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

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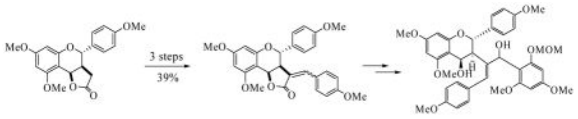
Abstract

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 KO^{t}Bu favored formation of the *E*-isomer, 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.

Graphical Abstract



Keywords

biflavonoids; donor-acceptor cyclopropanes; α-benzylidene lactones; chamaejasmine; 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 *B. 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 antimalarial activity.[3] Also isolated from more than one plant source, chamaejasmine has

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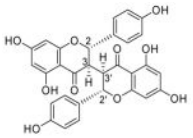
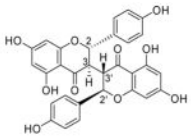
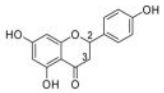
been shown to possess both anti-inflammatory activity and aldose reductase inhibiting activity,[4] suggesting that it could be a potential treatment for the complications associated with diabetic neuropathy and related conditions. Structurally, chamaejasmine and isochamaejasmine are dimers of the flavanone 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**),[7] which, we reasoned, should provide chalcones **5** upon cleavage with an *o*-alkoxy aryl lithium reagent.[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 have shown that the stereochemistry of Horner-Wadsworth-Emmons (HWE) olefinations of related α-phosphono-γ-lactones can be controlled to give either E- or Z-alkenes, depending on the reaction conditions used.[9]


Chamaejasmine (1)


Isochamaejasmine (2)


Naringenin (3)

Results and Discussion

Our starting materials were chromenes *rac*-**8a** and *rac*-**8b** (Scheme 2), which were prepared according to well-documented literature procedures.[10] We have previously shown that 2-aryl 2*H*-chromenes can be stereoselectively lactonized in a two-step cyclopropanation-rearrangement sequence.[11] 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 rearranged 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 unreactive to 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 unreactive to **9b** under rhodium catalysis. Osipov and coworkers have reported some success in the CuI-mediated cyclopropanations of alkenes with α-trifluoromethyl-diazophosphonate in refluxing toluene,[12] but this, too, failed in our hands. Instead, compound **14** was prepared by α-phosphorylation of lactone **13**,[13] obtained from compound **12** by decarboxylation with NaI in refluxing DMF.[14]

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. We reasoned that if the aldol is stereoselective, a stereospecific elimination step would provide the α-benzylidene lactone diastereomerically enriched. However, this approach proved to be challenging. The boron enolate of lactone **13** provided a single aldol stereoisomer[15] with *p*-anisaldehyde, but the yields were disappointing (Scheme 4).

By contrast, higher aldol yields were observed with the corresponding lithium enolate, although the reaction resulted in a mixture of stereoisomers **17** (Scheme 5). Moreover, base-induced elimination of the corresponding mesylates of this mixture was found to be base-dependent. With KO^{t}Bu, **16E** was the predominant product, while DBU showed a slight preference for the formation of **16Z**. Although the complete chromatographic separation of these stereoisomers was challenging, sufficient amounts of each 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 unreactive 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 two days in the presence of a large excess of the reducing agent. Fortunately, however, 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 separable 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.[16] Addition of aryllithium reagent **20**[17] then provided compound **21** as an inseparable mixture of isomers, possessing all the necessary functionality required for biflavonoid synthesis. The ^{1}H-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 the HRMS data.

Conclusions

We have described the first synthesis of 3-benzylidene dihydrofurochromen-2-ones, and we have identified a potential strategy for the synthesis of complex biflavonoids such as chamaejasmine and isochamaejasmine. Because asymmetric routes to 2-aryl 2*H*-chromenes are well-documented,[18] enantioselective syntheses of these natural products should eventually be possible using the methodologies described herein.

Experimental Details

All reactions were performed using oven-dried glassware under inert atmosphere (Ar or N_2). Flash purification of compounds was conducted using Biotage-Isolera™ One. 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 ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-Avance 300 or 600 MHz instrument in $CDCl_3$ and data are reported as chemical shift (δ) in ppm from tetramethylsilane as an internal standard. For ^{13}C NMR spectra data are reported as δ in ppm from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$, 77.16 ppm). HRMS analyses were conducted on a Bruker Ultimate 3000, using ESI.

