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Synthesis of 3-benzylidene-dihydrofurochromen-2-ones: promising intermediates for biflavonoid synthesis

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Abstract: A route to 3-benzylidene-dihydrofurochromen-2-ones from 2*H*-chromenes is described. Lactonization of 2*H*-chromenes was achieved using a two-step cyclopropanation-rearrangement sequence. Subsequent conversion of these intermediates to the corresponding α-benzylidene lactones was achieved by lithium enolate aldol reaction, followed by base-promoted elimination of the aldolate mesylates. The alkene geometry was found to be base-dependent. While the use of KOBu^t favored formation of the *E* isomer, the application of DBU showed a slight preference for the *Z* isomer. In further studies, these 3-benzylidene-dihydrofurochromen-2-ones were converted to polyaromatic structures possessing all the required functionality for biflavonoid synthesis.

Keywords: α-benzylidene lactones; biflavonoids; chamaejasmine; cyclopropanes; donor-acceptor; isochamaejasmine.

Introduction

Biflavonoids represent a class of natural products that continue to attract attention both for their structural complexities and diverse biological activities. Two examples are chamaejasmine (**1**) and the related isochamaejasmine (**2**). Isolated from the root of *Stellera chamaejasme L.*, a traditional Chinese herb, isochamaejasmine was found to alter several cell signaling pathways, which could explain its use in the treatment of solid tumors, as well as tuberculosis [1]. The same compound has been isolated from the yellow bark of *Brackenridgea zanguebarica* and was found to be active against several tumor cell lines including human myeloid leukemia cells [2]. Structurally related analogues of this compound have demonstrated anti-malarial activity [3]. Also isolated from more than one plant source, chamaejasmine has been shown to possess both anti-inflammatory activity and aldose reductase inhibiting activity [4], suggesting that it could be used in a potential treatment of the complications associated with diabetic neuropathy and related conditions. Structurally, chamaejasmine and isochamaejasmine are dimers of the flavanone narigenin (**3**) linked at C-3, giving them a C-3/C-3′ connectivity. Both natural products have a *trans-trans* configuration at the C-2/C-3 and C-2′/C-3′ positions, differing only in the absolute stereochemistry at C-2′ and C-3′. In 2005, Li and Ma reported the first synthesis of dl-chamaejasmine using a biomimetic strategy [5]. However, the key reductive dimerization step in this synthesis provided methyl-protected **1** in only a 10% yield. To date, a non-racemic synthesis of either compound has not been documented.

The goal of this research was to investigate a general strategy that could be used to target a range of biflavonoids, including compounds **1** and **2**. Addressing this challenge, we viewed chalcones **5** as potential precursors to the basic biflavonoid templates **4** (Scheme 1). The key step would be an intramolecular oxa-Michael reaction of the deprotected alkoxide, which has been shown to occur with complete *trans*-selectivity in related systems [6]. If these reactions prove to be stereospecific, cyclizations of the individual *Z*- and *E*-chalcones could result in the formation of *trans* products, but with opposite stereochemistries at C-2′ and C-3′. Chalcone structures such as compounds **5** then became our synthetic targets. Retrosynthetic analysis led us back to a new class of α-benzylidene lactones (**6**) (for the synthesis of a related α-methylene lactone, see [7]), which, we reasoned, should provide chalcones **5** upon cleavage with an *o*-alkoxyaryllithium reagent (for an example of a related reaction, see [8]). A number of strategies were considered for controlling the alkene stereochemistry in the α-benzylidene lactones, including the use of α-phosphonolactones such as **7**. Yu and Wiemer [9] have shown that the stereochemistry of Horner-Wadsworth-Emmons (HWE) olefinations of

