperature for 15 min. The reaction mixture was diluted with 6 M HCl, and extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica-gel column (hexane–EtOAc 2/1) to afford **15d** (0.44 g, quant.) as an oil: IR (NaCl) 3323, 2499, 1520, 1286 cm^{-1}; ^1H NMR δ 1.85 (2H, tt, $J = 7.3$, 7.8 Hz), 2.63 (2H, t, $J = 7.8$ Hz), 3.68 (2H, t, $J = 7.3$ Hz), 6.83–6.93 (3H, complex); ^{13}C NMR δ 31.1 (d, $J = 1.6$ Hz), 34.1, 62.1, 115.3 (d, $J = 17.4$ Hz), 117.0 (d, $J = 2.5$ Hz), 124.4 (d, $J = 3.3$ Hz), 134.5 (d, $J = 5.7$ Hz), 141.5 (d, $J = 14.2$ Hz), 150.8 (d, $J = 236$ Hz); HRMS found m/z 170.0738, calcd for $C_9H_{11}FO_2$: M, 170.0742.

Synthesis of 2-Chloro-4-(3-hydroxypropyl)phenol (15e): A mixture of **19**[11] (109 mg, 0.48 mmol) and K_2CO_3 (668 mg, 4.8 mmol) in MeOH (5 mL) was stirred at room temperature for 12 h. After extraction, the crude product was chromatographed on a silica-gel column (hexane–EtOAc 1/1) to afford **15e** (81.8 mg, 92%): mp 78.5–80 °C (needles, EtOAc–hexane); IR (NaCl) 3359, 2935, 1610, 1217, 1053 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 1.77 (2H, tt, $J = 6.4$, 7.6 Hz), 2.59 (2H, t, $J = 7.6$ Hz), 3.56 (2H, t, $J = 6.4$ Hz), 3.75 (1H, broad s), 6.90 (1H, d, $J = 8.4$ Hz), 6.99 (1H, dd, $J = 2.4$, 8.4 Hz), 7.16 (1H, d, $J = 2.4$ Hz), 8.51 (1H, broad s); ^{13}C NMR (CD_3COCD_3) δ 31.5, 35.3, 61.5, 117.3, 120.5, 128.6, 130.2, 135.5, 151.5; HRMS found m/z 186.0404, calcd for $C_9H_{11}{}^{35}ClO_2$: M, 186.0447.

Procedure of Anodic Oxidation: A solution of **5** (44.8 mg, 0.27 mmol) in $MeNO_2$ (135 mL) in the presence of n-Bu_4NClO_4 (4.70 g) was electrolyzed (1.6–2.2 V vs SCE, 30 mA, 4.0 F/mol). The reaction mixture was evaporated, and the residue was chromatographed on a silica-gel column (hexane–EtOAc 1/1) to give oily **7**[5] (15.8 mg, 36%) and unreacted **5** (2.9 mg, 6%).

Procedure of PIFA Oxidation: To a solution of **15b** (51.2 mg, 0.23 mmol) in MeCN (5 mL) was added PIFA (161 mg, 0.38 mmol) at 0 °C; the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on a silica-gel column (hexane–EtOAc 4/1) to afford **20b** (23.6 mg, 47%): IR (NaCl) 2983, 2881, 1687, 1651, 1398, 1298, 1140, 1034 cm^{-1}; ^1H NMR δ 2.15 (2H, complex), 2.22 (2H, complex), 4.13 (2H, complex), 6.18 (1H, d, $J = 10$ Hz), 6.86 (1H, dd, $J = 3.2$, 10 Hz), 7.27 (1H, broad s); ^{13}C NMR δ 26.8, 37.0, 69.8, 77.0, 121.2 (q, $J = 267.0$ Hz), 126.9, 127.1 (q, $J = 29.6$ Hz), 149.3, 150.0 (q, $J = 4.9$ Hz), 179.7; HRMS found m/z 218.0562, calcd for $C_{10}H_9F_3O_2$: M, 218.0554.

9-Chloro-7-methyl-1-oxaspiro[4.5]deca-6,9-dien-8-one (20a): IR (NaCl) 2954, 1672, 1612, 1328, 1032 cm^{-1}; ^1H NMR δ 1.93 (3H, d, $J = 1.5$ Hz), 2.07–2.19 (4H, complex), 4.07 (2H, complex), 6.59 (1H, dd, $J = 1.5$, 2.9 Hz), 6.96 (1H, d, $J = 2.9$ Hz); ^{13}C NMR δ 16.1, 26.8, 36.8, 69.2, 78.8, 131.3, 133.1, 145.1, 145.2, 179.2; HRMS found m/z 200.0399, calcd for $C_{10}H_{11}{}^{37}ClO_2$: M, 200.0417. Found: C, 60.41; H, 5.57%. Calcd for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58%.

