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Total Syntheses of *ent*-Heliespirones A and C

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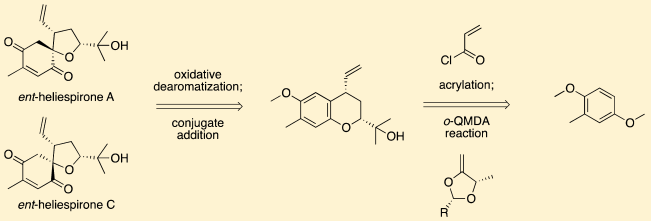
Supporting Information

ABSTRACT: Stereodivergent total syntheses of *ent*-heliespirone A and C were both completed in 11 vessels and ∼24% combined overall yield (A + C). These syntheses employed an identical inverse demand Diels–Alder reaction between a surrogate for an extendedly conjugated $\gamma-\delta$ unsaturated *ortho*-quinone methide and L-lactic-acid-derived exocyclic enol ether. Novel reactions of special note include a diastereoselective reduction of a chroman spiroketal by combination of borontrifluoride etherate and triethyl silane, along with oxidative rupture of a chroman etherial ring into the corresponding *p*-quinone by argentic oxide (AgO). In addition, an unusual *intramolecular* etherification of a 3° alcohol caused by cerium ammonium nitrate was observed.



INTRODUCTION

A new family of bioactive spirosesquiterpenes, heliespirones **1**–**3**, was recently isolated from aqueous leaf extracts of the sunflower *Helianthus annus* (Figure 1).[1] These compounds

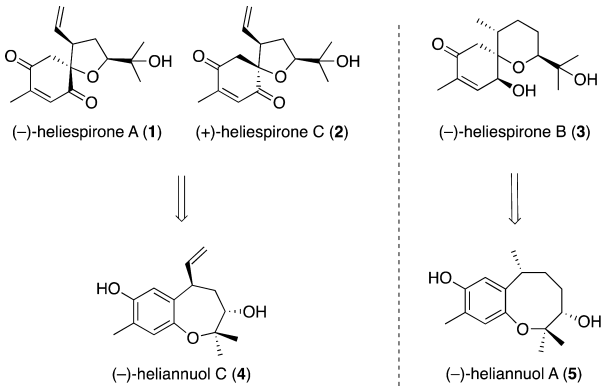
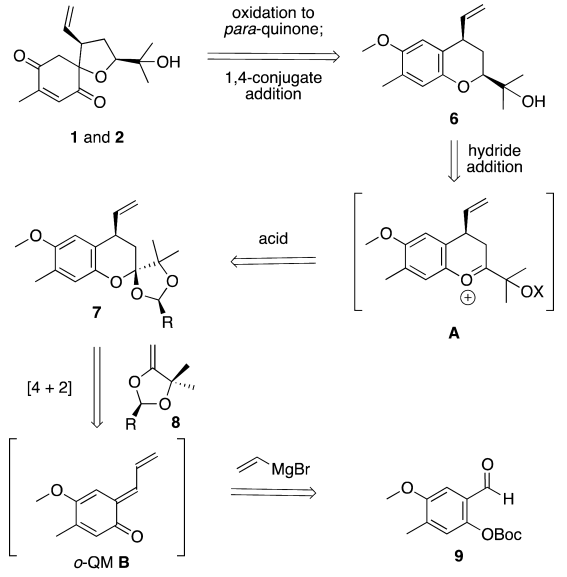


Figure 1. Proposed biosynthesis of the heliespirane family.

display an intriguing oxaspirocyclic motif previously unknown among sesquiterpenes. The heliespiranes exhibited significant inhibition in the coleoptile bioassay, suggesting use as novel allelopathic agrochemicals. Given the previous isolation of heliannuol C (**4**) and A (**5**) from the same species, their biosynthesis has been envisioned to proceed by oxidative rupture of their respective benzofused cyclic ethers to the corresponding quinones, followed by an intramolecular 1,4-conjugate addition of their respective secondary alcohols. A synthetic approach along these lines of thinking would be orthogonal to Liu's, which had formed the penultimate quinone from an acyclic hydroquinone precursor.[2]

In our strategy, we targeted the chroman **6**, a structural isomer of heliannuol C (**4**),[3] as the penultimate intermediate, thereby mimicking the supposed divergent biosynthesis of heliespirones A (**1**) and C (**2**) (Scheme 1). We further chose this chroman intermediate based upon a hypothesis that the

Scheme 1. Synthetic Plan



benzylic vinyl substituent could guide the reduction of the intermediate oxonium **A** that would arise from application of Lewis acid to the chroman spiroketal **7**. If this stereochemical relay proved diastereoselective, it would then provide us with a general stereochemical approach to *cis*-oriented chroma motifs. We further suspected that the key spiroketal **7** could arise from a diastereoselective inverse electron demand *ortho*-quinone

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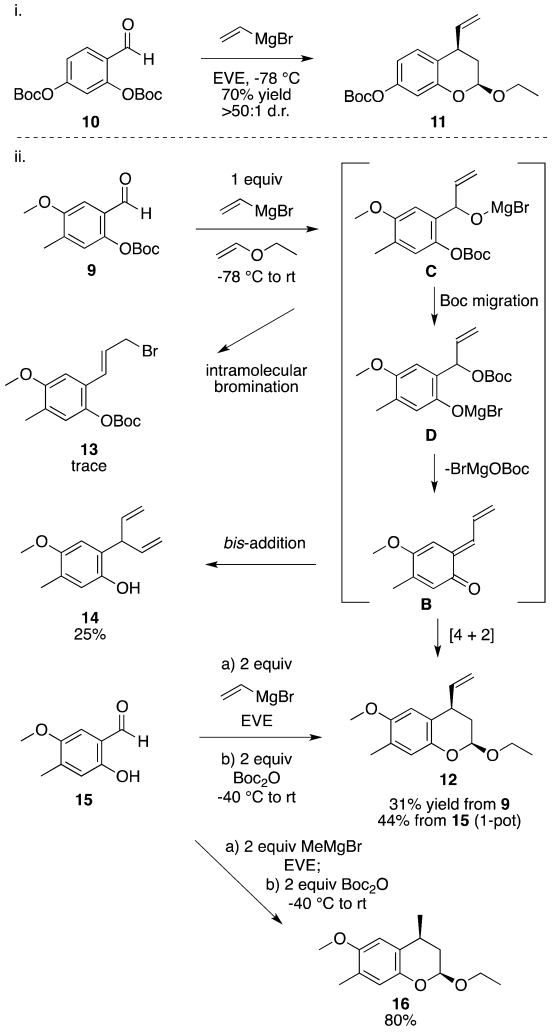
methide Diels–Alder (*o*-QMDA) reaction between the exocyclic enol ether **8** and the intermediate *o*-QM **B** generated from addition of vinylmagnesium bromide to the OBoc salicylaldehyde **9**.[4] If all went as planned, then we would arrive at the heliespirones **1** and **2** in just three pots from the OBoc salicylaldehyde **9**.

RESULTS AND DISCUSSION

In 2002, we reported that addition of vinylmagnesium bromide to aldehyde **10** triggered an *o*-QMDA reaction to occur with ethyl vinyl ether (EVE) to afford the respective chroman acetal **11** in 70% yield (>50:1 d.r.) (Scheme 2i).[4c] While this specific

Scheme 2. Cascades Triggered by Vinylmagnesium Bromide



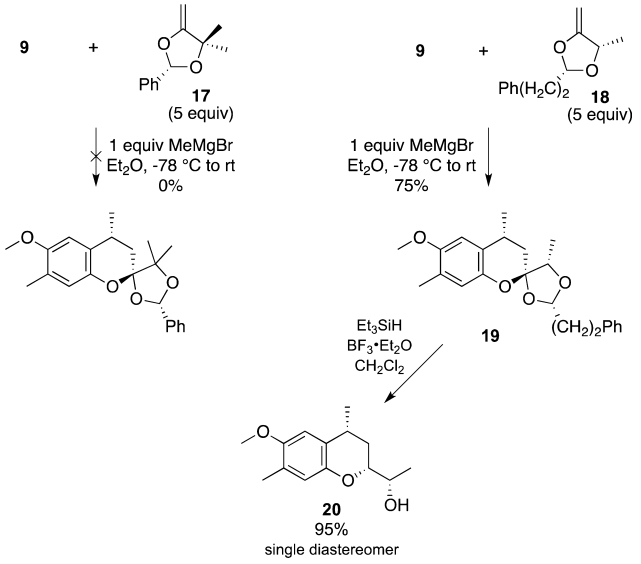
example used EVE as the solvent, we have also shown that these cycloadditions proceed with as few as 2 equiv of an enol ether as the dienophile. Before examining more elaborate exocyclic enol ethers, we found that application of similar conditions, using EVE as the solvent for addition of vinylmagnesium bromide to aldehyde **9**, afforded a meager 31% yield of the desired adduct **12**, albeit as a single diastereomer (Scheme 2ii). Isolated alongside the chroman were two unanticipated side products. We believe the bromide **13** resulted from an intramolecular delivery of a bromide within intermediate **C**. On the other hand, the phenol **14** (25% yield) most likely arose from a 1,4-conjugate addition of residual vinylmagnesium bromide to the *o*-QM **B** rapidly formed by facile elimination within species **D**.

