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Expedient synthesis of [5,5]- and [6,5]-benzannulated spiroketals from 1,1-diacyl-2-vinyl cyclopropanes

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Dedicated with respect and admiration to Professor Samir Zard

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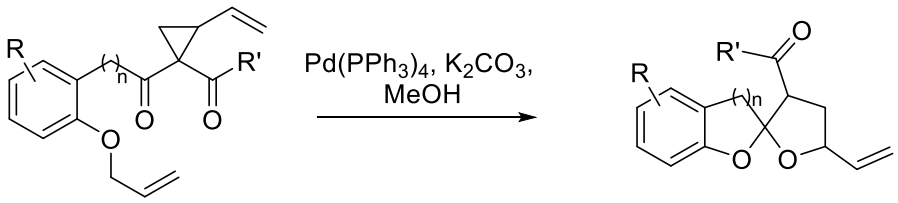
Abstract

Palladium-mediated oxidative spirocyclization of 1,1-diacyl-2-vinylcyclopropanes afforded a small series of benzannulated 6,5- and 5,5-spiroketals. The rapid construction of these scaffolds proceeded in moderate to good yield (27-63%). However, efforts to thoroughly examine scope were hampered by both poor diastereoselectivity and, in the case of the 5,5-benzannulated spiroketal series, access to the requisite 1,3-dicarbonyl starting materials.



Keywords: Spiroketal, vinyl cyclopropane, donor-acceptor, benzannulation

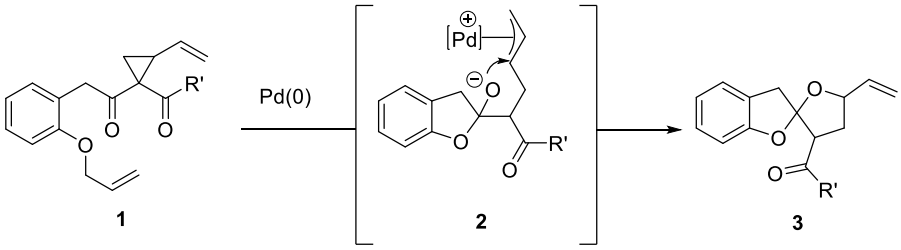
Introduction

Cyclopropanes, with their unique strained structure, have emerged as valuable building blocks in the synthesis of high-value compounds. [1-5] The strained three-membered ring of cyclopropane imparts reactivity that distinguishes it from other cycloalkanes, making it a versatile and powerful tool for chemical synthesis.[6-9] Benzannulated spiroketal often possess diverse biological activities and have been studied for their potential medicinal applications. The three-dimensional arrangement of benzannulated spiroketal can be crucial for interacting with biological targets, with this unique spatial arrangement often leading to specific and potent biological activities.[9,10]

Recently we reported the use of 1,1-diacyl-2-vinyl cyclopropanes to access benzannulated 6,5-spiroketals in high yield and diastereoselectvity.[12] While this was an efficient method for the synthesis of a small scope of vinyl substituted tetrahydrofuran containing 6,5-benzannulated spiroketals, it was not clear at the outset of this study exactly how broad of a substrate scope this methodology could be applied to. Herein, we report our efforts to extend our previously reported method to the construction of benzannulated 5,5-spiroketals, as well as additional benzannulated 6,5-spiroketals.

Results and Discussion

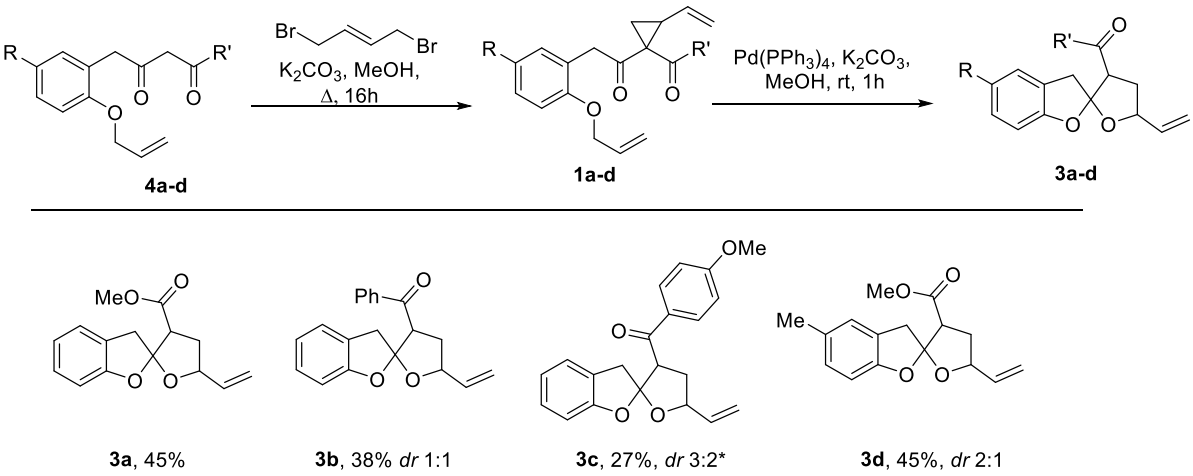
In an analogous fashion to our reported synthesis of benzannulated 6,5-spiroketals, we speculated that the intermediate lactol would be generated by oxidative addition of the palladium (0) to vinylcyclopropane **1** (Scheme 1). The oxygen anion of zwitterion **2** would then attack the π-allyl complex to afford benzannulated 5,5-spiroketals **3**.



Scheme 1. Proposed oxidative spirocyclization to afford benzannulated 5,5-spiroketal **3**.

To establish if our previously reported method to access benzannulated 6,5-spiroketals could be applied to the synthesis of 5,5-benzannulated spiroketals, a small series of 1,3-dicarbonyl compounds **4a-d** were synthesized from the appropriate 2-allyloxy phenylacetic acid derivatives using adapted literature methods (Scheme 2).[12,13] After some screening of the reaction conditions for the desired cyclopropanation, it was found that treatment of the corresponding 1,3-dicarbonyl compound **4** with 1,4-dibromobut-2-ene with potassium carbonate in refluxing methanol provided the desired vinyl cyclopropanes **1a-d** in acceptable yields. Pleasingly, treatment of the vinyl cyclopropane **1a** with Pd(0) and potassium carbonate in methanol at room temperature for 1 h, smoothly provided the benzannulated 5,5-spiroketal **3a** in 45% isolated yield, as a single diastereoisomer (Scheme 2). Moving from the β-ketoester to the phenyl ketone **1b** system had little impact on the efficiency of the spiroketalization but did remove the diastereoselectivity leading to a 1:1 mixture of inseparable diastereomers, as determined by analysis of the ^{1}H NMR spectrum. The 4-methoxyphenyl ketone

1c was found to be unstable on silica gel and could not be isolated, so the crude residue was reacted on immediately to established spirocyclization reaction conditions to afford the benzannulated spiroketal **3c** as an inseparable 3:2 mixture of diastereomers in a 27% yield over two steps. Returning to the beta keto ester analogs, the tolyl system **1d** smoothly provided the benzannulated spiroketal analog **3d** in comparable yield and as a 2:1 mixture of diastereoisomers.

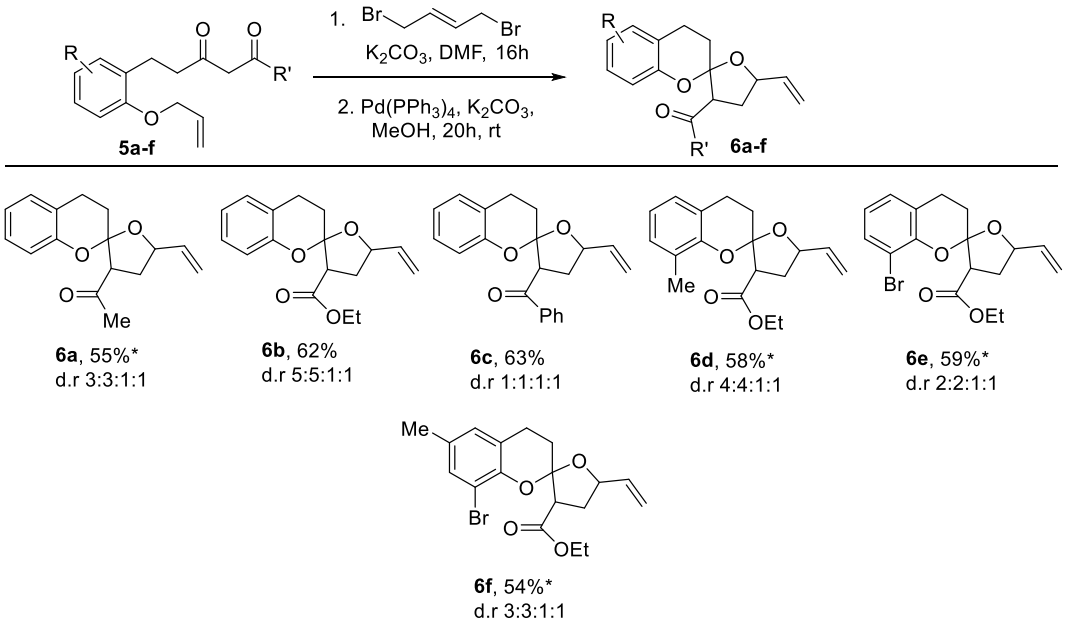


Scheme 2. Synthesis of benzannulated 5,5-spiroketals **3a-d**, yields are reported for final step **1** to **3** *vinyl cyclopropane **1c** was not stable to silica gel chromatography, yield is reported over 2 steps.