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

To a solution of chromene **8a** (175 mg, 0.55 mmol) and Rh_2(*S*-TBSP)$_4$ (8 mg, 0.055 mmol in DCM (5 mL) was added a solution of *tert*-butyl methyl malonate diazo (347 mg, 1.73 mmol) in DCM (3.3 mL) via syringe pump over a period of 3–4 hours. 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 Et_2O/hexane system as the eluent. Yield: 170 mg (66%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.7 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-3,3a,4,9b-tetrahydro-2*H*-furo[3,2-c]chromene-3-carboxylate (12)[11a]

To a solution of cyclopropane **10** (51 mg, 0.11 mmol) in dry DCM (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 DCM (x3). 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, $CDCl_3$): 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)-3,3a,4,9b-tetrahydro-2H-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). Afte refluxing for 5 hours the solvent was removed under reduced pressure. The residue was then dissolved in water the 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, $CDCl_3$): δ 7.34 (d, *J* = 8.6 Hz, 2H) 6.96-6.94 (d, *J*=8.6 Hz, 2H), 6.14 (d, *J* = 2.1Hz, 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, 7.9 Hz, 1H), 2.25 (d, *J* = 17.8 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): 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) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_6$, 357.1333; found, 357.1328.

Diethyl (7,9-dimethoxy-4-(4-methoxyphenyl)-2-oxo-3,3a,4,9b-tetrahydro-2H-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, 1M in THF). After stirring the solution at that temperature for 2 hours TMEDA (20 μL, 0.13 mmol) and diethylchlorophosphite (20 μL, 0.14 mmol) was added and the reaction mixture was allowed to warm to room temperature over 3 hours. The reaction was then quenched by the slow addition of 1 M acetic acid in Et_2O (2 mL). The resulted mixture was filtered through a celite pad and the pad was washed with $E_{t2}O$. After concentration under reduced pressure the residue was stirred overnight with the flask was left open to air. The mixture was dissolved in Et_2O, washed with saturated $NaHCO_3$ and brine respectively and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. Yield: 13 mg (43%) as a mixture of diastereomers; clear oil; 1H NMR (300 MHz, CDCl3): δ 7.37(d, J = 8.7 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* = 2.1 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, 1H), 1.31 (t, *J* = 7.1, 3 H), 1.23 (t, *J* = 7.0, 3H).

3-(hydroxy(4-methoxyphenyl)methyl)-7,9-dimethoxy-4-(4-methoxyphenyl)-3,3a,4,9b-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 hours at that temperature, *p*-anisaldehyde (200 μL, 1.65 mmol) was added. The solution was stirred for an additional 2 hours at −78 °C, after which the reaction was quenched by the addition of saturated aqueous NH_4Cl and warmed to room temperature. The resultant mixture was then extracted with

EtOAc (x3), 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 purified by flash column chromatography. Yield: 308 mg (76%) as a mixture of diastereomers; clear oil; ^{1}H NMR (600 MHz, $CDCl_3$): 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, 5.5 Hz,1H), 2.46 (s, 1H), 2.25 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): 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**: δ 6.97 (d, *J* = 7.7 Hz, 2H), 6.95 (d, *J* = 7.68 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* = 10.9 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, 5.4 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): 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) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_6$, 493.1857; found, 493.1855.

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

Procedure A—To a solution of aldol product **17** (308 mg, 0.63 mmol) in DCM (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 hour, the reaction mixture was cooled to 0 °C and DBU (668 μL, 3.13 mmol) was added. The reaction was warmed to room temperature and stirred overnight. It was then diluted by the addition of distilled water and the layers were separated. The aqueous layer was extracted with DCM (x3), 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 purified by flash column chromatography. Yield: 242.9 mg (82%); yellow oil.

Procedure B—To a solution of of aldol product **17** (27 mg, 0.055 mmol) in DCM (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 and stirred for 1 hour. It was then quenched by the addition of distilled water. The layers were separated and the aqueous phase was extracted with DCM. 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 dissolved in dry THF (7 mL). Potassium *tert*-butoxide (19 mg, 0.17 mmol) was then added and the mixture was refluxed until reaction was complete, as indicated by TLC. After completion the reaction mixture was diluted with distilled water and was 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, $CDCl_3$): δ 7.53 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.8 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 (600 MHz, $CDCl_3$): 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) m/z: $[M+Na]^+$ calcd for $C_{28}H_{26}NaO_7$, 497.1571; found, 497.1623. ***Z*- alkene (16Z)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.8 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 (600 MHz, $CDCl_3$): 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** (242.9 mg, 0.51 mmol) in THF (4.2 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 3 hours. The reaction was then cooled to 0 °C and a saturated solution of Rochelle's salt was added dropwise. 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 Et_2O (x3), followed by washing of the combined organic layers with brine. The organic layer 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, $CDCl_3$): 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* = 11.1 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* = 12.4 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, *J* = 11.0, 3.42 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): 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) m/z: $[M]^+$ calcd for $C_{28}H_{30}O_7$, 478.1992; found, 478.1963. **Z Isomer (18Z)**: ^{1}H NMR (600 MHz, $CDCl_3$): 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, 3.2 Hz, 1H); ^{13}C NMR (600MHz, $CDCl_3$): 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) m/z: $[M]^+$ calcd for $C_{28}H_{30}O_7$, 478.1992; found, 478.1963.