When forming species resembling the *o*-QM **B** in our prior studies with vinylmagnesium bromide, we had never encountered this bromination adduct nor seen more than traces of the corresponding *bis*-addition product. Moreover, in all cascades initiated by addition of an aromatic or aliphatic Grignard reagent in the presence of enol ether, the cycloaddition reaction had always predominated, even if excess (>2.0 equiv of RMgBr) of the organometallic reagent were used to initiate the cascade. To ensure complete consumption of the Grignard reagent prior to formation of *o*-QM **B**, we added 2 equiv of vinylmagnesium bromide to the commercially available phenol **15** followed by the addition of Boc_2O.[5] While this modified procedure intercepted intermediate **D** and eliminated the formation of the phenol **14**, we still observed the brominated product **13** in 49% yield. If no enol ether was added during the course of the reaction, then the bromide **13** was formed as the major product (90% yield).

However, when our best cycloaddition conditions were implemented using the aldehyde **15** in combination with MeMgBr, the chroman acetal **16** arose in better than 80% yield as a single diastereomer. Suspecting chemical collusion between the vinyl substituent and this particular aromatic core, which perhaps resulted in rapid elimination of intermediate **D** and subdued reactivity of intermediate **B**, we reasoned that a surrogate for the vinyl residue would be required. In the interest of time, we moved forward to test the diastereoselectivity of the desired cycloaddition reaction with some easily accessible exocyclic enol ethers.

Our first attempt involved addition of methylmagnesium bromide to aldehyde **9** so as to trigger the *o*-QMDA reaction with the enol ether **17**, prepared in just two steps from 2-hydroxyisobutyric acid by condensation with benzaldehyde and Petasis methylenation (Scheme 3). The desired cyclo-

Scheme 3. Some Early Model Studies with *o*-QMDA



addition reaction failed, presumably because of steric interactions caused by the *gem*-dimethyl substituent, as related analogs were known by us to participate in similar reactions.[4f] We were fortunate to find that the cycloaddition proceeded with the less sterically congested enol ether **18** derived

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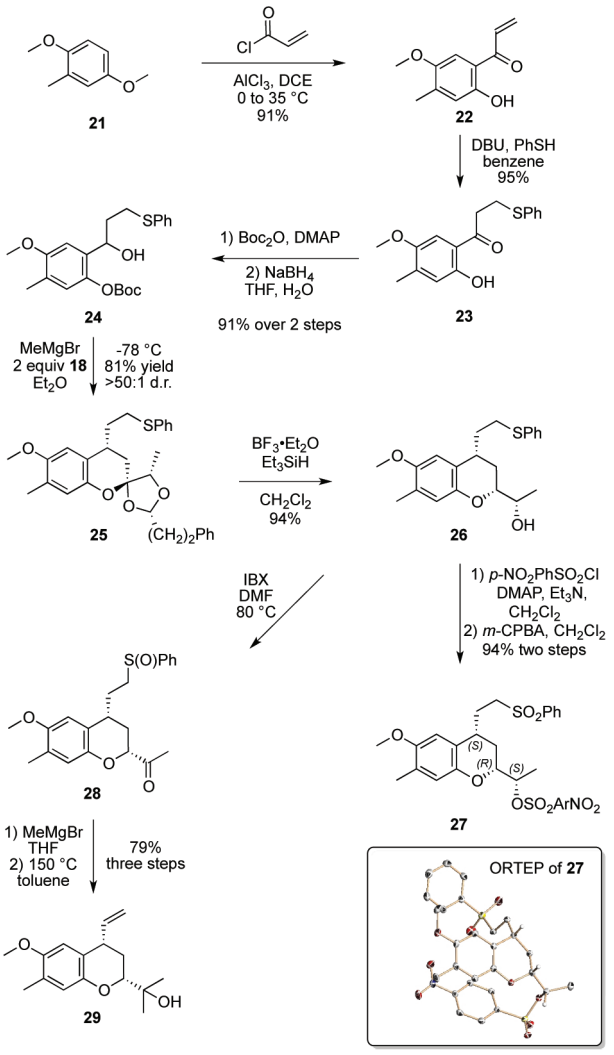
analogously from L-lactic acid.[6] Its reaction afforded the desired spiroketal **19** in 75% yield (>50:1 overall d.r.). As expected for the subsequent reduction, A-1,3 interactions served to position the benzylic methyl substituent in a pseudo-axial orientation on the oxonium intermediate so that the hydride addition proceeded from the face opposite the methyl residue, affording chroman **20** as a single diastereomer in a 95% yield. Thus, we had established a two-step process for the controlled construction of chromans of interest from OBoc salicylaldehyde via a chroman spiroketal intermediate.

In light of the problems caused by the vinyl substituent, we set out to construct its surrogate. The route began by regioselective acylation of 1,4-dimethoxy-2-methylbenzene **21** with acryloyl chloride mediated by aluminum trichloride (Scheme 4). The Friedel–Crafts reaction proceeded at 0 °C

Scheme 4. Enantioselective Synthesis of (+)-29

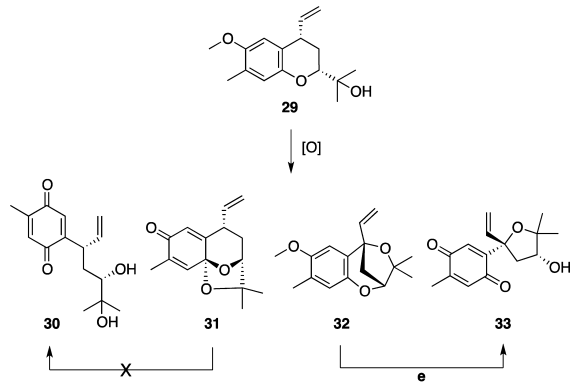


over the course of 1 h, whereupon warming to 35 °C for an additional 2 h resulted in cleavage of the more labile aryl methyl ether, affording the phenol **22** in 91% yield. The aryl acrylate moiety in **22** underwent 1,4-conjugate addition with thiophenol with the aid of DBU (1,8-diazobicycloundec-7-ene) to produce the thioether **23** in 95% yield. Carbonate formation followed by reduction of the ketone with sodium borohydride furnished the *o*-QMDA precursor **24** in 91% overall yield for the two steps. Subsequent deprotonation with methylmagnesium bromide triggered the desired cascade and provided the chroman spiroketal **25** in 81% yield (>50:1 d.r.). Reduction of ketal moiety proceeded as before and afforded the alcohol **26** in 94% yield. Its relative and absolute stereochemistry was secured by a two-step conversion to the sulfone **27** and X-ray analysis.[7]

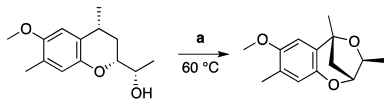
To complete the construction of the vinyl chroman, the thioether and secondary alcohol in compound **26** were concurrently oxidized to the corresponding sulfoxide and ketone in nearly quantitative yield by prolonged exposure to IBX (2-iodoxybenzoic acid).[8] To the best of our knowledge, this is the first such example of a concurrent oxidation. Subsequent treatment of the ketone in **28** with methylmagnesium bromide followed by thermolysis gave our desired chroman **29** in 79% yield over the two steps.