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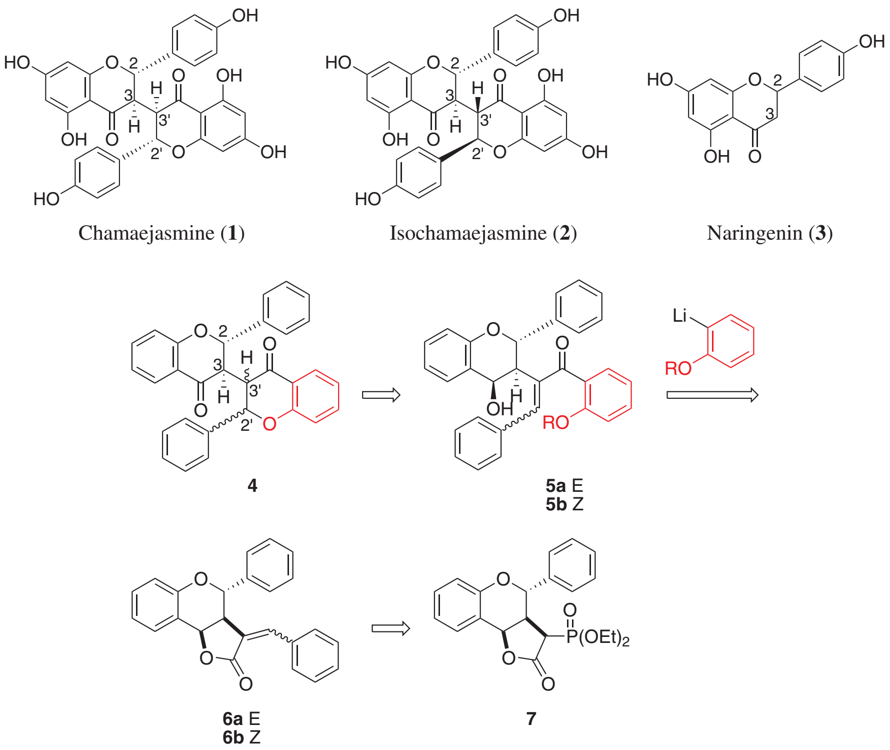
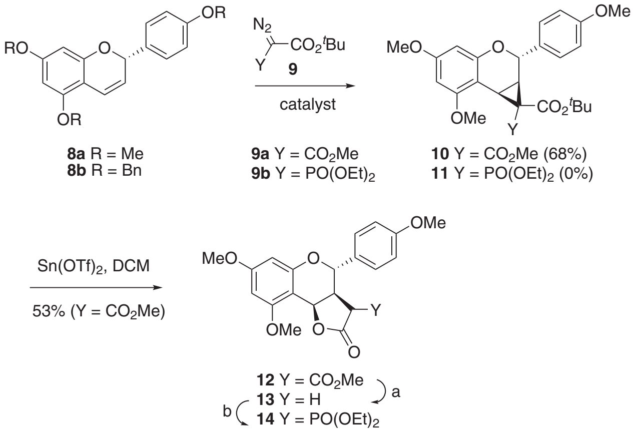


Scheme 1

related α-phosphono-γ-lactones can be controlled to give either *E*- or *Z*-alkenes, depending on the reaction conditions used.

Results and discussion

The starting materials were chromenes *rac*-**8a** and *rac*-**8b** (Scheme 2), which were prepared according to well-documented literature procedures [10–12]. We have previously shown that 2-aryl 2*H*-chromenes can be stereoselectively lactonized in a two-step cyclopropanation-rearrangement sequence [11, 13]. Thus, treatment of chromene **8a** with the diazo derivative **9a** in the presence of catalytic Rh$_2$(S-TBSP)$_4$ gave the donor-acceptor cyclopropane **10**, which underwent rearrangement to the α-carbomethoxy lactone **12** on treatment with Sn(OTf)$_2$. Originally, we intended to use benzyl protective groups, but unfortunately, chromene **8b** was inert in the attempted cyclopropanation. An equal lack of reactivity was observed when MOM protective groups were used. A reaction we were particularly interested in was the cyclopropanation of **8a** with phosphono-substituted diazo derivative **9b**, as rearrangement of the product **11** would have given direct access to the target lactone **14**. However, chromene **8a** was completely inert in the presence of **9b** under rhodium catalysis conditions. Osipov and coworkers [14] have reported some success in the CuI-mediated cyclopropanations of alkenes with α-trifluoromethyl-diazophosphonate in refluxing toluene [14], but this, too, failed in our hands. Instead, compound **14** was prepared by α-phosphorylation of lactone **13** [15], obtained from compound **12** by decarboxylation in the presence of NaI in refluxing DMF [16].