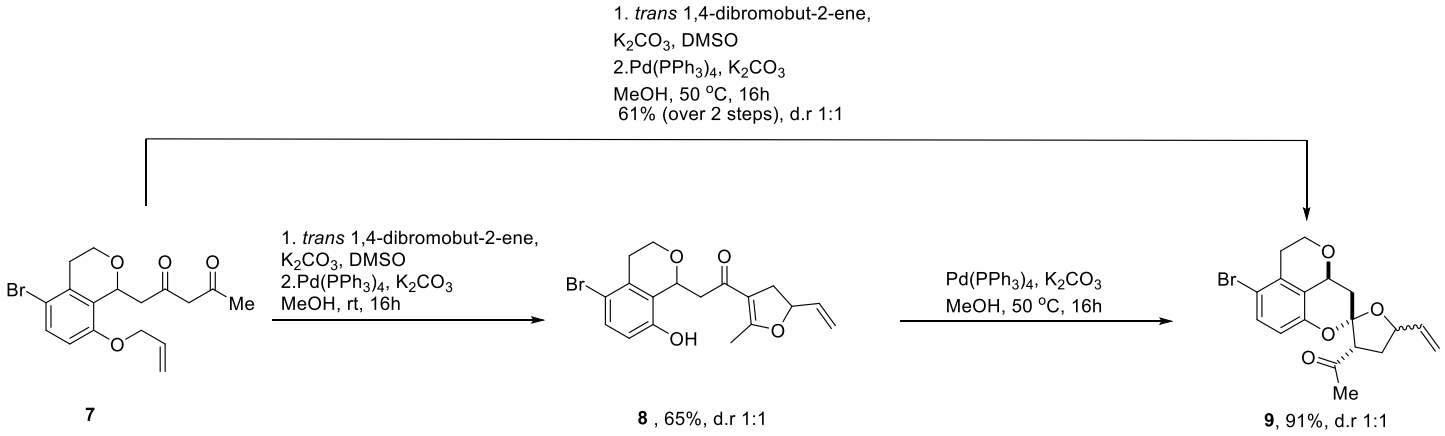
Given the varying diastereoselectivities observed between structurally similar substrates, and the difficulties encountered trying to access additional 1,3-dicarbonyl analogues we decided to shift focus to the more synthetically tractable one carbon homologs **5**.

Access to the dicarbonyl starting materials **5a-e** and their respective vinylcyclopropanes proved relatively straightforward using adapted literature procedures.[12] The efficiency of the oxidative spirocyclization did not appear to vary with the type of 1,3-dicarbonyl substructure with the methylketone **5a**, β-keto ester **5b** and benzoyl **5c** all providing the requisite benzannulated [6,5]-spiroketal in 55-63% yield, over 2 steps (Scheme 3). Given the highest diastereoselectivity was observed with the β-keto ester **5b**, we next examined substituents on the aromatic portion both the tolyl **5d** and bromobenzene **5e** derivatives performed similarly with good yields and moderate diastereoselectivity. The bromotolyl derived substrate **5f** also performed well providing the spiroketal **6f** in a 55% with modest diastereoselectivity. Notably, during the isolation attempts of benzannulated spiroketals **6**, we observed significant mass recovery deviation of the expected diastereomers based off analysis of the proton NMR of the reaction mixtures. To probe this further we treated isolated diastereomers to acidic and basic conditions, including stirring with silica, and no epimerization products were detected. In several cases (**6a, d, e** and **f**) only 3 diastereomers were isolated after silica gel chromatography leading us to the conclusion that they were decomposing during purification (Scheme 3).

As previously reported,[12] the methylketone **7** could be efficiently elaborated to the berkelic acid analogue **9** using the reaction conditions outlined in Scheme 4. However, when the reaction was conducted at room temperature the dihydrofuran **8** was isolated in a 65%, with only traces of the spiroketal **9**. This intermediate was then subjected to the same oxidative spirocyclization reaction conditions with an elevated reaction temperature to afford the berkelic acid analogue **9** as the thermodynamic product. Not only does this provide access to heavily substituted dihydrofurans but it also provides support to our mechanistic suggestions in our original communication.[12]



Scheme 3. Synthesis of benzannulated 6,5-spiroketals **6a-f**, yield over 2 steps, d.r calculated from ^{1}H NMR of crude reaction mixture. * Only 3 diastereomers isolated, the other isomer presumably decomposed during purification.



Scheme 4. Synthesis of berkelic acid derivative **9** can proceed via the dihydrofuran **8**.

Conclusions

Extension of our methodology to benzannulated 5,5-spiroketals provided a small series of analogues, these preliminary results show the spirocyclization strategy was successful however, access to the requisite 1,3-dicarbonyl substrate proved difficult and highlights the need for additional methods to access this structure type, before the generality of this method can be fully assessed. The substrate scope for benzannulated 6,5-spiroketal was expanded and the impact of benzylic substitution on diastereoselectivity was demonstrated.

Experimental Section

General. Thin layer chromatography (TLC) was performed on ALUGRAM® aluminium-backed UV_{254} silica gel 60 (0.20 mm) plates. Compounds were visualized with either p-anisaldehyde or 20% w/w phosphomolybdic acid in ethanol. Column chromatography was performed using silica gel 60. Infrared spectra were recorded on a Bruker Optics Alpha ATR FT-IR spectrometer. High resolution mass-spectra (HRMS) were recorded on a Bruker microTOFQ mass spectrometer using an electrospray ionisation (ESI) source in either the positive or negative modes. ^{1}H NMR spectra were recorded at either 400 MHz on a Varian 400-MR NMR system or at 500 MHz on a Varian 500 MHz AR premium shielded spectrometer. All spectra were recorded from samples in $CDCl_3$ at 25 °C in 5 mm NMR tubes. Chemical shifts are reported relative to the residual chloroform singlet at δ 7.26 ppm. Resonances were assigned as follows: chemical shift (multiplicity, coupling constant(s), number of protons, assigned proton(s)). Multiplicity abbreviations are reported by the conventions: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), td (triplet of doublets), q (quartet), qd (quartet of doublets), m (multiplet). Proton decoupled ^{13}C NMR spectra were recorded at either 100 MHz on a Varian 400-MR NMR system or at 125 MHz on a Varian 500 MHz AR premium shielded spectrometer under the same conditions as the ^{1}H NMR spectra. Dichloromethane (CH_2Cl_2), tetrahydrofuran and diethyl ether were dried using a PURE SOLV MD-6 solvent purification system. Melting points were measured on a DigiMelt MPA 161 apparatus. Unless otherwise noted, all experiments were conducted at room temperature.

General Procedures

General Procedure A. Cyclopropanation of 1,3-diketones (vinyl cyclopropanes). To a solution of 1,3-diketone (1.0 eq) in MeOH or acetone (1 mmol/3 mL) was added K_2CO_3 (3.2 eq) and trans-1,4-dibromo-2-butene (1.2 eq) with stirring and heated under reflux for 17 hours. After this time the reaction mixture was allowed to cool to room temperature. The reaction was quenched with water at room temperature and extracted with Et_2O (x3). The combined organic layer was washed with water (x3) and brine (x1), dried over Na_2SO_4 and reduced in vacuo. The crude residue was purified by flash chromatography.

General Procedure B. Spirocyclization 1 and de-allylation. To a solution of vinyl cyclopropane (1.0 eq) in degassed MeOH (1 mmol/5 mL) was added $Pd(PPh_3)_4$ (0.05 eq) with stirring for 10 minutes followed by the addition of K_2CO_3 (3.0 eq) with stirring for a further 1-2 hours. The reaction was quenched with 2M HCl and extracted with DCM (x 3). The combined organic layer was washed with water (x1) and brine (x1), dried over Na_2SO_4 and reduced in vacuo. The crude residue was purified by flash chromatography.

General Procedure C. Synthesis of 1,3-diketone derivatives. To a solution of NaH in THF (0.3mmol/mL) at 0 °C was added ethyl acetoacetate or 1,3-diketone derivatives (1 eq) dropwise. The reaction mixture was stirred for 10 minutes, at which time n-BuLi (1.1 eq) was added dropwise. After a further 10 minutes stirring at 0°C, a solution of 1-bromomethyl or 1-bromoethyl benzene derivatives (1.3-1.5 eq) in THF (2.5 mmol/mL) was added quickly to the reaction mixture and this mixture was allowed to warm to room temperature for an additional 30 minutes stirring. After this time, the reaction was quenched with 3.5M HCl and extracted with Et_2O (x3). The combined organic layer was washed with saturated $NaHCO_3$ (x3) water (x3) and brine (x1), dried over Na_2SO_4 and reduced in vacuo. The crude residue was purified by chromatography.