We were now poised to test what we suspected to be a very challenging oxidative rupture of the chroman etherial ring so as to cede the corresponding *p*-quinone in the presence of the unprotected tertiary alcohol appendage. Submission of compound **29** to cerium ammonium nitrate (CAN), which was well-known to convert hydroquinone ethers into their corresponding *p*-quinones,[9] afforded instead the unexpected tricyclic ether **32** in 81% yield (Table 1, entry a). We suspect

Table 1. Efforts Toward Oxidative Rupture of the Chroman Ring



Entry	Oxid	Equiv	Yield 30	Yield 31	Yield 32	Yield 33
a	CAN	1.7	-	-	81%	-
b	CAN	2.5	23%	24%	23%	6%
c	CAN	5.0	21%	40%	-	24%
d	(AgO)	6.0	62%	18%	-	9%



[a]CAN (1.7 equiv), ($MeCN/H_2O$ 3/1), 0 °C, 30 min. [b]CAN (2.5 equiv), ($MeCN/H_2O$ 3/1), 0 °C, 30 min. [c]CAN (5.0 equiv), ($MeCN/H_2O$ 3/1), 0 °C, 30 min. [d]AgO (6.0 equiv), 6 M HNO_3 (9 equiv), dioxane, rt, 3 min. [e]CAN (2.5 equiv), ($MeCN/H_2O$ 3/1), 0 °C, 30 min. 90% yield.

this etherification starts by formation of a tertiary cerium alkoxide **A** followed by fragmentation to the corresponding alkoxy radical **B** (Scheme 5). However, because of the stereochemical positioning of the reacting groups, we speculate oxidation of the methine between the vinyl and aryl residues proceeds in an unprecedented fashion, via an *intermolecular*

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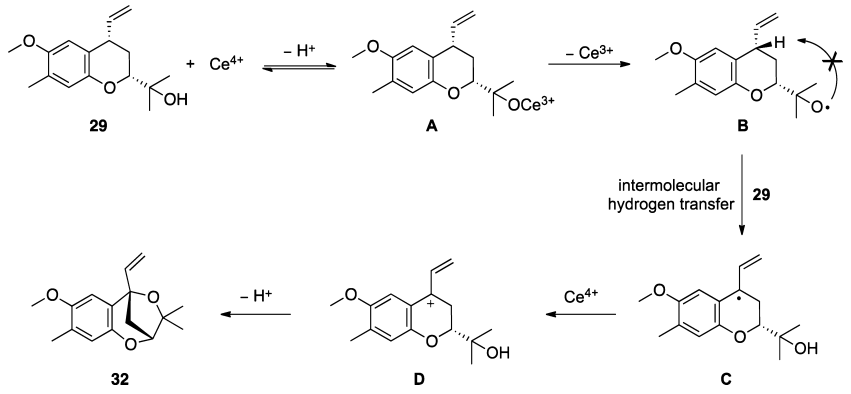
Scheme 5. Proposed Mechanism for Formation of Compound 32

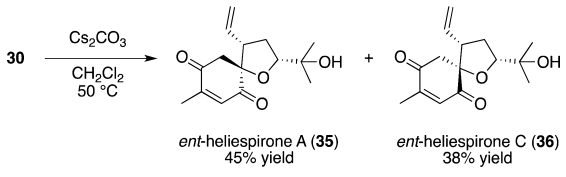


hydrogen transfer, followed by conventional radical oxidation and ether formation.[10] Interested to see whether a vinyl substituent was necessary for this outcome, we applied similar conditions to the methyl alcohol analog **20**. If the solution of the alcohol **20** was preheated to 60 °C prior to addition of the oxidant, then a similar etherification was observed to produce the cyclic ether **34**.

The desired quinone **30** was obtained along with a few other products upon increasing the equivalents of the oxidant (Table 1, entry b). We speculate that the *p*-quinone **30** and the *p*-quinone ketal **31** both formed from the same oxonium intermediate produced by oxidative dearomatization of **29** but diverged because of competing *intermolecular* addition of water verses *intramolecular* addition of the tertiary alcohol. On the other hand, the *p*-quinone **33** likely emerged from oxidative hydrolysis of the unusual ether **32**. Indeed, we found that upon resubjecting compound **32** to CAN afforded the *p*-quinone **33** in nearly quantitative yield (Table 1, e). However, upon adding more oxidant at the beginning of the reaction and thereby increasing the water content, the yield of the desired quinone **30** could not be improved (Table 1, entry c). Moreover, hydrolysis of the ketal **31** to the *p*-quinone **30** proved impossible in our hands under a myriad of conditions. After a rather exhaustive search of oxidative demethylation methods thought to proceed by different mechanisms, we were fortunate to find that exposure of the chroman **29** to argentic oxide (AgO),[11] a mixture of Ag^{I} and Ag^{III} species ($Ag_2O{\cdot}Ag_2O_3$), afforded the desired *p*-quinone **30** in a 62% yield (Table 1, entry d). We speculated that the tertiary alcohol is protected as its corresponding silver alkoxide, as very little of the benzylic oxidation products **32** and **33** were observed.

Treatment of quinone **30** with cesium carbonate furnished *ent*-heliespirone A (**35**) and *ent*-heliespirone C (**36**) in 45 and 38% yield, respectively (Scheme 6),[12] which could be

Scheme 6. Cesium Carbonate Mediated Conjugate Addition



easily separated by chromatography. This is a significant improvement over the Lewis acidic conditions previously employed for this transformation.[2] All spectral data were identical with the data of the corresponding natural products **1** and **2**, except for the optical rotations, which were equal and opposite.

CONCLUSION

In summary, we have completed the total syntheses of *ent*-heliespirone A (**35**) and *ent*-heliespirone C (**36**) from a chroman spiroketal that was produced in enantiomerically pure manner from L-lactic acid. Key steps were an *o*-QMDA reaction used to set the benzylic stereocenter that subsequently guided a diastereoselective reduction of oxonium generated from the chroman spiroketal. The final oxaspirocyclic ethereal bond was generated via an unusual oxidative rupture of the chroman ethereal ring mediated by argentic oxide and base-mediated Michael addition of the freed secondary alcohol.

EXPERIMENTAL SECTION

General Procedures. In reactions, where water was *not* present as solvent, reagent, or byproduct, vented vessels were flame-dried under a slow nitrogen flow. A slight positive pressure of dry nitrogen was maintained via rubber septa seal during the course of the reaction. Reactions were monitored by analytical thin-layer chromatography on hard layer silica gel 60 F_{250} plates cut into 1 × 2.5 cm pieces. Visualization was effected by ultraviolet light (254 nm), followed by staining (Seebach or permanganate). Removal of solvents was accomplished using a rotary evaporator. If the product was nonvolatile, trace solvents were removed at a pressure of approximately 0.03 mmHg. Ethyl acetate (anhydrous) was utilized directly from the bottle. Deuterated chloroform was filtered through basic alumina prior to use. Solvents were distilled before use under a slight positive pressure of nitrogen. Diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, benzene, and toluene were distilled from sodium and benzophenone. Dichloromethane, 1,2-dichloroethane, and nitromethane were distilled from CaH_2. Chloroform was filtered through alumina before being fractionally distilled. ^{1}H NMR spectra were recorded on 200, 400, 500, or 600 MHz instruments. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance of $CDCl_3$ (7.27 ppm). ^{13}C NMR spectra were recorded on 400, 500, 600, and 800 MHz instruments with a solvent resonance of $CDCl_3$ (77.00 ppm). High resolution mass spectra (HRMS) were recorded by electrospray ionization/time-of-flight experiments. Melting points are uncorrected.

***tert*-Butyl (2-Formyl-4-methoxy-5-methylphenyl) carbonate (9).** Boc_2O (646.9 mg, 2.96 mmol, 1.2 equiv) was added in one portion to a solution of compound **15** (410 mg, 2.47 mmol, 1 equiv), *i*-Pr_2NEt (0.43 mL, 2.47 mmol, 1 equiv), and DMAP (30.2 mg, 0.25 mmol, 0.1 equiv) in DCM (20 mL, 0.1 M) at room temperature. The solution was allowed to stir for 30 min and then quenched with saturated aqueous NH_4Cl. The solution was extracted with DCM, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl

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acetate) to afford compound **9** (624 mg, 2.35 mmol, 95%). White solid: mp 80−82 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.28 (s, 1H), 7.05 (s, 1H), 3.89 (s, 3H), 2.28 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.0, 155.9, 152.0, 146.4, 136.1, 126.4, 125.0, 108.5, 84.4, 55.9, 27.7, 16.9; HRMS (EI) m/z calculated for $C_{14}H_{18}O_5Na$ $[M + Na]^+$ 289.1052, found 289.1044; IR (neat) cm^{-1} 2985, 2870, 1751, 1688, 1609, 1370, 1255, 1144; R_f = 0.35 (90% hexanes, 10% ethyl acetate).

***cis*-2-Ethoxy-6-methoxy-7-methyl-4-vinylchroman (12). Procedure 1 from OBoc salicylaldehyde**: Vinylmagnesium bromide (0.53 mL, 0.39 mmol, 0.7 M in THF, 1.05 equiv) was added slowly to a solution of compound **9** (100 mg, 0.37 mmol, 1 equiv) in ethyl vinyl ether (3.6 mL, 0.1 M) at −78 °C. The reaction was warmed to room temperature over 3 h and then quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl acetate) to afford compound **12** (29 mg, 0.12 mmol, 31%), compound **14** (19.1 mg, 0.09 mmol, 25%), and compound **13** (trace). **Procedure 2 from salicylaldehyde**: Vinylmagnesium bromide (0.84 mL, 0.62 mmol, 0.7 M in THF, 2.05 equiv) was added slowly to a solution of compound **15** (50 mg, 0.30 mmol, 1 equiv) in ethyl vinyl ether (3 mL, 0.1 M) at 0 °C. The reaction was stirred at this temperature for 20 min and then cooled to −40 °C. Boc_2O (131 mg, 0.60 mmol, 2 equiv) was added to the reaction in one portion, and then the reaction was warmed to room temperature over 3 h and quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl acetate) to afford chroman acetal **12** (31.4 mg, 0.13 mmol, 44%) and compound **13** (50.1 mg, 0.14 mmol, 49%).

