Accepted Manuscript

Expedient synthesis of xanthones and multi-functionalized chromones from 1,1-diacyl cyclopropanes

Sarah A. French, Mitchell R. Clark, Robert J. Smith, Thomasin Brind, Bill C. Hawkins

PII: S0040-4020(18)30371-5

DOI: 10.1016/j.tet.2018.04.003

Reference: TET 29418

To appear in: *Tetrahedron*

Received Date: 28 February 2018

Revised Date: 29 March 2018

Accepted Date: 3 April 2018

Please cite this article as: French SA, Clark MR, Smith RJ, Brind T, Hawkins BC, Expedient synthesis of xanthones and multi-functionalized chromones from 1,1-diacyl cyclopropanes, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.04.003.

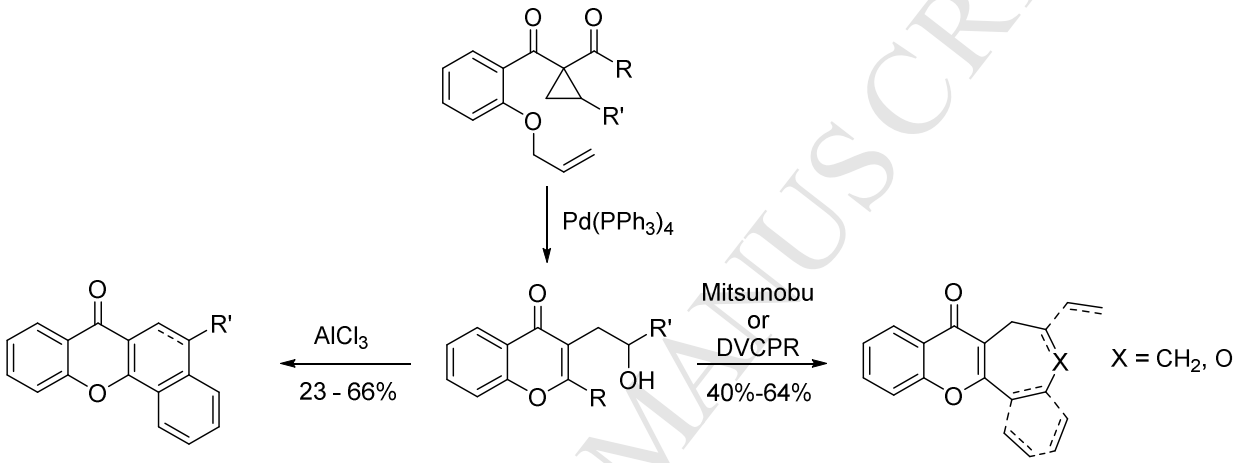
Expedient Synthesis of Xanthones and Multi-Functionalized Chromones from 1,1-Diacyl Cyclopropanes.

Sarah A. French, Mitchell R. Clark, Robert J. Smith, Thomasin Brind and Bill C. Hawkins

Department of Chemistry, University of Otago, Dunedin, New Zealand

bhawkins@chemistry.otago.ac.nz

Graphical Abstract



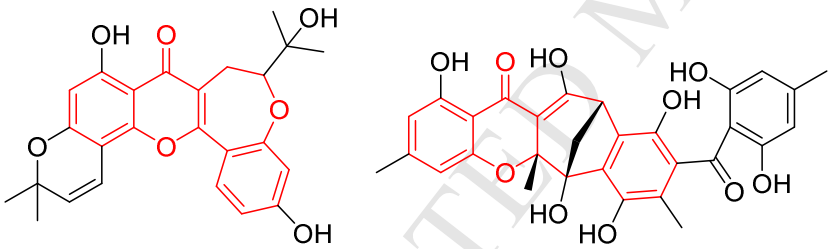
Abstract

We report the rapid synthesis of various cycloheptane-fused chromones and an oxepine fused flavone in 5 steps from the corresponding 2-hydroxy acetophenone. Furthermore, we describe the synthesis of xanthones, in moderate to good yield, from 2,3-disubstituted flavones using a Friedel Crafts alkylation strategy.

Introduction

The rich chemical diversity of natural products and their often useful biological activity has provided a wealth of structures that lend themselves to the discovery of potential medicines. In fact, nearly 50% of all clinically used drugs are natural products or directly derived from them.[1] Within this, terrestrial natural products are the most explored, constituting the majority of the naturally derived drugs on the market.[2] Central to the continued success is the development of organic synthetic methodology and its application to efficiently produce these, and yet to be discovered, natural products and pharmaceutically optimized analogues.

In humans, chromones, xanthones and more broadly, benzopyrans, have been shown to possess a diverse range of biological activity such as antioxidant,[3] antidiabetic,[4] anticancer and antibacterial properties.[5-8] This has attracted a lot of attention from the biological and synthetic chemistry disciplines, and as a result significant efforts have been invested into the synthesis of chromone analogues to further investigate their biological properties.[9-12] The *Moraceae* are a large family of flowering plants (which includes fig and mulberry trees) which have long been used in herbal medicines to treat a variety of illnesses. Studies on the chemical constituents present in the root bark of this family has led to the identification of numerous natural products, including many which contain a 2-phenyl chromone (flavone) core. Of particular interest to us are the oxepine-fused flavones like neocyclomorusin (**1**, Figure 1) which has been reported to possess anticancer[13] and antimicrobial[14] activities amongst others.[15-16] Another structurally related compound is microsphaerin D (**2**, Figure 1) a hexacyclic natural product found in the soil anamorph *Microspaeropsis* sp. which was isolated along with three other compounds (microsphaerin A-C). All four compounds were shown to possess low µM activity against Methicillin-resistant Staphylococcus aureus (MRSA).[17]

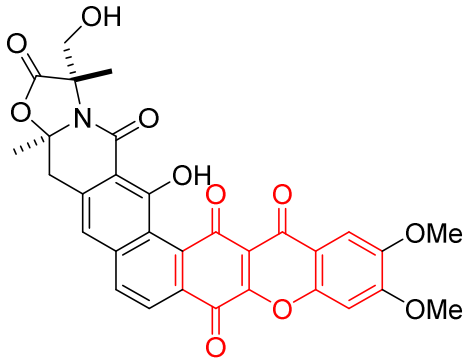


neocyclomorusin (**1**) microsphaerin D (**2**)

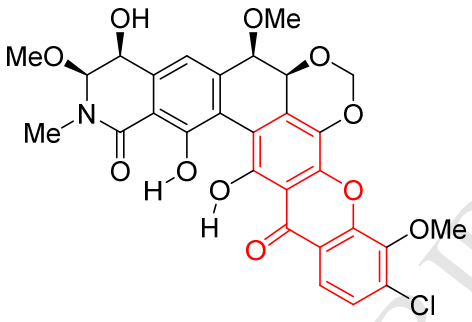
Figure 1. Antimicrobial natural products containing chromones.

A related benzopyran subclass which incorporates a further fused cyclohexane ring, of varying degrees of saturation, are the xanthones (Figure 2), which are present in fungi and higher plant families.[18-19] Xanthones can be highly cytotoxic and have shown anti-inflammatory, antimalarial and antimicrobial activities.[19-21] Examples of bioactive xanthone containing natural products include citreamicin η (**3**) which was isolated from a culture of *Micromonosporacitrea* and is a potent antibiotic possessing an MIC value below 30 nM against several gram positive strains of bacteria (Figure 2).[22] Lysolipin I (**4**) is also a potent antibacterial against a variety of multidrug resistant pathogens, originally isolated from *Streptomyces violaceoniger* Tü 96.[23] In recent years, structure-activity relationships (SAR) of

the xanthone scaffold has been a focus of much research, with several promising xanthone based compounds having been identified.[24]