9-Bromo-7-(trifluoromethyl)-1-oxaspiro[4.5]deca-6,9-dien-8-one (20c): IR (NaCl) 2881, 1691, 1381, 1290, 1146, 1022 cm^{-1}; ^1H NMR δ 2.23 (4H, complex), 4.14 (2H, complex), 7.28 (2H, s);

^{13}C NMR δ 26.8, 36.9, 70.0, 78.8, 120.8 (q, J = 273 Hz), 122.5 (q, J = 2.4 Hz), 126.2 (q, J = 30.6 Hz), 149.5, 150.2 (q, J = 4.1 Hz), 173.1; HRMS found m/z 295.9649, calcd for $C_{10}H_8{}^{79}BrF_3O_2$: M, 295.9659.

7-Fluoro-1-oxaspiro[4.5]deca-6,9-dien-8-one (20d): IR (NaCl) 2981, 2879, 1685, 1365, 1161, 1034 cm^{-1}; ^{1}H NMR δ 2.12–2.21 (4H, complex), 4.09 (2H, complex), 6.16 (1H, dd, J = 7.3, 9.8 Hz), 6.36 (1H, dd, J = 3, 12.7 Hz), 6.83 (1H, dd, J = 3, 9.8 Hz); ^{13}C NMR δ 26.7, 37.1 (d, J = 2.5 Hz), 69.3, 79.5 (d, J = 8.3 Hz), 125.0 (d, J = 0.8 Hz), 125.8 (d, J = 2.7 Hz), 150.5 (d, J = 2.5 Hz), 152.1 (d, J = 264 Hz), 178.2 (d, J = 19.9 Hz); HRMS found m/z 168.0596, calcd for $C_9H_9FO_2$: M, 168.0586.

7-Chloro-1-oxaspiro[4.5]deca-6,9-dien-8-one (20e): IR (NaCl) 2956, 1676, 1604, 1340, 1032 cm^{-1}; ^{1}H NMR δ 2.08–2.23 (4H, complex), 4.10 (2H, complex), 6.24 (1H, d, J = 10 Hz), 6.83 (1H, dd, J = 2.8, 10 Hz), 6.99 (1H, d, J = 2.8 Hz); ^{13}C NMR δ 26.8, 37.0, 69.5, 79.3, 126.1, 131.3, 145.4, 150.0, 178.4; HRMS found m/z 184.0258, calcd for $C_9H_9{}^{35}ClO_2$: M, 184.0290.

Procedure of the Ring Expansion: To a solution of **20d** (23.3 mg, 0.139 mmol) in CH_2Cl_2 (1.4 mL) was added $BF_3 \cdot Et_2O$ (52.8 μL, 0.42 mmol) at 0 °C; the mixture was stirred at room temperature until the starting material was disappeared. The reaction was diluted with EtOAc (30 mL), washed with H_2O and brine (30 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica-gel column (hexane–EtOAc 8/1) to afford **22d** (14.7 mg, 63%).

A Mixture of 5-Chloro-7-methylchroman-6-ol (21a) and 5-Chloro-7-methylchroman-6-ol (22a): IR (NaCl) 3456, 2952, 1483, 1415, 1157, 1066 cm^{-1}; ^{1}H NMR δ 2.00 (3H, complex), 2.15 (1.5H, s), 2.22 (3H, s), 2.62 (1H, m), 2.71 (2H, complex), 4.07 (3H, complex), 5.20 (0.5H, broad s), 5.23 (1H, broad s), 6.55 (1H, s), 6.68 (0.5H, s); ^{13}C NMR δ 11.9, 16.3, 22.2, 22.4, 22.9, 23.3, 65.8, 65.8, 113.6, 117.1, 117.6, 119.2, 123.6, 143.3, 148.4; HRMS found m/z 198.0470, calcd for $C_{10}H_{11}{}^{35}ClO_2$: M, 198.0447. Found: C, 60.84; H, 5.76%. Calcd for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58%.

7-(Trifluoromethyl)chroman-6-ol (21b): mp 82–83 °C (needles, hexane); IR (KBr) 3377, 2974, 1618, 1458, 1375, 1275, 1124, 1072 cm^{-1}; ^{1}H NMR δ 1.98 (2H, complex), 2.88 (2H, complex), 4.12 (2H, complex), 6.74 (1H, d, J = 8.8 Hz), 6.88 (1H, d, J = 8.8 Hz); ^{13}C NMR δ 21.9, 22.8 (q, J = 4.1 Hz), 65.6, 113.4 (q, J = 27.3 Hz), 117.6, 120.8, 122.3, 125.6 (q, J = 273.1 Hz), 147.9 (q, J = 2.5 Hz), 148.9; HRMS found m/z 218.0571, calcd for $C_{10}H_9F_3O_2$: M, 218.0554.