***cis*-2-Ethoxy-6-methoxy-7-methyl-4-vinylchroman (12).** Colorless liquid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.55 (s, 1H), 6.00−5.93 (m, 1H), 5.21 (ddd, J = 17.0, 1.8, 0.8 Hz, 1H), 5.15 (dd, J = 6.6, 2.5 Hz, 1H), 5.10 (dd, J = 9.9, 1.8 Hz, 1H), 3.98 (dq, J = 9.6, 7.1 Hz, 1H), 3.76 (s, 3H), 3.63 (dq, J = 9.6, 7.1 Hz, 1H), 3.50 (q, J = 7.8 Hz, 1H), 2.20 (ddd, J = 13.5, 6.7, 2.5 Hz, 1H), 2.17 (s, 3H), 1.92 (ddd, J = 13.5, 7.9, 6.6 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.0, 145.5, 141.8, 126.7, 121.3, 119.1, 115.2, 110.3, 98.2, 64.0, 55.8, 39.5, 34.4, 15.9, 15.2; HRMS (EI) m/z calculated for $C_{15}H_{20}O_3$ 248.1412, found 248.1397; IR (neat) cm^{-1} 2975, 2929, 1497, 1404, 1204, 1143, 1061, 1037; R_f = 0.8 (88% hexanes, 12% ethyl acetate).

4-Methoxy-5-methyl-2-(penta-1,4-dien-3-yl)phenol (14). Colorless liquid: ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.67 (s, 1H), 6.59 (s, 1H), 6.10 (ddd, J = 17.2, 10.3, 6.2 Hz, 2H), 5.25 (dt, J = 10.3, 1.5 Hz, 2H), 5.17 (dt, J = 17.3, 1.6 Hz, 2H), 4.73 (s, 1H), 4.26−4.24 (m, 1H), 3.78 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 152.0, 147.1, 138.5, 126.5, 124.7, 119.1, 116.3, 111.3, 56.0, 47.8, 15.8; HRMS (EI) m/z calculated for $C_{13}H_{16}O_2$ 204.1150, found 204.1141; IR (neat) cm^{-1} 3457, 2933, 1756, 1505, 1464, 1407, 1201, 1150; R_f = 0.45 (88% hexanes, 12% ethyl acetate).

(*E*)-2-(3-Bromoprop-1-en-1-yl)-4-methoxy-5-methylphenyl *tert*-Butyl Carbonate (13). Vinylmagnesium bromide (0.84 mL, 0.62 mmol, 0.7 M in THF, 2.05 equiv) was added slowly to a solution of compound **15** (50 mg, 0.30 mmol, 1 equiv) in diethyl ether (3 mL, 0.1 M) at 0 °C. The reaction was stirred at this temperature for 20 min and then cooled to −40 °C. Boc_2O (78.6 mg, 0.36 mmol, 1.2 equiv) was added to the reaction in one portion, and then the reaction was warmed to room temperature over 3 h and quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl acetate) to afford compound **13** (96.1 mg, 0.27 mmol, 90%). Colorless liquid: ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.91 (s, 1H), 6.89 (s, 1H), 6.70 (d, J = 15.5 Hz, 1H), 6.38 (dt, J = 15.6, 7.8 Hz, 1H), 4.16 (dd, J = 7.8, 1.0 Hz, 2H), 3.85 (s, 3H), 2.21 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 155.6, 152.1, 141.8, 128.6, 128.1, 126.5, 126.1, 124.3, 107.3, 83.6, 55.7, 33.4, 27.7, 16.2; HRMS (EI) m/z calculated for $C_{16}H_{21}O_4Br$ 356.0623, found 356.0636; IR (neat) cm^{-1} 2980, 2960, 1756, 1505, 1370, 1253, 1203, 1147; R_f = 0.5 (83% hexanes, 17% ethyl acetate).

***cis*-2-Ethoxy-6-methoxy-4,7-dimethylchroman (16).** The procedure yielding compound **16** was the same as **procedure 2**. 80% yield. Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.66 (s, 1H), 6.63 (s, 1H), 5.14 (dd, J = 6.6, 2.4 Hz, 1H), 3.98 (dq, J = 9.6, 7.1 Hz, 1H), 3.79 (s, 3H), 3.61 (dq, J = 9.6, 7.1 Hz, 1H), 2.97 (q, J = 7.1 Hz, 1H), 2.17 (s, 3H), 2.17−2.15 (m, 1H), 1.75 (ddd, J = 13.5, 7.9, 6.7 Hz, 1H), 1.39 (d, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.2, 145.6, 126.2, 125.0, 119.1, 109.2, 98.8, 64.1, 56.0, 36.0, 28.2, 21.8, 15.9, 15.3; HRMS (EI) m/z calculated for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ 259.1310, found 259.1294; IR (neat) cm^{-1} 2930, 1496, 1406, 1206, 1137, 1053, 1010, 883; R_f = 0.75 (83% hexanes, 17% ethyl acetate).

4,4-Dimethyl-5-methylene-2-phenyl-1,3-dioxolane (17)[13]. TsOH (86 mg, 0.5 mmol, 0.05 equiv) was added to a solution of 2-hydroxyisobutyric acid (1.56 g, 15 mmol, 1.5 equiv) and PhCHO (1.06 g, 10 mmol, 1 equiv) in DCM (58.6 mL, 0.17 M) at room temperature. The solution was allowed to stir for 15 h under azeotropic reflux at 45 °C before it was cooled and quenched at room temperature with saturated aqueous $NaHCO_3$. The solution was then extracted with DCM, and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl acetate) to afford 5,5-dimethyl-2-phenyl-1,3-dioxolan-4-one[14] (1.56 g, 8.1 mmol, 81%). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.52−7.51 (m, 2H), 7.47−7.45 (m, 3H), 6.45 (s, 1H), 1.59 (s, 3H), 1.57 (s, 3H); R_f = 0.4 (90% hexanes, 10% ethyl acetate). Petasis reagent[15] (4.3 mL, 1.72 mmol, 0.4 M in Tol, 2.2 equiv) was added to a solution of this intermediate lactone (150 mg, 0.78 mmol, 1 equiv) in toluene (5 mL, 0.08 M) under N_2 at room temperature. The solution was allowed to stir for 1.5 h at 78 °C and then cooled down to room temperature. The solution was purified by column chromatography (SiO_2, eluent: first 100% hexanes to remove toluene; then 95% hexanes, 5% ethyl acetate) to afford the enol ether **17** (115 mg, 0.61 mmol, 78%). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.53−7.51 (m, 2H), 7.43−7.41 (m, 3H), 6.15 (s, 1H), 4.31 (d, J = 2.5 Hz, 1H), 3.90 (d, J = 2.5 Hz, 1H), 1.58 (s, 3H), 1.52 (s, 3H); R_f = 0.75 (96% hexanes, 4% ethyl acetate).

(2*S*,4*S*)-4-Methyl-5-methylene-2-phenethyl-1,3-dioxolane (18). $Sc(OTf)_3$ (40 mg, 0.08 mmol, 0.001 equiv) was added to a solution of L-lactic acid (8.1 g, 90 mmol, 1.5 equiv) and $Ph(CH_2)_2CHO$ (8.04 g, 60 mmol, 1 equiv) in DCM (350 mL, 0.17 M) at room temperature. The solution was allowed to stir for 10 h under azeotropic reflux at 45 °C before it was cooled and quenched at room temperature with saturated aqueous $NaHCO_3$. The solution was extracted with DCM, and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by distillation to remove $Ph(CH_2)_2CHO$ (95−98 °C/1 mmHg), followed by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl acetate) to afford (2*S*,5*S*)-5-methyl-2-phenethyl-1,3-dioxolan-4-one6 (9.27 g, 45 mmol, 75%%, d.r. = 10:1). Colorless liquid: ^{1}H NMR (200 MHz; $CDCl_3$) δ 7.30−7.12 (m, 5H), 5.45 (td, J = 4.8, 1.0 Hz, 1H), 4.29 (qd, J = 6.7, 1.1 Hz, 1H), 2.79−2.71 (m, 2H), 2.15−2.05 (m, 2H), 1.46 (d, J = 6.8 Hz, 3H); R_f = 0.45 (93% hexanes, 7% ethyl acetate); $[\alpha]^{23}_D$ +5.3 (c = 1.6, $CHCl_3$). The procedure of Petasis methylenation to afford enol ether (−)-**18** is the same as shown above. Colorless liquid (d.r. = 10:1): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.32 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.9 Hz, 3H), 5.23 (t, J = 4.5 Hz, 1H), 4.57 (dddt, J = 8.2, 6.2, 4.2, 2.0 Hz, 1H), 4.31 (t, J = 2.2 Hz, 1H), 3.84 (t, J = 2.1 Hz, 1H), 2.83−2.79 (m, 2H), 2.12−2.08 (m, 2H), 1.47 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 161.3, 141.2, 128.50, 128.45, 126.0, 104.0, 77.4, 74.6, 35.3, 29.5, 18.6; HRMS (EI) m/z calculated for $C_{13}H_{16}O_2$ 204.1150, found 204.1143; IR (neat) cm^{-1} 3027, 2932,

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2866, 1685, 1496, 1298, 1241, 1133; R_f = 0.75 (96% hexanes, 4% ethyl acetate); $[\alpha]^{23}_D$ −26.4 (c = 2.5, $CHCl_3$).

