Environmentally benign, one-pot synthesis of pyrans by domino Knoevenagel/6π-electrocyclization in water and application to natural products

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In water medium, environmentally benign, facile, and efficient synthesis of pyrans was achieved in good yields by the reactions of a variety of cyclic 1,3-dicarbonyls with several α,β-unsaturated aldehydes. The key strategy was a formal [3+3] cycloaddition by domino Knoevenagel/6π- electrocyclization. This methodology was applied to the synthesis of biologically interesting pyranocoumarin, pyranoquinolinone, and pyranonaphthoquinone derivatives along with selected natural and non-natural products.

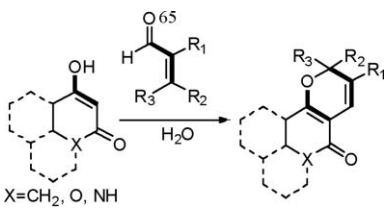
Introduction

Currently, there exists an increasing need to develop environmentally benign processes in the chemical industry.[1] For such green chemical technologies, water has received considerable attention for many years as an environmentally benign solvent and potent catalyst for various organic reactions.[2] Moreover, water has many unique physical and chemical properties, including extensive hydrogen bonding, high heat capacity, large dielectric constant, and optimum oxygen solubility.[3] Many of the traditional, volatile organic solvents are ecologically toxic and harmful while water is nontoxic, nonflammable, abundantly available, and inexpensive.[4] Accordingly, water is generally used as a cheap, safe, and environmentally benign solvent. Water also has the advantages of simplicity of reaction conditions and ease of workup and product isolation. In particular, water is also known to enhance and accelerate reaction rates and increase the selectivity of a wide variety of organic reactions.[5]

Many reactions in water have been reported, including Diels–Alder reactions,[6] 1,3-dipolar reactions,[7] Claisen rearrangements,[8] Ugi reactions,[9] nucleophilic reactions,[10] oxidations,[11] reductions,[12] and transformations catalyzed by transition metals.[13] However, although a number of reactions in water have been developed and described, one-pot synthesis for pyran formation by formal [3+3] cycloaddition in water has not been reported so far.

Formal [3+3] cycloaddition reactions are one of the most powerful methods for the construction of heterocycles.[14] Among these, the reactions of 1,3-dicarbonyl equivalents with enals or α,β-unsaturated iminiums for the synthesis of heterocycles or natural products bearing a pyran core have been already reported by Hsung.[15] The computational study of this kind of formal [3+3] cycloaddition reaction has been investigated by Fang.[16] Pyrans are important core units in a number of natural products[17] and photochromic materials.[18] Molecules bearing a pyran moiety have a variety of interesting biological activities and potential medical applications.[18] This lab previously developed new methodologies for the synthesis of pyrans using indium(III) chloride- or EDDA-catalyzed formal [3+3] cycloadditions as a strategy.[19] Later, novel approaches were also developed by other groups using BF_3-Et_2O, $TiCl_4$, and $In(OTf)_3$ Lewis acids as catalysts,[20] phosphoric acids as a Brønsted acid catalyst,[21] and EDDA/$ZnCl_2$ as co-catalysts.[22] Although several synthetic approaches for constructing pyranyl rings have been reported by this lab and other groups, environmentally benign and cost-effective approaches are still in demand.

We report herein a simple and environmentally innocuous one-pot synthesis of pyrans by a formal [3+3] cycloaddition in water (Scheme 1). The key strategy developed begins with reactions of readily available cyclic 1,3-dicarbonyls (**1–14**) to α,β-unsaturated aldehydes in water as a green and inexpensive reaction (Fig. 1).



Scheme 1

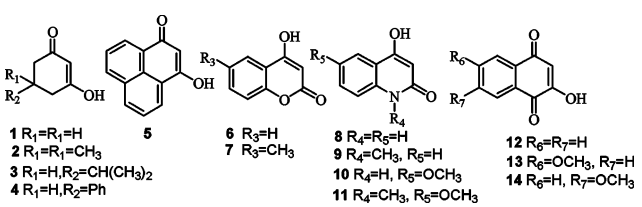


Fig. 1

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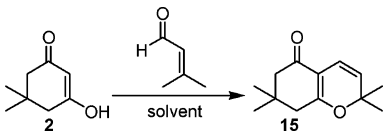
Table 1 Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1**) with 3-methyl-2-butenal in several solvents



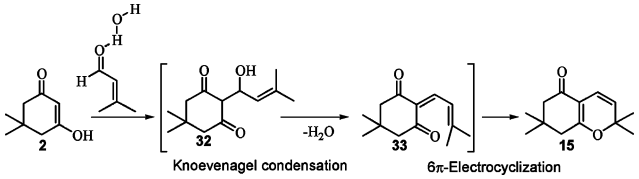
Solvent	Condition	Yield (%)
CH_2Cl_2	rt, 12 h	0
toluene	reflux, 12 h	45
xylene	reflux, 12 h	60
THF	reflux, 12 h	43
DMF	80 °C, 12 h	62
DMSO	80 °C, 12 h	70
EtOH	reflux, 6 h	75
AcOH	80 °C, 4 h	86
H_2O	80 °C, 4 h	91

Results and discussion

To demonstrate the advantages of the reactions in water, the reaction of 5,5-dimethyl-1,3-cyclohexanedione (**2**) with 3-methyl-2-butenal in the absence of any catalysts, compared with several solvents, was first investigated (Table 1). Treatment of **2** with 3-methyl-2-butenal in dichloromethane at room temperature for 12 h did not afford pyran **15**. However, when **2** was reacted in heated solvents, the best yield (91%) was produced in water at 80 °C for 4 h. Other solvents studied include toluene (reflux, 12 h, 45%), xylene (reflux, 12 h, 60%), THF (reflux, 12 h, 43%), DMF (80 °C, 12 h, 65%), DMSO (80 °C, 12 h, 70%), EtOH (reflux, 6 h, 75%), and AcOH (80 °C, 4 h, 86%). Polar solvents were superior over nonpolar solvents in yielding pyran **15**. As described previously, this result is due likely to the beneficial hydrophobic effects and hydrogen bonding in water.[3c–e]