General Procedure D. **Synthesis of 5,6-spiroketals.** To a solution of 1,3-diketone derivatives (1.0 eq) in DMSO (0.6 mmol/mL) was added K_2CO_3 (3.2 eq) and trans-1,4-dibromo-2-butene (1.2 eq) with stirring at room temperature for 24 hours. After this time the reaction was quenched with water and extracted with Et_2O (x3). The combined organic layer was washed with water (x3) and brine (x1), dried over Na_2SO_4 and reduced in vacuo. The crude residue was used for the next step without further purification.

To a solution of crude vinyl cyclopropane (1.0 eq) in degassed EtOH or MeOH (0.1 mmol/mL) was added $Pd(PPh_3)_4$ (0.05 eq) with stirring for 10 minutes followed by the addition of K_2CO_3 (3.0 eq) with stirring for a further 16 hours under the nitrogen atmosphere. The reaction was quenched with 2M HCl and extracted with DCM (x3). The combined organic layer was washed with water (x1) and brine (x1), dried over Na_2SO_4 and reduced in vacuo. The crude residue was purified by flash chromatography or preparative thin layer chromatography.

1-[2-(2-Allyloxy-phenyl)-acetyl]-2-vinyl-cyclopropanecarboxylic acid methyl ester (1a). Following **general procedure A**: to a solution of 4-(2-allyloxy-phenyl)-3-oxo-butyric acid methyl ester **4a** (140 mg, 0.56 mmol) in MeOH (3 mL) was added K_2CO_3 (235 mg, 1.7 mmol) and *trans*-1,4-dibromo-2-butene (150 mg, 0.68 mmol) with stirring and heated under reflux for 17 hours to give a crude residue. The crude residue was purified by a quick flash chromatography (1:15 Et_2O/40−60 Pet. Ether, unstable during purification) to afford **1a** as a yellow oil (57 mg, 34%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.20 (m, 1H), 7.10 (dd, *J* 7.6, 1.6, 1H), 6.93-6.89 (m, 1H), 6.83 (d, *J* 8.4, 1H), 6.04-5.95 (m, 1H), 5.52-5.43 (m, 1H), 5.36 (dq, *J* 17.2, 3.2, 1.6, 1H), 5.29-5.24 (m, 2H), 5.12 (dq, *J* 10.0, 1.6, 0.4, 1H), 4.50 (dt, *J* 5.2, 1.6, 2H), 4.04 (d, *J* 7.6, 2H), 3.71 (s, 3H), 2.69-2.62 (m, 1H), 1.71-1.68 (m, 1H), 1.57-1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 169.2, 156.4, 133.2, 133.1, 131.6, 128.5, 123.4, 120.6, 118.7, 117.1, 111.4, 68.6, 52.2, 44.0, 42.7, 33.5, 23.2; IR: 2951.0, 1697.8, 1492.9, 1317.0, 1242.8, 1196.9, 1111.5, 994.6, 920.2, 752.1 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{20}O_4Na^+$ 323.1254; Found 323.1245.

5'-Vinyl-4',5'-dihydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'- acetic acid methyl ester (3a). Following **general procedure B**: to a solution of vinyl cyclopropane **1a** (66 mg, 0.22 mmol) in degassed MeOH (2 mL) was added $Pd(PPh_3)_4$ (13 mg, 0.01 mmol) and K_2CO_3 (92 mg, 0.66 mmol) with stirring for a 1 hour to give a crude residue. The crude residue was purified by flash chromatography (1:30 Et_2O/40−60 Pet. Ether) to afford **3a** as a yellow oil (15 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* 7.6, 1H), 7.09 (t, *J* 15.6, 1H), 6.85 (t, *J* 14.8, 1H), 6.76 (d, *J* 8.0, 1H), 6.03-5.94 (m, 1H), 5.25 (d, *J* 17.2, 1H), 5.14 (d, *J* 10.0, 1H), 4.65-4.59 (m, 1H), 3.75 (d, *J* 16.4, 1H), 3.54 (s, 3H), 3.33-3.25 (m, 2H), 2.58-2.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 157.5, 138.9, 127.8, 125.7, 124.3, 120.7, 116.7, 116.04, 109.4, 80.6, 52.9, 52.0, 38.3, 32.8; IR: 2953.0, 2913.0, 1740.5, 1480.5, 1460.9, 1239.6, 974.0, 867.3, 749.5 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{16}O_4Na^+$ 283.0941; Found 283.0938.

2-(2-Allyloxy-phenyl)-1-(1-benzoyl-2-vinyl-cyclopropyl)-ethanone (1b). Following **general procedure A**: to a solution of 1,3-diketone **4b** (355 mg, 1.35 mmol) in MeOH (5 mL) was added K_2CO_3 (600 mg, 4.3 mmol) and *trans*-1,4-dibromo-2-butene (355 mg, 1.62 mmol) with stirring and heated under reflux for 17 hours to give a crude residue. The crude residue was purified by flash chromatography (1:20 Et_2O/40−60 Pet. Ether, unstable during purification) to afford **1b** as a yellow oil (75 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* 7.2, 2H), 7.59 (t, *J* 14.8, 1H), 7.47 (t, *J* 15.6, 2H), 7.21-7.16 (m, 1H), 6.83 (d, *J* 4.4, 2H), 6.77 (d, *J* 8.4, 1H), 6.00-5.91 (m, 1H), 5.35-5.16 (m, 4H), 4.98 (dd, *J* 9.6, 2.0, 1H), 4.44 (d, 5.2, 2H), 3.73 (d, *J* 16.8, 1H), 3.50 (d, *J* 16.8, 1H), 3.12-3.05 (m, 1H), 1.95-1.92 (m, 1H), 1.54-1.51 (m, 1H); IR: 2912.5, 1671.8, 1597.5, 1493.0, 1450.1, 1245.2, 1021.3, 998.4, 753.4, 710.2, 691.4 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{22}O_3Na^+$ 369.1461; Found 369.1437.

Phenyl(5'-vinyl-4',5'-dihydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'-yl)methanone (3b). Following **general procedure B**: to a solution of vinyl cyclopropane **1b** (72 mg, 0.21 mmol) in degassed MeOH (3 mL) was added $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and K_2CO_3 (87 mg, 0.63 mmol) with stirring for a 1 hour to give a crude residue. The crude residue was purified by flash chromatography (1:10 Et_2O/40−60 Pet. Ether) to afford **3b** as a yellow oil (20 mg, 37%, two inseparable diastereoisomers, 1:1): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.98 (m, 4H), 7.61-7.54 (m, 2H), 7.50-7.42 (m, 4H), 7.15-7.03 (m, 4H), 6.85-6.80 (m, 4H), 6.06-5.97 (m, 2H), 5.37-5.14 (m, 4H), 4.96-4.90 (m, 1H), 4.84-4.78 (m, 1H), 4.63 (t, *J* 15.6, 1H), 4.54 (dd, *J* 8.0, 2.0, 1H), 3.31-3.06 (m, 4H), 2.58-2.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 198.4, 157.3, 157.0, 139.1, 136.8, 136.6, 136.2, 133.7, 133.6,

132.3, 132.2, 128.9, 128.9, 128.7, 128.6, 127.9, 127.9, 125.7, 125.7, 124.6, 124.6, 121.0, 120.8, 118.6, 118.2, 117.7, 116.6, 109.5, 109.4, 81.9, 79.8, 54.0, 53.8, 37.5, 36.9, 35.5, 35.5; IR: 2921.2, 1681.1, 1595.5, 1478.6, 1356.9, 1221.4, 1085.22, 989.0, 925.0, 865.5, 750.6, 711.3, 690.9 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{18}O_3Na^+$ 329.1148; Found 329.1129.