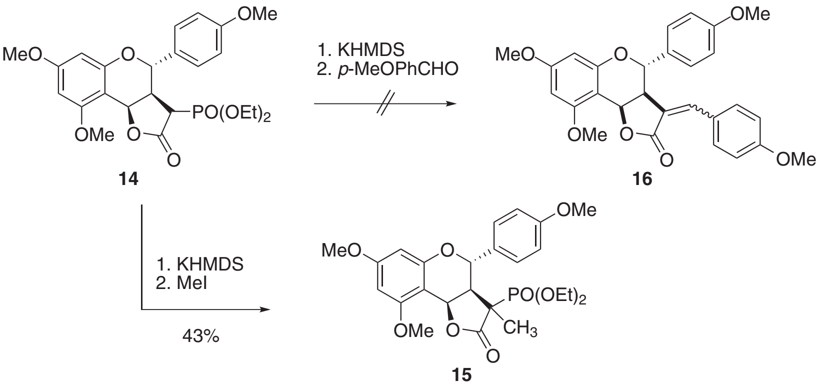
Conditions: [a]NaI, DMF, reflux, 5h (91%);
[b]1) LHMDS, THF, -78 oC; 2) PCl(OEt)2, TMEDA; 3) Air oxidation (43%, 3 steps)

Scheme 2

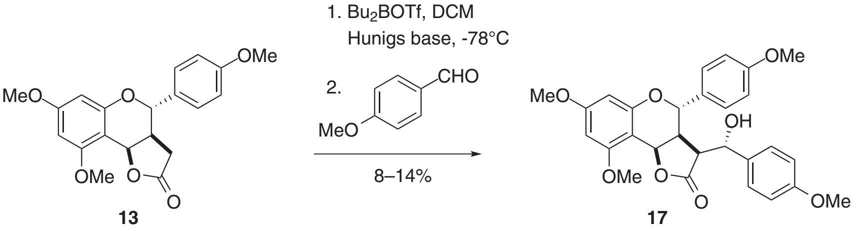
Unfortunately, all attempts at the HWE olefination of **14** with *p*-anisaldehyde using either the conditions reported by Yu and Wiemer (KHMDS, 18-crown-6) [9] or other conditions (NaH, refluxing THF) failed to produce either of the desired α-benzylidene lactone products **16** (Scheme 3). Successful methylation of **14** to give **15**, albeit in low yield, showed that enolate formation was occurring, which indicated that reaction with the aldehyde was problematic.

To try to circumvent this obstacle, we looked at an aldol route to the same derivatives. It was reasoned that if the aldol reaction is stereoselective, a stereospecific elimination step would provide the diastereomerically enriched α-benzylidene lactone. However, this approach proved to be challenging. The use of a boron enolate of lactone **13** provided **17** as a single stereoisomer with *p*-anisaldehyde, but the yields were disappointing (Scheme 4) (the stereochemistry was assigned by comparison to related aldol reactions, see [17]).

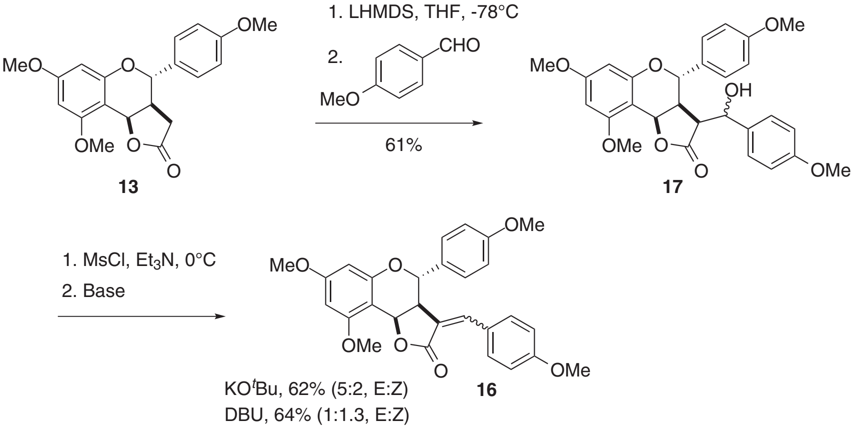
By contrast, higher aldol yields were observed with the corresponding lithium enolate, although the reaction resulted in a mixture of stereoisomers of **17** (Scheme 5). Moreover, base-induced elimination of the corresponding mesylates of this mixture was found to be base-dependent. With KOBu^t, **16E** was the predominant product, while DBU showed a slight preference for the formation of **16Z.**