Next, additional reactions of a variety of cyclic carbonyls with several α,β-unsaturated aldehydes such as crotonaldehyde, 3-methyl-2-butenal, citral, *trans*,*trans*-farnesal, and 1-cyclohexene-1-carboxaldehyde were attempted in water. The results are summarized in Table 2. Reactions of 1,3-cyclohexanedione (**1**) and 5,5-dimethyl-1,3-cyclohexanedione (**2**) with crotonaldehyde in water at 80 °C afforded the desired pyrans **16** and **17** in 70% and 71% yields, respectively (entries 1–2). Similarly, reactions of 1,3-cyclohexanedione (**1**), 5-isopropyl-1,3-cyclohexanedione (**3**), 5-phenyl-1,3-cyclohexanedione (**4**), 3-hydroxy-1*H*-phenalen-1-one (**5**), and 4-hydroxycoumarin (**6**) with 3-methyl-2-butenal provided cycloadducts **18–22** in 70–91% yields (entries 3–7). Compound **22** has been clearly shown to be angular by spectral analysis and comparison with previously reported data.[23] With citral (entries 8–12), the desired cycloadducts **23–27** were produced in 64–81% yields. In addition, reaction of **2** with *trans*,*trans*-farnesal in water afforded adduct **28** with a long chain on the pyranyl ring in 60% yield (entry 13). In the case of 1-cyclohexene-1-carboxaldehyde with a ring system (entries 14–16), the desired pyrans **29–31** were produced in 61%, 77%, and 70% yields, respectively. These reactions provided a rapid synthetic route to various kinds of pyran formation in good yields.

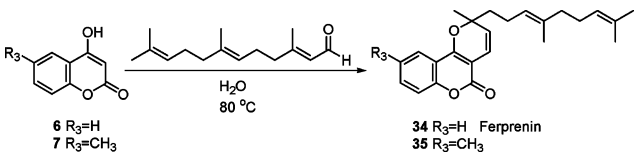
The proposed mechanism for the formation of **15** may be explained through domino Knoevenagel/6π-electocyclization as shown in Scheme 2. Water first activates the carbonyl oxygen



Scheme 2 Proposed mechanism for the formation of **15**.

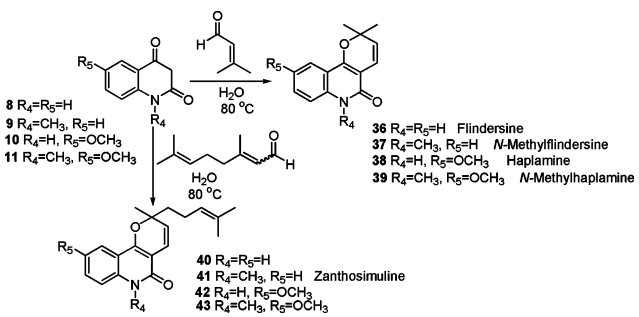
of the 3-methyl-2-butenal through hydrogen bonding.[3c] The dimedone (**2**) then attacks the activated aldehyde to yield intermediate **32**, which is dehydrated upon heating to give **33**. The intermediate **33** further undergoes 6π-electrocyclization to give cycloadduct **15**.

As an application of this methodology, the environmentally benign synthesis of natural products bearing 2*H*-pyrans and their non-natural derivatives were examined in water. One-step synthesis of ferprenin (**34**) and its derivative **35** was first attempted (Scheme 3). Ferprenin (**34**), a sesquiterpenoid pyranocoumarin, was isolated from *Ferula communis*.[24] The toxic variety of this plant was thought to be responsible for a lethal hemorrhagic syndrome, which mainly affects sheep and goats, cattle, and horses.[25] Reaction of 4-hydroxycoumarin (**6**) and 4-hydroxy-6-methylcoumarin (**7**) with *trans*,*trans*-farnesal in water at 80 °C for 6 h provided ferprenin (**34**) and its derivative **35** in 61% and 65% yields, respectively.



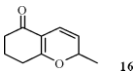
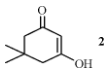
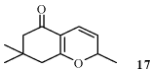
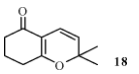
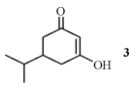
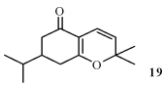
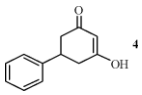
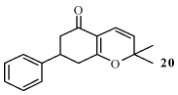
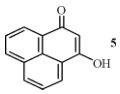
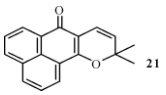
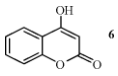
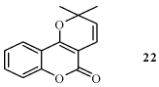
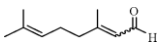
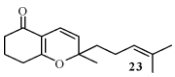
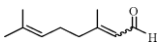
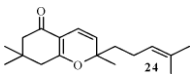
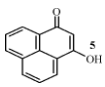
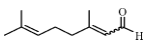
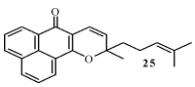
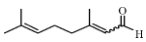
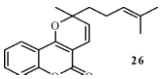
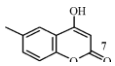
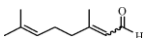
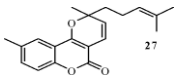
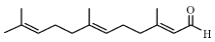
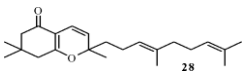
Scheme 3

Next, one-step synthesis of pyranoquinolinone alkaloids such as flindersine (**36**), *N*-methylflindersine (**37**), haplamine (**38**), *N*-methylhaplamine (**39**), zanthosimuline (**41**), and non-natural zanthosimuline derivatives **40**, **42**, and **43** were next attempted (Scheme 4). Total synthesis of other pyranoquinoline alkaloids such as simulenoline, huajiaosimuline, and (±)-7-demethoxyzanthodioline has been already reported by Hsung through formal [3+3] cycloaddition as a key step.[26] Flindersine (**36**) and *N*-methylflindersine (**37**) were primarily isolated from Rutaceous plants, *Fagara heitzii*[27] and *Orixa japonica*.[28] Haplamine (**38**) has been isolated from *Haplophyllum acutifolium*[29] and *Vepris bilocularis*,[30] while *N*-methylhaplamine (**39**) was isolated from *Agathosma barosmaefolia*.[31] The extracts



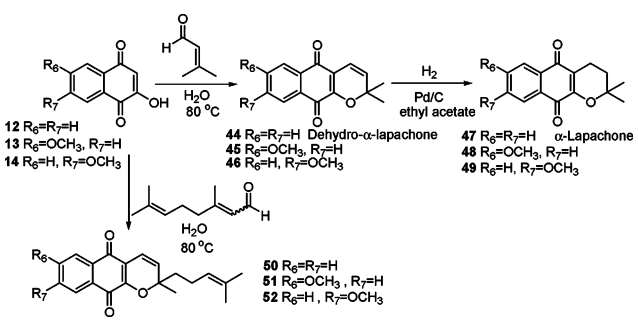
Scheme 4

Table 2 Reactions of cyclic 1,3-dicarbonyls with α,β-unsaturated aldehydes

Entry	Starting material	α,β-unsaturated aldehyde	Time/h	Product	Yield (%)
1			6		70
2			6		71
3			4		91
4			4		80
5			4		72
6			4		90
7			4		70
8			6		65
9			4		81
10			6		68
11			6		64
12			6		67
13			6		60
14			6		61
15			6		77
16			6		70