(2*R*,2′*S*,4*R*,5′*S*)-6-Methoxy-4,5′,7-trimethyl-2′-phenethylspiro[chroman-2,4′-[1,3]dioxolane] (19). Methylmagnesium bromide (0.73 mL, 0.73 mmol, 1 M in Et_2O, 1.15 equiv) was added slowly to a solution of compound **9** (168 mg, 0.63 mmol, 1 equiv) and enol ether (−)-**18** (642 mg, 3.15 mmol, 5 equiv) in Et_2O (6.3 mL, 0.1 M) at −78 °C. The reaction was warmed to room temperature over 3 h and then quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: first 75% hexanes, 25% DCM to remove excess (−)-**18**; then 95% hexanes, 5% ethyl acetate) to afford compound (−)-**19** (173 mg, 0.47 mmol, 75%, dr >50:1). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.29 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 3H), 6.70 (s, 1H), 6.65 (s, 1H), 5.28 (t, J = 4.5 Hz, 1H), 4.27 (q, J = 6.5 Hz, 1H), 3.83 (s, 3H), 3.06 (quintet, J = 7.2, 2.1 Hz, 1H), 2.77 (t, J = 8.4 Hz, 3H), 2.21 (s, 3H), 2.10 (dd, J = 13.7, 7.3 Hz, 1H), 2.04−2.01 (m, 2H), 1.90 (dd, J = 13.7, 2.5 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 152.5, 145.1, 141.7, 128.48, 128.44, 126.3, 125.9, 124.7, 119.5, 110.0, 104.9, 101.7, 81.1, 56.0, 35.4, 33.1, 29.8, 28.1, 23.5, 16.3, 16.0; HRMS (EI) m/z calculated for $C_{23}H_{28}O_4Na$ $[M + Na]^+$ 391.1885, found 391.1866; IR (neat) cm^{-1} 2957, 2928, 1496, 1409, 1224, 1196, 1139, 1042; R_f = 0.82 (83% hexanes, 17% ethyl acetate); $[\alpha]^{23}_D$ −64.4 (c = 0.45, $CHCl_3$).

(*S*)-1-((2*R*,4*R*)-6-Methoxy-4,7-dimethylchroman-2-yl)ethanol (20). $BF_3{\cdot}Et_2O$ (0.17 mL, 1.35 mmol, 5 equiv) was added slowly to a solution of compound (−)-**19** (100 mg, 0.27 mmol, 1 equiv) and Et_3SiH (0.22 mL, 1.26 mmol, 5 equiv) in DCM (7 mL, 0.04 M) at −78 °C. The reaction was stirred for 2 h at 0 °C and then quenched with saturated aqueous $NaHCO_3$. The solution was extracted with DCM, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 87% hexanes, 13% ethyl acetate) to afford compound (−)-**20** (60.5 mg, 0.25 mmol, 95%). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.69 (s, 1H), 6.64 (s, 1H), 4.03 (qd, J = 6.5, 3.6 Hz, 1H), 3.91 (ddd, J = 11.6, 3.6, 1.8 Hz, 1H), 3.80 (s, 3H), 2.99 (dquintet, J = 12.4, 6.2 Hz, 1H), 2.34 (s, 1H), 2.17 (s, 3H), 2.02 (ddd, J = 13.4, 5.8, 1.8 Hz, 1H), 1.57 (dt, J = 13.3, 11.8 Hz, 1H), 1.36 (d, J = 6.6 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 152.0, 148.0, 126.1, 124.8, 118.7, 108.9, 79.3, 69.3, 56.1, 31.4, 29.4, 20.6, 17.8, 15.9; HRMS (EI) m/z calculated for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ 259.1310, found 259.1298; IR (neat) cm^{-1} 3437, 2959, 2872, 1509, 1464, 1210, 1176, 1058; R_f = 0.2 (83% hexanes, 17% ethyl acetate); $[\alpha]^{22}_D$ −53.4 (c = 0.5, $CHCl_3$).

1-(2-Hydroxy-5-methoxy-4-methylphenyl)prop-2-en-1-one (22). Acryloyl chloride (0.13 mL, 1.64 mmol, 1.1 M in DCM, 1 equiv) was added slowly to a solution of $AlCl_3$ (440 mg, 3.28 mmol, 2 equiv) and compound **21** (250 mg, 1.64 mmol, 1 equiv) in DCE (1.5 mL, 1.1 M) at 0 °C. The reaction was stirred for 1 h at 0 °C and then warmed to 35 °C for 2 h. The reaction was then cooled down to room temperature and poured into ice water. The solution was then extracted with DCM, and the combined organic solutions were washed with water, brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl acetate) to afford compound **22** (286.5 mg, 1.49 mmol, 91%). Yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ 12.33 (s, 1H), 7.25 (dd, J = 16.8, 10.5 Hz, 1H), 7.05 (s, 1H), 6.80 (s, 1H), 6.54 (dd, J = 16.8, 1.7 Hz, 1H), 5.93 (dd, J = 10.5, 1.5 Hz, 1H), 3.81 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 193.3, 158.4, 150.3, 138.9, 130.8, 130.2, 120.3, 116.6, 108.8, 55.8, 17.0; HRMS (EI) m/z calculated for $C_{11}H_{12}O_3Na$ $[M + Na]^+$ 215.0684, found 215.0679; IR (neat) cm^{-1} 3582, 2961, 1645, 1587, 1504, 1408, 1254, 1208; R_f = 0.5 (90% hexanes, 10% ethyl acetate).

1-(2-Hydroxy-5-methoxy-4-methylphenyl)-3-(phenylthio)-propan-1-one (23). Compound **22** (35 mg, 0.18 mmol, 0.9 M in benzene, 1 equiv) was added slowly to a solution of DBU (31 μL, 0.22 mmol, 1.2 equiv) and PhSH (22 μL, 0.22 mmol, 1.2 equiv) in benzene (1 mL, 0.22 M). The reaction was stirred for 1 h at room temperature and quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 87% hexanes, 13% ethyl acetate) to afford compound **23** (51.6 mg, 0.17 mmol, 95%). Yellow solid: mp 64−65 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 11.93 (s, 1H), 7.40−7.38 (m, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 6.89 (s, 1H), 6.80 (s, 1H), 3.76 (s, 3H), 3.35−3.27 (m, 4H), 2.24 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 202.9, 157.2, 150.4, 138.7, 135.6, 129.5, 129.1, 126.4, 120.3, 116.4, 108.4, 55.8, 37.9, 28.1, 16.9; HRMS (EI) m/z calculated for $C_{17}H_{18}O_3NaS$ $[M + Na]^+$ 325.0874, found 325.0869; IR (neat) cm^{-1} 3041, 2934, 1613, 1481, 1368, 1299, 1233, 1027; R_f = 0.3 (90% hexanes, 10% ethyl acetate).