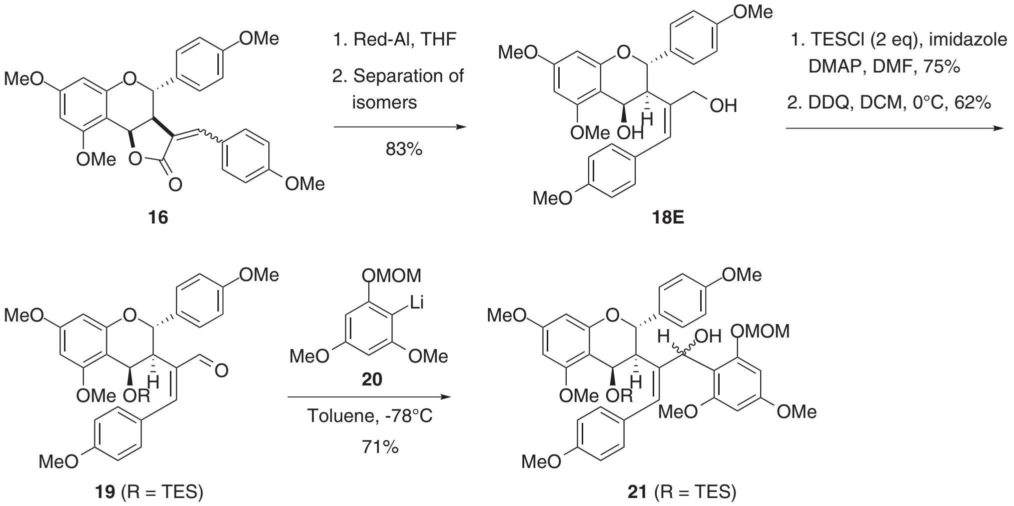
Scheme 3



Scheme 4



Scheme 5



Scheme 6

Although the complete chromatographic separation of these stereoisomers was challenging, sufficient amounts of each compound were isolated to allow full spectral characterizations. Based on well-established literature precedent [9], **16E** was identified by the presence of an olefinic proton downfield (δ=7.53 ppm) relative to the corresponding *Z* isomer (δ=5.89 ppm). Using this information, the *E*/*Z* isomeric ratio in product mixtures was determined from the integration of these olefinic protons in the NMR spectra.

The next goal was to transform these lactones into our chalcone targets using ring cleavage methodology (see Scheme 1). However, lactones **16** proved to be surprisingly resistant to modification. The mixture of lactones **16E** and **16Z**, for example, was completely inert to aryllithium reagents, thereby thwarting our original plans (see Scheme 1) and forcing us to consider alternative strategies. Hydrolysis with lithium hydroxide progressed to completion by TLC, but all attempts to isolate the hydroxy acid products led to ring closure back to the lactones. By comparison, reaction with $LiAlH_4$ never went to completion, even after 2 days in the presence of a large excess of the reducing agent. Fortunately, reduction with Red-Al went to completion and gave a mixture of the diols **18E** and **18Z** in 83% yield (Scheme 6). These isomers were easily separated by column chromatography, and their stereochemical assignments were made by direct correlation with the previously determined structures of **16E** and **16Z**. All attempts to oxidize diol **18E** to the corresponding keto-aldehyde resulted in conversion back to its lactone form. However, protection of both alcohol groups as their TES ethers, followed by DDQ oxidation, gave aldehyde **19** by selective oxidation of the protected allylic alcohol [18]. Addition of aryllithium reagent **20** [19] then provided compound **21** as an inseparable mixture of isomers, possessing all the necessary functionality required for biflavonoid synthesis. The ^1H NMR spectrum of this mixture was complex but showed the expected loss of the aldehyde signal along with a gain of aromatic signals. The structure assignment was further supported by HRMS data.

Conclusions

The first synthesis of 3-benzylidene-dihydrofurochromen-2-ones was described, and a potential strategy for the synthesis of complex biflavonoids such as chamaejasmine and isochamaejasmine was delineated. Because asymmetric routes to 2-aryl 2*H*-chromenes are well documented [20], enantioselective syntheses of these natural products should eventually be possible using the methodologies described herein.

Experimental

All reactions were performed under inert atmosphere (Ar or N_2) using oven-dried glassware. Flash purification of compounds was conducted using a Biotage-Isolera™ One column. Anhydrous DMSO, DMF, and toluene were purchased from Sigma Aldrich in a SureSeal™ bottle and used without further purification. Other solvents and reagents (THF, DCM, Et_3N, CH_3CN) were dried over sodium benzophenone ketyl or calcium hydride and distilled before use. The ^1H NMR (300 or 600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on Bruker-Avance 300 or 600 MHz instruments in $CDCl_3$. HRMS analyses were conducted on a Bruker Ultimate 3000, using ESI.