of these plants have shown cytotoxic, antifungal, and antimicrobial activities.[32] Zanthosimuline (**41**), a monoterpenoid pyranoquinoline alkaloid, has been isolated from the root bark of Taiwanese *Zanthoxylum simulans*.[33] It has potent cytotoxic activity when evaluated with a variety of cultured human cancer cell lines and the expression of cellular makers associated with cell differentiation in cultured HL-60 cells.[34] Reactions of 4-hydroxy-2(1*H*)-quinolone (**8**) and 4-hydroxy-1-methyl-2(1*H*)-quinolone (**9**) with 3-methyl-2-butenal in water at 80 °C for 6 h gave flindersine (**36**) and *N*-methylflindersine (**37**) in 70% and 64% yields, respectively, whereas those of **10** and **11** gave haplamine (**38**) and *N*-methylhaplamine (**39**) in 62% and 69% yields, respectively. Similarly, treatment of **8–11** with citral in water produced cycloadducts **40–43** in 71%, 62%, 64%, and 65% yields, respectively. The spectral data of synthetic zanthosimuline (**41**) are in agreement with those reported in the literature.[33]

Finally, the synthesis of naturally occurring pyranonaphthoquinones and their non-natural derivatives was attempted (Scheme 5). Dehydro-α-lapachone (**44**) and α-lapachone (**47**) were isolated from *Catalpa ovata*[35] and *Tabebuia avellanedae*.[36] These compounds possess antibacterial, antifungal, antimalarial, and antitumor activities and are used in traditional medicines for the treatment of pyrexia, jaundice, and edema by nephritis in Japan and China.[37] Their biological properties include reduction of HIV-1 replication, suppression of both acute and chronic infections, inhibition of DNA topoisomerase I, induction of chromosomal alterations, inhibition of reverse transcriptase and DNA polymerase-α, and blocking of activation of NF-κB and AP-1.[38] They also have potential clinical utility in the treatment of human leukemia and prostate cancer.[39] Reactions of 2-hydroxy-1,4-naphthoquinone (**12**), 2-hydroxy-6-methoxy-1,4-naphthoquinone (**13**), and 2-hydroxy-7-methoxy-1,4-naphthoquinone (**14**) with 3-methyl-2-butenal in water at 80 °C for 6 h gave dehydro-α-lapachone (**44**) and its non-natural derivatives **45** and **46** in 80%, 66%, and 70% yields, respectively. Hydrogenation of compounds **44–46** in the presence of 10% Pd/C (20 psi, 20 min) in ethyl acetate afforded α-lapachone (**47**) and its derivatives **48** and **49** in 91%, 88%, and 80% yields, respectively. Similarly, treatment of **12–14** with citral in water provided cycloadducts **50–52** with pyranokunthone B skeleton in 72%, 65%, and 63% yields, respectively.[40]



Scheme 5

Conclusions

In summary, we have developed a new and efficient method for the synthesis of a variety of pyrans starting from cyclic 1,3-dicarbonyls and α,β-unsaturated aldehydes in water. The method is endowed with several unique merits including environmentally friendly conditions, no metal catalysis, and simple procedure. This method has been successfully applied to the synthesis of biologically interesting and naturally occurring pyranocoumarins, pyranoquinolinone alkaloids, and pyranonaphthoquinones in good yields.

Experimental

All experiments were carried out in aqueous medium. 1,3-Dicarbonyl compounds and α,β-unsaturated aldehydes were obtained from Aldrich Chemicals. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS spectra were measured at the Korea Basic Science Institute on a Jeol JMS 700 spectrometer.

General procedure for the synthesis of pyrans

To a solution of 1,3-dicarbonyl compound (1.0 mmol) in water (5.0 ml) was added α,β-unsaturated aldehyde (2.0 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 4–6 h and then cooled to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 20 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude residue. Purification of the residue by column chromatography on silica gel gave product.

2,2,7,7-Tetramethyl-2,6,7,8-tetrahydrochromen-5-one (15). Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**2**) (140 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **15** (188 mg, 91%) as a solid: mp 38–40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, 1H, J = 9.9 Hz), 5.19 (d, 1H, J = 9.9 Hz), 2.23 (s, 2H), 2.21 (s, 2H), 1.35 (s, 6H), 1.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 170.1, 122.7, 115.8, 109.6, 79.8, 50.4, 42.5, 32.2, 28.4, 28.3; IR (KBr) 2959, 2870, 1645, 1633, 1586, 1454, 1416, 1351, 1324, 1299, 1251, 1206, 1131, 1090, 1047, 976, 928 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1310.

2-Methyl-2,6,7,8-tetrahydro-chromen-5-one (16). Reaction of 1,3-cyclohexanedione (**1**) (112 mg, 1.0 mmol) with crotonaldehyde (140 mg, 2.0 mmol) afforded **16** (115 mg, 70%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, 1H, J = 10.0 Hz), 5.26 (dd, 1H, J = 10.0, 3.0 Hz), 4.99 (m, 1H), 2.42–2.34 (m, 4H), 2.02–1.90 (m, 2H), 1.38 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 172.3, 118.8, 117.1, 111.1, 73.8, 36.3, 28.2, 21.5, 20.5; IR (neat) 2960, 1651, 1633, 1422, 1408, 1370, 1224, 1140, 1054, 947 cm^{-1}; HRMS m/z (M^+) calcd for $C_{10}H_{12}O_2$: 164.0837. Found: 164.0839.

2,7-Dimethyl-2, 6,7,8-tetrahydro-chromen-5-one (17). Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**2**) (140 mg, 1.0 mmol) with crotonaldehyde (140 mg, 2.0 mmol) afforded **17** (136 mg, 71%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, 1H, J = 10.0 Hz), 5.24 (dd, 1H, J = 10.0, 3.1 Hz), 4.96 (m, 1H), 2.31–2.17 (m, 4H), 1.36 (d, 3H, J = 6.5 Hz), 1.03 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 170.7,

118.5, 117.0, 110.1, 73.9, 50.2, 41.9, 32.1, 28.3, 28.2, 21.5; IR (neat) 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1152.

2,2-Dimethyl-2,6,7,8-tetrahydrochromen-5-one (18). Reaction of 1,3-cyclohexanedione (**1**) (112 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **18** (162 mg, 91%) as a liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, 1H, J = 10.0 Hz), 5.21 (d, 1H, J = 10.0 Hz), 2.38–2.33 (m, 4H), 1.95–1.91 (m, 2H), 1.36 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 171.5, 122.9, 115.8, 110.6, 79.7, 36.4, 28.6, 28.4, 20.6; IR (neat) 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{11}H_{14}O_2$: 178.0994. Found: 178.0991.