(4-Methoxyphenyl)(5'-vinyl-4',5'-dihydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'-yl) methanone (3c). Following **general procedure A and B**: to a solution of 1,3-diketone **1c** (324 mg, 1 mmol) in MeOH (8 mL) was added K_2CO_3 (442 mg, 3.2 mmol) and *trans*-1,4-dibromo-2-butene (262 mg, 1.2 mmol) with stirring and heated under reflux for 17 hours to give a crude residue which was unstable during flash chromatography purification. To a solution of crude vinyl cyclopropane (230 mg, 0.61 mmol) in degassed MeOH (6 mL) was added $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) and K_2CO_3 (253 mg, 1.83 mmol) with stirring for one hour to give the crude residue. The crude residue was purified by flash chromatography (1:15 Et_2O/40−60 Pet. Ether) to afford **3c** as yellow oil (55 mg, 27%, two inseparable diastereoisomers, 3:2): ^1H NMR (400 MHz, $CDCl_3$): δ 7.99-7.92 (m, 3.4H), 7.15-7.08 (m, 1.7H), 7.08-7.02 (m, 1.7H), 6.93-6.88 (m, 3.4H), 6.85-6.79 (m, 3.4H), 6.05-5.97 (m, 1.7H), 5.36-5.12 (m, 3.4), 4.96-4.91 (m, 1H), 4.82-4.77 (m, 0.7H), 4.58 (t, *J* 16.0, 0.7H), 4.49-4.46 (m, 1H), 3.86 (s, 3H), 3.83 (s, 2H), 3.27-3.09 (m, 3.3H), 2.53-2.46 (m, 1H), 2.41-2.35 (m, 1H) 2.25-2.16 (m, 1.3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 196.7, 163.9, 163.4, 157.3, 157.1, 139.2, 136.9, 131.1, 131.0, 129.7, 129.3, 127.9, 127.8, 126.3, 125.8, 124.6, 124.4, 120.9, 120.7, 118.8, 118.4, 117.6, 116.4, 114.1, 113.6, 109.8, 109.4, 82.0, 79.8, 55.5, 55.4, 53.5, 53.3, 37.5, 36.9, 35.5, 34.7; IR: 2923, 1672, 1597, 1478, 12.8, 1171, 1024, 926, 866, 749 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{20}O_4Na^+$ 359.1254; Found 359.1239.

1-[2-(2-Allyloxy-5-methyl-phenyl)-acetyl]-2-vinyl-cyclopropanecarboxylic acid methyl ester (1d). Following **general procedure A**: to a solution of 4-(2-allyloxy-5-methyl-phenyl)-3-oxo-butyric acid methyl ester **4d** (355 mg, 1.35 mmol) in MeOH (5 mL) was added K_2CO_3 (600 mg, 4.3 mmol) and *trans*-1,4-dibromo-2-butene (355 mg, 1.62 mmol) with stirring and heated under reflux for 17 hours to give a crude residue. The crude residue was purified by flash chromatography (1:20 Et_2O/40−60 Pet. Ether, unstable during purification) to afford **1d** as a yellow oil (75 mg, 20%): ^1H NMR (400 MHz, $CDCl_3$): δ 7.02-6.99 (m, 1H), 6.91 (d, *J* 2.4, 1H), 6.74-6.71 (m, 1H), 6.03-5.94 (m, 1H), 5.41-5.18 (m, 4H), 5.14-5.10 (m, 1H), 4.47 (dt, *J* 4.8, 1.6, 2H), 4.00 (d, *J* 5.6, 2H), 3.71 (s, 3H), 2.68-2.62 (m, 1H), 2.26 (s, 3H), 1.70-1.67 (m, 1H), 1.56-1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (201.7, 169.2, 154.3, 137.0, 133.3, 132.4, 129.8, 128.8, 123.1, 118.6, 117.0, 111.4, 82.2, 68.8, 52.2, 43.9, 33.4, 23.2, 20.4; IR: 2949.7, 1730.8, 1697.8, 1502.0, 1315.9, 1226.1, 1119.6, 993.9, 804.2 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{22}O_4Na^+$ 337.1410; Found 337.1410.

5-Methyl-5'-vinyl-4',5'-dihydro-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-3'-acetic acid methyl ester (3d). Following **general procedure B:** to a solution of vinyl cyclopropane **1d** (68 mg, 0.22 mmol) in degassed MeOH (3 mL) was added $Pd(PPh_3)_4$ (13 mg, 0.01 mmol) and K_2CO_3 (91 mg, 0.65 mmol) with stirring for a 1 hour to give a crude residue. The crude residue was purified by flash chromatography (1:10 Et_2O/40−60 Pet. Ether) to afford **3d** as yellow oil (26 mg, 45%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* 2.4, 1H), 6.97-6.95 (m, 1H), 6.81 (d, *J* 8.4, 1H), 6.02-5.93 (m, 1H), 5.25 (d, *J* 17.2, 1H), 5.14 (d, *J* 10.0, 1H), 4.63-4.57 (m, 1H), 3.72 (d, *J* 16.4, 1H), 3.55 (s, 3H), 3.28-3.23 (m, 2H), 2.54-2.45 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 152.7, 136.3, 132.0, 129.3, 128.1, 124.9, 120.7, 116.7, 109.0, 83.2, 52.8, 51.7, 35.0, 29.3, 20.4; IR: 2951., 2923, 1743, 1491, 1438, 1228, 1057, 974, 940, 822 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{18}O_4Na^+$ 297.1097; Found 297.1102.

6-(2-Allyloxy-phenyl)-hexane-2,4-dione (5a). Following **general procedure C**: To a solution of NaH (66 mg, 1.65 mmol) in THF (5 mL) was added acetylacetone (0.155 mL, 1.5 mmol) followed by n-BuLi (1.65 mL, 1M) and 1-allyloxy-2-bromomethyl-benzene (476 mg, 2.1 mmol) to give a crude residue. The crude residue was purified by flash chromatography (1:15 EtOAc/40−60 Pet. Ether) to afford **5a** as a colourless oil (315 mg, 4

steps from 2-hydroxybenzaldehyde, as 6 :1 mixture of enol :keto tautomers, overall yield 81%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.13 (m, 2.3H), 6.91-6.83 (m, 2.3H), 6.12-6.03 (m, 1.2H), 5.49 (s, 1H), 5.46-5.41 (m, 1.2H), 5.30-5.27 (m, 1.2H), 4.57-4.55 (m, 2.3H), 3.55 (s, 0.3H), 2.98-2.91 (m, 2.3H), 2.85-2.83 (m, 0.3H), 2.60 (t, *J* 15.6, 2H), 2.20 (s, 0.5H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 202.1, 193.8, 191.1, 156.4, 133.4, 133.4, 130.2, 130.0, 129.3, 129.0, 127.5, 127.5, 120.7, 120.6, 117.1, 116.9, 111.5, 111.5, 110.0, 99.8, 68.6, 68.5, 58.0, 43.6, 38.4, 38.3, 30.8, 26.7, 24.9, 24.9; IR: 2928, 2868, 1707, 1600, 1492, 1452, 1422, 1359, 1239, 1110, 996, 751 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{18}O_3Na^+$ $[M+Na]^+$: 269.1148; found: 269.1175

1-(5'-Vinyl-4',5'-dihydro-3'*H*-spiro[chromane-2,2'-furan]-3'-yl)ethan-1-one (6a). Following **general procedure D**: 6-(2-Allyloxy-phenyl)-hexane-2,4-dione **5a** (74 mg, 0.3 mmol), K_2CO_3 (133 mg, 0.96 mmol) and *trans*-1,4-dibromo-2-butene (79 mg, 0.36 mmol) were combined in DMSO (1 mL) to provide the crude vinyl cyclopropane compound which was used for the next step without further purification. This crude vinyl cyclopropane, $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol) and K_2CO_3 (124 mg, 0.9 mmol) were combined in MeOH (5 mL) to provide a crude residue. The crude residue was purified by flash chromatography (1:50−1:20 Et_2O/40−60 Pet. Ether) to afford **6a**.

6ai (yellow oil, 6 mg, 8%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.05 (m, 2H), 6.90-6.82 (m, 2H), 5.95-5.87 (m, 1H), 5.26 (d, *J* 17.2, 1H), 5.14 (d, *J* 10.4, 1H), 4.69-4.63 (m, 1H), 3.66 (t, *J* 8.6, 1H), 3.14-3.05 (m, 1H), 2.71-2.65 (m, 1H), 2.33-2.26 (m, 4H), 2.18-2.15 (m, 1H), 1.97-1.91 (m, 1H), 1.81-1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 152.6, 137.2, 129.1, 127.2, 122.1, 121.0, 116.9, 116.9, 106.2, 79.1, 61.2, 34.2, 31.4, 28.0, 21.6; IR: 2920, 2854, 1713, 1611, 1488, 1454, 1427, 1358, 1220, 1116, 1030, 989, 924, 874, 754 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{18}O_3Na^+$ 281.1148; Found 281.1150.

6aii (yellow oil, 19 mg, 24%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.06 (m, 2H), 6.87 (t, *J* 7.4, 1H), 6.76 (d, *J* 8, 1H), 5.87-5.79 (m, 1H), 5.26 (d, *J* 16.8, 1H), 5.12 (d, *J* 10.4, 1H), 4.76-4.71 (m, 1H), 3.20-3.11 (m, 2H), 2.97-2.90 (m, 1H), 2.75 (dd, *J* 15.6, 5.2, 1H), 2.37-2.27 (m, 1H), 2.25 (s, 3H), 2.21-2.17 (m, 1H), 1.93-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6, 152.1, 137.7, 129.1, 127.2, 121.8, 120.9, 117.0, 116.1, 105.5, 78.6, 60.1, 32.5, 30.4, 29.9, 22.2; IR: 2919, 2851, 1713, 1582, 1489, 1455, 1357, 1220, 1121, 1071, 978, 943, 880, 755 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{18}O_3Na^+$ 281.1148; Found 281.1145.