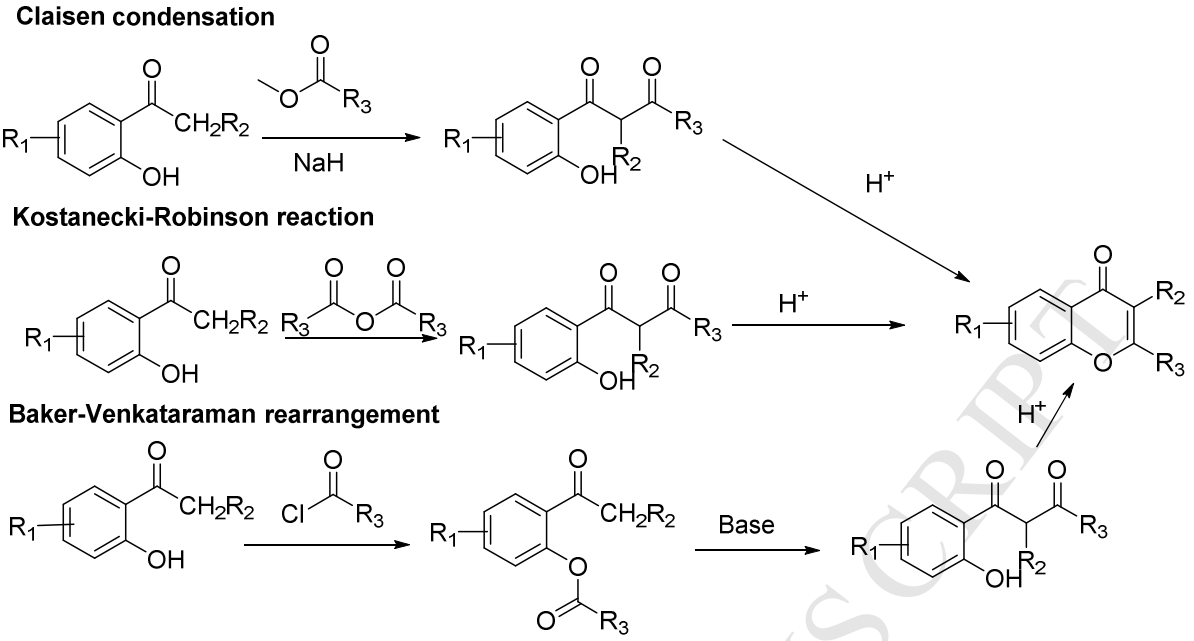
citreamicin η **(3)**



lysolipin **I** (**4**)

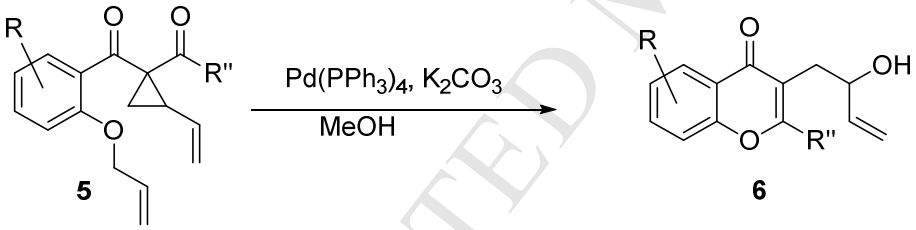
Figure 2. Potent antibiotics containing a xanthone core.

While there are several well established methods to synthesize chromone structures all the currently available methods have limitations (Scheme 1) and several sites on the scaffold remain difficult to functionalize.[7, 25] Significant limitations include: acidic reaction condition are often required to drive the dehydration step of the intermediary lactol and long reaction times with elevated temperatures are usually needed.[26-27] Since these structures are present in a plethora of biologically active natural and non-natural compounds, any new synthetic methods which allows for the rapid generation of analogues would be highly valued. Furthermore, if new methods allowed access to chemical space beyond the scope of the current methodology they may prove to be a useful tool in furthering medicinal chemistry programs.



Scheme 1. Common methods to synthesis chromones.

Recently we reported a rapid, acid-free, method to access various 2,3-substituted chromones from various 1,1-diacylcyclopropanes (Scheme 2).[28] The reaction proceeds under ambient temperature in 90 mins.

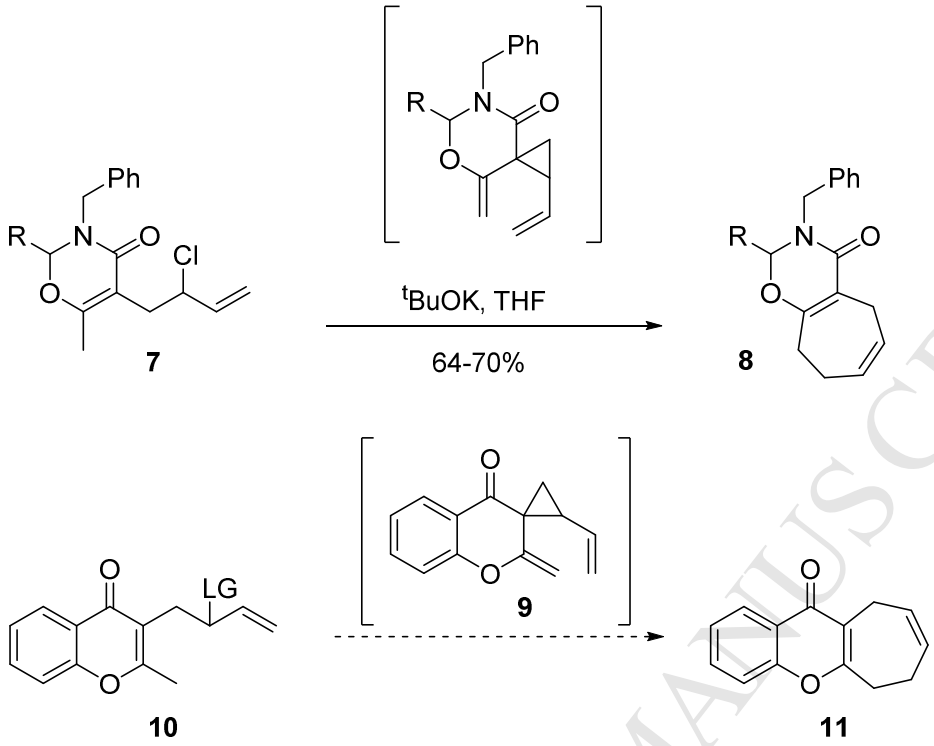


Scheme 2. Synthesis of 2,3-substituted chromones from 1,1-diacylcyclopropanes.

Results and Discussion

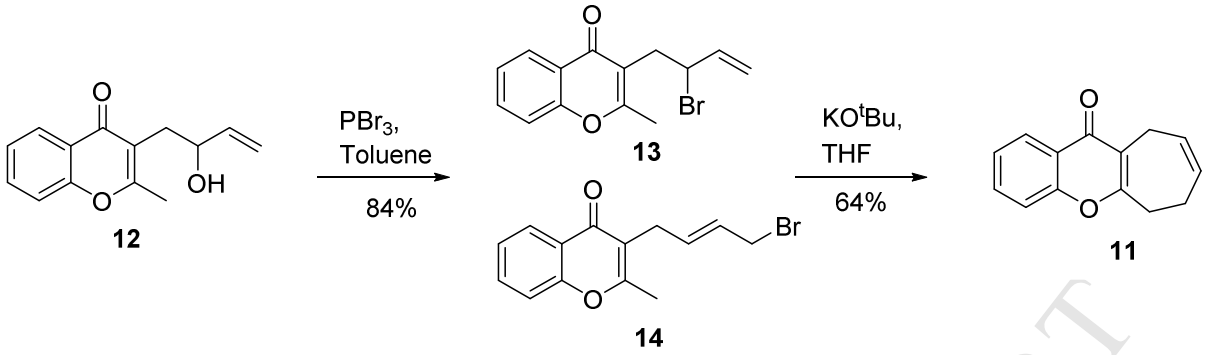
Herein we disclose our efforts to expand the reaction scope and also use these chromones as intermediates for the construction of structurally diverse natural product inspired scaffolds. Given the prevalence of bioactive natural products containing cyclohepta- and oxepine- fused chromones (for example, see Figure 1), our first study was focussed on extending our established chemistry to the synthesis of such structures. Given our previous success in synthesizing cycloheptane-fused oxazinones (Scheme 3),[29] we postulated that the electronically similar chromone system may also undergo *in situ* formation of the divinyl

cyclopropane **9** and a subsequent rearrangement would provide the cycloheptane-fused chromone **11**.



Scheme 3. Synthesis of cycloheptadienes via a divinyl cyclopropane rearrangement (DVCPR).

To this end, the known allylic alcohol **12**[28] was smoothly converted to the corresponding allylic bromides **13** and **14** by treatment with phosphorous tribromide (Scheme 4). The inconsequential mixture of bromides **13** and **14**, which presumably arose from an S_N2 and S_N2' reaction pathway, respectively. Treatment of the mixture of bromides **13** and **14** with potassium *tert*-butoxide at low temperature for 3 h, provided the cycloheptadiene fused chromone **11** in a 64% yield. Attempts to improve the efficiency by mesylation of the allylic alcohol and treatment of the crude residue with base did not result in an improved yield. The established procedure was also used to synthesise both the cycloheptane-fused 7-methoxychromone (**19**) as well as the cycloheptane-fused 6-bromochromone (**20**, Table 1).



Scheme 4. Synthesis of the cycloheptane-fused chromone **11**.