7-Isoprpyl-2,2-dimethyl-2,6,7,8-tetrahydro-chromen-5-one (19). Reaction of 5-isopropyl-1,3-cyclohexanedione (**3**) (154 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **19** (176 mg, 80%) as a liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, 1H, J = 9.9 Hz), 5.20 (d, 1H, J = 9.9 Hz), 2.49–2.41 (m, 1H), 2.40–2.32 (m, 1H), 2.22–2.03 (m, 2H), 1.89–1.76 (m, 1H), 1.60–1.49 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 0.90 (d, 6H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 171.6, 122.7, 115.7, 110.0, 79.8, 53.4, 40.5, 39.4, 32.4, 31.9, 28.6, 28.1, 19.5; IR (neat) 2964, 2878, 1651, 1594, 1462, 1416, 1331, 1252, 1203, 1144, 1093, 1048, 1002, 910, 872, 820 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{14}H_{20}O_2$: 220.1463. Found: 2201467.

2,2-Dimethyl-7-phenyl-2,6,7,8-tetrahydro-chromen-5-one (20). Reaction of 5-phenyl-1,3-cyclohexanedione (**4**) (188 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **20** (183 mg, 72%) as a liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2H), 7.26–7.21 (m, 3H), 6.43 (d, 1H, J = 9.9 Hz), 5.26 (d, 1H, J = 9.9 Hz), 3.39–3.28 (m, 1H), 2.65–2.57 (m, 4H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 170.7, 142.6, 128.7, 126.9, 126.6, 123.0, 115.0, 110.2, 80.2, 43.5, 38.7, 36.1, 28.6, 28.2; IR (neat) 3487, 3056, 2971, 2925, 1723, 1644, 1590, 1454, 1415, 1330, 1252, 1203, 1142, 1090, 1048, 919, 887, 819 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1304.

10,10-Dimethyl-10*H*-11-oxa-benzo[de]anthracen-7-one (21). Reaction of 3-hydoxy-1*H*-phenalen-1-one (**5**) (196 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **21** (236 mg, 90%) as a solid: mp 87–88 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (dd, 1H, J = 7.3, 1.2 Hz), 8.21 (dd, 1H, J = 7.3, 1.2 Hz), 8.10 (dd, 1H, J = 8.1, 1.1 Hz), 8.01 (dd, 1H, J = 8.1, 1.1 Hz), 7.69 (dd, 1H, J = 8.1, 7.3 Hz), 7.60 (dd, 1H, J = 8.1, 7.3 Hz), 6.83 (d, 1H, J = 9.9 Hz), 5.56 (d, 1H, J = 9.9 Hz), 1.54 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 159.3, 134.0, 132.2, 131.7, 129.7, 128.5, 126.7, 126.2, 126.1, 125.8, 124.3, 117.0, 112.0, 79.3, 28.3; IR (KBr) 2975, 2927, 1632, 1578, 1506, 1458, 1425, 1387, 1331, 1259, 1152, 1127, 898 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{18}H_{14}O_2$: 262.0994. Found: 262.0995.

2,2-Dimethyl-2*H*-pyrano[3,2-*c*]chromen-5-one (22). Reaction of 4-hydroxycoumarin (**6**) (162 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **22** (160 mg, 70%) as a liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, 1H, J = 7.8, 1.6 Hz), 7.50 (m, 1H), 7.30–7.23 (m, 2H), 6.53 (d, 1H, J = 9.9 Hz), 5.52 (d, 1H, J = 9.9 Hz), 1.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 158.8, 153.1, 132.0, 126.1, 123.9, 122.7, 116.7, 115.5, 100.2, 80.5, 28.5; IR (neat) 3073, 2978, 2930, 1715, 1642, 1566, 1493, 1458, 1416, 1362, 1327, 1281, 1217, 1192, 1157, 1115, 1038, 992, 909 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{14}H_{12}O_3$: 228.0786. Found: 228.0785.

2-Methyl-2-(4-methyl-pent-3-enyl)-2,6,7,8-tetrahydro-chromen-5-one (23). Reaction of 1,3-cyclohexanedione (**1**) (112 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **23** (160 mg, 65%) as a liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (d, 1H, J = 9.9 Hz), 5.14 (d, 1H, J = 9.9 Hz), 5.07–5.02 (m, 1H), 2.38–2.32 (m, 4H), 2.05–1.89 (m, 4H), 1.74–1.17 (m, 1H), 1.64 (s, 3H), 1.55 (s, 3H), 1.59–1.49 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 171.9, 131.9, 123.7, 121.7, 116.5, 110.3, 82.4, 41.7, 36.5, 28.6, 27.4, 25.7, 22.6, 20.7, 17.6; IR (neat) 2966, 2928, 1648, 1596, 1442, 1416, 1354, 1303, 1261, 1228, 1164, 1070, 1019,920, 861,0832, 794, 762, 707 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{16}H_{22}O_2$: 246.1620. Found: 246.1622.

2,7,7-Trimethyl-2-(4-methyl-pent-3-enyl)-2,6,7,8-tetrahydro-chromen-5-one (24). Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**2**) (140 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **24** (222 mg, 81%) as a liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (d, 1H, J = 9.9 Hz), 5.14 (d, 1H, J = 9.9 Hz), 5.08–5.02 (m,1H), 2.24–2.21 (m, 4H), 2.05–1.97 (m, 2H), 1.79–1.66 (m, 1H), 1.64 (s, 3H), 1.55 (s, 3H), 1.53–1.48 (s, 1H), 1.33 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 170.5, 131.9, 126.6, 121.4, 116.2, 109.1, 82.5, 50.4, 42.4, 41.7, 32.2, 28.6, 28.2, 27.5, 25.6, 22.5, 17.6; IR (neat) 3386, 2961, 2930, 1719, 1646, 1596, 1415, 1356, 1234, 1194, 1142, 1067, 931, 889, 748 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{18}H_{26}O_2$: 274.1933. Found: 274.1935.