5-(Trifluoromethyl)chroman-6-ol (22b): mp 96.5–97 °C (needles, hexane); IR (KBr) 3394, 2924, 1639, 1434, 1329, 1277, 1115, 1030 cm^{-1}; ^{1}H NMR δ 1.99 (2H, complex), 2.75 (2H, complex), 4.15 (2H, complex), 6.64 (1H, s), 6.94 (1H, s); ^{13}C NMR δ 22.0, 24.9, 66.4, 114.5 (q, J = 4.9 Hz), 115.4 (q, J = 29.8 Hz), 118.4, 123.8 (q, J = 270.8 Hz), 127.8, 146.1 (q, J = 2.5 Hz), 148.4; HRMS found m/z 218.0541, calcd for $C_{10}H_9F_3O_2$: M, 218.0554.

5-Bromo-7-(trifluoromethyl)chroman-6-ol (21c): mp 99–100 °C (needles, hexane–Et_2O); IR (NaCl) 3487, 1460, 1107, 1070 cm^{-1}; ^{1}H NMR δ 1.97 (2H, complex), 2.89 (2H, complex), 4.11 (2H, complex), 7.15 (1H, s); ^{13}C NMR δ 21.7 (q, J = 1.6 Hz), 23.0 (q, J = 4.1 Hz), 65.7, 110.3, 115.4 (q, J = 29 Hz), 122.1 (q, J = 1.7 Hz), 123.9, 124.3 (q, J = 275 Hz), 144.5 (q, J = 1.6 Hz), 148.9; HRMS found m/z 295.9666, calcd for $C_{10}H_8F_3{}^{79}BrO_2$: M, 295.9660.

7-Bromo-5-(trifluoromethyl)chroman-6-ol (22c): mp 89–90 °C (needles, hexane–Et_2O); IR (KBr) 3456, 2941, 1487, 1433, 1117, 1039 cm^{-1}; ^{1}H NMR δ 2.05 (2H, complex), 2.76 (2H, complex), 4.12 (2H, complex), 7.03 (1H, s); ^{13}C NMR δ 22.0, 26.6, 65.9, 114.4 (q, J = 4.9 Hz), 115.7 (q, J = 32.2 Hz), 122.8 (q, J = 271.7 Hz), 126.6, 126.6, 143.4 (q, J = 1.6 Hz), 148.8; HRMS found m/z 295.9676, calcd for $C_{10}H_8F_3{}^{79}BrO_2$: M, 295.9660.

7-Fluorochroman-6-ol (22d): IR (NaCl) 3381, 2937, 1610, 1508, 1288, 1153 cm^{-1}; ^{1}H NMR δ 1.96 (2H, complex), 2.69 (2H, complex), 4.11 (2H, complex), 6.55 (1H, d, J = 11.7 Hz), 6.66 (1H, d, J = 9.8 Hz); ^{13}C NMR δ 22.2, 24.4, 66.3, 103.9 (d, J = 21.5 Hz), 117.0 (d, J = 3.3 Hz), 118.0 (d, J = 4.0 Hz), 136.6, 148.1 (d, J = 23.1 Hz), 149.3 (d, J = 248 Hz); HRMS found m/z 168.0579, calcd for $C_9H_9FO_2$: M, 168.0586.

5-Chlorochroman-6-ol (21e): IR (NaCl) 3438, 2927, 1483, 1176, 1066 cm^{-1}; ^{1}H NMR δ 2.02 (2H, complex), 2.76 (2H, complex), 4.09 (2H, complex), 5.16 (1H, broad s), 6.67 (1H, d, J = 8.9 Hz), 6.80 (1H, d, J = 8.9 Hz); HRMS found m/z 184.0277, calcd for $C_9H_9{}^{35}ClO_2$: M, 184.0290.

7-Chlorochroman-6-ol (22e): IR (NaCl) 3423, 2935, 1489, 1180, 1061 cm^{-1}; ^{1}H NMR δ 1.97 (2H, complex), 2.72 (2H, complex), 4.12 (2H, complex), 5.07 (1H, broad s), 6.69 (1H, s), 6.77 (1H, s); ^{13}C NMR δ 22.1, 24.6, 66.3, 116.0, 116.3, 117.6, 122.4, 144.5, 148.6; HRMS found m/z 184.0301, calcd for $C_9H_9{}^{35}ClO_2$ 184.0290.

Bioassay. Effects for Coleoptile and Root Growth of Oat (*Avena sativa* L.): Ten seeds of oat were put on a dish, in which 1 mL of a test solution was added. After incubation at 25 °C for 3 days in the dark, the lengths of coleoptiles and roots of the seedlings were measured. Oat incubated without test samples during the same period was used as control.

Effects for Hypocotyl and Root Growth of Cress (*Lepidium sativum* L.): Ten seeds of cress in the presence of a 0.5 mL solution of a test sample were incubated at 23 °C in the dark. After 2 days, the length of the roots was measured, and hypocotyls were measured after being incubated one more day.

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