Significant decreases in isolated yield were observed upon increase in steric bulk at the 2-position of the chromone. For example, extension from methyl to ethyl resulted in the isolated yield of the corresponding cycloheptane-fused chromone **21**, dropping from 64% to 16%, under the standard reaction conditions (Table 1). Likewise, the 2-benzylchromone provided the cycloheptane **22** in low yield. This was attributed to significant 1,4- flagpole interactions expected in the boat-like transition state (Figure 3). Efforts to optimise the reaction via increased formation of the O (*Z*) enolate, thereby minimising 1,4-flagpole interactions in the transition state, only resulted in modest increases in yield of the corresponding cycloheptadienes (Table 1). Interestingly, under reversible enolate formation conditions (sodium methoxide in methanol) a significant increase in the isolated yield of **21** and **22**, to 40% and 38%, respectively, was observed. This suggests that the kinetic and thermodynamic enolate is the O (*Z*) enolate with the O (*E*) enolate being unfavoured due to steric clashing between the 2 and 3 substituents on the chromone. This reaction pathway was inaccessible to 2-methylchromones disubstituted at the methyl group, as shown by exposure of the 2-isopropylchromone **23** to the standard reaction conditions, which provided the eliminated product **24** and no traces of the cycloheptyl adduct (Scheme 5).

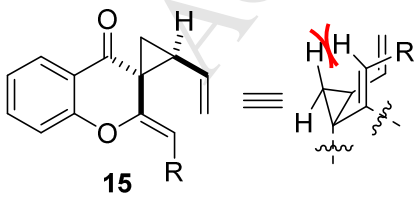
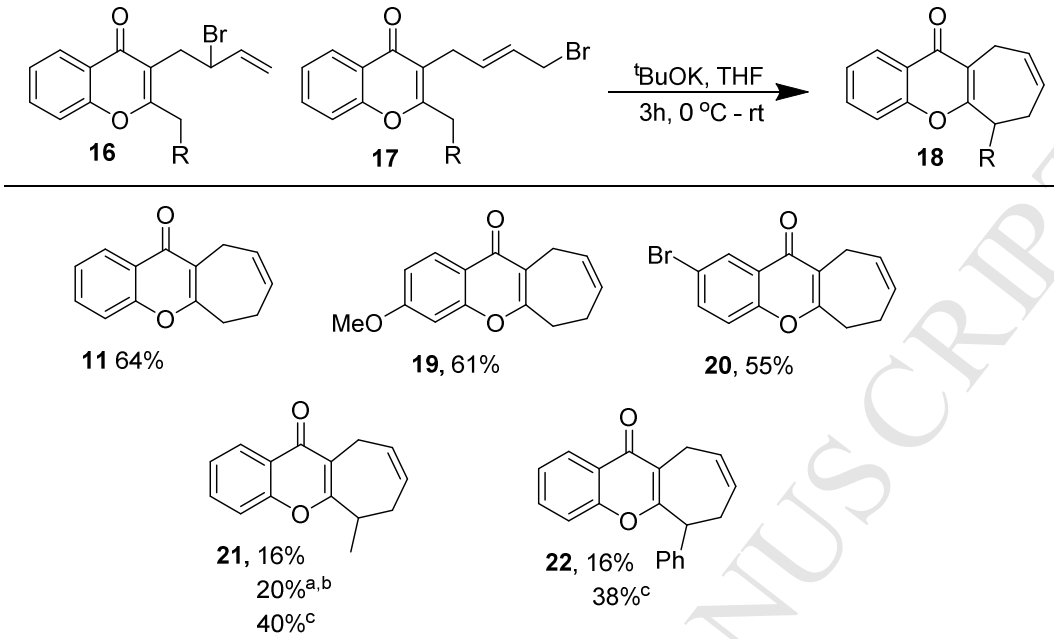
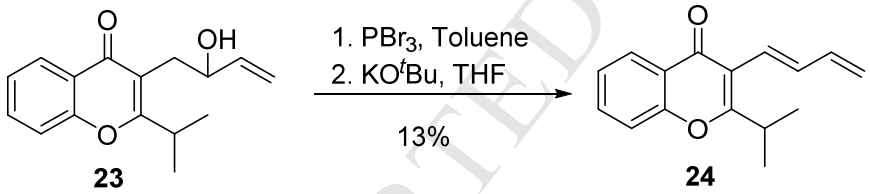


Figure 3. 1,4-Flag pole interactions can be minimized through the O (*Z*) enolate.

Table 1. Reaction scope of the divinyl cyclopropane rearrangement (DVCPR).



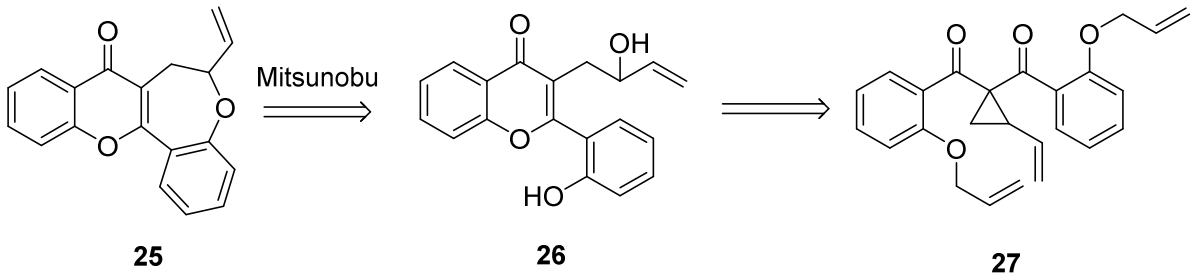
Use of alternate bases [a] NaHMDS, THF, [b] LDA, HMPA, THF [c] NaOMe, MeOH



Scheme 5. Synthesis of 3-dienyl-2-isopropylchromone (**24**).

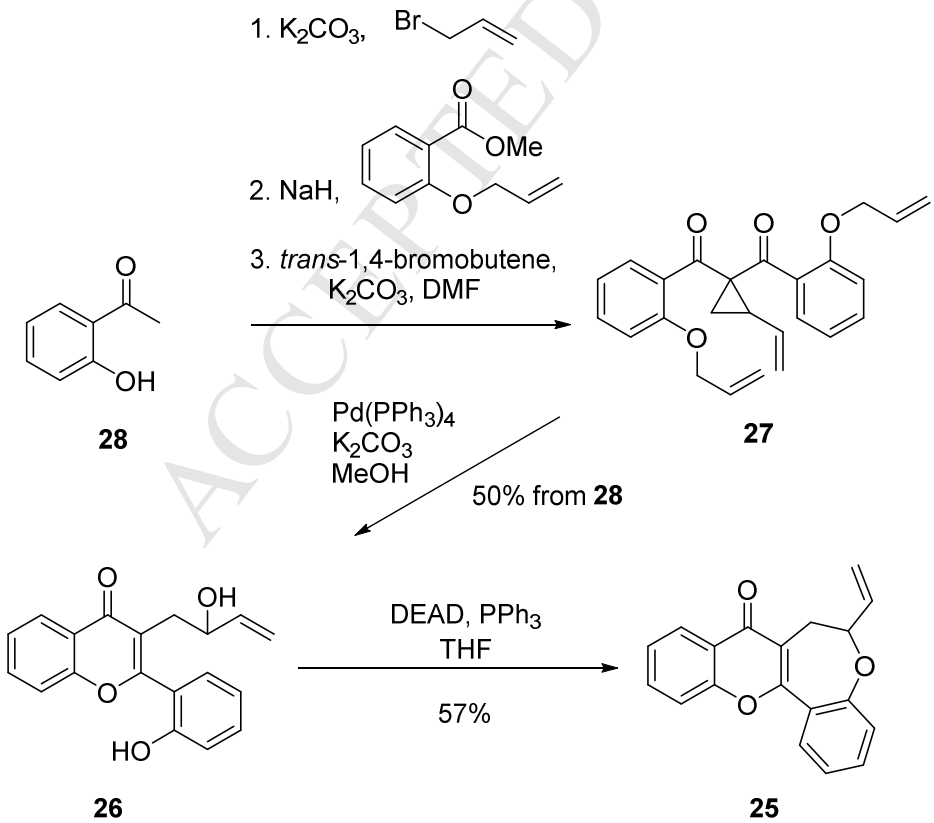
The rapid and facile entry into the substrate makes this method attractive for the synthesis of cycloheptane-fused chromones. However, limitations in scope around the vinyl handles of the incipient cyclopropane limit widespread adoption of this method.

Given the prevalence of natural products containing oxepine-fused flavones,[13-16] like neocyclomorusin (Figure 1), we next sought to apply our methodology to the synthesis of such structures. Specifically access to the oxepine was envisaged through an intramolecular Mitsunobu reaction on the precursor flavone, itself accessible from the vinyl cyclopropane **27** (Scheme 6).



