A Concise Route for the Synthesis of Pyranonaphthoquinone Derivatives

Yong Rok Lee,*[a] Jung Hyun Choi,[a] Dinh Thi Lan Trinh,[a] Nam Woo Kim[b]

[a] School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea
Fax +82(53)8104631; E-mail: yrlee@yu.ac.kr

[b] Department of Herbal Biotechnology, Daegu Hanny University, Gyeongsan 712-751, Korea

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Abstract: An efficient synthesis of pyranonaphthoquinones is achieved by ethylenediamine diacetate-catalyzed reactions of 4-hydroxy-2-quinolones with a variety of α,β-unsaturated aldehydes in moderate yields. This method provides a rapid entry into biologically interesting α-lapachone derivatives with a variety of substituents on the pyran ring.

Key words: pyranonaphthoquinones, ethylenediamine diacetate, tandem Knoevenagel–electrocyclic reaction, α-lapachone derivatives

Pyranonaphthoquinones are widely distributed in nature and play important physiological roles in animals and plants.[1] Among these, α-lapachone (**1**) and β-lapachone (**2**) are primarily isolated from *Tabebuia avellanedae* in Central and South America (Figure 1).[2] α-Lapachone derivatives **3**–**7** are isolated from *Catalpa ovata*, which is in found in Japan and China.[3] Dehydro-α-lapachone (**8**) and α-caryopterone (**9**) were isolated from *Zeyhera tuberculosa* and *Caryopteris clandonensis*.[4] They have antibacterial, antifungal, antitrypanosomal, antimalarial, and antitumor activities and are used in traditional medicines for the treatment of pyrexia, jaundice, and edema by nephritis in Japan and China.[5] 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-*k*B and AP-1.[6–12] They also have potential clinical utility in the treatment of human leukemia and prostate cancer.[13,14] In particular, a combination of β-lapachone (**2**) and taxol is combined synergistically to induce cell death in so many types of human carcinoma cells such as ovarian, breast, prostate, lung, melanoma, colon and pancreatic cells.[15]

Pyranokunthone A (**10**) and B (**11**) with pyranonaphthoquinone skeleton were isolated from the root bark extract of *Stereospermum kunthianum.*[16] They have been used as a valuable remedy to treat fever in Uganda and they have also shown a strong antimalarial activity.[16]

Several synthetic approaches of pyranonaphthoquinone derivatives including α-lapachone (**1**) and β-lapachone (**2**) have been reported.[17] The common protocol was made by the acid-catalyzed cyclization of lapachol which was synthesized from 2-hydroxy-1,4-naphthoquinone (**12**). However, this synthetic exploitation has been limited due to many reaction steps, strong reaction conditions, and side reactions involving O-alkylation product. The necessity for overcoming these problems has prompted research for improved synthetic methods of pyranonaphthoquinone derivatives. We have recently reported one-pot synthesis of 2*H*-pyrans using a tandem Knoevenagel–electrocyclic reaction in the presence of $Yb(OTf)_3$ or $InCl_3$.[18] We ex-

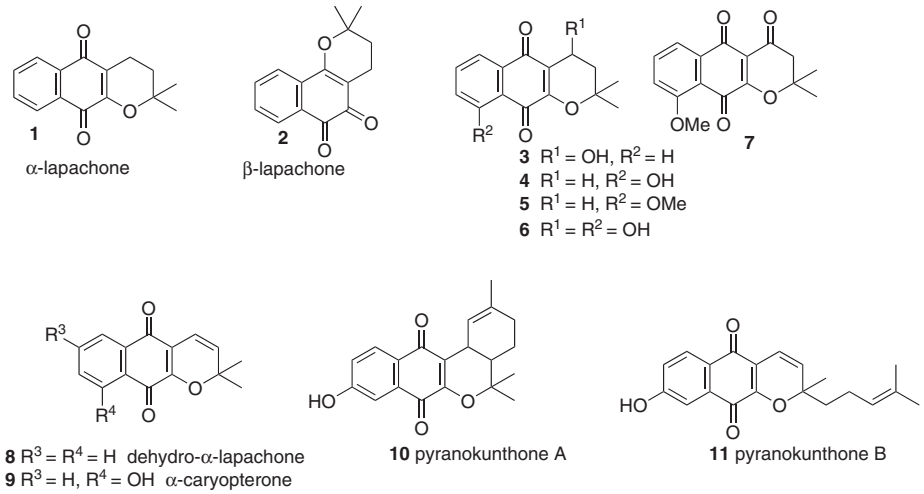

Figure 1

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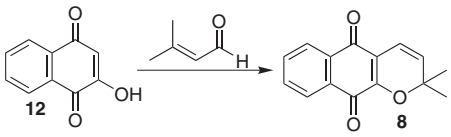
pand this work to the synthesis of pyranonaphthoquinone derivatives by using other catalysts.

First, synthesis of dehydro-α-lapachone (**8**) was attempted starting from 2-hydroxy-1,4-naphthoquinone (**12**) and 3-methyl-2-butenal under several catalysts (Table 1). Both indium(III) chloride (10 mol%) and ytterbium(III) triflate (10 mol%) catalysts in MeCN afforded a small fraction of product **8** in 5% and 10% yields, respectively. The higher yield (55%) was obtained in DMF at 100 °C for five hours in the presence of $Yb(OTf)_3$. In order to obtain optimal reaction conditions, we surveyed other catalysts. With pyridine, cycloadduct **8** was produced in 54% yield. With ethylenediamine diacetate (10 mol%), cycloadduct was obtained in increased yield. There was a solvent dependence. The best yield was obtained in benzene (80%). Other solvents included THF (47%) and MeOH (75%). Our finding was very surprising in comparison with the reported results that ethylenediamine diacetate-catalyzed reactions of 1,3-dicarbonyl compounds with enals have usually been carried out in polar solvent such as MeCN or MeOH.[19] The spectral data of synthetic material **8** are in good agreement with those of natural product reported in the literature.[2a]