***tert*-Butyl (2-(1-Hydroxy-3-(phenylthio)propyl)-4-methoxy-5-methylphenyl) Carbonate (24).** Boc_2O (646.9 mg, 2.96 mmol, 1.2 equiv) was added slowly to a solution of compound **23** (746 mg, 2.47 mmol, 1 equiv), i-Pr_2NEt (0.43 mL, 2.47 mmol, 1 equiv), and DMAP (30.2 mg, 0.25 mmol, 0.1 equiv) in DCM (20 mL, 0.1 M) at room temperature. The solution was allowed to stir for 30 min and then quenched with saturated aqueous NH_4Cl. The solution was extracted with DCM, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 84% hexanes, 16% ethyl acetate) to afford the corresponding alcohol **23a**: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.37−7.35 (m, 2H), 7.31−7.27 (m, 2H), 7.18 (s, 1H), 7.20−7.16 (m, 1H), 6.96 (s, 1H), 3.84 (s, 3H), 3.31−3.22 (m, 4H), 2.24 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 197.2, 155.4, 151.9, 143.0, 136.1, 133.6, 129.00, 128.98, 128.2, 126.0, 125.5, 109.9, 83.9, 55.7, 41.9, 27.80, 27.66, 16.4; HRMS (EI) m/z calculated for $C_{22}H_{26}O_5NaS$ $[M + Na]^+$ 425.1399, found 425.1397; IR (neat) cm^{-1} 2980, 1759, 1682, 1498, 1397, 1275, 1205, 1148; R_f = 0.28 (90% hexanes, 10% ethyl acetate). $NaBH_4$ (280.8 mg, 7.37 mmol, 0.63 M in H_2O, 3 equiv) precooled to 0 °C was then added slowly to a solution of this alcohol intermediate in THF (23 mL, 0.1 M) at 0 °C. The reaction was stirred at 0 °C and monitored carefully by TLC. After the starting material disappeared, the reaction was quenched with 0.5 N HCl. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 80% hexanes, 20% ethyl acetate) to afford compound **24** (910 mg, 2.25 mmol, 91% over two steps). Colorless liquid: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.36−7.34 (m, 2H), 7.27 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 4.98 (dd, J = 8.4, 4.7 Hz, 1H), 3.81 (s, 3H), 3.08−2.98 (m, 2H), 2.19 (s, 3H), 2.18−2.11 (m, 1H), 2.05−1.97 (m, 1H), 1.55 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 155.9, 152.8, 140.7, 136.5, 133.8, 129.1, 128.9, 127.2, 125.9, 124.0, 107.7, 83.6, 67.4, 55.7, 36.8, 30.1, 27.7, 16.0; HRMS (EI) m/z calculated for $C_{22}H_{28}O_5NaS$ $[M + Na]^+$ 427.1555, found 427.1559; IR (neat) cm^{-1} 3452, 2932, 1754, 1501, 1370, 1255, 1201, 1149; R_f = 0.18 (90% hexanes, 10% ethyl acetate).

(2*R*,2′*S*,4*S*,5′*S*)-6-Methoxy-5′,7-dimethyl-2′-phenethyl-4-(2-(phenylthio)ethyl)spiro[chroman-2,4′-[1,3]dioxolane] (25). Methylmagnesium bromide (0.52 mL, 0.26 mmol, 0.5 M in Et_2O, 1.05 equiv) was added slowly to a solution of compound **24** (100 mg, 0.25 mmol, 1 equiv) and compound (−)-**18** (102 mg, 0.5 mmol, 2 equiv) in Et_2O (2 mL, 0.13 M) at −78 °C. The reaction was warmed to room temperature over 3 h and then quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: first 75% hexanes, 25% DCM to remove excess (−)-**18**; then 95% hexanes, 5% ethyl acetate) to afford compound (−)-**25** (99 mg, 0.2 mmol, 81%, d.r. > 50:1). Colorless liquid: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.32−7.28 (m, 4H), 7.23−7.18 (m, 4H), 6.70 (s, 1H), 6.52 (s, 1H), 5.25 (t, J = 4.5 Hz, 1H), 4.26 (q, J = 6.5 Hz, 1H), 3.74 (s, 3H), 3.23 (ddd, J = 12.9, 7.5, 5.5 Hz, 1H), 3.16 (dt, J = 10.0, 5.0 Hz, 1H), 3.06 (dt, J = 12.8, 7.5 Hz, 1H), 2.76−2.73 (m, 2H), 2.46−2.38 (m, 1H), 2.20 (s, 3H), 2.17−2.10 (m, 1H), 2.06−1.96 (m, 4H), 1.34 (d, J = 6.5 Hz, 3H);

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^{13}C NMR (125 MHz; $CDCl_3$) δ 152.3, 145.1, 141.5, 136.4, 129.5, 128.9, 128.42, 128.39, 126.5, 126.06, 125.89, 122.7, 119.4, 110.1, 104.5, 101.7, 81.3, 55.8, 35.4, 35.1, 31.85, 31.78, 30.0, 28.9, 16.01, 15.95; HRMS (EI) m/z calculated for $C_{30}H_{34}O_4NaS$ $[M + Na]^+$ 513.2076, found 513.2052; IR (neat) cm^{-1} 3025, 2928, 1497, 1410, 1225, 1195, 1122, 1046; R_f = 0.65 (96% hexanes, 4% ethyl acetate); $[\alpha]^{22}_D$ −83.3 (c = 0.50, $CHCl_3$).

(*S*)-1-((2*R*,4*S*)-6-Methoxy-7-methyl-4-(2-(phenylthio)ethyl)-chroman-2-yl)ethanol (26). $BF_3{\cdot}Et_2O$ (0.63 mL, 5 mmol, 25 equiv) was added slowly to a solution of compound (−)-**25** (100 mg, 0.20 mmol, 1 equiv) and Et_3SiH (0.8 mL, 5 mmol, 25 equiv) in DCM (5 mL, 0.04 M) at −78 °C. The reaction was stirred for 2 h at 0 °C and then quenched with saturated aqueous $NaHCO_3$. The solution was extracted with DCM, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 87% hexanes, 13% ethyl acetate) to afford compound (−)-**26** (67.3 mg, 0.19 mmol, 94%). Colorless liquid: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40−7.37 (m, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.24−7.19 (m, 1H), 6.64 (s, 1H), 6.53 (s, 1H), 4.08−4.01 (m, 1H), 3.83 (ddd, J = 11.5, 3.6, 1.7 Hz, 1H), 3.71 (s, 3H), 3.17−3.11 (m, 1H), 3.11−3.05 (m, 1H), 2.97−2.91 (m, 1H), 2.33−2.24 (m, 1H), 2.15 (s, 3H), 2.09 (td, J = 6.4, 1.6 Hz, 1H), 1.93−1.82 (m, 1H), 1.58 (q, J = 12.4 Hz, 1H), 1.27 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 152.1, 148.5, 136.1, 129.8, 129.0, 128.4, 126.2, 122.5, 119.0, 108.5, 79.0, 69.2, 55.9, 34.4, 33.0, 30.7, 27.7, 17.9, 15.8; HRMS (EI) m/z calculated for $C_{21}H_{26}O_3NaS$ $[M + Na]^+$ 381.1500, found 381.1497; IR (neat) cm^{-1} 3442, 2926, 1584, 1501, 1408, 1211, 1176, 1043; R_f = 0.35 (75% hexanes, 25% ethyl acetate); $[\alpha]^{22}_D$ −52.5 (c = 0.50, $CHCl_3$).

(*S*)-1-((2*R*,4*S*)-6-Methoxy-7-methyl-4-(2-(phenylsulfonyl)-ethyl)chroman-2-yl)ethyl Nitro Sulfonate (27). 4-Nitrobenzene-sulfonyl chloride (26 mg, 0.12 mmol, 4 equiv) was added in one portion to a solution of compound (−)-**26** (10 mg, 0.03 mmol, 1 equiv), Et_3N (40 μL, 0.30 mmol, 10 equiv), and DMAP (7 mg, 0.06 mmol, 2.0 equiv) in DCM (0.25 mL, 0.1 M) at room temperature. The solution was allowed to stir for 30 min and then quenched with saturated aqueous NH_4Cl. The solution was extracted with DCM, and the combined organic solutions were washed with 1 N HCl, brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was dissolved in DCM (0.25 mL), followed by adding mCPBA (14 mg, 0.07 mmol, 70% wet, 2.5 equiv) at 0 °C. The solution was allowed to stir for 30 min and then quenched with water. The solution was extracted with DCM, and the combined organic solutions were washed with saturated aqueous $Na_2S_2O_3$, brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 50% hexanes, 50% ethyl acetate) to afford compound (−)-**27** (16.2 mg, 0.028 mmol, 94% for two steps). Yellow solid: mp 160−162 °C; ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.35 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 8.9 Hz, 2H), 7.93 (dd, J = 8.2, 1.0 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.8 Hz, 2H), 6.47 (s, 1H), 6.15 (s, 1H), 4.87 (qd, J = 6.6, 3.3 Hz, 1H), 3.83 (ddd, J = 11.5, 3.2, 1.6 Hz, 1H), 3.71 (s, 3H), 3.12−3.08 (m, 1H), 3.07−2.98 (m, 2H), 2.38−2.32 (m, J = 6.4, 3.6 Hz, 1H), 2.11−2.06 (m, 1H), 2.08 (s, 3H), 1.96 (ddd, J = 13.1, 6.0, 1.5 Hz, 1H), 1.44 (d, J = 6.6 Hz, 3H), 1.39 (q, J = 12.4 Hz, 1H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 152.5, 150.6, 147.3, 142.7, 139.0, 133.9, 129.43, 129.29, 128.0, 127.1, 124.2, 119.9, 118.8, 107.7, 81.6, 76.3, 55.9, 52.5, 32.3, 27.5, 26.3, 16.9, 15.7; HRMS (EI) m/z calculated for $C_{27}H_{29}NO_9NaS_2$ $[M + Na]^+$ 598.1181, found 598.1160; IR (neat) cm^{-1} 3105, 2925, 1735, 1532, 1350, 1147, 1186, 1087; R_f = 0.5 (50% hexanes, 50% ethyl acetate); $[\alpha]^{22}_D$ −33.8 (c = 0.26, $CHCl_3$).