Scheme 6. Retrosynthetic analysis of the scaffold present in numerous bioactive compounds isolated from *Moraceae,* including neocyclomorusin (**1**).

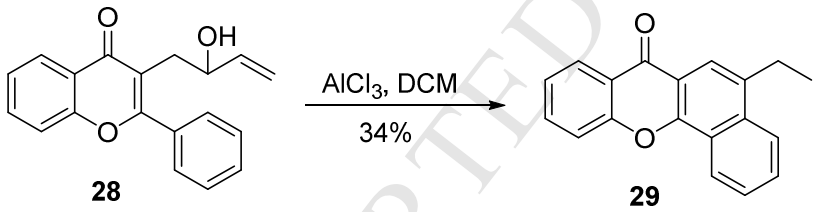
In a forward synthetic sense the vinyl cyclopropane substrate **27** was prepared from 2-hydroxyacetophenone (**28**) in three steps using an adapted literature procedure (Scheme 7).[28] Treatment of the crude vinylcyclopropane **27** with Pd(0) under the standard reaction conditions provided the hydroxyl flavone **26** in a 50% overall yield from 2-hydroxyacetophenone. The intramolecular Mitsunobu reaction on the flavone was achieved using DEAD and triphenylphosphine to form the oxepine **25** and thereby the scaffold of neocyclomorusin in 57%. This provides a general strategy to access this scaffold, which is prevalent in numerous natural products. Efforts towards the synthesis of these compounds remains ongoing and will be reported in due course.



Scheme 7. Synthesis of an oxepine-fused flavone, a structure embedded in numerous natural products.

Despite many bioactive xanthones being known there remains relatively few methods to synthesise them.[30-32] The most common method for synthesis of xanthones is through benzophenone or diaryl ether intermediates with the subsequent ring closures requiring harsh reaction conditions.[33] Other methods include Hauser type cyclizations on chromones,[34-35] coupling of arynes with benzoates,[33] or more recently photochemical induced electrocyclizations of flavone derivatives.[36]

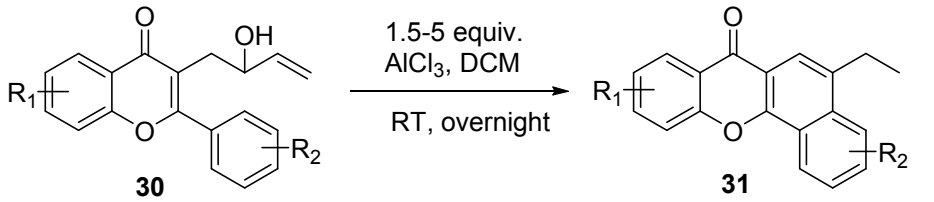
In continuing efforts to expand our methodology to access bioactive natural product scaffolds, we next examined the possibility of creating xanthones using an intramolecular Friedel Crafts alkylation strategy (Scheme 8). After the unsuccessful screening of various Lewis Acids (TMSI, $BF_3.OEt_2$, $FeCl_3$, $SnCl_2$ and ytterbium triflate) it was found that treatment of a solution of the flavone **28**[28] in dichloromethane with three molar equivalents of aluminium trichloride smoothly provided the corresponding xanthone **29** in 34%.

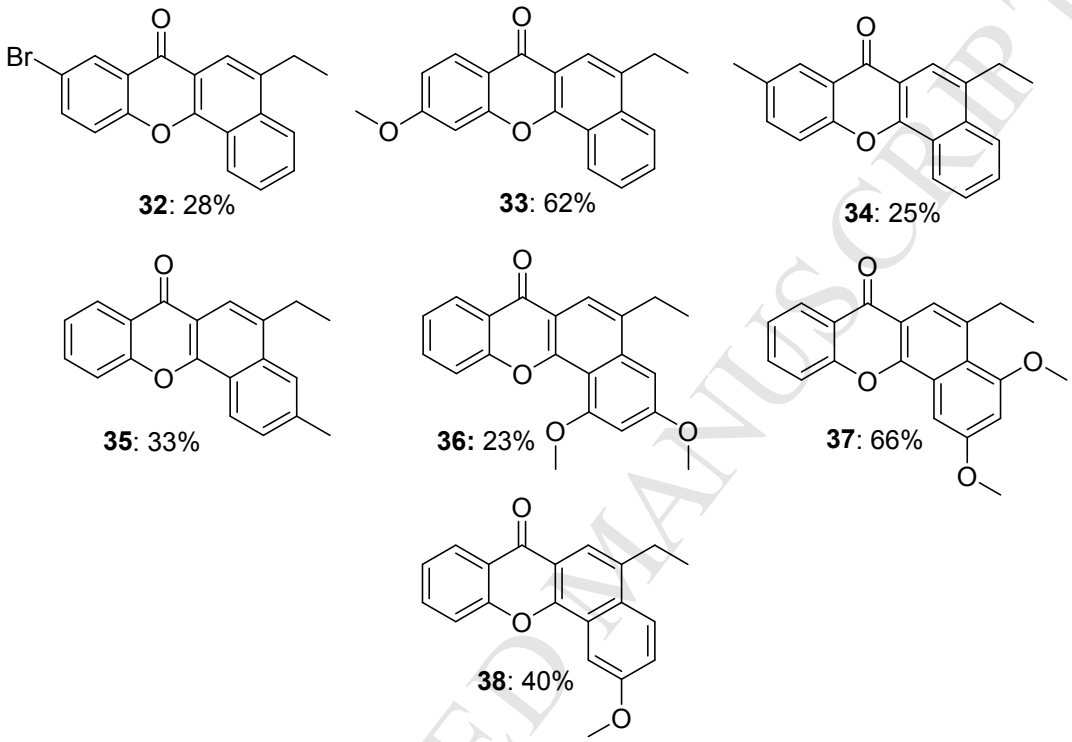


Scheme 8. Synthesis of xanthone **29**.

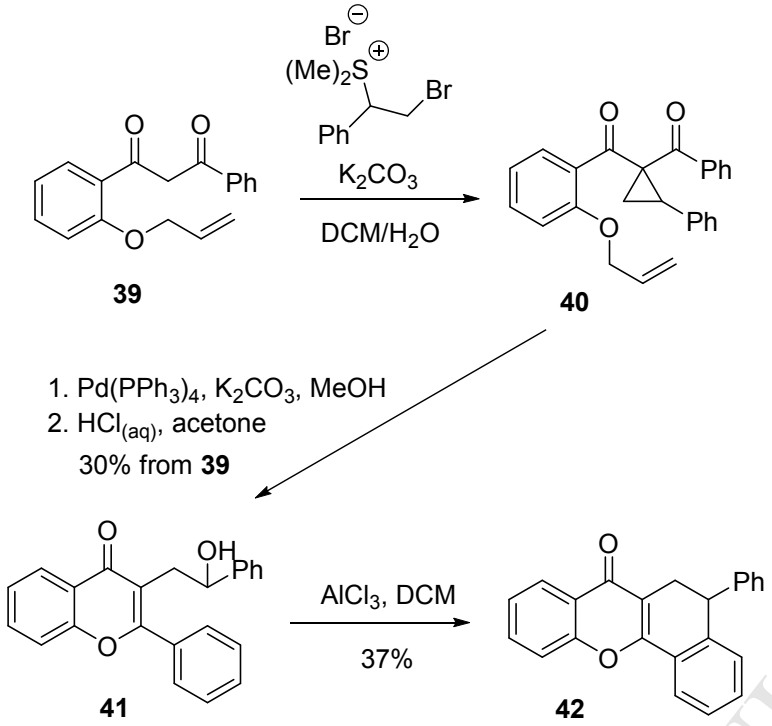
With the reaction conditions established we next examined substrate scope. As expected the more electron rich aromatic systems in the 2-position of the chromone underwent the Friedel Crafts alkylation with increased efficiency providing the corresponding xanthones in good yields (**35**, 33%, **37**, 66% and **38**, 40%, Table 2). While substitution on the benzene ring of the chromone scaffold appeared to be tolerated with electron poor (**32**, 28%) and electron rich (**33**, 62%) substituents. Interestingly, in the case of xanthone **35** the intermediate dihydroxanthone could be isolated.[37] However, no general procedure to enable routine isolation of the dihydroxanthone was developed.

Table 2. Substrate scope





Cognizant of the limitations of an alkyl chain in terms of future functionalization, we next examined the use of a phenylcyclopropane as a replacement for the vinyl cyclopropane. To this end the diketone **39** was treated with an *in situ* generated sulfonium ylide,[38] to provide the phenylcyclopropane **40** (Scheme 9). Deallylation, provided the free phenol (not shown) which was subsequently heated at reflux in aqueous acid to afford the flavone **41** in a 30% overall yield from **39**. Treatment of the flavone **41** under the standard reaction conditions smoothly provided the dihydroxanthone **42** in a 37% yield.