Table 1 Effect of Catalysts and Solvents on the Reaction of **12** and 3-Methyl-2-butenal



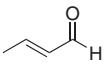
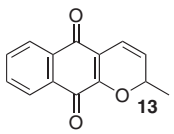
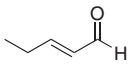
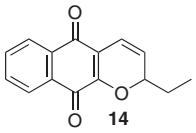
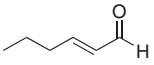
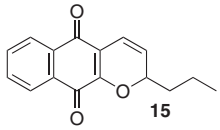
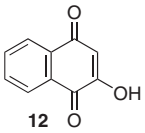
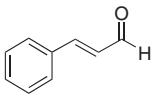
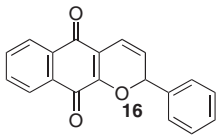
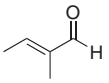
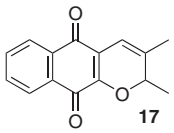
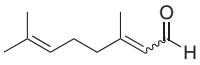
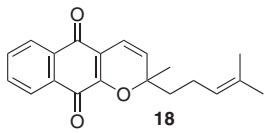
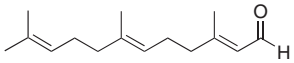
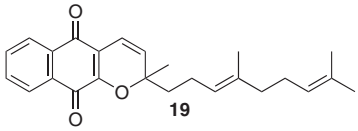
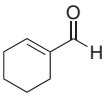
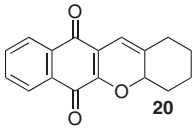
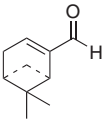
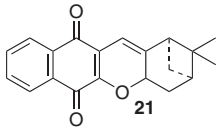
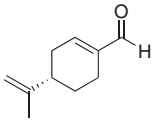
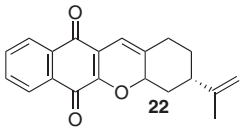
Catalyst	Conditions	Yield (%)
$InCl_3$ (10 mol%)	MeCN, reflux, 5 h	5
$Yb(OTf)_3$ (10 mol%)	MeCN, reflux, 5 h	10
$Yb(OTf)_3$ (10 mol%)	DMF, 100 °C, 5 h	55
pyridine (excess)	$MgSO_4$, reflux, 5 h	54
ethylenediamine diacetate (10 mol%)	$InCl_3$ (10 mol%)	47
ethylenediamine diacetate (10 mol%)	MeOH, r.t., 5 h	75
ethylenediamine diacetate (10 mol%)	benzene, reflux, 5 h	80

In order to extend the utility of this cycloaddition, further reactions with other types of α,β-unsaturated aldehydes were next investigated (Table 2). Reaction with crotonaldehyde in the presence of ethylenediamine diacetate (10 mol%) in refluxing benzene afforded **13** in 49% yield (entry 1). With *trans*-2-pentenal and *trans*-2-hexenal, cycloadducts **14** and **15** were produced in 74% and 60% yields, respectively (entries 2 and 3). With *trans*-cinnamaldehyde and *trans*-2-methyl-2-butenal, expected addition products **16** and **17** were obtained in 40% and 49% yields, respectively (entries 4 and 5). In the cases of citral and *trans*,*trans*-farnesal with a long chain, the reaction was successful. When **12** was treated with citral, adduct **18** was obtained in 64% yield (entry 6). This reaction provides a rapid route to the synthesis of skeleton of biologically interesting pyranokunthone B (**11**).[17a] Similarly, reaction with *trans*,*trans*-farnesal afforded product **19** in 60% yield (entry 7). With other α,β-unsaturated aldehydes with cyclic ring, cycloaddition reaction was also successful. For example, treatment of **12** with 1-cyclohexene-1-carboxaldehyde afforded the product **20** with tetracyclic ring in 92% yield (entry 8). Similarly, reactions with chiral (–)-myrtenol and (–)-perillaldehyde afforded products **21** and **22** in 97% and 87% yields, respectively (entries 9 and 10). These reactions provide a rapid route to the synthesis of pyranonaphthoquinone derivatives, which are known to have a number of biological activities.

The synthesized dehydro-α-lapachone (**8**) can be readily converted to α-lapachone derivatives with a variety of substituents on the pyran ring as shown in Scheme 1. For example, dehydro-α-lapachone (**8**) can be selectively hydrogenated in the presence of 10% Pd/C (10 psi, 20 min) to produce α-lapachone (**1**) in 99% yield.[20] Spectroscopic data of our synthetic material **1** are same as the values reported in the literature for the natural product.[4a] Oxidation of **8** with dimethyl dioxirane in acetone at room temperature leads to product **23** with epoxide ring in 87% yield. When **8** was treated with NBS in aqueous THF at 0 °C for seven hours, bromohydrin **24** was produced in 50% yield. Compound **24** can be used in the synthesis of naturally occurring compound **3** by reduction of bromide. Treatment with osmium tetroxide–NMO at room temperature for three hours afforded *cis*-diol **25** in 52% yield.