10-Methyl-10-(4-methyl-pent-3-enyl)-10*H*-11oxa-benzo[*de*]-anthracen-7-one (25). Reaction of 3-hydoxy-1*H*-phenalen-1-one (**5**) (196 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **25** (224 mg, 68%) as a liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, 1H, J = 7.2 Hz), 8.20 (d, 1H, J = 7.2 Hz), 8.09 (d, 1H, J = 8.1 Hz), 8.00 (d, 1H, J = 8.1 Hz), 7.68 (t, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 7.8 Hz), 6.87 (d, 1H, J = 9.9 Hz), 5.50 (d, 1H, J = 9.9 Hz), 5.09 (t, 1H, J = 6.8 Hz), 2.20–2.12 (m, 2H), 1.98–1.71 (m, 2H), 1.59 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 159.6, 134.0, 132.2, 132.0, 131.6, 129.7, 128.4, 126.7, 126.1, 124.7, 124.2, 123.7, 117.5, 111.7, 81.9, 41.6, 27.1, 27.1, 25.6, 22.6, 17.6; IR (neat) 3056, 2968, 2923, 2823, 2855, 1712, 1671, 1632, 1313, 1577, 1506, 1425, 1377, 1331, 1223, 1189, 1155, 1118, 1073, 1019, 904, 845, 791, 763, 722 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{23}H_{22}O_2$: 330.1620. Found: 330.1620.

2-Methyl-2-(4-methyl-pent-3-enyl)-2*H*-pyrano[3,2-*c*]chromen-5-one (26). Reaction of 4-hydroxycoumarin (**6**) (162 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **26** (189 mg, 64%) as a liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 1H, J = 7.8 Hz), 7.45 (t, 1H, J = 7.8 Hz), 7.23–7.18 (m, 2H), 6.51 (d, 1H, J = 9.9 Hz), 5.40 (d, 1H, J = 9.9 Hz), 5.01 (t, 1H, J = 6.8 Hz), 2.11–2.03 (m, 2H), 1.86–1.63 (m, 2H), 1.54 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 159.3, 153.5, 132.4, 125.5, 124.4, 123.8, 123.1, 117.6, 116.9,

115.8, 100.2, 83.6, 42.1, 27.9, 26.0, 22.9, 18.0; IR (neat) 3061, 2971, 2922, 1718, 1642, 1608, 1565, 1451, 1365, 1279, 1178, 1111, 1034, 986, 910, 758, 726 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{19}H_{20}O_3$: 296.1412. Found: 296.1413.

2,9-Dimethyl-2-(4-methyl-pent-3-enyl)-2*H*-pyrano[3,2-*c*]chromen-5-one (27). Reaction of 4-hydroxy-6-methylcoumarin (**7**) (176 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **27** (208 mg, 67%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.30 (d, 1H, *J* = 7.8 Hz), 7.16 (d, 1H, *J* = 7.8 Hz), 6.56 (d, 1H, *J* = 9.9 Hz), 5.44 (d, 1H, *J* = 9.9 Hz), 5.07 (t, 1H, *J* = 6.6 Hz), 2.39 (s, 3H), 2.15–2.08 (m, 2H), 1.92–1.82 (m, 1H), 1.77–1.67 (m, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 158.9, 151.2, 133.5, 132.9, 132.0, 124.8, 123.3, 122.1, 117.7, 116.3, 114.9, 99.7, 82.9, 41.6, 27.4, 25.4, 22.4, 20.7, 17.5; IR (neat) 3056, 2969, 2922, 2860, 1715, 1642, 1571, 1496, 1448, 1421, 1358, 1316, 1276, 1210, 1162, 1120, 1040, 1017, 919, 817, 725 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{20}H_{22}O_3$: 310.1569. Found: 310.1566.

2-(4,8-Dimethyl-nona-3,7-direnyl)-2,7,7-trimethyl-2,6,7,8-tetrahydro-chromen-5-one (28). Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**2**) (140 mg, 1.0 mmol) with *trans*,*trans*-farnesal (440 mg, 2.0 mmol) afforded **28** (205 mg, 60%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (d, 1H, *J* = 9.9 Hz), 5.15 (d, 1H, *J* = 9.9 Hz), 5.09–5.05 (m, 2H), 2.24 (s, 2H), 2.22 (s, 2H), 2.04–1.91 (m, 6H), 1.77–1.50 (m, 2H), 1.65 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 170.4, 135.6, 131.4, 124.2, 123.5, 121.4, 116.3, 109.1, 82.4, 50.4, 42.4, 41.7, 39.6, 32.2, 28.6, 28.3, 27.5, 26.6, 25.6, 22.4, 17.7, 15.9; IR (neat) 2936, 1648, 1425, 1357, 1228, 1140, 1056, 888, 831, 743, 670 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{23}H_{34}O_2$: 342.2559. Found: 342.2558.

2,3,4,5,6,7,8,10a-Octahydro-xanthen-1-one (29). Reaction of 1,3-cyclohexanedione (**1**) (112 mg, 1.0 mmol) with 1-cylohexene-1-carboxaldehyde (220 mg, 2.0 mmol) afforded **29** (125 mg, 61%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.91 (dd, 1H, *J* = 10.9, 4.9 Hz), 2.35–2.30 (m, 6H), 1.95–1.24 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 171.5, 141.3, 122.9, 115.8, 79.7, 36.6, 36.4, 33.3, 31.0, 28.6, 28.4, 20.6; IR (neat) 2942, 1645, 1518, 1404, 1171, 1073, 1019, 939, 869 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1150

3,3-Dimethyl-2,3,4,5,6,7,8,10a-octahydro-xanthen-1-one (30). Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**2**) (140 mg, 1.0 mmol) with 1-cylohexene-1-carboxaldehyde (220 mg, 2.0 mmol) afforded **30** (179 mg, 77%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.92 (dd, 1H, *J* = 10.9, 4.9 Hz), 2.37–2.05 (m, 6H), 1.95–1.20 (m, 6H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 170.1, 122.7, 115.8, 109.6, 79.8, 50.4, 42.5, 35,1, 33.0, 32.2, 28.3, 26.8, 24.3; IR (neat) 2955, 1644, 1630, 1617, 1404, 1258, 1231, 1146, 1074, 1041, 1008, 945 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{15}H_{20}O_2$: 232.1463. Found: 232.1464.

10,11,12,12a-Tetrahydro-9*H*-13-oxa-benzo[de]naphthacen-7-one (31). Reaction of 3-hydoxy-1*H*-phenalen-1-one (**5**) (196 mg, 1.0 mmol) with 1-cylohexene-1-carboxaldehyde (220 mg, 2.0 mmol) afforded **31** (202 mg, 70%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, 1H, *J* = 7.3 Hz), 8.13 (d, 1H, *J* = 7.3 Hz), 8.07 (d, 1H, *J* = 8.1 Hz), 7.97 (d, 1H, *J* = 8.1 Hz), 7.67 (dd, 1H, *J* = 8.1, 7.3 Hz), 7.57 (dd, 1H, *J* = 8.1, 7.3 Hz), 6.51 (s, 1H), 5.17 (dd, 1H, *J* = 11.1, 5.1 Hz), 2.51–1.34 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 180.7, 158.3, 133.7, 133.6, 131.6, 131.3, 129.3, 128.1, 126.3, 126.0, 125.9, 125.6, 123.5, 111.1, 109.9, 79.1, 35.1, 33.0, 26.8, 24.4; IR (neat) 3060, 2933, 2857, 1632, 1577, 1422, 1383, 1296, 1198, 1026, 941, 861 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{20}H_{16}O_2$: 288.1150. Found: 288.1147.