Scheme 9. Synthesis of the pentacycle **42**.

In conclusion, we have disclosed our efforts towards the synthesis of cycloheptane- and oxepine-fused chromones present in numerous bioactive natural products. The syntheses are relatively rapid, 5 steps from the 2-hydroxyacetophenone, and required only 2 chromatographic separations. Future efforts will focus on applying this methodology to the synthesis of neocyclomorusin and microsphaerin A. Furthermore, we have shown that a series of flavone can be readily converted into the corresponding xanthones in moderate to good yield (23- 66%).

Experimental Section

General

Thin layer chromatography (tlc) was performed on ALUGRAM® aluminium-backed UV254 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 1H NMR spectra. Chemical shifts have been reported relative to the $CDCl_3$ triplet at δ 77.16 ppm. Dichloromethane (CH_2Cl_2) was dried using a PURE SOLV MD-6 solvent purification system. All other solvents and reagents were used as received. Melting points were measured using a DigiMelt MPA 161.

Chromone procedure To a solution of 1,3-diketone (1 equiv) in DMSO at rt was added K_2CO_3 (3 equiv) and trans-1,4-dibromo-2-butene (1.1 equiv) the suspension was stirred for 24 h. After this time the reaction was diluted with water and extracted with ethyl acetate (×3). The combined organic extracts were washed with water (×3) and brine (×1), dried over $MgSO_4$, and reduced *in vacuo* to provide the desired cyclopropane. The residue was of sufficient purity to be used in the next step. To a solution of cyclopropane (1 equiv) in degassed MeOH was added $Pd(PPh_3)_4$ (0.05 equiv) with stirring for 5 min followed by the addition of K_2CO_3 (2 equiv) with stirring for a further 45 min. 1M HCl was added and stirred for 15 min then extracted with EtOAc (×2). The combined organic extracts were washed with

water (×1) and brine (×1), dried, and reduced *in vacuo*. The crude residue was purified by flash

Xanthone procedure. To the chromone (1 equiv) in DCM, $AlCl_3$ (1.5 equiv) was added and stirred at rt for 30 minutes. If starting material remained a further 1.5 equivalents of $AlCl_3$ was added. This was repeated until all the starting material was consumed. The solution was diluted with water and the aqueous phase was extracted with DCM. The combined organic fractions were washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (typically 1:9−1:4 EtOAc/40−60 Pet. Ether), yielding the desired xanthone.

Cycloheptadiene general procedure. To a solution of the appropriate chromone (1 equiv) in THF at $0^{O}C$ was added $^{t}BuOK$ (1.3 equiv). The reaction was warmed to rt and stirred for 3 h. The reaction mixture was then quenched with water and extracted with EtOAc which was further washed with brine. The solvent was removed *in vacuo* to give the crude cycloheptadiene which was be purified by silica gel column chromatography.

Cyclohept-11-ene[2,3]-benzopyran-4-one 11

Following the cycloheptadiene procedure, a mixture of the appropriate allylic bromides (0.063 g, 0.22 mmol) was reacted with $^{t}BuOK$ (0.032 g, 0.29 mmol) in dry THF (1 mL) to give a crude residue which was then subjected to column chromatography elution with 1:19 to 1:9 EtOAc/petrol provided the title compound (30 mg, 64%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (m, 1H). 7.61 (m, 1H), 7.38 (m, 2H), 5.79 (m, 1H), 5.67 (m, 1H), 3.46 (m, 2H), 3.03 (m, 2H), 2.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 167.0, 156.0, 133.1, 128.9, 126.8, 126.2, 124.8, 122.9, 121.5, 117.8, 31.6, 24.9, 20.8. FTIR (ATR / cm^{-1}):

1608, 1464, 1141, 756. HRMS-ESI calculated for $C_{14}H_{12}O_2Na^+$ $[M + Na]^+$: 235.0730; found: 235.0745.

Cyclohept-11-ene[2,3]-7-methoxy-benzopyran-4-one 19

To a solution of the appropriate allylic bromides (0.350 g, 1.08 mmol) in dry THF (4 mL) was added ^{t}BuOK (0.158 g, 1.41 mmol) at 0 ^{o}C. The reaction mixture was warmed to room temperature and left to stir for 3 h. The reaction was then quenched with aqueous ammonium chloride and extracted with EtOAc. The organic layer was separated washed with brine before the solvent was removed under reduced pressure to give a crude residue which was then subjected to column chromatography elution with 1:19 to 1:9 EtOAc/petrol provided the title compound **19** (0.160 g, 61%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 1H), 6.91 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.77 (m, 1H), 5.79 (m, 1H), 5.67 (m, 1H), 3.87 (m, 4H), 3.42 (m, 2H), 2.97 (m, 2H), 2.42 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.04, 166.07, 163.50, 157.49, 128.74, 127.45, 126.90, 120.92, 116.76, 113.97, 99.86, 55.69, 31.35, 24.70, 20.51. FTIR (ATR / cm^{-1}): 1606, 1437, 1118, 722, 538. HRMS-ESI calculated for $C_{15}H_{14}O_3Na^+$ $[M + Na]^+$: 265.0835; found: 265.0869.

Cyclohept-11-ene[2,3]-6-bromo-benzopyran-4-one 20

To a solution of the appropriate allylic bromides (0.150 g, 0.40 mmol) in dry THF (2 mL) was added ^{t}BuOK (0.09 g, 0.81 mmol) at 0 ^{o}C. The reaction mixture was warmed to room temperature and left to stir for 3 h. The reaction was then quenched with aqueous ammonium chloride and extracted with EtOAc. The organic layer was separated washed with brine before the solvent was removed under reduced pressure to give a crude residue which was then subjected to column chromatography elution with 1:19 to 1:9 EtOAc/petrol provided the title compound **20** (0.065 g, 55%) a light yellow oil:

^{1}H NMR (400 MHz, CDCl3) δ 8.33 (d, *J* = 2.5 Hz, 1H), 7.69 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 5.80 (m, 1H), 5.69 (m, 1H), 3.44 (dd, *J* = 5.3, 2.4 Hz, 2H), 3.02 (m, 2H),

2.45 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.24, 166.99, 154.57, 135.89, 128.80, 128.73, 126.55, 124.19, 121.61, 119.72, 117.98, 31.45, 24.64, 20.63. FTIR (ATR / cm^{-1}): 2923, 1634, 1463, 816, 756. HRMS-ESI calculated for $C_{14}H_{11}BrO_2Na^+$ $[M + Na]^+$: 312.9942; found: 312.9936.

14-Methyl-cyclohept-11-ene[2,3]-7-methoxy-benzopyran-4-one 21

Following the cycloheptadiene procedure, a mixture of the appropriate allylic bromides (0.260 g, 0.85 mmol) was reacted with ^{t}BuOK (0.124 g, 1.10 mmol) in dry THF (3 mL). The reaction mixture was warmed to room temperature and left to stir for 3 h. The reaction was then quenched with aqueous ammonium chloride and extracted with EtOAc. The organic layer was separated washed with brine before the solvent was removed under reduced pressure to give a crude residue which was then subjected to column chromatography elution with 1:19 to 1:9 EtOAc/petrol provided the title compound **21** (30 mg, 16%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.38 (m, 2H), 5.83 (m, 1H) 5.65 (m, 1H),3.65 (m, 1H), 3.47 (m, 1H), 3.28 (m, 1H), 2.37 (m, 2H), 1.41 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 168.4, 155.7, 132.8, 128.1, 127.0, 126.0, 124.6, 122.4, 120.6, 118.3, 117.6, 35.7, 20.7, 16.8. FTIR (ATR / cm^{-1}): 1614, 1464, 757. HRMS-ESI calculated for $C_{15}H_{14}O_2Na^+$ $[M + Na]^+$: 249.0886; found: 249.0878.