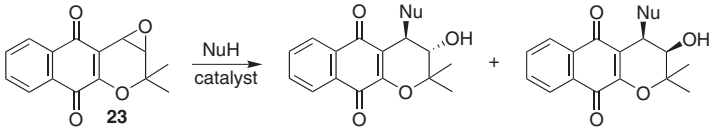
Further conversion to α-lapachone derivatives was carried out by ring opening reaction of epoxide **23** with several nucleophiles in basic and acidic conditions. The epoxide **23** was then reacted with oxygen, nitrogen and sulfur-containing nucleophiles at room temperature in neat or in a suitable solvent as shown in Table 3. Reaction of **23** with water in the presence of catalytic amount of $InCl_3$ at room temperature for five hours afforded both *cis*-diol **25** and *trans*-diol **26** in 30% and 42% yields, respectively, whereas treatment with NaOH in water at room temperature for two hours afforded *trans*-diol **26** as the sole product in 62% yield. The *cis*- and *trans*-isomers were easily separated by silica gel column chromatography and are assigned by spectral data. The ^1H NMR spectrum of *cis*-diol **25** showed two characteristic methine signals at δ = 4.95 (d, *J* = 4.8 Hz, 1 H) and 4.04 (d, *J* = 4.8 Hz, 1 H), which are in agreement with product obtained from osmylation reaction of **8**. The *trans*-diol **26** showed two methine protons of pyran ring at δ = 4.74 (d, *J* = 7.5 Hz, 1 H) and 3.76 (d, *J* = 7.5 Hz, 1 H). Similarly, indium(III)-catalyzed ring opening with MeOH afforded *cis*-product **27** and *trans*-product **28** in 41% and 45% yields, respectively, whereas opening with NaOMe in MeOH gave **28** in 68% yield. Treatment with NaOEt in EtOH also afforded **29** in 60% yield. To further expand the utility of this conversion, other nucleophiles were investigated in the presence of $InCl_3$. When **23** was treated with phenol in CH_2Cl_2, two products **30** and **31** were also obtained in 34% and 40% yields, re-

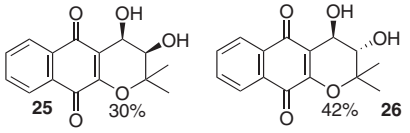
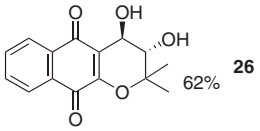
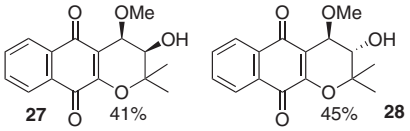
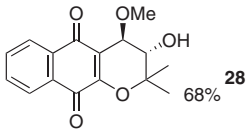
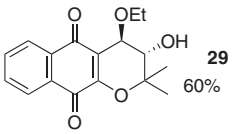
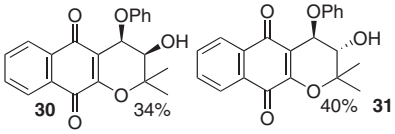
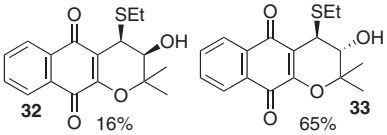
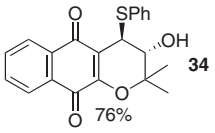
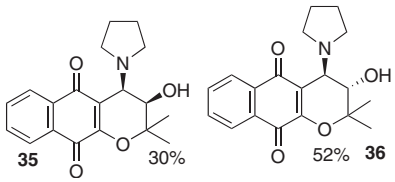
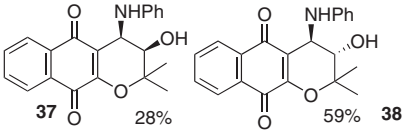
Table 2 Reaction of 2-Hydroxy-1,4-naphthoquinone (**12**) with α,β-Unsaturated Aldehydes

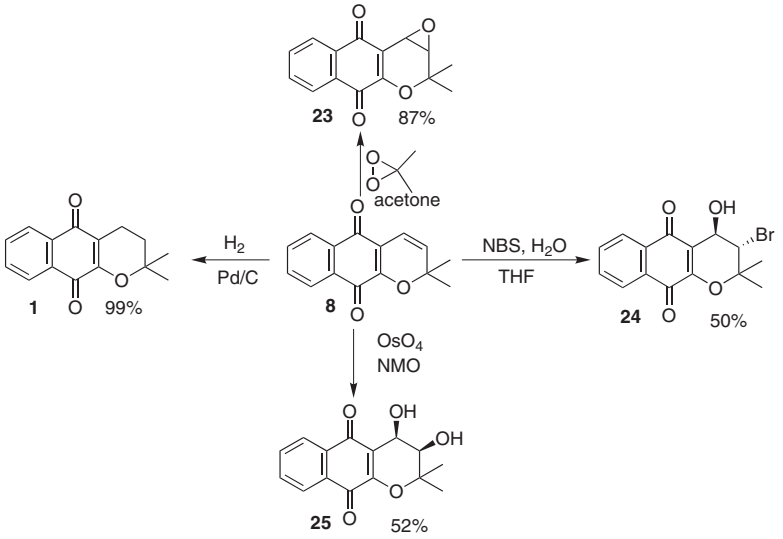
Entry	Starting material	α,β-Unsaturated aldehyde	Product	Yield (%)
1			 **13**	49
2			 **14**	74
3			 **15**	60
4	 **12**		 **16**	40
5			 **17**	49
6			 **18**	64
7			 **19**	60
8			 **20**	92
9			 **21**	97
10			 **22**	87

spectively. Treatment with ethanethiol afforded products **32** and **33** in 16% and 65% yields, respectively. In this case, *trans*-product was obtained as the major component. More interestingly, reaction with thiophenol afforded *trans*-product **34** as the single compound in 75% yield. Last, a series of aliphatic and aromatic amines were investigated. Treatment with pyrrolidine at room temperature for two hours resulted in products **35** and **36** in 30% and 52% yields, respectively. Similarly, reaction with aniline afforded the corresponding products **37** and **38** in 28% and 59% yields, respectively. In view of our results, *trans*-adducts were obtained as the major component in basic conditions. As contrasted with base-catalyzed cleavage, reactions with the indium(III) catalyst mainly afforded both *cis* and *trans* products. These transformations pro-