tert-Butyl methyl 5,7-dimethoxy-2-(4-methoxyphenyl)-1*a*,2-dihydrocyclopropa[*c*]chromene-1,1(7b*H*)-dicarboxylate (10) [11]

To a solution of chromene **8a** (175 mg, 0.55 mmol) and Rh_2(*S*-TBSP)$_4$ (8 mg, 0.055 mmol in dichloromethane (5 mL) was added a solution of *tert*-butyl methyl diazomalonate (347 mg, 1.73 mmol) in dichloromethane (3.3 mL) *via* a syringe pump over a period of 3–4 h. After the addition was complete, the reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using the ether/hexanes system as an eluent: yield 170 mg (66%); pale yellow oil; ^{1}H NMR (300 MHz): δ 7.82 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.10 (d, *J* = 2.2 Hz, 1H), 5.84 (d, *J* = 2.2 Hz, 1H), 5.49 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.25 (d, *J* = 9.6 Hz, 1H), 2.52 (d, *J* = 9.6 Hz, 1H), 1.49 (s, 9H).

Methyl 7,9-dimethoxy-4-(4-methoxyphenyl)-2-oxo-3,3*a*,4,9*b*-tetrahydro-2*H*-furo[3,2-*c*]chromene-3-carboxylate (12) [11]

To a solution of cyclopropane **10** (51 mg, 0.11 mmol) in dry dichloromethane (2.2 mL) at 0°C was added tin(II) triflate (23 mg, 0.054 mmol). The resulting solution was allowed to warm up to room temperature overnight. It was then quenched with water and the layers were separated. The aqueous layer was extracted with dichloromethane (×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography: yield 45 mg (78%); yellow oil; ^{1}H NMR (600 MHz): δ 7.36 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.14 (d, *J* = 2.1 Hz, 1H), 6.10 (d, *J* = 2.1 Hz, 1H), 5.83 (d, *J* = 4.8 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.76 (s, 6H), 3.29 (dd, *J* = 11.5, 4.9 Hz), 1H), 3.23 (s, 1H).

7,9-Dimethoxy-4-(4-methoxyphenyl)-3,3*a*,4,9*b*-tetrahydro-2*H*-furo[3,2-*c*]chromen-2-one (13)

To a solution of lactone **12** (54 mg, 0.13 mmol) in DMF (2 mL) was added sodium iodide (58 mg, 0.39 mmol). After refluxing for 5 h, the solvent was removed under reduced pressure. The residue was then dissolved in water, then extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by flash column chromatography: yield 42 mg (91%); yellow oil; ^{1}H NMR (600 MHz): δ 7.34 (d, *J* = 8.6 Hz, 2H) 6.96–6.94 (d, *J* = 8.6 Hz, 2H), 6.14 (d, *J* = 2.1 Hz, 2H), 6.11 (d, *J* = 2.1 Hz, 2H), 5.60 (d, *J* = 4.8 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 2.86–2.82 (m, 1H), 2.78 (dd, *J* = 17.8 Hz, 7.9 Hz, 1H), 2.25 (d, *J* = 17.8 Hz, 1H); ^{13}C NMR: δ 175.4, 162.5, 160.5, 160.2, 157.5, 129.2, 129.1, 114.3, 99.9, 93.1, 92.4, 72.2, 55.8, 55.4, 55.3, 39.1, 32.4. HRMS (ESI-TOF). Calcd for $C_{20}H_{21}O_6$ ([M+H]$^+$): *m/z* 357.1333. Found: *m/z* 357.1328.

Diethyl (7,9-dimethoxy-4-(4-methoxyphenyl)-2-oxo-3,3*a*,4,9*b*-tetrahydro-2*H*-furo[3,2-*c*]chromen-3-yl) phosphonate (14)

To a solution of lactone **13** (22 mg, 0.062 mmol) in THF (0.5 mL) at -78°C was added LHMDS (0.13 mL, 0.13 mmol, 1 m in THF). After stirring the solution at that temperature for 2 h, TMEDA (20 µL, 0.13 mmol) and diethylchlorophosphite (20 µL, 0.14 mmol) were added, and the reaction mixture was allowed to warm to room temperature over 3 h. The mixture was then quenched by a slow addition of 1 m acetic acid in ether (2 mL), filtered through a celite pad, and the pad was washed with ether. After concentration under reduced pressure, the residue was stirred overnight in the flask, left open to air, then dissolved in ether. The solution was washed with saturated $NaHCO_3$ and brine, and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography: yield 13 mg (43%) of a mixture of diastereomers; clear oil; ^{1}H NMR (300 MHz): δ 7.37 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.14 (d, *J* = 2.2 Hz, 1H), 6.09 (d, *J* = 2.2 Hz, 1H), 5.90 (d, *J* = 2.2 Hz, 1H), 4.53 (d, *J* = 5.0 Hz, 1H), 4.17–4.01 (m, 4H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.25–3.20 (m, 1H) 2.74 (d, *J* = 24.7 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.0 Hz, 3H).