14-Benzo-cyclohept-11-ene[2,3]-7-methoxy-benzopyran-4-one 22

Following the cycloheptadiene procedure, a solution of the appropriate allylic bromides (0.330 mg, 0.89 mmol) was reacted with ^{t}BuOK (0.130 g, 1.16 mmol) in dry THF (3 mL). The reaction mixture was warmed to room temperature and left to stir for 3 h. The reaction was then quenched with aqueous ammonium chloride and extracted with EtOAc. The organic layer was separated washed with brine before the solvent was removed under reduced pressure to give a crude residue which was then subjected to column chromatography elution with 1:19 to 1:9 EtOAc/petrol provided the title compound **22** (0.040 g, 16%). ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.20 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.55 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.32 (m, 6H), 7.22 (m, 1H), 5.79 (m, 1H), 5.74 (dt, *J* = 10.8, 5.5 Hz, 1H), 4.40 (dd, *J* = 7.3, 4.9 Hz, 1H), 3.47 (m, 2H), 2.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 166.5, 155.9, 140.4, 133.2, 129.6, 128.6, 128.2, 128.1, 127.2, 126.2, 124.8, 122.7, 121.5, 117.9, 47.4, 31.2, 20.6. FTIR (ATR / cm^{-1}): 3232, 1615, 1466, 1073, 756, 698. HRMS-ESI calculated for $C_{20}H_{16}O_2Na^+$ $[M + Na]^+$: 311.1043; found: 311.1017.

2-Isopropyl-3-(2'hydroxy-3'-buten-1'-yl)-benzopyran-4-one 23

Following the chromone general procedure 1, to a suspension of the appropriate diketone (0.687 g, 2.79 mmol) and K_2CO_3 (1.16 g, 8.37 mmol) in DMSO (7 mL) was added *trans*-1,4-dibromo-2-butene (0.629 g, 3.35 mmol) with stirring for 24 hours. Upon completion the reaction was worked up and the crude residue was dried, redissolved in MeOH (10 mL) and degassed. To this solution was added of K_2CO_3 (1.29 g, 9.31 mmol) and $Pd(PPh_3)_4$ (0.179 g, 0.16 mmol) with stirring for 45 min. After this time the reaction was diluted with 1M HCl stirred for a further 15 min then extracted with EtOAc. Following work up crude residue was purified by silica gel column chromatography (1:9-1:3 EtOAc:40-60 pet. Ether) to provide the title compound (230 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.64 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.39 (m, 2H), 5.93 (ddd, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.28 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.10 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.36 (m, 1H), 3.28 (p, *J* = 6.8 Hz, 1H), 2.85 (m, 2H), 1.33 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 170.8, 155.9, 140.6, 133.4, 125.8, 124.7, 122.5, 117.5, 116.2, 114.5, 72.8, 32.5, 30.5, 20.2, 19.8. FTIR (ATR / cm^{-1}): 3413, 1619, 1466, 758. HRMS-ESI calculated for $C_{16}H_{18}O_3Na^+$ $[M + Na]^+$: 281.1148; found: 281.1144.

2-Isopropyl-3-(1',3'-butadiene)-benzopyran-4-one 24

To a mixture of the appropriate allylic bromides (0.200 g, 0.62 mmol) in THF (2 mL) was added ^{t}BuOK (0.090 mg, 0.81 mmol) the solution was stirred for 3 h before being quenched with water (5 mL). Ethyl acetate (10 mL) was added and the organic layer was collected and concentrated *in vacuo* to provide a crude residue. Subjection of the crude residue column chromatography using 1:9 EtOAc/Pet Ether provided **24** (0.020 g, 13%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 6.5 Hz, 1H), 7.36 (m, 3H), 6.48 (m, 2H), 5.36 (d, *J* = 16.9 Hz, 1H), 5.19 (d, *J* = 9.8 Hz, 1H), 3.46 (h, *J* = 6.8 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 170.2, 155.2, 138.0, 136.1, 135.6, 133.0, 126.0, 124.7, 123.1, 122.8, 117.9, 117.4, 116.6, 30.2, 20.0. FTIR (ATR / cm^{-1}): 1614, 1464, 1069, 758. HRMS-ESI calculated for $C_{16}H_{16}O_2Na^+$ $[M + Na]^+$: 263.1043; found: 263.1023.

2-(2'-Phenol)-3-(2''-hydroxy-buten-1''-yl)-benzopyran-4-one 26

Following the chromone general procedure 1, to a suspension of 1,3-bis(2-allyloxyphenyl)-1,3-propandione (1.85 g, 5.50 mmol) and K_2CO_3 (2.28 g, 16.5 mmol) in DMSO (20 mL) was added *trans*-1,4-dibromo-2-butene (1.18 g, 5.50 mmol) with stirring for 24 hours. Upon completion the reaction was worked up and crude residue was dried, redissolved in MeOH (20 mL) and degassed. To this solution was added of K_2CO_3 (2.61 g, 18.9 mmol) and $Pd(PPh_3)_4$ (0.437 g, 0.378 mmol) with stirring for 45 min. After this time the reaction was diluted with 1M HCl stirred for a further 15 min then extracted with EtOAc. Following work up the crude residue was purified by silica gel column chromatography (1:4-2:3 EtOAc:40-60 pet. Ether) to provide the title compound (830 mg, 50%).Melting point: 162-166^{O}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (ddd, *J* = 7.9, 1.6, 0.52 Hz, 1H), 7.67 (ddd, *J* = 8.5, 7.1, 1.7 Hz, 1H), 7.44 - 7.39 (m, 3H), 7.30 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.08 - 7.02 (m, 2H), 5.86 (ddd, *J* = 17.1, 10.4, 6.1 Hz, 1H), 5.30 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.10 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.80 (m, 1H), 2.92 (dd, *J* = 14.4, 3.3 Hz, 1H), 2.39 (dd, *J* = 14.3, 10.0 Hz, 1H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 181.5, 163.4, 159.2, 156.1, 142.8, 136.5, 134.7, 132.7, 128.4, 127.7, 125.5, 123.7, 123.3, 122.9, 121.2, 118.1, 73.5, 37.0. FTIR (ATR / cm^{-1}): 3475, 3062, 2927, 2870, 1611, 1590, 1425, 999, 926, 753. HRMS-ESI calculated for $C_{19}H_{15}O_4^-$ $[M]^-$: 307.0976; found: 307.0957.

2'-Ethene-benzooxapine[5',4',-*b*]-benzopyran-4-one 25

To a solution of triphenylphosphine (1.28 g, 4.9 mmol) in THF (10 mL) maintained at 0 ^oC was added diethylazodicarboxylate (0.847 g, 4.86 mmol), followed by addition of chromone **26** (1.25 g, 4.05 mmol) in THF (10 mL). The reaction was heated to 50 °C with stirring until consumption of starting material (as indicated by TLC, ~2 hours). Solvent was removed *in vacuo* and the crude residue purified by column chromatography (1:4 - 3:2 EtOAc:Pet Ether) to provide the title compound as a yellow solid (673 mg, 57%). Melting point: 116-118^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (ddd, 1H, *J* = 8.0, 1.7, 0.4 Hz), 7.90 (dd, 1H, *J* = 7.9, 1.7 Hz), 7.69 (ddd, 1H, *J* = 8.4, 7.1, 1.7 Hz), 7.53 (ddd, 1H, *J* = 8.5, 1.0, 0.4 Hz), 7.47 (ddd, 1H, *J* = 8.2, 7.4, 1.7 Hz), 7.42 (ddd, 1H, *J* = 8.0, 7.1, 1.0 Hz), 7.27 (ddd, 2H, *J* = 7.9, 7.4, 1.2 Hz), 7.18 (dd, 1H, *J* = 8.2, 1.1 Hz), 6.05 (ddd, 1H, *J* = 17.2, 10.6, 5.8 Hz), 5.4 (dt, 1H, *J* = 17.2, 1.3 Hz), 5.25 (dt, 1H, *J* = 10.6, 1.3 Hz), 5.14 (m, 1H), 3.19 (dd, 1H, *J* = 15.4, 4.0 Hz), 2.79 (dd, 1H, *J* = 15.4, 8.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 159.3, 156.4, 156.1, 136.9, 133.7, 133.7, 132.5, 128.5, 126.3, 126.0, 125.1, 123.6, 122.9, 118.8, 118.1, 116.8, 88.7, 28.1. FTIR (ATR / cm^{-1}): 3080, 3013, 2922, 2854, 1632, 1605, 1565, 991, 935, 755. HRMS-ESI calculated for $C_{19}H_{14}O_3Na^+$ $[M+Na]^+$: 313.0835; found: 313.0841.

1'-Ethyl-naptha[4',3'-*b*]-benzopyran-4-one 29

Following the xanthone general procedure, to a solution of the appropriate chromone (85 mg, 0.291 mmol) in dry DCM (2 mL) was added $AlCl_3$ (58 mg, 0.436 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:4 EtOAc/40-60 Pet. Ether) to afford the title compound **29** (27 mg, 34%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.42 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.14 (d, *J* = 7.9 Hz, 2H), 7.77 (dddd, *J* = 8.4, 6.7, 5.1, 1.6 Hz, 2H), 7.74 – 7.67 (m, 2H), 7.45 (td, *J* = 7.5, 7.1, 1.2 Hz, 1H), 3.16 (q, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 155.9, 152.7, 136.5, 135.4, 134.3, 129.6, 126.74, 126.6, 124.6, 124.4, 124.4, 123.7, 122.6, 119.5, 118.2, 117.4, 25.7, 14.8. FTIR (ATR / cm^{-1}); 2969, 1721, 1626, 1468, 1434, 754. HRMS-ESI calculated for $C_{19}H_{15}O_2$ $[M+H]^+$: 275.1067; found: 275.1057.