Table 3 Ring-Opening Reaction of Epoxide **23** with Several Nucleophiles



Entry	NuH/catalyst	Solvent	Product (yield)
1	H_2O–$InCl_3$	CH_2Cl_2	 **25** 30% 42% **26**
2	NaOH	H_2O	 62% **26**
3	MeOH–$InCl_3$	MeOH	 **27** 41% 45% **28**
4	MeONa	MeOH	 68% **28**
5	EtONa	EtOH	 **29** 60%
6	PhOH–$InCl_3$	CH_2Cl_2	 **30** 34% 40% **31**
7	EtSH	CH_2Cl_2	 **32** 16% 65% **33**
8	PhSH	CH_2Cl_2	 **34** 76%
9	pyrrolidine	CH_2Cl_2	 **35** 30% 52% **36**
10	aniline	CH_2Cl_2	 **37** 28% 59% **38**



Scheme 1

vided a rapid entry to the synthesis of biologically interesting α-lapachone derivatives.

In conclusion, the synthesis of pyranonaphthoquinones is achieved by reactions of 4-hydroxy-1,4-naphthoquinone and a variety of α,β-unsaturated aldehydes in the presence of ethylenediamine diacetate in moderate yields. The adduct obtained by this methodology is readily converted to biologically interesting pyranonaphthoquinone derivatives with a variety of substituents on the pyran ring.

All experiments were carried out under a N_2 atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined in capillary tubes on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Bruker Model ARX (300 MHz) spectrometer. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS spectra measurements were carried out at Korea Basic Science Institute.

Synthesis of 8 and 13–22; General Procedure

2-Hydroxy-1,4-naphthoquinone (**12**; 174 mg, 1 mmol) and α,β-unsaturated aldehydes (2 mmol) were dissolved in benzene (10 mL), and ethylenediamine diacetate (18 mg, 0.1 mmol) was added at r.t. The mixture was refluxed for 4–7 h and then cooled to r.t. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give the products.

Dehydro-α-lapachone (8)

Reaction of **12** (174 mg, 1 mmol) with 3-methyl-2-butenal (168 mg, 2 mmol) in benzene (10 mL) afforded **8** (192 mg, 80%) as a solid; mp 145–146 °C (Lit.[2d] 148 °C).

IR (KBr): 3079, 3017, 2976, 2922, 1676, 1647, 1593, 1570, 1416, 1331, 1275, 1211, 1190, 1134, 968, 947 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.05 (m, 2 H), 7.70–7.64 (m, 2 H), 6.64 (d, *J* = 10.0 Hz, 1 H), 5.71 (d, *J* = 10.0 Hz, 1 H), 1.54 (s, 6 H).

2-Methyl-2*H*-benzo[*g*]chromene-5,10-dione (13)

Reaction of **12** (174 mg, 1 mmol) with crotonaldehyde (140 mg, 2 mmol) in benzene (10 mL) afforded **13** (111 mg, 49%) as a solid; mp 96 °C.

IR (KBr): 3067, 2924, 2855, 2361, 2342, 1674, 1647, 1634, 1593, 1572, 1408, 1366, 1337, 1304, 1260, 1130, 966 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (m, 2 H), 7.71–7.67 (m, 2 H), 6.69 (dd, *J* = 10.0, 1.6 Hz, 1 H), 5.78 (dd, *J* = 10.0, 3.4 Hz, 1 H), 5.30–5.25 (m, 1 H), 1.53 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.6, 179.6, 152.6, 134.0, 133.2, 131.3, 131.2, 127.1, 126.2, 126.1, 118.3, 116.5, 74.2, 21.5.

HRMS: *m*/*z* [M$^+$] calcd for $C_{14}H_{10}O_3$: 226.0630; found: 226.0632.

2-Ethyl-2*H*-benzo[*g*]chromene-5,10-dione (14)

Reaction of **12** (174 mg, 1 mmol) with *trans*-2-pentenal (168 mg, 2 mmol) in benzene (10 mL) afforded **14** (178 mg, 74%) as a solid; mp 65 °C.

IR (KBr): 2971, 2926, 2876, 1674, 1649, 1593, 1572, 1335, 1300, 1258, 1202, 1119, 997, 720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (m, 2 H), 7.72–7.66 (m, 2 H), 6.71 (dd, *J* = 10.0, 1.6 Hz, 1 H), 5.79 (dd, *J* = 10.0, 3.4 Hz, 1 H), 5.14–5.09 (m, 1 H), 1.90–1.81 (m, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7, 179.6, 153.0, 134.0, 133.2, 131.4, 131.3, 126.2, 126.1, 125.8, 118.5, 117.1, 78.9, 28.7, 8.4.

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{12}O_3$: 240.0786; found: 240.0787.

2-Propyl-2*H*-benzo[*g*]chromene-5,10-dione (15)

Reaction of **12** (174 mg, 1 mmol) with *trans*-2-hexenal (196 mg, 2 mmol) in benzene (10 mL) afforded **15** (153 mg, 60%) as a solid; mp 56 °C.

IR (KBr): 2959, 2924, 2870, 1672, 1643, 1589, 1566, 1412, 1337, 1294, 1254, 1200, 968, 718 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (m, 2 H), 7.72–7.59 (m, 2 H), 6.69 (dd, *J* = 10.0, 1.5 Hz, 1 H), 5.79 (dd, *J* = 10.0, 3.5 Hz, 1 H), 5.20–5.10 (m, 1 H), 1.89–1.69 (m, 2 H), 1.60–1.40 (m, 2 H), 0.95 (t, *J* = 7.3 Hz, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{16}H_{14}O_3$: 254.0943; found: 254.0939.