3-(Hydroxy(4-methoxyphenyl)methyl)-7,9-dimethoxy-4-(4-methoxyphenyl)-3,3*a*,4,9*b*-tetrahydro-2*H*-furo[3,2-*c*]chromen-2-one (17)

To a solution of lactone **13** (295 mg, 0.83 mmol) in THF (2 mL) was added LHMDS (1.65 mL, 1.65 mmol, 1 m in THF) at -78°C. After stirring for 2 h at that temperature, *p*-anisaldehyde (200 µL, 1.65 mmol) was added. The solution was stirred for an additional 2 h at -78°C, after which the mixture was quenched by the addition of saturated aqueous solution of NH_4Cl and warmed to room temperature. The mixture was then extracted with EtOAc (×3), and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography: yield 308 mg (76%) of a mixture of diastereomers; clear oil.

One diastereomer ^{1}H NMR (600 MHz): δ 6.91 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.60 (d, *J* = 8.3 Hz, 2H), 6.11 (s, 1H), 6.03 (s, 1H), 5.76 (d, *J* = 5.5 Hz, 1H), 5.31 (s, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H), 2.83 (dd, *J* = 11.5 Hz, 5.5 Hz, 1H), 2.46 (s, 1H), 2.25 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR: 177.2, 162.2, 160.8, 159.6, 158.8, 157.3, 132.7, 128.8, 128.1, 125.8, 113.8, 113.7, 100.3, 99.9, 93.0, 92.4, 77.2, 72.9, 72.7, 55.7, 55.3, 55.1, 52.5, 39.1.

Other diastereomer ^{1}H NMR (600 MHz): δ 6.97 (d, *J* = 7.7 Hz, 2H), 6.95 (d, *J* = 7.7 Hz, 2H), 6.77 (d, *J* = 7.7 Hz, 2H), 6.72 (d, *J* = 7.7 Hz, 2H), 6.10 (s, 1H), 6.04 (s, 1H), 5.50 (d, *J* = 5.3 Hz, 1H), 4.91 (d, *J* = 9.0 Hz, 1H), 4.42 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.22 (s, 1H), 2.59 (d, *J* = 9.1, 1H), 2.56 (dd, *J* = 10.8, 5.3 Hz, 1H); ^{13}C NMR: 177.0, 162.5, 160.6, 160.0, 159.6, 157.2, 131.7, 129.0, 128.2, 127.6, 114.1, 114.0, 99.7, 93.1, 92.5, 76.7, 72.3, 71.5, 55.8, 55.4, 55.3, 55.2, 51.3, 41.7. HRMS (ESI-TOF). Calcd for $C_{20}H_{21}O_6$ ([M+H]$^+$): *m/z* 493.1857. Found: *m/z* 493.1855.

7,9-Dimethoxy-3-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-3,3*a*,4,9*b*-tetrahydro-2*H*-furo[3,2-*c*] chromen-2-one (16)

Procedure A To a solution of aldol product **17** (308 mg, 0.63 mmol) in dichloromethane (4 mL) at 0°C was added mesyl chloride (98 µL, 1.26 mmol) and Et_3N (437 µL, 3.14 mmol). After stirring at room temperature for 1 h, the mixture was cooled to 0°C and DBU (668 µL, 3.13 mmol) was added. The mixture was warmed to room temperature, stirred overnight, then diluted with distilled water, and the layers were separated. The aqueous layer was extracted with dichloromethane (×3), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography: yield 243 mg (82%); yellow oil.

Procedure B To a solution of aldol product **17** (27 mg, 0.055 mmol) in dichloromethane (0.5 mL) at 0°C was added Et_3N (38 µL, 0.27 mmol) and mesyl chloride (9 µL, 0.11 mmol). The mixture was warmed to room temperature, stirred for 1 h, and then quenched by the addition of distilled water. The layers were separated, and the aqueous phase was extracted with dichloromethane. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was the removed *in vacuo* and the residue was dissolved in dry THF (7 mL). Potassium *tert*-butoxide (19 mg, 0.17 mmol) was then added and the mixture was heated under reflux until reaction was completed, as indicated by TLC analysis. The mixture was diluted with distilled water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography: yield 16.2 mg (62%); pale yellow oil.