6aiii (yellow oil, 18 mg, 23%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.05 (m, 2H), 6.89-6.85 (m, 1H), 6.74 (d, *J* 8, 1H), 5.90-5.81 (m, 1H), 5.12 (d, *J* 17.2, 1H), 5.03 (d, *J* 10, 1H), 4.58-4.52 (m, 1H), 3.16-3.01 (m, 2H), 2.74 (dd, *J* 16, 4.8, 1H), 2.66-2.58 (m, 1H), 2.46-2.39 (m, 1H), 2.34-2.25 (m, 4H), 2.11-2.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 152.0, 139.3, 129.1, 127.2, 121.9, 120.8, 116.9, 116.0, 105.1, 80.1, 61.3, 33.5, 29.8, 29.5, 22.1; IR: 2918, 2851, 1709, 1582, 1489, 1455, 1358, 1222, 1129, 1036, 975, 924, 880, 754 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{18}O_3Na^+$ 281.1148; Found 281.1156.

5-(2-Allyloxy-phenyl)-3-oxo-pentanoic acid ethyl ester (5b). Following **general procedure C**: to a solution of NaH (169 mg, 4.2 mmol) in THF (10 mL) was added ethyl acetoacetate (0.49 mL, 3.8 mmol) followed by n-BuLi (2.2 mL, 2M) and 1-allyloxy-2-bromomethyl-benzene (1135 mg, 5 mmol) to give a crude residue. The crude residue was purified by flash chromatography (1:15 EtOAc/40−60 Pet. Ether) to afford **5b** as a colourless oil (875 mg, 4 steps from 2-hydroxybenzaldehyde, overall yield 83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.13 (m, 2H), 6.89-6.81(m, 2H), 6.10-6.01(m, 1H), 5.40 (dq, *J* 17.2, 3.2, 1.6, 1H), 5.27 (dq, *J* 10.4, 2.8, 1.6, 1H), 4.55 (dt, *J* 4.8, 1.6, 2H), 4.18 (q, *J* 7.2, 2H), 3.42 (s, 2H), 2.96-2.92 (m, 2H), 2.88-2.84 (m, 2H), 1.26 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 167.1, 156.3, 133.3, 130.1, 129.0, 127. 5, 120.6, 117.0, 111.4, 68.5, 61.2, 49.3, 42.9, 24.8, 14.0; IR: 2982, 2933, 1741, 1714, 1493, 1453, 1410, 1366, 1239, 1188, 1023, 928, 753 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{20}O_4Na^+$ 299.1254; Found 299.1276.

5'-Vinyl-4',5'-dihydro-3'*H*-spiro[chromane-2,2'-furan]-3'-carboxylic acid ethyl ester (6b). Following **general procedure D**: 5-(2-Allyloxy-phenyl)-3-oxo-pentanoic acid ethyl ester **5b** (306 mg, 1.11 mmol), K_2CO_3 (486 mg,

3.5 mmol) and *trans*-1,4-dibromo-2-butene (288 mg, 1.3 mmol) were combined in DMSO (2 mL) to provide the crude vinyl cyclopropane compound which was used for the next step without further purification. This crude vinyl cyclopropane, $Pd(PPh_3)_4$ (64 mg, 0.056 mmol) and K_2CO_3 (460 mg, 3.3 mmol) were combined in EtOH (6 mL) to provide a crude residue. The crude residue was purified by flash chromatography (1:60−1:20 Et_2O/40−60 Pet. Ether) and preparative layer chromatography plate (1:60 Et_2O/40−60 Pet. Ether) to afford **6b.**

6bi and 6biv (pale yellow oil, 110 mg, an inseparable 1:2 mixture of two diastereoisomers, 34%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.05 (m, 2H), 6.89-6.84 (m, 1H), 6.78-6.74 (m, 1H), 5.90-5.80 (m, 1H), 5.25 (d, *J* 16.8, 0.4H), 5.16-5.10 (m, 1H), 5.20 (d, *J* 10, 0.7H), 4.94-4.88 (m, 0.65H), 4.80-4.75 (m, 0.35H), 4.26-4.13 (m, 2H), 3.32 (d, *J* 6.4, 0.6H), 3.16-2.93 (m, 2H), 2.82-2.71 (m, 1H), 2.54-2.40 (m, 1H), 2.34-2.27 (m, 0.8H), 2.12-1.93 (m, 2H), 1.30 (t, *J* 7.2, 2H), 1.19 (t, *J* 7.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 169.4, 152.4, 139.8, 137.9, 129.0, 129.0, 127.2, 127.1, 122.0, 121.8, 120.7, 120.7, 117.0, 116.9, 115.9, 115.8, 107.2, 105.6, 82.0, 78.4, 61.0, 60.9, 54.1, 52.7, 34.1, 32.4, 30.3, 29.6, 27.3, 22.2, 22.2, 14.2; IR: 2925, 1734, 1582, 1489, 1454, 1369, 1229, 1181, 1096, 989, 921, 869, 753 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{20}O_4Na^+$ 311.1254; Found 311.1236.

6bii (pale yellow oil, 65 mg, 20%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.05 (m, 2H), 6.85 (t, *J* 7.4, 1H), 6.75 (d, *J* 8, 1H), 5.89-5.81 (m, 1H), 5.10 (d, *J* 17.2, 1H), 5.01 (d, *J* 10.4, 1H), 4.58-4.52 (m, 1H), 4.16 (q, *J* 7.2, 2H), 3.14-3.04 (m, 2H), 2.76-2.71 (m, 1H), 2.70-2.61 (m, 1H), 2.51-2.39 (m, 2H), 2.06-2.00 (m, 1H), 1.21 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 152.3, 139.5, 128.9, 127.1, 122.0, 120.5, 117.0, 115.9, 105.1, 80.1, 60.9, 53.9, 32.8, 29.2, 22.1, 14.2; IR: 2930, 1736, 1582, 1448, 1368, 1218, 1182, 1132, 1036, 986, 942, 882, 754 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{20}O_4Na^+$ 311.1254; Found 311.1238.

6biii (pale yellow oil, 29 mg, 9%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.05 (m, 2H), 6.87 (t, *J* 7.4, 1H), 6.80 (d, *J* 8, 1H), 6.02-5.93 (m, 1H), 5.25 (d, *J* 17.2, 1H), 5.14 (d, *J* 10.4, 1H), 4.69-4.63 (m, 1H), 4.23-4.17 (m, 2H), 3.41-3.38 (m, 1H), 3.12-3.03 (m, 1H), 2.75-2.69 (m, 1H), 2.54-2.47 (m, 1H), 2.22-2.19 (m, 1H), 2.02-1.98 (m, 2H), 1.29 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 152.5, 137.3, 129.1, 127.1, 122.0, 120.8, 117.1, 116.9, 107.0, 79.4, 61.1, 54.4, 34.7, 27.3, 22.0, 14.2; IR: 2935, 1729, 1590, 1435, 1360, 1223, 1180, 1139, 1030, 996, 938, 880, 763 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{20}O_4Na^+$ $[M+Na]^+$: 311.1254; Found 311.1225.

5-(2-Allyloxy-phenyl)-1-phenyl-pentane-1,3-dione (5c). Following **general procedure C**: to a solution of NaH (88 mg, 2.2 mmol) in THF (7 mL) was added 1-phenyl-1,3-butanedione (324 mg, 2 mmol) followed by n-BuLi (2.2 mL, 1M) and 1-allyloxy-2-bromomethyl-benzene (590 mg, 2.6 mmol) to give a crude residue. The crude residue was purified by flash chromatography (1:40 Et_2O/40−60 Pet. Ether) to afford **5c** as a yellow oil in a 10 :1 mixture of enol/keto tautomers (290 mg, 4 steps from 2-hydroxybenzaldehyde, overall yield 47%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* 7.6, 0.2H), 7.86 (d, *J* 7.6, 2H), 7.54-7.43 (m, 3.3H), 7.21-7.17 (m, 2.2H), 6.92-6.81 (m, 2.2 H), 6.15 (s, 1H), 6.14-6.04 (m, 1H), 5.49-5.43 (m, 1H), 5.41-5.36 (m, 0.1H), 5.31-5.28 (m, 1H), 5.27-5.23 (m, 0.1H), 4.58 (d, *J* 4.8, 2H), 4.53 (d, *J* 4.8, 0.2H), 4.07 (s, 0.2H), 3.05 (t, *J* 15.6, 2.2H), 2.96-2.92 (m, 0.2H), 2.76 (t, *J* 15.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 196.5, 183.0, 156.4, 135.0, 133.6, 133.4, 132.1, 130.2, 130.0, 129.2, 128.7, 128.7, 128.5, 127.5, 127.5, 126.9, 120.7, 120.6, 117.0, 116.9, 111.5, 111.5, 96.2, 68.5, 54.0, 43.2, 39.3, 26.8, 24.9; IR: 2927, 1598, 1491, 1453, 1422, 1239, 1108, 996, 925, 750, 692 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{20}O_3Na^+$ 331.1305; Found 331.1340.