2-Phenyl-2*H*-benzo[*g*]chromene-5,10-dione (16)
Reaction of **12** (174 mg, 1 mmol) with *trans*-cinnamaldehyde (264 mg, 2 mmol) in benzene (10 mL) afforded **16** (115 mg, 40%) as a solid; mp 98 °C.

IR (KBr): 3069, 2924, 1654, 1647, 1585, 1331, 1292, 1258, 1188, 1107, 958, 717 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.03 (m, 2 H), 7.73–7.63 (m, 2 H), 7.47–7.44 (m, 2 H), 7.40–7.34 (m, 3 H), 6.91 (dd, *J* = 10.0, 1.5 Hz, 1 H), 6.15 (dd, *J* = 3.8, 1.5 Hz, 1 H), 5.96 (dd, *J* = 10.0, 3.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7, 179.3, 152.2, 138.5, 134.0, 133.3, 131.4, 131.3, 129.3, 129.3, 128.9, 128.9, 127.5, 126.3, 126.2, 124.9, 118.0, 117.0, 78.8.

HRMS: *m*/*z* [M^+] calcd for $C_{19}H_{12}O_3$: 288.0786; found: 288.0786.

2,3-Dimethyl-2*H*-benzo[*g*]chromene-5,10-dione (17)
Reaction of **12** (174 mg, 1 mmol) with *trans*-2-methyl-2-butenal (168 mg, 2 mmol) in benzene (10 mL) afforded **17** (118 mg, 49%) as a solid; mp 107 °C.

IR (KBr): 2967, 1671, 1647, 1591, 1572, 1385, 1337, 1304, 1256, 1202, 966, 720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.03 (m, 2 H), 7.75–7.63 (m, 2 H), 6.43 (s, 1 H), 5.08 (q, *J* = 6.6 Hz, 1 H), 1.88 (s, 3 H), 1.45 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.9, 179.6, 150.2, 137.3, 133.7, 133.1, 131.4, 131.3, 126.1, 125.9, 119.2, 111.7, 76.6, 19.6, 19.1.

HRMS: *m*/*z* [M^+] calcd for $C_{15}H_{12}O_3$: 240.0786; found: 240.0786.

2-Methyl-2-(4-methylpent-3-enyl)-2*H*-benzo[*g*]chromene-5,10-dione (18)
Reaction of **12** (174 mg, 1 mmol) with citral (304 mg, 2 mmol) in benzene (10 mL) afforded **18** (197 mg, 64%) as a liquid.

IR (neat): 2978, 2926, 1676, 1651, 1595, 1572, 1449, 1412, 1339, 1273, 1211, 1115, 966, 901, 797, 720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2 H), 7.71–7.63 (m, 2 H), 6.68 (d, *J* = 10.0 Hz, 1 H), 5.65 (d, *J* = 10.0 Hz, 1 H), 5.09–5.03 (m, 1 H), 2.15–2.05 (m, 2 H), 1.99–1.89 (m, 1 H), 1.71–1.64 (m, 1 H), 1.60 (s, 3 H), 1.53 (s, 3 H), 1.50 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.6, 179.5, 152.6, 133.8, 133.0, 132.1, 131.3, 131.2, 129.6, 126.0, 126.0, 123.3, 117.3, 115.8, 82.9, 41.4, 27.4, 25.5, 22.5, 17.5.

HRMS: *m*/*z* [M^+] calcd for $C_{20}H_{20}O_3$: 308.1412; found: 308.1414.

2-(4,8-Dimethylnona-3,7-dienyl)-2-methyl-2*H*-benzo[*g*]chromene-5,10-dione (19)
Reaction of **12** (174 mg, 1 mmol) with *trans*,*trans*-farnesal (441 mg, 2 mmol) in benzene (10 mL) afforded **19** (226 mg, 60%) as a liquid.

IR (neat): 2969, 2926, 1676, 1653, 1597, 1572, 1449, 1410, 1337, 1273, 1211, 966, 720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 2 H), 7.72–7.63 (m, 2 H), 6.68 (d, *J* = 10.0 Hz, 1 H), 5.66 (d, *J* = 10.0 Hz, 1 H), 5.10–5.01 (m, 2 H), 2.15–1.85 (m, 8 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.53 (s, 3 H), 1.50 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{25}H_{28}O_3$: 376.2038; found: 376.2038.

2,3,4,4a-Tetrahydro-1*H*-benzo[*b*]xanthene-6,11-dione (20)
Reaction of **12** (174 mg, 1 mmol) with 1-cyclohexene-1-carboxaldehyde (220 mg, 2 mmol) in benzene (10 mL) afforded **20** (245 mg, 92%) as a solid; mp 156 °C.

IR (KBr): 2940, 1672, 1649, 1597, 1574, 1395, 1345, 1204, 1007, 721 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.06–8.02 (m, 2 H), 7.70–7.62 (m, 2 H), 6.32 (s, 1 H), 5.18 (dd, *J* = 11.6, 5.7 Hz, 1 H), 2.57–2.49 (m, 1 H), 2.37–2.31 (m, 1 H), 2.11–1.76 (m, 4 H), 1.50–1.32 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.9, 179.3, 151.3, 140.6, 133.7, 133.0, 131.2, 131.1, 125.9, 125.8, 117.6, 108.5, 79.9, 35.1, 33.5, 26.9, 24.3.

HRMS: *m*/*z* [M^+] calcd for $C_{17}H_{14}O_3$: 266.0943; found: 266.0946.