***E*-Alkene (16E)** ^{1}H NMR (300 MHz): δ 7.53 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 6.17 (s, 2H), 5.5 (d, *J* = 4.7 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H); ^{13}C NMR: 172.0, 162.5, 160.7, 160.3, 159.7, 157.5, 139.8, 131.0, 129.4, 128.2, 126.2, 122.5, 113.6, 113.6, 99.9, 93.1, 92.5, 76.7, 70.1, 55.8, 55.4, 55.2, 55.0, 44.4; HRMS (ESI-TOF). Calcd for $C_{28}H_{26}NaO_7$ ([M+Na]$^+$): 497.1571. Found: *m*/*z* 497.1623.

***Z*-Alkene (16Z)** ^{1}H NMR (300 MHz): δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.16 (s, 2H), 5.90 (s, 1H), 5.60 (d, 5.1 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.23 (dd, *J* = 11.0, 5.0 Hz, 1H); ^{13}C NMR: 168.7, 162.4, 160.9, 160.8, 160.0, 157.6, 143.2, 133.0, 129.5, 129.1, 126.1, 121.3, 113.9, 113.5, 100.2, 93.1, 92.6, 77.6, 69.2, 55.8, 55.4, 55.4, 55.3, 48.5.

3-(3-Hydroxy-1-(4-methoxyphenyl)prop-1-en-2-yl)-5,7-dimethoxy-2-(4-methoxyphenyl) chroman-4-ol (18)

Red-Al (0.66 mL, 2.05 mmol, 60% weight in toluene) was added dropwise to a solution of α-benzylidene lactone **16** (243 mg, 0.51 mmol) in THF (4.2 mL) at 0°C. The mixture was warmed to room temperature and stirred for 3 h, then cooled to 0°C, and treated dropwise with a saturated solution of Rochelle's salt. The layers were separated and the organic layer was washed with a saturated solution of Rochelle's salt. The combined aqueous layers were extracted with ether (×3), followed by washing of the combined organic layers with brine. The organic solution was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography: yield 204 mg (83%); clear oil (*Z* isomer, 73 mg; *E* isomer, 125 mg; mixture, 6 mg).

***E* isomer (18E)** ^{1}H NMR (600 MHz): δ 7.11 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.55 (s, 1H), 6.10 (d, *J* = 2.2 Hz, 1H), 6.02 (d, *J* = 2.2 Hz, 1H), 5.35 (d, *J* = 11.0 Hz, 1H), 5.12 (d, *J* = 3.3 Hz, 1H), 4.11 (d, *J* = 12.0 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (d, *J* = 12.0 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, *J* = 11.0, 3.42 Hz, 1H); ^{13}C NMR: δ 161.4, 159.8, 158.8, 158.5, 155.9, 138.0, 134.8, 130.2, 129.8, 129.5, 129.4, 113.8, 113.7, 105.9, 93.1, 91.7, 75.8, 65.1, 64.1, 60.3, 55.6, 55.3, 55.2, 55.1, 44.3. HRMS (ESI-TOF). Calcd for $C_{28}H_{30}O_7$ ([M]$^+$): *m*/*z* 478.1992. Found: *m*/*z* 478.1963.

***Z* isomer (18Z)** ^{1}H NMR (600 MHz)): δ 7.35 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.47 (s, 1H), 5.40 (d, *J* = 11.2 Hz, 1H), 5.11 (d, *J* = 3.4 Hz, 1H), 3.88 (s, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.15 (dd, *J* = 11.2 Hz, 3.4 Hz, 1H); ^{13}C NMR: δ 161.5, 159.9, 158.9, 158.7, 155.9, 136.7, 135.3, 130.4, 130.4, 129.5, 129.1, 113.9, 113.5, 105.9, 93.2, 91.7, 75.6, 64.9, 58.2, 55.6, 55.4, 55.2, 52.7. HRMS (ESI-TOF). Calcd for $C_{28}H_{30}O_7$ ([M]$^+$): *m*/*z* 478.1992. Found: *m*/*z* 478.1963.