1'-Ethyl-naptha[4',3'-*b*]-6-bromo-benzopyran-4-one 32

Following the xanthone general procedure, to a solution of the appropriate chromone (38 mg, 0.102 mmol) in dry DCM (2 mL) was added $AlCl_3$ (68 mg, 0.512 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:4 EtOAc/40-60 Pet. Ether) to afford the title compound **32** (8 mg, 28%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.66 (m, 1H), 8.52 (d, *J* = 2.5 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.08 (s, 1H), 7.84 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 3.15 (q, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 154.6, 152.7, 137.2, 137.0, 135.5, 129.9, 129.2, 126.7, 124.4, 124.4, 123.9, 123.6, 120.2, 119.3, 117.7, 117.1, 25.7, 14.7. FTIR (ATR / cm^{-1}); 2965, 1628, 1465, 1444. HRMS-ESI calculated for $C_{19}H_{13}BrNaO_2$ $[M+Na]^+$: 374.9991; found: 374.9957.

1'-Ethyl-naptha[4',3'-*b*]-7-methoxy-benzopyran-4-one 33

Following the xanthone general procedure, to a solution of the appropriate chromone (80 mg, 0.248 mmol) in dry DCM (2 mL) was added $AlCl_3$ (165 mg, 1.241 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:4 EtOAc/40-60 Pet. Ether) to afford the title compound **33** (50 mg, 62%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.3 Hz, 1H), 8.29 (d, *J* = 8.9 Hz, 1H), 8.14 – 8.10

(m, 2H), 7.72 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.65 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.96 (s, 3H), 3.15 (q, *J* = 7.6 Hz, 2H), 1.44 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 164.7, 157.7, 152.5, 136.3, 135.1, 129.3, 128.1, 126.4, 124.5, 124.3, 123.4, 119.6, 117.3, 116.6, 113.8, 100.4, 56.0, 25.7, 14.8. FTIR (ATR / cm^{-1}); 2965, 1629, 1613, 1441, 788. HRMS-ESI calculated for $C_{20}H_{16}NaO_3$ $[M+Na]^+$: 327.0992; found: 327.0967.

1'-Ethyl-naptha[4',3'-*b*]-6-methyl-benzopyran-4-one 34

Following the xanthone general procedure, to a solution of the appropriate chromone (30 mg, 0.10 mmol) in dry DCM (2 mL) was added $AlCl_3$ (65 mg, 4.8 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:4 EtOAc/40-60 Pet. Ether) to afford the title compound **34** (7 mg, 25%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.4Hz, 1H), 8.21 – 8.18 (s, 1H), 8.13 (m, 2H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.58 (s, 2H), 3.15 (q, *J* = 7.5 Hz, 2H), 2.51 (s, 3H), 1.45 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 154.2, 152.7, 136.3, 135.6, 135.4, 134.3, 129.5, 126.5, 126.0, 124.6, 124.4, 123.7, 122.3, 119.6, 118.0, 117.3, 25.7, 21.1, 14.8. FTIR (ATR / cm^{-1}); 2923, 1651, 1627, 1487, 1447, 767. HRMS-ESI calculated for $C_{20}H_{17}O_2$ $[M+H]^+$: 289.1223; found: 289.1211.

1'-Ethyl-8'-methyl-naptha[4',3'-*b*]-benzopyran-4-one 35

Following the xanthone general procedure, to a solution of the appropriate chromone (31 mg, 0.102 mol) in dry DCM (2 mL) was added $AlCl_3$ (68 mg, 0.512 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:4 EtOAc/40-60 Pet. Ether) to afford the title compound **35** (10 mg, 33%) as a brown solid. Melting point: 114 – 115^{O}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.45 – 8.39 (m, 1H), 8.10 (s, 1H), 7.90 (s, 1H), 7.77 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1H), 7.68 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.53 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.44 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 3.14

(q, *J* = 7.5 Hz, 2H), 2.63 (s, 3H), 1.45 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 155.9, 152.9, 139.9, 135.9, 135.7, 134.2, 128.56, 126.7, 124.3, 123.8, 123.5, 122.7, 122.5, 119.6, 118.2, 116.8, 25.7, 22.5, 14.8. FTIR (ATR / cm^{-1}); 2922, 2362, 1620, 1467, 1387, 760. HRMS-ESI calculated for $C_{20}H_{17}O_2$ $[M+H]^+$: 289.1223; found: 289.1207.

1'-Ethyl-6',8'-dimethoxy-naptha[4',3'-*b*]-benzopyran-4-one 36

Following the xanthone general procedure, to a solution of the appropriate chromone (100 mg, 0.28 mmol) in dry DCM (5 mL) was added $AlCl_3$ (187 mg, 1.4 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:3 EtOAc/40-60 Pet. Ether) to afford the title compound **36** (22 mg, 23%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.9 Hz, 1H), 8.17 (s, 1H), 7.76 – 7.69 (m, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 4.10 (s, 3H), 3.99 (s, 3H), 3.05 (q, *J* = 7.5 Hz), 1.45 (t, *J* = 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 161.3, 160.4, 155.9, 154.4, 139.4, 134.8, 133.9, 126.3, 124.1, 122.3, 121.4, 118.6, 116.4, 111.1, 99.4, 96.6, 56.5, 55.6, 26.5, 14.1. FTIR (ATR / cm^{-1}): 2924, 1608, 1466. HRMS-ESI calculated for $C_{21}H_{18}NaO_4$ $[M+Na]^+$: 357.1097; found: 357.1117.

1'-Ethyl-7',9'-dimethoxy-naptha[4',3'-*b*]-benzopyran-4-one 37

Following the xanthone general procedure, to a solution of the appropriate chromone (67 mg, 0.190 mmol) in dry DCM (2 mL) was added $AlCl_3$ (127 mg, 0.951 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:4 EtOAc/40-60 Pet. Ether) to afford the title compound **37** (42 mg, 66%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.87 (s, 1H), 7.75 (ddd, *J* = 8.6, 7.0, 1.7 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 2.5 Hz, 1H), 7.42 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 4.04 (s, 3H), 3.96 (s, 3H), 3.30 (q, *J* = 7.3 Hz, 2H), 1.31 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 159.0, 158.7, 156.0, 151.3, 137.9, 134.2, 134.2, 127.6, 126.7, 124.2, 123.3, 122.5, 119.1, 118.2, 117.9, 101.8, 94.5, 55.7,

30.7, 16.9. FTIR (ATR / cm^{-1}); 2930, 1612, 1557, 1467, 1208. HRMS-ESI calculated for $C_{21}H_{19}O_4$ $[M+H]^+$: 335.1278; found: 335.1252.

1'-Ethyl-7'methoxy-naptha[4',3'-*b*]-benzopyran-4-one 38

Following the xanthone general procedure, to a solution of the appropriate chromone (183 mg, 0.57 mmol) in dry DCM (2 mL) was added $AlCl_3$ (378 mg, 2.83 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:9 EtOAc/40-60 Pet. Ether) to afford a 81:19 mixture isomers of title compound **38** (70 mg, 40%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.98 (s, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 7.77 (ddd, *J* = 8.6, 6.9, 1.7 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 9.2, 2.7 Hz, 1H), 4.06 (s, 3H), 3.11 (q, *J* = 7.5 Hz, 2H), 1.42 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 158.2, 155.9, 151.8, 136.4, 134.3, 130.6, 126.7, 126.0, 125.7, 124.3, 122.5, 121.2, 118.2, 117.9, 117.2, 102.5, 55.7, 25.8, 14.9. FTIR (ATR / cm^{-1}): 2963, 1650, 1613, 1469, 759. HRMS-ESI calculated for $C_{20}H_{16}NaO_3$ $[M+Na]^+$: 327.0992; found: 327.0977.