Phenyl(5'-Vinyl-4',5'-dihydro-3'*H*-spiro[chromane-2,2'-furan]-3'-yl)methanone (6c). Following **general procedure D**: 5-(2-Allyloxy-phenyl)-1-phenyl-pentane-1,3-dione **5c** (100 mg, 0.32 mmol), K_2CO_3 (146 mg, 1.1 mmol) and *trans*-1,4-dibromo-2-butene (86 mg, 0.39 mmol) were combined in DMSO (1 mL) to provide the crude vinyl cyclopropane compound which was used for the next step without further purification. This crude vinyl cyclopropane, $Pd(PPh_3)_4$ (19 mg, 0.016 mmol) and K_2CO_3 (133 mg, 0.96 mmol) were combined in MeOH (5 mL) to provide a crude residue. The crude residue was purified by flash chromatography (1:60−1:10 Et_2O/40−60 Pet. Ether) to afford **6c**.

6ci (yellow oil, 16 mg, 16%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* 8, 2H), 7.59-7.55 (m, 1H), 7.46 (t, *J* 7.6, 2H), 7.13 (t, *J* 7.6, 1H), 7.15 (d, *J* 7.6, 1H), 6.93-6.85 (m, 2H), 6.05-5.96 (m, 1H), 5.32 (d, *J* 17.2, 1H), 5.19 (d, *J* 7.6, 1H), 4.79-4.74 (m, 1H), 4.55 (t, *J* 8.6, 1H), 3.09-3.01 (m, 1H), 2.58-2.47 (m, 2H), 2.38-2.32 (m, 1H), 1.91-1.86 (m, 1H), 1.62-1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 152.8, 137.2, 137.1, 133.5, 129.1, 128.8, 127.1, 122.3, 120.8, 117.1, 116.9, 106.9, 79.3, 56.0, 35.2, 28.3, 21.7; IR: 2919, 2851, 1681, 1582, 1489, 1451, 1357, 1222, 1117, 1020, 925, 867, 753, 690 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{20}O_3Na^+$ 343.1305; Found 343.1288.

6cii (yellow oil, 5 mg, 5%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8 Hz, 2H), 7.59 (t, *J* 7.6, 1H), 7.48 (t, *J* 7.8, 2H), 7.12 (t, *J* 7.6, 1H), 7.02 (d, *J* 7.2, 1H), 6.88-6.82 (m, 2H), 6.00-5.89 (m, 1H), 5.19 (d, *J* 16.8, 1H), 5.06 (d, *J* 10.4, 1H), 5.00-4.94 (m, 1H), 4.51-4.48 (m, 1H), 3.06-2.97 (m, 1H), 2.73-2.67 (m, 1H), 2.60-2.54 (m, 1H), 2.37-2.30 (m, 1H), 1.88-1.83 (m, 1H), 1.76-1.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 152.6, 139.7, 137.1, 133.6, 129.1, 128.8, 128.7, 127.2, 122.1, 120.8, 116.8, 115.7, 107.5, 81.7, 54.5, 34.7, 28.1, 21.9; IR: 2924, 2853, 1727, 1680 1582, 1489, 1451, 1358, 1224, 1118, 993, 919, 868, 754, 690 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{20}O_3Na^+$ 343.1305; Found 343.1281.

6ciii (yellow oil, 27 mg, 26%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* 7.2, 2H), 7.52-7.48 (m, 1H), 7.43-7.40 (m, 2H), 7.03-6.95 (m, 2H), 6.79 (t, *J* 7.4, 1H), 6.68 (d, *J* 8, 1H), 5.95-5.86 (m, 1H), 5.31 (d, *J* 17.2, 1H), 5.16 (d, *J* 10.4, 1H), 4.87-4.82 (m, 1H), 4.17-4.13 (m, 1H), 3.19-3.07 (m, 2H), 2.60 (dd, *J* 15.2, 4.8, 1H), 2.21-2.16 (m, 1H), 2.01-1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 152.2, 138.4, 137.9, 132.6, 128.8, 128.5, 128.1, 127.1, 121.6, 120.7, 117.2, 116.1, 105.2, 78.9, 54.4, 33.3, 30.8, 22.2; IR: 2925, 2851, 1729, 1685, 1582, 1488, 1452, 1356, 1215, 1118, 984, 927, 885, 755, 692 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{20}O_3Na^+$ 343.1305; Found 343.1287.

6civ (yellow solid, 16 mg, 16%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* 7.6, 2H), 7.53 (t, *J* 7.4, 1H), 7.43 (t, *J* 7.8, 2H), 7.04 (t, *J* 7.8, 1H), 6.95 (d, *J* 7.6, 1H), 6.81-6.74 (m, 2H), 5.94-5.85 (m, 1H), 5.12 (d, *J* 17.2, 1H), 5.03 (d, *J* 10.4, 1H), 4.68-4.62 (m, 1H), 4.12-4.07 (m, 1H), 3.11-2.95 (m, 2H), 2.58 (dd, *J* 16, 5.6, 1H), 2.45-2.38 (m, 1H), 2.11-2.06 (m, 1H), 1.86-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 152.2, 139.5, 138.2, 132.8, 128.8, 128.5, 128.3, 127.1, 121.6, 120.6, 117.2, 115.9, 104.4, 80.2, 55.6, 33.1, 30.3, 22.2; IR: 2918, 2850, 2281, 1685, 1582, 1490, 1452, 1217, 1125, 990, 926, 884, 754, 704 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{20}O_3Na^+$ 343.1305; Found 343.1274; m.p. = 101.8 °C-102.9 °C.

5-(2-Allyloxy-3-methyl-phenyl)-3-oxo-pentanoic acid ethyl ester (5d). Following **general procedure C**: to a solution of NaH (85 mg, 2.1 mmol) in THF (6 mL) was added ethyl acetoacetate (0.24 mL, 1.9 mmol) followed by n-BuLi (1.6 mL, 1.35M) and 2-allyloxy-1-bromomethyl-3-methyl-benzene (2.5 mmol) to give a crude residue. The crude residue was purified by flash chromatography (1:15 EtOAc/40−60 Pet. Ether) to afford **5d** as a colourless oil (428 mg, 4 steps from 2-hydroxy-3-methylbenzaldehyde, overall yield 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05-6.93 (m, 3H), 6.14-6.05(m, 1H), 5.42 (dq, *J* 17.2, 3.6, 2.0, 1H), 5.26 (dq, *J* 10.8, 2.8, 1.6, 1H), 4.32 (dt, *J* 5.6, 1.6, 2H), 4.18 (q, *J* 7.2, 2H), 3.42 (s, 2H), 2.94-2.85 (m, 4H), 2.28 (s, 3H), 1.26 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 167.1, 155.7, 133.9, 133.5, 131.3, 129.6, 127.7, 124.1, 117.2, 73.6, 61.3, 49.3, 43.7, 24.5, 16.4, 14.0; IR: 2982, 2930, 2864, 1742, 1716, 1646, 1467, 1418, 1367, 1315, 1256, 1197, 1088, 990, 928, 773 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{22}O_4Na^+$ 313.1410; Found 313.1427.

8-Methyl-5'-vinyl-4',5'-dihydro-3'*H*-spiro[chromane-2,2'-furan]-3'-carboxylic acid ethyl ester (6d). Following **general procedure D**: 5-(2-Allyloxy-3-methyl-phenyl)-3-oxo-pentanoic acid ethyl ester **5d** (339 mg, 1.17 mmol), K_2CO_3 (517 mg, 3.74 mmol) and *trans*-1,4-dibromo-2-butene (306 mg, 1.40 mmol) were combined in DMSO (2 mL) to provide the crude vinyl cyclopropane compound which was used for the next step without further purification. This crude vinyl cyclopropane, $Pd(PPh_3)_4$ (68 mg, 0.06 mmol) and K_2CO_3 (485 mg, 3.5 mmol) were

combined in EtOH (10 mL) to provide a crude residue. The crude residue was purified by flash chromatography (1:60−1:20 Et_2O/40−60 Pet. Ether) to afford **6d**.

6di (colourless oil, 139 mg, 40%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96-6.90 (m, 2H), 6.77 (t, *J* 7.2, 1H), 5.88-5.80 (m, 1H), 5.09 (d, *J* 17.2, 1H), 5.01 (d, *J* 10.4, 1H), 4.62-4.56 (m, 1H), 4.16 (q, *J* 7.2, 2H), 3.14-3.05 (m, 2H), 2.76-2.67 (m, 2H), 2.49-2.40 (m, 2H), 2.13 (s, 3H), 2.06-2.01 (m, 1H), 1.22 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 150.1, 139.6, 128.2, 126.5, 126.0, 121.3, 119.9, 115.5, 105.0, 79.9, 60.8, 54.0, 33.0, 29.1, 22.2, 15.7, 14.1; IR: 2979, 2941, 1737, 1594, 1466, 1368, 1263, 1187, 1125, 985, 932, 854, 762 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{22}O_4Na^+$ 325.1410; Found 325.1387.