Ferprenin (34)[24]. Reaction of 4-hydroxycoumarin (**6**) (162 mg, 1.0 mmol) with *trans*,*trans*-farnesal (440 mg, 2.0 mmol) afforded **34** (222 mg, 61%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 1H, *J* = 7.8 Hz), 7.45 (t, 1H, *J* = 7.8 Hz), 7.24–7.18 (m, 2H), 6.51 (d, 1H, *J* = 9.9 Hz), 5.41 (d, 1H, *J* = 9.9 Hz), 5.06–4.96 (m, 2H), 2.12–2.04 (m, 2H), 1.98–1.91 (m, 2H), 1.87–1.77 (m, 2H), 1.74–1.63 (m, 2H), 1.59 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 158.9, 153.0, 135.8, 131.9, 131.2, 125.0, 124.1, 123.8, 123.4, 123.0, 122.5, 117.1, 116.6, 115.3, 99.8, 83.0, 41.6, 39.5, 27.4, 26.5, 25.5, 22.3, 17.5, 15.8; IR(neat) 2955, 2919, 1719, 1625, 1564 1489, 1444, 1371, 1283, 1178, 1107, 1033, 909, 751 cm^{-1}.

2-(4,8-Dimethyl-nona-3,7-dienyl)-2,9-dimethyl-2*H*-pyrano-[3,2-c]chromen-5-one (35). Reaction of 4-hydroxy-6-methyl-coumarin (**7**) (176 mg, 1.0 mmol) with *trans*,*trans*-farnesal (440 mg, 2.0 mmol) afforded **35** (246 mg, 65%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.30 (d, 1H, *J* = 8.1 Hz), 7.16 (d, 1H, *J* = 8.1 Hz), 6.55 (d, 1H, *J* = 9.9 Hz), 5.50 (d, 1H, *J* = 9.9 Hz), 5.11–5.01 (m, 2H), 2.39 (s, 3H), 2.16–2.08 (m, 2H), 2.03–1.96 (m, 2H), 1.92–1.83 (m, 2H), 1.77–1.17 (m, 2H), 1.64 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 159.9, 151.3, 135.8, 133.6, 133.0, 131.3, 124.8, 124.1, 123.1, 122.2, 117.3, 116.4, 115.0, 99.8, 83.0, 41.7, 19.5, 27.4, 26.5, 25.6, 22.4, 20.8, 17.6, 15.9; IR(neat) 2920, 1714, 1637, 1435, 1367, 1205, 1124, 1027, 912, 821, 730 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{30}O_3$: 378.2195. Found: 378.2195.

Flindersine (36)[27]. Reaction of 4-hydroxy-2(1*H*)-quinolone (**8**) (161 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **36** (159 mg, 70%) as a solid: mp 195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.5 (s,1H), 7.87 (d, 1H, *J* = 8.1 Hz), 7.46 (dd, 1H, *J* = 8.2, 7.4 Hz), 7.31 (d, 1H, *J* = 8.2 Hz), 7.17 (dd, 1H, *J* = 8.1, 7.4 Hz), 6.75 (d, 1H, *J* = 9.9 Hz), 5.54 (d, 1H, *J* = 9.9 Hz), 1.53 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 157.5, 137.9, 130.9, 126.2, 122.5, 122.2, 117.0, 116.2, 115.3,105.5, 79.2, 28.3; IR (KBr) 3152, 2975, 1651, 1630, 1599, 1499, 1433, 1411, 1361, 1278, 1132, 872 cm^{-1}.

***N*-Methylflindersine (37)[28].** Reaction of 4-hydroxy-1-methyl-2(1*H*)-quinolone (**9**) (175 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **37** (154 mg, 64%) as a solid: mp 80–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 1H, *J* = 8.0 Hz), δ 7.51 (dd, 1H, *J* = 8.3, 7.3 Hz), 7.28 (d, 1H, *J* = 8.3 Hz), δ 7.19 (dd, 1H, *J* = 8.0, 7.3 Hz), 6.73 (d, 1H, *J* = 10.0 Hz), 5.51 (d, 1H, *J* = 10.0 Hz), 3.67 (s, 3H), 1.49 (s, 6H); IR (KBr) 2976, 1645, 1505, 1464, 1418, 1360, 1325, 1211, 1154, 1123, 1092, 1044, 1005, 987, 895 cm^{-1}.

Haplamine (38). Reaction of 6-methoxyl-1*H*-quinoline-2,4-dione (**10**) (190 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **38** (159 mg, 62%) as a solid: mp 202–203 °C;

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.89 (s, 1H), 7.33 (d, 1H, J = 9.0 Hz), 7.25 (d, 1H, J = 3.0 Hz), 7.10 (dd, 1H, J = 9.0, 3.0 Hz), 6.75 (d, 1H, J = 10.0 Hz), 5.54 (d, 1H, J = 10.0 Hz), 3.86 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 156.8, 154.9, 132.7, 126.3, 120.6, 117.6, 117.2, 115.6, 105.8, 103.2, 79.0, 55.6, 28.3; IR (KBr) 3448, 2927, 2846, 2353, 1660, 1498, 1347, 1220, 1122, 1033, 905, 833, 717 cm^{-1}; HRMS m/z (M^+) calcd for $C_{15}H_{15}NO_3$: 257.1052. Found: 257.1054.

***N*-Methylhaplamine (39).** Reaction of 6-methoxy-1-methyl-1*H*-quinoline-2,4-dione (**11**) (205 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **39** (187 mg, 69%) as a solid: mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H, J = 2.0 Hz), 7.25 (d, 1H, J = 9.0 Hz), 7.15 (dd, 1H, J = 9.0, 2.0 Hz), 6.76 (d, 1H, J = 9.9 Hz), 5.53 (d, 1H, J = 9.9 Hz), 3.89 (s, 3H), 3.68 (s, 3H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 154.5, 154.4, 133.8, 126.3, 119.4, 117.9, 116.5, 115.3, 106.1, 104.5, 78.6, 55.5, 29.2, 28.0; IR (KBr) 3461, 2963, 1624, 1509, 1459, 1327, 1216, 1035, 817, 727 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{17}NO_3$: 271.1208. Found: 271.1205.