2-Benzo-3-(2'-hydroxy-2'-benzoethyl)-benzopyran-4-one 41

To a solution of the appropriate diketone (8.13 g, 29 mmol) in 1:1 DCM/H_2O (80 mL) was added K_2CO_3 (12.10 g, 87 mmol) and (2-bromo-1-phenyl ethyl)dimethyl sulphonium bromide (10.0 g, 44 mmol) to stir for 24 h. Upon completion the reaction was worked up and crude residue was dried, redissolved in MeOH (90 mL) and degassed. To this solution was added of K_2CO_3 (12.2 g, 88 mmol) and $Pd(PPh_3)_4$ (0.57 g, 0.49 mmol) with stirring for 45 min. After this time the reaction was diluted with 1M HCl stirred for a further 15 min then extracted with EtOAc. The crude extracts were refluxed overnight in 1M HCl:acetone (80 mL) then diluted with 1M HCl and extracted with DCM. Following work up the crude residue was purified by flash chromatography (1:3 EtOAc/40−60 Pet. Ether) to afford the title compound (2.65 g, 30%) as orange crystals. Melting point: 114 - 115^{o}C. ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.34 – 8.28 (dd, 1H), 7.71 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 7.55 – 7.43 (m, 7H), 7.26 – 7.18 (m, 5H), 5.07 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.07 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.94 (dd, *J* = 14.5, 3.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.9, 164.5, 156.4, 144.9, 134.2, 133.0, 130.6, 129.0, 128.7, 128.6, 128.4, 127.3, 126.2, 125.7, 125.4, 122.8, 119.4, 118.1, 74.6, 36.9. FTIR (ATR / cm^{-1}): 3417, 3060, 1617, 1387. HRMS-ESI calculated for $C_{23}H_{18}NaO_3$ $[M+Na]^+$: 365.1148; found: 365.1125.

1'-Benzo-naptha[4',3'-*b*]-benzopyran-4-one 42

Following the xanthone general procedure, to a solution **41** (101 mg, 0.29 mol) in dry DCM (3 mL) was added $AlCl_3$ (59 mg, 0.44 mmol) and stirred over night at room temperature. The crude residue was purified by flash chromatography (1:3 EtOAc/40-60 Pet. Ether) to afford the title compound **42** (37 mg, 39%) as pale white crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.08 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.68 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.58 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.42 – 7.37 (m, 3H), 7.32 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 7.06 (d, *J* = 7.4 Hz, 1H), 4.33 – 4.27 (m, 1H), 3.32 (dd, *J* = 16.4, 6.9 Hz, 1H), 3.24 (dd, *J* = 16.4, 9.1 Hz, 1H). NMR data were consistent with those found in the literature.[39]

Acknowledgements

The authors thank the University of Otago for funding and Prof. David Larsen (University of Otago) for helpful discussions.

References

1. Newman, D. J.; Cragg, G. M., *J. Nat. Prod.* **2016,** *79* (3), 629-661.
2. Montaser, R.; Luesch, H., *Future Med. Chem.* **2011,** *3* (12), 1475-1489.
3. Middleton, E., Jr.; Kandaswami, C.; Theoharides, T. C., *Pharmacol. Rev.* **2000,** *52* (4), 673-751.
4. Snijman, P. W.; Joubert, E.; Ferreira, D.; Li, X.-C.; Ding, Y.; Green, I. R.; Gelderblom, W. C. A., *Journal of Agricultural and Food Chemistry* **2009,** *57* (15), 6678-6684.
5. Ahmed, D.; Kumar, V.; Sharma, M.; Verma, A., *BMC Complementary Altern. Med.* **2014,** *14* (1), 1-13.
6. Romagnolo, D. F.; Selmin, O. I., *Journal of Nutrition in Gerontology and Geriatrics* **2012,** *31* (3), 206-238.
7. Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G., *Eur. J. Med. Chem.* **2014,** *78*, 340-374.

8. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J., *J. Med. Chem.* **1988,** *31* (12), 2235-2246.
9. Katsuyama, Y.; Funa, N.; Miyahisa, I.; Horinouchi, S., *Chemistry & Biology* **2007,** *14* (6), 613-621.
10. Selepe, A. M.; Van Heerden, R. F., *Molecules* **2013,** *18* (4).
11. Sum, T. J.; Sum, T. H.; Galloway, W. R. J. D.; Spring, D. R., *Synlett* **2016,** (EFirst).
12. Zhang, X.; Zhang, L.; Liu, Y.; Bao, B.; Zang, Y.; Li, J.; Lu, W., *Tetrahedron* **2015,** *71* (29), 4842-4845.
13. Oke-Altuntas, F.; Kapche, G. D. W. F.; Nantchouang Ouete, J. L.; Demirtas, I.; Koc, M. B.; Ngadjui, B. T., *Med. Chem. Res.* **2016,** *25* (10), 2250-2257.
14. Mbaveng, A. T.; Sandjo, L. P.; Tankeo, S. B.; Ndifor, A. R.; Pantaleon, A.; Nagdjui, B. T.; Kuete, V., *SpringerPlus* **2015,** *4* (1), 823.
15. Kim, J. Y.; Lee, W. S.; Kim, Y. S.; Curtis-Long, M. J.; Lee, B. W.; Ryu, Y. B.; Park, K. H., *J. Agric. Food Chem.* **2011,** *59* (9), 4589-4596.
16. Liao, Y.-R.; Kuo, P.-C.; Tsai, W.-J.; Huang, G.-J.; Lee, K.-H.; Wu, T.-S., *Bioorganic & Medicinal Chem. Lett.* **2017,** *27* (2), 309-313.
17. Yoganathan, K.; Cao, S.; Crasta, S. C.; Aitipamula, S.; Whitton, S. R.; Ng, S.; Buss, A. D.; Butler, M. S., *Tetrahedron* **2008,** *64* (44), 10181-10187.
18. Roberts, J. C., *Chem. Rev.* **1961,** *61* (6), 591-605.
19. Negi, J. S.; Bisht, V. K.; Singh, P.; Rawat, M. S. M.; Joshi, G. P., *J. Appl. Chem.* **2013,** *2013*, 9.
20. Koh, J.-J.; Qiu, S.; Zou, H.; Lakshminarayanan, R.; Li, J.; Zhou, X.; Tang, C.; Saraswathi, P.; Verma, C.; Tan, D. T. H.; Tan, A. L.; Liu, S.; Beuerman, R. W., *Biochim. Biophys. Acta, Biomembr.* **2013,** *1828* (2), 834-844.
21. Singha, A.; Kaurb, N.; Sharmaa, S.; Bedi, P. M. S., *J. Chem. Pharm. Res.* **2016,** *8* (1), 75-131.
22. Carter, G.; Nietche, J.; Williams, D.; Borders, D., *The Journal of Antibiotics* **1990,** *43*, 504-512.
23. Drautz, H.; Keller-Schierlein, W.; Zahner, H., *Arch. Microbiol.* **1975,** *106* (3), 175-90.
24. Turner, P. A.; Griffin, E. M.; Whatmore, J. L.; Shipman, M., *Org. Lett.* **2011,** *13* (5), 1056-1059.
25. Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F., *Chem. Rev.* **2014,** *114* (9), 4960-4992.
26. Baker, W., *J. Chem. Soc.* **1933,** 1381-1389.
27. Heywang, R.; Kostanecki, S. v., *Ber. Dtsch. Chem. Ges.* **1902,** *35* (3), 2887-2891.
28. Smith, R. J.; Nhu, D.; Clark, M. R.; Gai, S.; Lucas, N. T.; Hawkins, B. C., *J. Org. Chem.* **2017,** *82* (10), 5317-5327.
29. Smith, R. J.; Mills, D. A.; Nhu, D.; Tan, E. W.; Lucas, N. T.; Hawkins, B. C., *J. Org. Chem.* **2016,** *81* (5), 2099-2105.
30. Masters, K.-S.; Bräse, S., *Chem. Rev.* **2012,** *112* (7), 3717-3776.
31. Khanna, R.; Dalal, A.; Kumar, R.; Kamboj, R. C., *ChemistrySelect* **2016,** *1* (4), 840-851.
32. Sousa, M. E.; Pinto, M. M. M., *Curr. Med. Chem.* **2005,** *12* (21), 2447-2479.
33. Zhao, J.; Larock, R. C., *J. Org. Chem.* **2007,** *72* (2), 583-588.
34. Hauser, F. M.; Dorsch, W. A., *Org. Lett.* **2003,** *5* (20), 3753-3754.
35. Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M., *J. Org. Chem.* **1988,** *53* (1), 223-224.
36. Han, J.; Wang, T.; Liang, Y.; Li, Y.; Li, C.; Wang, R.; Feng, S.; Zhang, Z., *Org. Lett.* **2017,** *19* (13), 3552-3555.
37. *See supporting information*.
38. Gopinath, P.; Chandrasekaran, S., *J. Org. Chem.* **2011,** *76* (2), 700-703.
39. Rocha, D. H. A.; Pinto, D. C. G. A.; Silva, A. M. S.; Patonay, T.; Cavaleiro, J. A. S., *Synlett* **2012,** *2012* (04), 559-564.