Compound (21)
Reaction of **12** (174 mg, 1 mmol) with (1*R*)-(–)-myrtenal (300 mg, 2 mmol) in benzene (10 mL) afforded **21** (297 mg, 97%) as a solid; mp 125 °C; $[\alpha]^{22}_D$ –372.0 (*c* = 1, $CHCl_3$).

IR (KBr): 2948, 2912, 2867, 1650, 1566, 1335, 1287, 1252, 1196, 1049, 984, 806, 718 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2 H), 7.71–7.64 (m, 2 H), 6.35 (d, *J* = 2.6 Hz, 1 H), 5.21–5.15 (m, 1 H), 2.77–2.67 (m, 2 H), 2.45–2.37 (m, 1 H), 2.28–2.21 (m, 1 H), 2.18–2.13 (m, 1 H), 1.60–1.52 (m, 1 H), 1.32 (s, 3 H), 0.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.9, 179.8, 153.5, 144.0, 134.2, 133.7, 131.9, 131.8, 126.6, 126.5, 123.0, 111.2, 72.4, 49.7, 42.9, 40.4, 32.2, 25.9, 25.2, 22.2.

HRMS: *m*/*z* [M^+] calcd for $C_{20}H_{18}O_3$: 306.1256; found: 306.1255.

3-Isopropenyl-2,3,4,4a-tetrahydro-1*H*-benzo[*b*]xanthene-6,11-dione (22)
Reaction of **12** (174 mg, 1 mmol) with (*S*)-(–)-perillaldehyde (300 mg, 2 mmol) in benzene (10 mL) afforded **22** (267 mg, 87%) as a solid; mp 120 °C; $[\alpha]^{22}_D$ +210.3 (*c* = 1, $CHCl_3$).

IR (KBr): 3073, 2924, 2856, 1649, 1593, 1444, 1389, 1339, 1296, 1250, 1200, 995, 890, 714 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.07–8.03 (m, 2 H), 7.68–7.64 (m, 2 H), 6.35 (s, 1 H), 5.27 (dd, *J* = 11.5, 6.2 Hz, 1 H), 4.74 (s, 1 H), 4.72 (s, 1 H), 2.64–2.57 (m, 1 H), 2.46–2.39 (m, 1 H), 2.25–2.07 (m, 2 H), 1.93–1.85 (m, 1 H), 1.83–1.75 (m, 1 H), 1.72 (s, 3 H), 1.42–1.28 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.3, 179.7, 151.8, 147.8, 140.2, 134.2, 133.5, 131.7, 131.6, 126.4, 126.4, 118.1, 110.2, 109.2, 78.0, 43.5, 40.2, 33.1, 32.1, 21.2.

HRMS: *m*/*z* [M^+] calcd for $C_{20}H_{18}O_3$: 306.1256; found: 306.1258.

α-Lapachone (1)
To the synthetic material **8** (300 mg, 1.25 mmol) in a Parr bottle in EtOAc (10 mL) was added 10% Pd/C (20 mg). The bottle was shaken for 20 min at 10 psi of H_2. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **1** (299 mg, 99%) as a solid; mp 113–114 °C (Lit.[2d] 116 °C, Lit.[17e] 112–115 °C).

IR (KBr): 2974, 2948, 1682, 1638, 1613, 1578, 1391, 1341, 1310, 1273, 1208, 1119, 961 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.02 (m, 2 H), 7.70–7.62 (m, 2 H), 2.60 (t, *J* = 6.6 Hz, 2 H), 1.80 (t, *J* = 6.6 Hz, 2 H), 1.42 (s, 6 H).

2,2-Dimethyl-3,4-epoxy-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (23)
A stirred mixture of **8** (0.5 g, 2.08 mmol) in acetone (10 mL) was treated with dimethyldioxirane (25 mL, 0.09 M in acetone) at r.t. for 4 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel afforded **23** (464 mg, 87%) as a solid; mp 139–140 °C.

IR (KBr): 2987, 2936, 1682, 1651, 1618, 1595, 1578, 1435, 1399, 1341, 1314, 1277, 1211, 1154, 1086, 965, 851, 725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.07 (m, 2 H), 7.76–7.65 (m, 2 H), 4.33 (d, *J* = 4.4 Hz, 1 H), 3.52 (d, *J* = 4.4 Hz, 1 H), 1.68 (s, 3 H), 1.43 (s, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{12}O_4$: 256.0736; found: 256.0738.

3-Bromo-4-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (24)

To a solution of **8** (240 mg, 1 mmol) in THF (5 mL) and H_2O (5 mL) was added NBS (214 mg, 1.2 mmol). The reaction mixture was stirred for 7 h at 0 °C, the reaction mixture was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **24** (169 mg, 50%) as a solid; mp 176 °C.

IR (KBr): 3453, 2926, 1686, 1638, 1618, 1595, 1576, 1460, 1308, 1271, 1208, 1175, 1119, 1034, 953, 727 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2 H), 7.76–7.69 (m, 2 H), 5.06 (d, *J* = 6.9 Hz, 1 H), 4.13 (d, *J* = 6.9 Hz, 1 H), 4.08 (s, 1 H), 1.70 (s, 3 H), 1.55 (s, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{13}BrO_4$: 335.9997; found: 335.9998.

3,4-Dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (25)

To a solution of osmium tetroxide (10 mg, 0.04 mmol) and NMO (0.165 g, 1.1 mmol) in *t*-BuOH–THF–H_2O (10:3:1, 10 mL) was added **8** (240 mg, 1 mmol) and the reaction mixture was stirred at r.t. for 12 h. Saturated $NaHSO_3$ solution (50 mL) was added, the mixture was stirred for 1 h, and extracted with CH_2Cl_2. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **25** (143 mg, 52%) as a solid; mp 63 °C.