2-Methyl-2-(4-methyl-pent-3-enyl)-2,6-dihydro-pyrano[3,2-c]quinolin-5-one (40). Reaction of 4-hydroxy-2(1*H*)-quinolone (**8**) (161 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **40** (209 mg, 71%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.03 (s, 1H), 7.86 (d, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 7.6 Hz), 7.17 (t, 1H, J = 7.6 Hz), 6.79 (d, 1H, J = 9.9 Hz), 5.48 (d, 1H, J = 9.9 Hz), 5.08 (t, 1H, J = 6.8 Hz), 2.18–2.10 (m, 2H), 1.90–1.67 (m, 2H), 1.60 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 157.5, 138.1, 132.0, 125.0, 123.7, 122.4, 122.0, 177.7, 116.2, 115.1, 105.3, 81.6, 41.6, 27.1, 25.6, 22.6, 17.6; IR(neat) 2967, 2922, 1657, 1599, 1561, 1497, 1432, 1413, 1360, 1275, 1183, 1128, 1075, 1080, 988, 918, 887, 758 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1574.

Zanthosimuline (41). Reaction of 4-hydroxy-1-methyl-2(1*H*)-quinolone (**9**) (175 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **41** (192 mg, 62%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 1H, J = 7.8 Hz), 7.52 (t, 1H, J = 7.8 Hz), 7.29 (d, 1H, J = 7.8 Hz), 7.20 (t, 1H, J = 7.8 Hz), 6.77 (d, 1H, J = 9.9 Hz), 5.45 (d, 1H, J = 9.9 Hz), 5.07 (t, 1H, J = 6.6 Hz), 3.7 (s, 3H), 2.16–2.08 (m, 2H), 1.88–1.67 (m, 2H), 1.60 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 155.2, 139.2, 131.7, 130.7, 125.1, 123.6, 122.9, 121.5, 118.2, 115.8, 113.8, 105.3, 81.1, 41.4, 29.1, 26.9, 25.5, 22.4, 17.4; (neat) 3052, 2968, 2923, 1649, 1587, 1570, 1502, 1461, 1418, 1361, 1324, 1208, 1162, 1121, 1094, 1075, 1042, 1002, 752, 727 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{23}NO_2$: 309.1729. Found: 309.1730.

9-Methoxy-2-methyl-2-(4-methyl-pent-3-enyl)-2,6-dihydro-pyrano[3,2-c]quinolin-5-one (42). Reaction of 6-methoxy-1*H*-quinoline-2,4-dione (**10**) (190 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **42** (208 mg, 64%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1H), 7.29–7.24 (m, 2H), 7.09 (dd, 1H, J = 8.7, 2.7 Hz), 6.79 (d, 1H, J = 9.9 Hz), 5.49 (d, 1H, J = 9.9 Hz), 5.09 (t, 1H, J = 6.6 Hz), 3.85 (s, 3H), 2.18–2.10 (m, 2H), 1.91–1.66 (m, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 157.0, 155.0, 132.6, 132.0, 125.2, 123.7, 120.5, 117.7, 117.4, 115.6, 105.5, 103.4, 81.7, 55.7, 41.6, 27.2, 25.6, 22.6, 17.6; IR(neat) 2968, 2925, 1657, 1625, 1505, 1453, 1423, 1377, 1351, 1327, 1274, 1224, 1183, 1116, 1036, 826, 742, 714, 637, 596 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{23}NO_3$: 325.1678. Found: 325.1681.

9-Methoxy-2,6-dimethyl-2-(4-methyl-pent-3-enyl)-2,6-dihydro-pyrano[3,2-c]quinolin-5-one (43). Reaction of 6-methoxy-1-methyl-1*H*-quinoline-2,4-dione (**11**) (205 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **43** (220 mg, 65%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.26 (d, 1H, J = 8.7 Hz), 7.16 (dd, 1H, J = 8.7, 2.7 Hz), 6.80 (d, 1H, J = 9.9 Hz), 5.48 (d, 1H, J = 9.9 Hz), 5.11 (t, 1H, J = 6.6 Hz), 3.89 (s, 3H), 3.68 (s, 3H), 2.19–2.11 (m, 2H), 1.91–1.69 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 154.8, 154.6, 134.0, 131.9, 125.3, 123.7, 119.4, 118.5, 116.6, 115.4, 105.9, 104.7, 81.3, 55.7, 41.5, 29.3, 27.0, 25.6, 22.5, 17.6; IR(neat) 3475, 2930, 1632, 1579, 1507, 1449, 1323, 1286, 1215, 1130, 906, 816, 703 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{25}NO_3$: 339.1834. Found: 339.1838.

Dehydro-α-lapachone (44)[35]. Reactions of 2-hydroxy-1,4-naphthoquinone (**12**) (174 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **44** (211 mg, 88%) as a solid: mp 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.06 (m, 2H), 7.68–7.66 (m, 2H), 6.64 (d, 1H, J = 9.9 Hz), 5.70 (d, 1H, J = 9.9 Hz), 1.53 (s, 6H); ^{13}C NMR (75 MHz, CDCl3) δ 181.6, 179.6, 152.2, 133.8, 133.0, 131.4, 131.3, 130.7, 126.0, 117.6, 115.3, 80.3, 28.2; IR (KBr) 2928, 1641, 1578, 1453, 1414, 1329, 1271, 1190, 1131, 953, 793, 708 cm^{-1}.

7-Methoxy-2,2-dimethyl-2*H*-benzo[g]chromene-5,10-dione (45). Reactions of 2-hydroxy-6-methoxy-[1,4]naphthoquinone (**13**) (203 mg, 1.0 mmol) with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **45** (178 mg, 66%) as a solid: mp 126–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, 1H, J = 8.5 Hz), 7.51 (s, 1H), 7.09 (d, 1H, J = 8.5 Hz), 6.61 (d, 1H, J = 9.9 Hz), 5.66 (d, 1H, J = 9.9 Hz), 3.91 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 178.9, 164.3, 152.8, 133.8, 130.2, 128.8, 124.9, 119.2, 117.5, 115.5, 110.1, 80.5, 55.9, 28.4; IR(KBr) 2976, 1651, 1588, 1448, 1325, 1245, 1123, 965, 843, 735 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{14}O_4$: 270.0892. Found: 270.0890.

8-Methoxy-2,2-dimethyl-2*H*-benzo[g]chromene-5,10-dione (46). Reactions of 2-hydroxy-7-methoxy-1,4-naphthoquinone (**14**) (203 mg, 1.0 mmol)with 3-methyl-2-butenal (168 mg, 2.0 mmol) afforded **46** (189 mg, 70%) as a solid: mp 120–121 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 1H, J = 8.7 Hz), 7.44 (s, 1H), 7.09 (d, 1H, J = 8.7 Hz), 6.58 (d, 1H, J = 9.9 Hz), 5.66 (d, 1H, J = 9.9 Hz), 3.87 (s, 3H), 1.49 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 179.8, 163.6, 152.0, 133.3, 130.8, 128.4, 124.7, 119.8, 117.6, 115.5, 109.9, 80.1, 55.8, 28.2; IR (KBr) 2973, 2924, 1643, 1593, 1493, 1459, 1437, 1405, 1330, 1167, 992, 913, 844, 736 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{14}O_4$: 270.0892. Found: 270.0893.