(*E*)-2-(5,7-dimethoxy-2-(4-methoxyphenyl)-4-((triethylsilyl)oxy)chroman-3-yl)-3-(4-methoxyphenyl) acrylaldehyde (19)

To a solution of diol **18E** (125 mg, 0.26 mmol), imidazole (110 mg, 1.62 mmol), and 4-DMAP (12.7 mg, 0.1 mmol) in dry DMF (8 mL) at 0°C was added TESCl (184 µL, 1.1 mmol). The mixture was warmed to room temperature, stirred overnight, and then poured onto a saturated solution of $NaHCO_3$. After extraction with ether (×3), the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue of this bis-trimethylsilyl ether was purified by flash column chromatography: yield 139 mg (75%); clear oil; ^{1}H NMR (600 MHz): 7.11 (d, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.82–6.81 (m, 4H), 6.65 (s, 1H), 5.99 (s, 1H), 5.93 (s, 1H), 5.49 (d, *J* = 11.6 Hz, 1H), 5.22 (s, 1H), 4.73 (d, *J* = 15.8 Hz, 1H), 3.91 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 3H), 3.792 (s, 3H), 3.784 (s, 3H), 3.680 (s, 3H), 3.46 (d, *J* = 11.6 Hz, 1H), 0.90 (t, *J* = 7.7 Hz, 9H), 0.85 (t, *J* = 7.7 Hz, 9H), 0.63–0.53 (m, 6H), 0.463 (q, *J* = 7.7 Hz, 6H); ^{13}C NMR: 161.1, 159.8, 157.8, 157.7, 155.9, 139.3, 130.9, 130.8, 129.8, 129.7, 125.1, 113.8, 113.7, 106.8, 92.8, 90.6, 75.3, 64.8, 55.3, 55.2, 55.1, 54.8, 43.7, 6.9, 6.7, 5.0, 4.3. HRMS (ESI-TOF). Calcd for $C_{40}H_{50}NaSi_2$: *m*/*z* 729.3613 ([M+Na]$^+$). Found: *m*/*z* 729.3606.

To a solution of this bis-protected triethylsiyl ether (36.4 mg, 0.05 mmol) in DCM at 0°C was added DDQ (12.8 mg, 0.06 mmol) and phosphate pH 7 buffer (0.18 mL). The solution was warmed to room temperature and monitored for completion. Upon completion, saturated $NaHCO_3$ was added and the layers were separated. The aqueous phase was extracted with ether (×3). The combined organic layers were then washed with brine and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue of **19** was purified by flash column chromatography: yield 20.7 mg (68%; 79% based on recovered starting material); clear oil; ^{1}H NMR (600 MHz):

δ 9.57 (s. 1H), 7.30 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.77 (d, *J* = 7.9 Hz, 2H), 6.14 (d, *J* = 11.0 Hz, 1H), 6.05 (s, 2H), 5.20 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.66 (d, *J* = 10.9 Hz, 1H), 0.85 (t, *J* = 8.0, 9 H), 0.62–0.49 (m, 6H); ^{13}C NMR: δ 193.0, 161.3, 160.3, 159.7, 159.7, 158.4, 145.2, 131.2, 130.7, 129.6, 114.4, 113.8, 106.3, 92.9, 91.0, 74.8, 64.1, 59.7, 55.3, 55.2, 55.2, 54.7, 6.9, 4.8; HRMS (ESI-TOF) m/z: [M+H]$^+$. Calcd for $C_{34}H_{43}O_7Si$: 591.2773. Found: 591.2721.

(*E*)-2-(5,7-Dimethoxy-2-(4-methoxyphenyl)-4-((triethylsilyl)oxy)chroman-3-yl)-1-(2,4-dimethoxy-6-(methoxymethoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-ol (21)

To a solution of aldehyde **19** (24.5 mg, 0.04 mmol) in toluene (0.3 mL) at -78°C was added a freshly prepared solution of aryllithium **20** (0.41 mL, 0.3 m in toluene, 0.12 mmol). The reaction mixture was stirred at -78°C for 15 min and then warmed to -50°C over 30 min and then to room temperature over 2 h. The mixture was then quenched by the addition of a saturated solution of NH_4Cl and extracted with EtOAc (×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography: yield 23.1 mg of a mixture of inseparable diastereomers (71%). HRMS (ESI-TOF). Calcd for $C_{44}H_{56}NaO_{11}$ (Si[M+Na]$^+$): *m/z* 811.3490. Found: *m/z* 811.3447.

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