(*E*)-((5,7-dimethoxy-2-(4-methoxyphenyl)-3-(1-(4-methoxyphenyl)-3-((triethylsilyl)oxy)prop-1-en-2-yl)chroman-4-yl)oxy)triethylsilane

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 reaction was then warmed to rt and stirred overnight. It was then poured into a saturated solution of $NaHCO_3$ and extracted with Et_2O (x3). The organic layer was then washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by flash column chromatography. Yield: 139 mg (75 %); clear oil. ^{1}H

NMR (600 MHz, $CDCl_3$): 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* = 7.6 Hz, 9H), 0.63-0.53 (m, 6H), 0.463 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR (600 MHz, $CDCl_3$): 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) m/z: $[M+Na]^+$ calcd for $C_{40}H_{50}NaSi_2$, 729.3613; found, 729.3606.

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

To a solution of 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 Et_2O (x3). 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 was purified by flash column chromatography. Yield: 20.7 mg (68%; 79% based on recovered starting material); clear oil. ^1H NMR (600 MHz, $CDCl_3$): 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 (600 MHz, $CDCl_3$): 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 mins and then warmed to −50 °C over 30 mins, and then to rt over 2 hours. The reaction was then quenched by the addition of a saturated solution of NH_4Cl and extracted with EtOAc (x3). The combined organic layers were then washed 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 as a mixture of inseparable diastereomers (71%); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{44}H_{56}NaO_{11}Si$, 811.3490; found, 811.3447.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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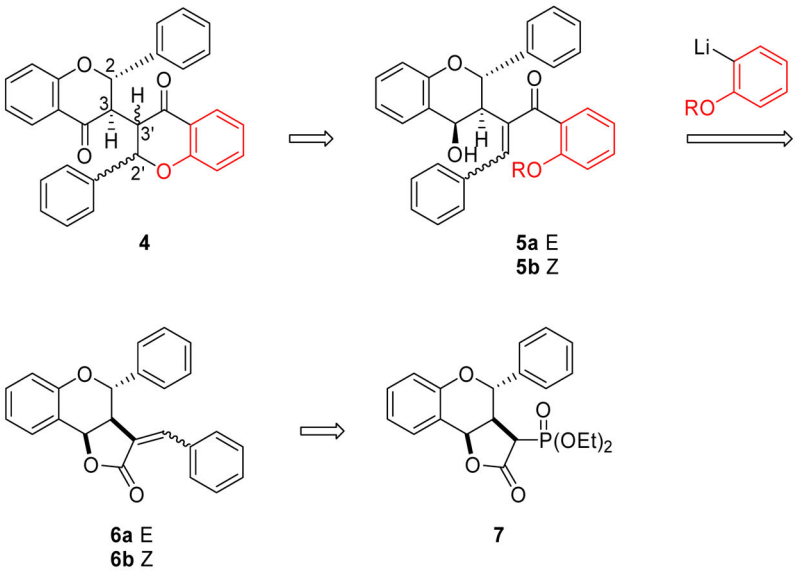
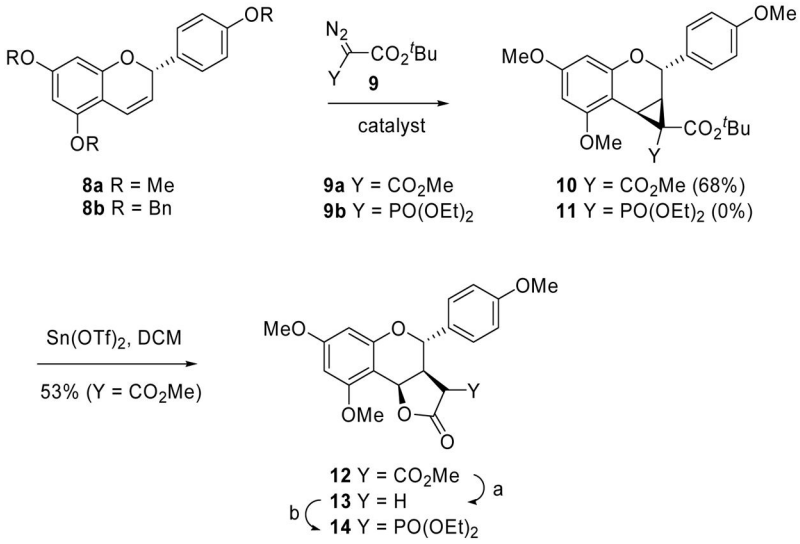


Scheme 1.