α-Lapachone (47)[36]. Hydrogenation of **44** (120 mg, 0.5 mmol) in the presence of 10% Pd/C (20 psi, 20 min) in ethyl acetate afforded **47** (110 mg, 91%) as a solid: mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15–8.11 (m, 2H), 7.77–7.68 (m, 2H), 2.67 (t, 2H, J = 6.6 Hz), 1.87 (t, 2H, J = 6.6 Hz), 1.48 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 179.8, 154.4, 133.7,

132.8, 131.9, 131.0, 126.1, 125.8, 78.0, 31.2, 26.4, 16.6; IR(KBr) 2943, 1677, 1607, 1452, 1376, 1319, 1264, 1180, 1109, 947, 799, 717, 539 cm^{-1}.

7-Methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[g]chromene-5,10-dione (48). Hydrogenation of **45** (135 mg, 0.5 mmol)in the presence of 10% Pd/C (20 psi, 20 min) in ethyl acetate afforded **48** (120 mg, 88%) as a solid: mp 163–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, 1H, J = 8.7 Hz), 7.44 (d, 1H, J = 2.7 Hz), 7.04 (dd, 1H, J = 8.7, 2.7 Hz), 3.88 (s, 3H), 2.54 (t, 2H, J = 6.6 Hz), 1.76 (t, 2H, J = 6.6 Hz), 1.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 178.9, 164.1, 154.8, 134.2, 128.7, 124.5, 119.4, 118.9, 109.7, 78.0, 55.7, 31.3, 26.4, 16.6; IR (KBr) 3459, 2975, 2938, 1662, 1592, 1495, 1448, 1377, 1331, 1305, 1254, 1230, 1157, 1104, 1020, 960 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1052.

8-Methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[g]chromene-5,10-dione (49). Hydrogenation of **46** (135 mg, 0.5 mmol) in the presence of 10% Pd/C (20 psi, 20 min) in ethyl acetate afforded **49** (109 mg, 80%) as a solid: mp 154–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (d, 1H, J = 8.7 Hz), 7.47 (d, 1H, J = 2.7 Hz), 7.10 (dd, 1H, J = 8.7, 2.7 Hz), 3.89 (s, 3H), 2.56 (t, 2H, J = 6.6 Hz), 1.77 (t, 2H, J = 6.6 Hz), 1.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.7, 179.9, 163.4, 154.3, 132.9, 128.2, 125.4, 119.9, 109.8, 77.8, 55.8, 31.4, 26.4, 16.7; IR (KBr) 2971, 2930, 1679, 1596, 1495, 1468, 1375, 1337, 1271, 1232, 1174, 1111, 1013, 979, 893, 843, 744 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1050.

2-Methyl-2-(4-methyl-pent-3-enyl)-2*H*-benzo[*g*]chromene-5,10-dione (50). Reaction of 2-hydroxyl-1,4-naphthoquinone (**12**) (174 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **50** (222 mg, 72%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07–8.04 (m,2H), 7.70–7.63 (m, 2H), 6.68 (d, 1H, J = 9.9 Hz), 5.64 (d, 1H, J = 9.9 Hz), 5.08–5.03 (m, 1H), 2.14–2.06 (m, 2H), 1.97–1.87 (m, 1H), 1.71–1.63 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 179.6, 152.7, 133.9, 133.1, 132.3, 131.5, 131.5, 129.7, 126.2, 123.4, 117.5, 116.0, 83.1, 41.6, 27.5, 25.6, 22.6, 17.6; IR (neat) 3058, 2921, 1656, 1587, 1445, 1332, 1272, 1197, 964, 897, 880, 719 cm^{-}; HRMS m/z (M^+) calcd for $C_{20}H_{20}O_3$: 308.1412. Found: 308.1414.

7-Methoxy-2-methyl-2-(4-methyl-pent-3-enyl)-2*H*-benzo[g]-chromene-5,10-dione (51). Reactions of 2-hydroxy-6-methoxy-[1,4]naphthoquinone (**13**) (204 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **51** (220 mg, 65%) as a solid: mp 89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 8.4 Hz), 7.46 (s, 1H), 7.06 (dd, 1H, J = 8.4, 2.4 Hz), 6.62 (d, 1H, J = 9.9 Hz), 5.33 (d, 1H, J = 9.9 Hz), 5.03 (t, 1H, J = 6.6 Hz), 3.88 (s, 3H), 2.13–2.03 (m, 2H), 1.95–1.85 (m, 1H), 1.68–1.60 (m, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.6, 178.6, 164.2, 153.1, 133.7, 132.1, 128.9, 128.6, 124.8, 123.4, 119.0, 117.0, 115.9, 109.9, 83.0, 55.8, 41.5, 27.5, 25.5, 22.6, 17.6; IR (KBr) 2925, 1653, 1586, 1447, 1326, 1249, 1111, 971, 827, 827, 736 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{22}O_4$: 338.1518. Found: 338.1514.

8-Methoxy-2-methyl-2-(4-methyl-pent-3-enyl)-2*H*-benzo[g]-chromene-5,10-dione (52). Reactions of 2-hydroxy-7-methoxy-1,4-naphthoquinone (**14**) (204 mg, 1.0 mmol) with citral (305 mg, 2.0 mmol) afforded **52** (213 mg, 63%) as a solid; mp 59–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 8.7 Hz), 7.47 (d, 1H, J = 2.7 Hz), 7.11 (dd, 1H, J = 8.7, 2.7 Hz), 6.64 (d, 1H, J = 9.9 Hz), 5.62 (d, 1H, J = 9.9 Hz), 5.04 (t, 1H, J = 6.3 Hz), 3.88 (s, 3H), 2.12–2.02 (m, 2H), 1.95–1.85 (m, 1H), 1.71–1.62 (m, 1H), 1.58 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 179.6, 163.6, 152.4, 133.3, 132.1, 129.8, 128.4, 124.8, 123.4, 119.9, 117.3, 116.1, 109.9, 82.8, 55.8, 41.5, 27.4, 25.5, 22.6, 17.6; IR (KBr) 2962, 1674, 1644, 1586, 1440, 1408, 1344, 1317, 1282, 1201, 1166, 1109, 980, 912, 835, 734 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{22}O_4$: 338.1518. Found: 338.1517.

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