2-((2*R*,4*S*)-6-Methoxy-7-methyl-4-vinylchroman-2-yl)-propan-2-ol (29).[3c] IBX (143 mg, 0.503 mmol, 6 equiv) was added to a solution of compound (−)-**26** (30 mg, 0.083 mmol, 1 equiv) in DMF (5 mL, 0.017 M) at room temperature. The reaction was stirred for 7 h at 80 °C before being cooled down to room temperature and then quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with water, brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was dissolved in THF (5 mL) and added MeMgBr (0.18 mL, 0.09 mmol, 0.5 M in Et_2O, 1.1 equiv) at 0 °C. The reaction was stirred for 30 min at 0 °C and then quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was dissolved in toluene (7.8 mL), sealed into a tube, and heated for 6 h at 150 °C. Then the reaction was cooled down to room temperature and quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with water, brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 83% hexanes, 17% ethyl acetate) to afford compound (+)-**29** (17.1 mg, 0.066 mmol, 79% for three steps). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.67 (s, 1H), 6.59 (s, 1H), 5.73 (dt, J = 17.4, 10.2 Hz, 1H), 5.29 (dd, J = 17.4, 1.2 Hz, 1H), 5.22 (dd, J = 10.2, 1.8 Hz, 1H), 3.82 (dd, J = 11.4, 1.8 Hz, 1H), 3.76 (s, 3H), 3.56−3.51 (m, 1H), 2.17 (s, 3H), 2.05 (ddd, J = 13.2, 6.0, 1.8 Hz, 1H), 1.68 (q, J = 12.4 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 151.8, 147.7, 141.0, 126.7, 121.2, 118.6, 116.7, 110.2, 81.5, 71.8, 55.9, 41.3, 30.1, 25.8, 24.3, 15.8; HRMS (EI) m/z calculated for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1467, found 285.1459; IR (neat) cm^{-1} 3438, 2928, 2855, 1728, 1497, 1406, 1209, 1120; R_f = 0.55 (75% hexanes, 25% ethyl acetate); $[\alpha]^{23}_D$ +34.1 (c = 0.20, $CHCl_3$).

2-((3*S*,5*S*)-5,6-Dihydroxy-6-methylhept-1-en-3-yl)-5-methyl-cyclohexa-2,5-diene-1,4-dione (30).[2] To a solution of compound (+)-**29** (10 mg, 0.038 mmol, 1 equiv) and AgO (28.4 mg, 0.229 mmol, 6 equiv) in 1,4-dioxane (1 mL, 0.04 M), HNO_3 (57 μL, 0.342 mmol, 6 N in H_2O, 9 equiv) was added. The reaction was stirred at room temperature for 3 min and then quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 67% hexanes, 33% ethyl acetate) to afford compound (+)-**30** (6.2 mg, 0.024 mmol, 62%) together with two minor products: compound (+)-**31** (1.8 mg, 0.007 mmol, 18%) and compound (−)-**33** (0.9 mg, 0.003 mmol, 9%). Yellow oil: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.60 (q, J = 1.6 Hz, 1H), 6.54 (s, 1H), 5.78 (ddd, J = 17.4, 10.2, 8.4 Hz, 1H), 5.22 (dt, J = 17.4, 1.2 Hz, 1H), 5.21 (dt, J = 10.2, 0.6 Hz, 1H), 3.73 (td, J = 9.1, 3.5 Hz, 1H), 3.46 (dd, J = 10.8, 1.2 Hz, 1H), 2.29 (s, 1H), 2.04 (d, J = 1.6 Hz, 3H), 1.74 (ddd, J = 13.8, 10.0, 1.8 Hz, 2H), 1.62 (s, 1H), 1.54 (ddd, J = 13.8, 10.8, 3.6 Hz, 1H), 1.21 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 188.4, 187.2, 151.4, 145.5, 137.3, 133.9, 131.9, 118.2, 75.9, 73.0, 39.5, 35.8, 26.4, 23.6, 15.5; HRMS (EI) m/z calculated for $C_{15}H_{20}O_4$ 264.1362, found 264.1357; IR (neat) cm^{-1} 3445, 2971, 2928, 1652, 1352, 1258, 1232, 915; R_f = 0.35 (50% hexanes, 50% ethyl acetate); $[\alpha]^{23}_D$ +33.1 (c = 0.10, $CHCl_3$).

(3*R*,5*S*,9a*R*)-2,2,8-Trimethyl-5-vinyl-4,5-dihydro-2*H*-3,9a-epoxybenzo[*b*]oxepin-7(3*H*)-one (31). To a solution of compound (+)-**29** (10 mg, 0.038 mmol, 1 equiv) in MeCN/H_2O (3/1) (1 mL, 0.04 M), CAN (103.2 mg, 0.11 M in H_2O, 0.19 mmol, 5 equiv) was added at 0 °C. The reaction was stirred at this temperature for 30 min and then quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 83% hexanes, 17% ethyl acetate) to afford compound (+)-**31** (4 mg, 0.015 mmol, 40%) together with two minor products: compound (+)-**30** (2.1 mg, 0.008 mmol, 21%) and compound (−)-**33** (2.4 mg, 0.009 mmol, 24%). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.40 (q, J = 1.5 Hz, 1H), 5.85 (d, J = 2.4 Hz, 1H), 5.65 (ddd, J = 17.4, 10.2, 8.4 Hz, 1H), 5.25 (dd, J = 10.2, 1.2 Hz, 1H), 5.18 (d, J = 17.4 Hz, 1H), 4.19 (d, J = 4.2 Hz, 1H), 3.55 (dtd, J = 10.8, 8.0, 2.5 Hz, 1H), 2.08 (ddd, J = 14.2, 7.5, 1.2 Hz, 1H), 1.94−1.91 (m, 1H), 1.90 (d, J = 1.5 Hz, 3H), 1.52 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 186.4, 156.9, 138.7, 138.5, 137.0, 121.4, 119.0, 98.0, 82.7, 80.8, 39.6, 32.9, 29.1, 21.9, 15.5; HRMS (EI) m/z calculated for $C_{15}H_{18}O_3$ 246.1256, found 246.1262; IR (neat) cm^{-1} 2925, 1684, 1647, 1292, 1148, 1070, 1053, 971; R_f = 0.75 (50% hexanes, 50% ethyl acetate); $[\alpha]^{24}_D$ +53.2 (c = 0.10, $CHCl_3$).

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(2*R*,5*S*)-7-Methoxy-3,3,8-trimethyl-5-vinyl-3,5-dihydro-2*H*-2,5-methanobenzo[*e*][1,4]dioxepine (32). To a solution of compound (+)-**29** (10 mg, 0.038 mmol, 1 equiv) in MeCN/H_2O (3/1) (1 mL, 0.04 M), CAN (35.4 mg, 0.11 M in H_2O, 0.065 mmol, 1.7 equiv) was added at 0 °C. The reaction was stirred at this temperature for 30 min and then quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 90% hexanes, 10% ethyl acetate) to afford compound (−)-**32** (8.0 mg, 0.031 mmol, 81%). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.60 (s, 1H), 6.57 (s, 1H), 6.29 (dd, J = 17.4, 10.8 Hz, 1H), 5.61 (dd, J = 17.4, 1.8 Hz, 1H), 5.40 (dd, J = 10.8, 1.8 Hz, 1H), 4.47 (d, J = 2.4 Hz, 1H), 3.74 (s, 3H), 2.43 (d, J = 12.0 Hz, 1H), 2.29 (dd, J = 12.0, 3.2 Hz, 1H), 2.16 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 151.1, 146.3, 136.8, 128.1, 127.0, 117.4, 115.9, 107.3, 86.4, 82.5, 80.5, 55.9, 37.6, 28.3, 24.0, 16.0; HRMS (EI) m/z calculated for $C_{16}H_{20}O_3Na$ $[M + Na]^+$ 283.1310, found 283.1298; IR (neat) cm^{-1} 2962, 2927, 2855, 1690, 1496, 1405, 1260, 1105; R_f = 0.7 (83% hexanes, 17% ethyl acetate); $[\alpha]^{22}_D$ −116.1 (c = 0.05, $CHCl_3$).