6dii (colourless oil, 27 mg, 8%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96-6.90 (m, 2H), 6.77 (t, *J* 7.4, 1H), 5.89-5.81 (m, 1H), 5.26 (d, *J* 17.2, 1H), 5.12 (d, *J* 10.4, 1H), 4.78-4.73 (m, 1H), 4.17-4.11 (m, 2H), 3.15-3.06 (m, 2H), 3.03-2.96 (m, 1H), 2.73 (dd, *J* 16, 5.2, 1H), 2.46-2.38 (m, 1H), 2.17 (d, *J* 11.2, 0.5H), 2.12 (s, 3H), 2.08 (d, *J* 5.6, 0.5H), 2.01-1.94 (m, 1H), 1.20 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 150.2, 137.9, 128.3, 126.5, 126.1, 121.3, 120.1, 115.9, 105.6, 78.4, 60.8, 52.9, 32.6, 29.5, 22.3, 15.6, 14.1; FTIR (ATR / cm^{-1}): 2940, 1737, 1594, 1466, 1368, 1341, 1187, 984, 947, 763 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{22}O_4Na^+$ 325.1410; Found 325.1390.

6diii (colourless oil, 35 mg, 10%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J* 7.6, 1H), 6.91 (d, *J* 7.2, 1H), 6.77 (t, *J* 7.4, 1H), 5.90-5.81 (m, 1H), 5.14 (d, *J* 17.2, 1H), 5.02 (d, *J* 10, 1H), 4.97-4.92 (m, 1H), 4.26-4.17 (m, 2H), 3.33 (d, *J* 6.4, 1H), 3.06-2.98 (m, 1H), 2.84-2.77 (m, 1H), 2.56-2.50 (m, 1H), 2.36-2.28 (m, 1H), 2.16 (s, 3H), 2.06-2.00 (m, 2H), 1.31 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 150.4, 139.8, 128.3, 126.6, 125.7, 121.0, 120.1, 115.7, 107.3, 81.9, 61.0, 54.1, 34.3, 27.3, 22.4, 16.0, 14.2; IR: 2922, 2852, 1734, 1641, 1468, 1443, 1370, 1344, 1222, 1181, 1111, 989, 925, 853, 768 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{22}O_4Na^+$ 325.1410; Found 325.1393.

5-(2-Allyloxy-3-bromo-phenyl)-3-oxo-pentanoic acid ethyl ester (5e). Following **general procedure C**: to a solution of NaH (68 mg, 1.7 mmol) in THF (5 mL) was added ethyl acetoacetate (0.2 mL, 1.53 mmol) followed by n-BuLi (0.85 mL, 2M) and 2-allyloxy-1-bromo-3-bromomethyl-benzene (2 mmol) to give a crude residue. The crude residue was purified by flash chromatography (1:10 EtOAc/40−60 Pet. Ether) to afford **5e** as a pale yellow oil (266 mg, 4 steps from 3-bromo-2-hydroxybenzaldehyde, overall yield 49%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, *J* 8.0, 1.6, 1H), 7.12 (dd, *J* 7.6, 1.6, 1H), 6.91 (t, *J* 8, 1H), 6.17-6.07 (m, 1H), 5.43 (ddd, *J* 17.2, 2.8, 1.6, 1H), 5.28 (ddd, *J* 10.4, 2.8, 1.6, 1H), 4.47 (dt, *J* 5.6, 1.6, 2H), 4.18 (q, *J* 7.2, 2H), 3.42 (s, 2H), 2.96-2.92 (m, 2H), 2.90-2.85 (m, 2H), 1.26 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 167.0, 154.1, 136.1, 133.3, 131.8, 129.5, 125.5, 118.1, 117.6, 74.1, 61.4, 49.3, 43.3, 24.9, 14.1; IR 2982, 2934, 1740, 1715, 1647, 1442, 1419, 1367, 1315, 1220, 1077, 983, 929, 776 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{19}BrO_4Na^+$ 377.0359; Found 377.0374

8-Bromo-5'-vinyl-4',5'-dihydro-3'*H*-spiro[chromane-2,2'-furan]-3'-carboxylic acid ethyl ester (6e). Following **general procedure D**: 5-(2-Allyloxy-3-bromo-phenyl)-3-oxo-pentanoic acid ethyl ester **5e** (251 mg, 0.706 mmol), K_2CO_3 (314 mg, 2.27 mmol) and *trans*-1,4-dibromo-2-butene (186 mg, 0.85 mmol) were combined in DMSO (2 mL) to provide the crude vinyl cyclopropane compound which was used for the next step without further purification. This crude vinyl cyclopropane, $Pd(PPh_3)_4$ (42 mg, 0.036 mmol) and K_2CO_3 (294 mg, 2.13 mmol) were combined in EtOH (8 mL) to provide a crude residue. The crude residue was purified by flash chromatography (1:60−1:10 Et_2O/40−60 Pet. Ether) and preparative layer chromatography plate (1:6 DCM/40−60 Pet. Ether) to afford **6e**.

6ei (pale yellow oil, 91 mg, 37%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* 8, 1H), 7.00 (d, *J* 7.6, 1H), 6.72 (t, *J* 7.8, 1H), 5.95-5.86 (m, 1H), 5.11 (d, *J* 16.8, 1H), 5.04 (d, *J* 10, 1H), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 2H), 3.11-3.06 (m, 2H), 2.81-2.72 (m, 2H), 2.53-2.44 (m, 2H), 2.07-2.02 (m, 1H), 1.24 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 168.6, 148.8, 139.4, 139.3, 130.7, 128.0, 123.7, 121.2, 116.3, 111.4, 105.8, 80.7, 61.0, 53.9, 32.7, 28.7, 22.4, 14.2; IR: 2980, 2934, 1731, 1567, 1450, 1367, 1233, 1178, 1119, 985, 933, 899, 764, 725 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{19}BrO_4Na^+$ 389.0359; Found 389.0346.

6eii (pale yellow oil, 34 mg, 13%) ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.35 (d, *J* = 8 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 5.97-5.88 (m, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 5.05 (d, *J* = 10 Hz, 1H), 4.97-4.91 (m, 1H), 4.26-4.17 (m, 2H), 3.40 (d, *J* = 7.2 Hz, 1H), 3.10-3.02 (m, 1H), 2.85-2.79 (m, 1H), 2.56-2.51 (m, 1H), 2.47-2.40 (m, 1H), 2.14-2.01 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 171.4, 148.9, 139.6, 130.8, 128.2, 123.6, 121.5, 116.5, 111.3, 107.8, 82.8, 61.1, 54.1, 34.0, 27.0, 22.6, 14.2; FTIR (ATR / cm^{-1}): 2926, 2853, 1733, 1567, 1450, 1368, 1238, 1181, 1109, 992, 925, 891, 765, 723 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{19}BrO_4Na^+$ 389.0359; Found 389.0346.

6eiii (pale yellow oil, 22 mg, 9%) ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* 8.4, 1H), 7.00 (d, *J* 7.2, 1H), 6.73 (t, *J* 7.4, 1H), 5.89-5.80 (m, 1H), 5.27 (d, *J* 17.2, 1H), 5.13 (d, *J* 10.4, 1H), 4.82-4.78 (m, 1H), 4.22-4.17 (m, 2H), 3.15-3.04 (m, 3H), 2.75 (dd, *J* 16.4, 6, 1H), 2.51-2.42 (m, 1H), 2.11 (dd, *J* 13.2, 5.6, 1H), 2.03-1.96 (m, 1H), 1.22 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 149.0, 137.6, 130.8, 128.0, 123.7, 121.4, 116.1, 111.4, 106.4, 78.7, 61.1, 52.8, 32.3, 29.3, 22.5, 14.2; IR: 2934, 1737, 1567, 1451, 1367, 1234, 1182, 1069, 985, 902, 764, 724 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{19}BrO_4Na^+$ 389.0359; Found 389.0341.

5-(2-Allyloxy-3-bromo-5-methyl-phenyl)-3-oxo-pentanoic acid ethyl ester (5f). Following **general procedure C**: to a solution of NaH (78 mg, 1.9 mmol) in THF (6 mL) was added ethyl acetoacetate (0.22 mL, 1.75 mmol) followed by n-BuLi (1.44 mL, 1.3M) and 2-allyloxy-3-bromo-1-bromomethyl-5-methylbenzene (2.28 mmol) to give a crude residue. The crude residue was purified by flash chromatography (1:20 EtOAc/40−60 Pet. Ether) to afford **5f** as a pale yellow oil (478 mg, 5 steps from 2-hydroxy-5-methylbenzaldehyde, overall yield 47%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* 2.4, 1H), 6.91 (d, *J* 2.4, 1H), 6.16-6.06 (m, 1H), 5.41 (dq, *J* 17.2, 3.6, 1.6, 1H), 5.27 (dq, *J* 10.4, 2.8, 1.6, 1H), 4.44 (dt, *J* 5.6, 1.6, 2H), 4.18 (q, *J* 7.2, 2H), 3.42 (s, 2H), 2.92-2.83 (m, 4H), 2.25 (s, 3H), 1.26 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 167.0, 151.8, 135.4, 133.4, 132.1, 130.2, 126.9, 118.0, 117.1, 74.2, 61.4, 49.3, 43.4, 24.9, 20.4, 14.1; IR: 2981, 2928, 1741, 1715, 1647, 1468, 1418, 1366, 1216, 1031, 984, 928, 656 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{21}BrO_4Na^+$ 391.0515; Found 391.0494.