IR (KBr): 3495, 2926, 1684, 1657, 1615, 1462, 1373, 1337, 1308, 1271, 1213, 1130, 1051, 961, 775 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.08 (m, 2 H), 7.70–7.69 (m, 2 H), 4.95 (d, *J* = 4.8 Hz, 1 H), 4.04 (d, *J* = 4.8 Hz, 1 H), 1.64 (s, 3 H), 1.46 (s, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{14}O_5$: 274.0841; found: 274.0842.

Ring Opening of Epoxide 23 with Nucleophiles; General Procedure

In(III)-Catalyzed Reaction: To a solution of epoxide **23** (128 mg, 0.5 mmol) and nucleophile in neat or in CH_2Cl_2 (5 mL) was added $InCl_3$ (11 mg, 0.05 mmol). The reaction mixture was stirred at r.t. for 5 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give the product.

Base-Catalyzed Reaction: Nucleophile was added to a solution of epoxide **23** (128 mg, 0.5 mmol) in a solvent (5 mL). The reaction mixture was stirred at r.t. for 2 h, the mixture was acidified by 2 N HCl solution, and extracted with EtOAc. Removal of the solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give the product.

***cis*-3,4-Dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (25) and *trans*-3,4-Dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (26)**

Reaction of **23** (128 mg, 0.5 mmol) with H_2O (36 mg, 2 mmol) using $InCl_3$ in CH_2Cl_2 (5 mL) afforded **25** (41 mg, 30%) and **26** (58 mg, 42%).

26

Mp 39–40 °C.

IR (KBr): 3495, 2984, 2922, 1684, 1645, 1595, 1580, 1372, 1341, 1308, 1273, 1211, 1132, 1096, 1042, 957, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.04 (m, 2 H), 7.73–7.69 (m, 2 H), 4.74 (d, *J* = 7.5 Hz, 1 H), 3.76 (d, *J* = 7.5 Hz, 1 H), 1.77 (s, 3 H), 1.27 (s, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{14}O_5$: 274.0841; found: 274.0843.

***trans*-3,4-Dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (26)**

Reaction of **23** (128 mg, 0.5 mmol) with 2 N NaOH (1 mL) using $InCl_3$ in H_2O (5 mL) afforded **26** (85 mg, 62%).

***cis*-3-Hydroxy-4-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (27) and *trans*-3-Hydroxy-4-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (28)**

Reaction of **23** (128 mg, 0.5 mmol) with MeOH (5 mL) using $InCl_3$ afforded **27** (59 mg, 41%) and **28** (65 mg, 45%).

27

Mp 145–147 °C.

IR (KBr): 3497, 2938, 1682, 1651, 1616, 1580, 1385, 1337, 1306, 1271, 1213, 1128, 1049, 976, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (m, 2 H), 7.73–7.66 (m, 2 H), 5.28 (s, 1 H), 4.49 (d, *J* = 4.9 Hz, 1 H), 3.76 (d, *J* = 4.9 Hz, 1 H), 3.69 (s, 3 H), 1.51 (s, 3 H), 1.44 (s, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{16}H_{16}O_5$: 288.0998; found: 288.0999.

28

Mp 197–199 °C.

IR (KBr): 3486, 3011, 2984, 2934, 2907, 2830, 1672, 1651, 1618, 1595, 1579, 1383, 1337, 1312, 1271, 1209, 1128, 972, 870 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.07 (m, 2 H), 7.74–7.63 (m, 2 H), 4.33 (d, *J* = 3.0 Hz, 1 H), 3.89 (d, *J* = 3.0 Hz, 1 H), 3.63 (s, 3 H), 1.56 (s, 3 H), 1.47 (s, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{16}H_{16}O_5$: 288.0998; found: 288.0996.

***trans*-3-Hydroxy-4-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (28)**

Reaction of **23** (128 mg, 0.5 mmol) with NaOMe (108 mg, 2 mmol) in MeOH (5 mL) afforded **28** (98 mg, 68%).

***trans*-4-Ethoxy-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (29)**

Reaction of **23** (128 mg, 0.5 mmol) with NaOMe (136 mg, 2 mmol) in EtOH (5 mL) afforded **29** (91 mg, 60%) as a solid; mp 187–189 °C.

IR (KBr): 3468, 2980, 1682, 1651, 1618, 1385, 1337, 1273, 1209, 1134, 1090, 964, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.07 (m, 2 H), 7.74–7.66 (m, 2 H), 4.43 (d, *J* = 3.0 Hz, 1 H), 3.95–3.80 (m, 3 H), 1.56 (s, 3 H), 1.50 (s, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H).

HRMS: *m*/*z* [M$^+$] calcd for $C_{17}H_{18}O_5$: 316.1311; found: 316.1314.

***cis*-3-Hydroxy-2,2-dimethyl-4-phenoxy-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (30) and *trans*-3-Hydroxy-2,2-dimethyl-4-phenoxy-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (31)**

Reaction of **23** (128 mg, 0.5 mmol) with PhOH (188 mg, 2 mmol) using $InCl_3$ in CH_2Cl_2 (5 mL) afforded **30** (60 mg, 34%) and **31** (70 mg, 40%).

30
Mp 183–185 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15–8.07 (m, 2 H), 7.71–7.67 (m, 2 H), 7.37–7.32 (m, 2 H), 7.22–7.19 (m, 2 H), 7.09–7.04 (m, 1 H), 5.54 (d, *J* = 4.7 Hz, 1 H), 3.96 (d, *J* = 4.7 Hz, 1 H), 1.54 (s, 3 H), 1.21 (s, 3 H).

IR (KBr): 3497, 2926, 2857, 1723, 1682, 1651, 1618, 1595, 1493, 1466, 1385, 1337, 1271, 1217, 1130, 1055, 976 cm^{-1}.