2-((2*S*,4*R*)-4-Hydroxy-5,5-dimethyl-2-vinyltetrahydrofuran-2-yl)-5-methylcyclohexa-2,5-diene-1,4-dione (33). To a solution of compound (−)-**32** (10 mg, 0.038 mmol, 1 equiv) in MeCN/H_2O (3/1) (1 mL, 0.04 M), CAN (51.6 mg, 0.11 M in H_2O, 0.095 mmol, 2.5 equiv) was added at 0 °C. The reaction was stirred at this temperature for 30 min and then quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 75% hexanes, 25% ethyl acetate) to afford compound (−)-**33** (8.9 mg, 0.034 mmol, 90%). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.02 (s, 1H), 6.53 (s, 1H), 6.13 (ddd, J = 17.4, 10.2, 0.6 Hz, 1H), 5.36 (d, J = 17.4 Hz, 1H), 5.04 (d, J = 10.2 Hz, 1H), 4.03 (t, J = 5.4 Hz, 1H), 2.71 (dd, J = 13.6, 6.0 Hz, 1H), 2.25 (dd, J = 13.6, 6.0 Hz, 1H), 2.03 (s, 3H), 1.63 (s, 1H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 188.9, 187.5, 152.5, 145.4, 141.7, 134.1, 130.4, 113.8, 83.5, 81.2, 77.4, 44.7, 27.4, 22.4, 15.4; HRMS (EI) m/z calculated for $C_{15}H_{18}O_4$ 262.1205, found 262.1195; IR (neat) cm^{-1} 3439, 2925, 1652, 1340, 1245, 1095, 1000, 921; R_f = 0.55 (50% hexanes, 50% ethyl acetate); $[\alpha]^{24}_D$ −52.3 (c = 0.10, $CHCl_3$).

(2*R*,3*S*,5*R*)-7-Methoxy-3,5,8-trimethyl-3,5-dihydro-2*H*-2,5 methanobenzo[*e*][1,4]dioxepine (34). To a solution of chroman (−)-**20** (10 mg, 0.04 mmol, 1 equiv) in MeCN/H_2O (3:1) (1 mL, 0.04 M), CAN (39.4 mg, 0.07 mmol, 0.11 M in H_2O, 1.7 equiv) was added at 60 °C. The reaction was stirred at this temperature for 10 min, cooled down to room temperature, and quenched with water. The solution was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: first 90% hexanes, 10% ethyl acetate and then 67% hexanes, 33% ethyl acetate) to afford compound (−)-**34** (5.9 mg, 0.025 mmol, 60%) and the corresponding *p*-quinone (2.2 mg, 0.009 mmol, 22%). Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.71 (s, 1H), 6.60 (s, 1H), 4.51 (d, J = 3.0 Hz, 1H), 4.37 (q, J = 6.6 Hz, 1H), 3.79 (s, 3H), 2.25 (d, J = 12.0 Hz, 1H), 2.16 (s, 3H), 1.96 (dd, J = 12.0, 3.6 Hz, 1H), 1.76 (s, 3H), 1.19 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 151.5, 145.8, 128.3, 125.7, 118.2, 106.0, 82.3, 81.5, 77.9, 56.0, 37.2, 20.7, 20.0, 16.0; HRMS (EI) m/z calculated for $C_{14}H_{18}O_3$ 234.1256, found 234.1251; IR (neat) cm^{-1} 2975, 2928, 1496, 1467, 1408, 1277, 1192, 1108; R_f = 0.72 (83% hexanes, 17% ethyl acetate); $[\alpha]^{22}_D$ −110.0 (c = 0.10, $CHCl_3$). The corresponding *p*-quinone product: 2-((2*R*,4*R*,5*S*)-4,5-dihydroxyhexan-2-yl)-5-methylcyclohexa-2,5-diene-1,4-dione. Colorless liquid: ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.60 (q, J = 1.2 Hz, 1H), 6.54 (d, J = 1.2 Hz, 1H), 3.78 (qd, J = 6.3, 3.5 Hz, 1H), 3.68 (d, J = 10.2 Hz, 1H), 3.15−3.09 (m, 1H), 2.37 (s, 1H), 2.04 (d, J = 1.2 Hz, 3H), 1.76 (s, 1H), 1.58 (ddd, J = 13.8, 10.2, 4.8 Hz, 1H), 1.48 (ddd, J = 13.8, 8.4, 2.4 Hz, 1H), 1.18 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.6 Hz, 2H); ^{13}C NMR (150 MHz; $CDCl_3$) δ 188.4, 187.6, 154.0, 145.4, 133.8, 131.0, 73.0, 70.6, 38.0, 28.7, 18.6, 17.1, 15.4; HRMS (EI) m/z calculated for $C_{13}H_{18}O_4$ 238.1205, found 238.1214; IR (neat) cm^{-1} 3405, 2967, 2927, 1653, 1377, 1260, 1072, 912; R_f = 0.36 (50% hexanes, 50% ethyl acetate); $[\alpha]^{23}_D$ +12.6 (c = 0.10, $CHCl_3$).

***ent*-Heliespirone A and C.** To a solution of compound **30** (26 mg, 0.098 mmol, 1 equiv) in DCM (1.5 mL, 0.065 M), Cs_2CO_3 (20 mg, 0.061 mmol, 0.63 equiv) was added at room temperature. The reaction was warmed to 50 °C and stirred for 8 h before cooled down to room temperature and quenched with water. The solution was extracted with DCM, and the combined organic solutions were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluent: 80% hexanes, 20% ethyl acetate) to afford *ent*-heliespirone A (**35**) (11.7 mg, 0.044 mmol, 45%) and *ent*-heliespirone C (**36**) (9.8 mg, 0.037 mmol, 38%).

***ent*-Heliespirone A (35).** Colorless liquid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.63 (q, J = 1.4 Hz, 1H), 5.31 (ddd, J = 16.8, 9.6, 9.6 Hz, 1H), 5.08 (d, J = 16.8 Hz, 1H), 4.98 (d, J = 10.2 Hz, 1H), 4.05 (dd, J = 10.8, 5.4 Hz, 1H), 3.25 (d, J = 15.6 Hz, 1H), 2.98 (d, J = 15.6 Hz, 1H), 2.93 (ddd, J = 12.6, 9.6, 6.6 Hz, 1H), 2.15 (ddd, J = 12.6, 12.6, 10.8 Hz, 1H), 1.97 (d, J = 1.4 Hz, 3H), 1.99−1.95 (m, 1H), 1.34 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.3, 195.5, 153.6, 137.1, 135.4, 118.5, 87.6, 86.8, 70.2, 57.1, 51.9, 31.9, 28.4, 25.3, 16.0; HRMS (FI) m/z calculated for $C_{15}H_{20}O_4$ 264.1362, found 264.1356; IR (neat) cm^{-1} 3447, 2973, 2924, 1678, 1622, 1242, 1061, 1005; R_f = 0.7 (50% hexanes, 50% ethyl acetate); $[\alpha]^{24}_D$ +23.2 (c = 0.09, $CHCl_3$) {lit.[2] $[\alpha]^{14.5}_D$ +17.6 (c = 0.09, $CHCl_3$); lit.[1a] $[\alpha]^{25}_D$ −29.0 (c = 0.10, $CHCl_3$)}.

***ent*-Heliespirone C (36).** Colorless liquid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (q, J = 1.4 Hz, 1H), 5.63 (ddd, J = 16.8, 10.2, 8.4 Hz, 1H), 5.13 (d, J = 9.6 Hz, 1H), 5.12 (d, J = 18.0 Hz, 1H), 3.96 (dd, J = 10.8, 5.4 Hz, 1H), 3.30 (dt, J = 11.4, 7.8 Hz, 1H), 2.96 (d, J = 16.2 Hz, 1H), 2.85 (d, J = 16.2 Hz, 1H), 2.06 (ddd, J = 12.2, 6.9, 5.3 Hz, 1H), 2.00 (d, J = 1.4 Hz, 3H), 1.98−1.91 (m, 1H), 1.25 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.7, 196.3, 151.9, 137.1, 134.6, 119.9, 86.9, 86.7, 70.3, 48.8, 47.1, 32.4, 27.7, 24.5, 16.2; HRMS (FI) m/z calculated for $C_{15}H_{20}O_4$ 264.1362, found 264.1353; IR (neat) cm^{-1} 3460, 2970, 1738, 1687, 1440, 1365, 1228, 1114; R_f = 0.6 (50% hexanes, 50% ethyl acetate); $[\alpha]^{23}_D$ −24.9 (c = 0.10, $CHCl_3$) {lit.[2] $[\alpha]^{14.5}_D$ −31.8 (c = 0.11, $CHCl_3$); lit.[1b] $[\alpha]^{25}_D$ +14.4 (c = 0.10, $CHCl_3$)}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Comparison of ^{1}H and ^{13}C NMR data of synthetic and natural heliespirone A and C; crystallographic details of **27**; and copies of ^{1}H NMR, ^{13}C NMR, and DEPTNOE spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

This paper is dedicated by Wen-Ju Bai to Professor Qi-Lin Zhou (Nankai University, P. R. China) for his contribution to development of privileged chiral spiro ligands and subsequent applications toward transition metal-catalyzed reactions.

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