8-Bromo-6-methyl-5'-vinyl-4',5'-dihydro-3'*H*-spiro[chromane-2,2'-furan]-3'-carboxylic acid ethyl ester (6f). Following **general procedure D**: 5-(2-Allyloxy-3-bromo-5-methyl-phenyl)-3-oxo-pentanoic acid ethyl ester **5f** (329 mg, 0.89 mmol), K_2CO_3 (394 mg, 2.85 mmol) and *trans*-1,4-dibromo-2-butene (233 mg, 1.07 mmol) were combined in DMSO (2 mL) to provide the crude vinyl cyclopropane compound which was used for the next step without further purification. This crude vinyl cyclopropane, $Pd(PPh_3)_4$ (51 mg, 0.044 mmol) and K_2CO_3 (365 mg, 2.6 mmol) were combined in EtOH (10 mL) to provide a crude residue. The crude residue was purified by flash chromatography (1:60−1:10 Et_2O/40−60 Pet. Ether) to afford **6f**.

6fii (yellow solid, 123 mg, 30%) ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (s, 1H), 6.80 (s, 1H), 5.94-5.85 (m, 1H), 5.10 (d, *J* 17.2, 1H), 5.03 (d, *J* 10, 1H), 4.59-4.53 (m, 1H), 4.21-4.15 (m, 2H), 3.10-3.01 (m, 2H), 2.80-2.67 (m, 2H), 2.50-2.42 (m, 2H), 2.22 (s, 3H), 2.04-2.00 (m, 1H), 1.23 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 146.6, 139.5, 131.1, 130.8, 128.6, 123.2, 116.2, 111.0, 105.7, 80.6, 61.0, 53.9, 32.7, 28.8, 22.4, 20.2, 14.2; IR: 2922, 1734, 1470, 1367, 1236, 1188, 1139, 990, 932, 895, 853, 805 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{21}BrO_4Na^+$ 403.0515; Found 403.0519; m.p. = 69.9 °C-71.2 °C.

6fi and 6fiii (yellow oil, 103 mg, an inseparable 1 :1 mixture of two diastereoisomers, 24%) ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* 8.4, 1.7H), 6.81 (s, 1.7H), 5.96-5.79 (m, 1.7H), 5.26 (d, *J* 17.2, 0.7H), 5.16-5.11 (m, 1.7H), 5.04 (d, *J* 10.4, 1H), 4.95-4.89 (m, 1H), 4.80-4.75 (m, 0.7H), 4.26-4.13 (m, 3.4H), 3.38 (d, *J* 6, 1H), 3.13-2.97 (m, 3.4H), 2.80-2.68 (m, 2H), 2.55-2.38 (m, 3H), 2.23 (s, 3H), 2.22 (s, 2.1H), 2.11-1.94 (m, 3.4H), 1.30 (t, *J* 7.2, 3H), 1.22 (t, *J* 7.2, 2.1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 169.1, 146.7, 146.6, 139.6, 137.7, 131.2, 131.2, 131.0,

130.9, 128.7, 128.5, 123.2, 123.1, 116.4, 116.0, 111.0, 110.8, 107.7, 106.3, 82.7, 78.6, 61.0, 61.0, 54.1, 52.8, 34.0, 32.3, 29.3, 27.1, 22.6, 22.5, 20.2, 20.2, 14.2, 14.2; IR: 2924, 1733, 1469, 1368, 1343, 1234, 1182, 1129, 990, 924, 854, 804 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{21}BrO_4Na^+$ 403.0515; Found 403.0508

2-(5-Bromo-8-hydroxy-isochroman-1-yl)-1-(2-methyl-5-vinyl-4,5-dihydro-furan-3-yl)-ethanone (8). Following **general procedure D**: 1,3-diketone **7** (135 mg, 0.37 mmol), K_2CO_3 (164 mg, 1.18 mmol) and *trans*-1,4-dibromo-2-butene (96 mg, 0.44 mmol) were combined in DMSO (1 mL) to provide the crude vinyl cyclopropane compound which was used for the next step without further purification. This crude vinyl cyclopropane, $Pd(PPh_3)_4$ (21.0 mg, 0.018 mmol) and K_2CO_3 (153 mg, 1.11 mmol) were combined in MeOH (5 mL) to provide a crude residue. The crude residue was purified by flash chromatography to afford **8** (91 mg, 65%); ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.30 (d, *J* 8.8, 1H), 6.67 (d, *J* 8.8, 1H), 5.97-5.86 (m, 1H), 5.43 (t, *J* 4.8, 1H), 5.35-5.22 (m, 2H), 5.14-5.06 (m, 1H), 4.00-3.94 (m, 1H), 3.88-3.83 (m, 1H), 3.24-3.05 (m, 3H), 2.86-2.69 (m, 3H), 2.31 (d, *J* 1.6, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.70, 197.61, 171.42, 171.36, 152.40, 136.21, 136.19, 133.72, 131.14, 127.02, 117.48, 117.39, 116.04, 114.40, 111.10, 111.02, 83.51, 83.46, 68.71, 68.61, 60.79, 60.78, 47.37, 35.72, 35.70, 29.44, 15.55, 15.54; IR: 3273, 2927, 1715, 1576, 1441, 1324, 1227, 1094, 1024, 947, 732 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{19}BrO_4Na^+$ 401.0359; Found 401.0356.

1-(7'-Bromo-5-vinyl-3',3a',4,5,5',6'-hexahydro-3*H*-spiro[furan-2,2'-pyrano[2,3,4-*de*]chromen]-3-yl)ethan-1-one (9). Dihydrofuran **8** (91 mg, 0.24 mmol) was treated with $Pd(PPh_3)_4$ (12 mg, 0.012 mmol) and K_2CO_3 (87 mg, 0.63 mmol) in MeOH (9 mL) at 50°C with stirring overnight to provide the crude residue which was purified by flash chromatography (1:20-1:10 EtOAc/40−60 Pet. Ether) to afford **9** (83 mg, 91%, two diastereoisomers 1:1).

9i (yellow oil, 27 mg) ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* 8.8, 1H), 6.53 (d, *J* 8.8, 1H), 5.88-5.80 (m, 1H), 5.29 (dt, *J* 17.2, 1.6, 1H), 5.16 (dt, *J* 10.4, 1.2, 1H), 4.85 (dd, *J* 12.0, 5.2, 1H), 4.79-4.73 (m, 1H), 4.37-4.31 (m, 1H), 4.00-3.93 (m, 1H), 3.23-3.18 (m, 1H), 2.97-2.87 (m, 2H), 2.73 (dd, *J* 17.6, 4.8, 1H), 2.52-2.47 (m, 1H), 2.35-2.29 (m, 1H), 2.19 (s, 3H), 1.93-1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 149.3, 137.2, 132.5, 131.7, 123.2, 116.5, 115.6, 115.4, 106.7, 79.3, 68.0, 65.6, 59.9, 36.3, 31.9, 29.9, 29.1; IR: 2927, 2857, 1716, 1579, 1454, 1339, 1256, 1087, 1047, 908, 811 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{19}BrO_4Na^+$ 401.0359; Found 401.0334.

9ii (yellow oil, 51 mg) ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 6.8 Hz, 1H), 6.51 (d, *J* 8.8, 1H), 5.91-5.82 (m, 1H), 5.18 (d, *J* 17.2, 1H), 5.08 (d, *J* 10.4, 1H), 4.83 (dd, *J* 12.0, 5.6, 1H), 4.61-4.55 (m, 1H), 4.35-4.30 (m, 1H), 3.99-3.92 (m, 1H), 3.11-3.06 (m, 1H), 2.96-2.87 (m, 1H), 2.72 (dd, *J* 17.6, 4.8, 1H), 2.60-2.52 (m, 1H), 2.44-2.37 (m, 2H), 2.33-2.27 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 149.3, 138.8, 132.4, 131.6, 123.3, 116.6, 115.5, 115.3, 106.4, 80.6, 68.1, 65.6, 61.0, 35.7, 32.7, 29.8, 29.1; IR: 2925, 2858, 1712, 1579, 1453, 1338, 1256, 1087, 901, 810 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{19}BrO_4Na^+$ 401.0359; Found 401.0340.

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Supplementary Material

^1H and ^{13}C NMR spectra for all new compounds are provided.

References

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