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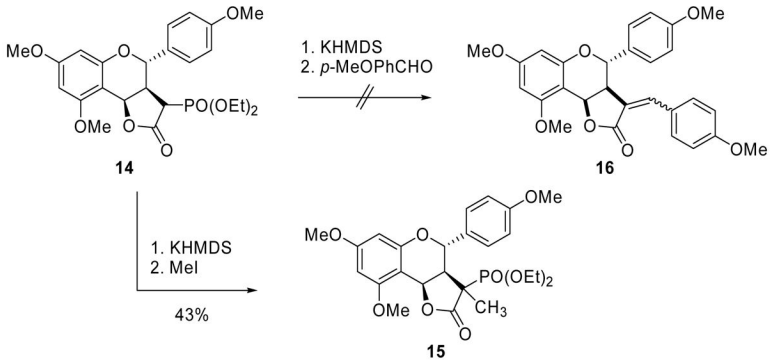

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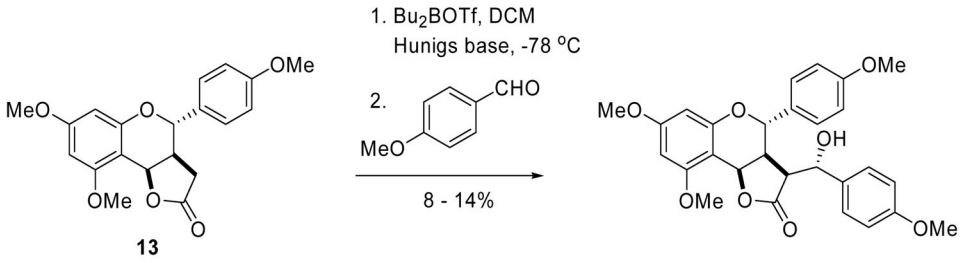

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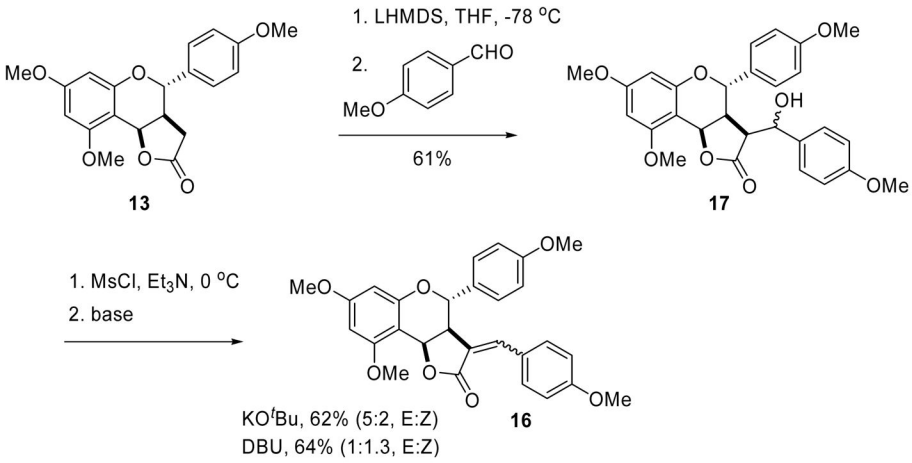
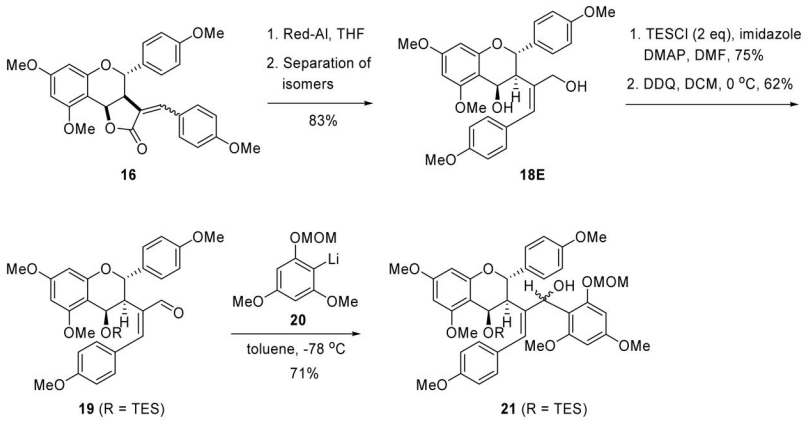


Scheme 5.



Scheme 6.