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{18}O_5$: 350.1154; found: 350.1155.

31
Mp 200–202 °C.

IR (KBr): 3488, 3069, 3011, 2982, 2934, 1676, 1649, 1628, 1591, 1489, 1385, 1341, 1275, 1221, 1128, 1073, 1026, 966 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.08 (m, 2 H), 7.75–7.62 (m, 2 H), 7.36–7.31 (m, 2 H), 7.15–7.13 (m, 2 H), 7.05–7.01 (m, 1 H), 5.41 (d, *J* = 2.4 Hz, 1 H), 3.98 (d, *J* = 2.4 Hz, 1 H), 1.59 (s, 3 H), 1.55 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{18}O_5$: 350.1154; found: 350.1157.

***cis*-4-Ethylsulfanyl-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (32) and *trans*-4-Ethylsulfanyl-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (33)**
Reaction of **23** (128 mg, 0.5 mmol) with EtSH (124 mg, 2 mmol) using $InCl_3$ in CH_2Cl_2 (5 mL) afforded **32** (25 mg, 16%) and **33** (103 mg, 65%).

32
Mp 139–141 °C.

IR (KBr): 3432, 2982, 1682, 1645, 1611, 1578, 1366, 1337, 1271, 1219, 1127, 1092, 1042, 974, 723 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (m, 2 H), 7.74–7.64 (m, 2 H), 4.06 (d, *J* = 6.2 Hz, 1 H), 3.92 (d, *J* = 6.2 Hz, 1 H), 3.06–2.97 (m, 2 H), 1.58 (s, 3 H), 1.36 (t, *J* = 7.4 Hz, 3 H), 1.28 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{17}H_{18}O_4S$: 318.0926; found: 318.0927.

33
Mp 167–169 °C.

IR (KBr): 3513, 2975, 2919, 1667, 1651, 1607, 1576, 1364, 1339, 1277, 1208, 1123, 1051, 961, 725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (m, 2 H), 7.74–7.63 (m, 2 H), 3.80 (d, *J* = 6.2 Hz, 1 H), 3.64 (d, *J* = 6.2 Hz, 1 H), 3.09–2.88 (m, 2 H), 1.57 (s, 3 H), 1.39 (s, 3 H), 1.34 (t, *J* = 7.4 Hz, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{17}H_{18}O_4S$: 318.0926; found: 318.0925.

***trans*-3-Hydroxy-2,2-dimethyl-4-phenylsulfanyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (34)**
Reaction of **23** (128 mg, 0.5 mmol) with PhSH (220 mg, 2 mmol) using $InCl_3$ in CH_2Cl_2 (5 mL) afforded **34** (143 mg, 78%) as a solid; mp 180–182 °C.

IR (KBr): 3505, 3065, 2984, 2922, 1669, 1655, 1610, 1578, 1480, 1366, 1335, 1308, 1277, 1211, 1123, 1057, 961, 727 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.06 (m, 2 H), 7.75–7.65 (m, 2 H), 7.60–7.57 (m, 2 H), 7.33–7.29 (m, 3 H), 4.10 (d, *J* = 5.7 Hz, 1 H), 3.86 (d, *J* = 5.7 Hz, 1 H), 2.40 (s, 1 H), 1.60 (s, 3 H), 1.41 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{18}O_4S$: 366.0926; found: 366.0929.

***cis*-3-Hydroxy-2,2-dimethyl-4-pyrrolidin-1-yl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (35) and *trans*-3-Hydroxy-2,2-dimethyl-4-pyrrolidin-1-yl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (36)**
Reaction of **23** (128 mg, 0.5 mmol) with pyrrolidine (142 mg, 2 mmol) using $InCl_3$ in CH_2Cl_2 (5 mL) afforded **35** (49 mg, 30%) and **36** (85 mg, 52%).

35
Mp 133–135 °C.

IR (KBr): 3447, 2973, 1682, 1649, 1611, 1578, 1337, 1306, 1271, 1211, 1130, 1044, 982, 729 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.04 (m, 2 H), 7.73–7.66 (m, 2 H), 4.25 (d, *J* = 5.7 Hz, 1 H), 3.86 (d, *J* = 5.7 Hz, 1 H), 3.37–3.28 (m, 2 H), 3.01–2.97 (m, 2 H), 1.89–1.77 (m, 4 H), 1.46 (s, 3 H), 1.43 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{19}H_{21}NO_4$: 327.1471; found: 327.1472.

36
Mp 140–141 °C.

IR (KBr): 3515, 2967, 2866, 1678, 1649, 1607, 1578, 1335, 1273, 1211, 1046, 974, 725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.03 (m, 2 H), 7.72–7.24 (m, 2 H), 3.82 (d, *J* = 7.6 Hz, 1 H), 3.66 (d, *J* = 7.6 Hz, 1 H), 3.10–3.00 (m, 2 H), 2.77–2.65 (m, 2 H), 1.79–1.72 (m, 4 H), 1.63 (s, 3 H), 1.34 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{19}H_{21}NO_4$: 327.1471; found: 327.1470.

***cis*-3-Hydroxy-2,2-dimethyl-4-phenylamino-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (37) and *trans*-3-Hydroxy-2,2-dimethyl-4-phenylamino-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (38)**
Reaction of **23** (128 mg, 0.5 mmol) with aniline (186 mg, 2 mmol) using $InCl_3$ in CH_2Cl_2 (5 mL) afforded **37** (49 mg, 28%) and **38** (103 mg, 59%).

37
Mp 178–180 °C.

IR (KBr): 3437, 3353, 1711, 1682, 1603, 1578, 1499, 1368, 1335, 1304, 1271, 1211, 1130, 1049, 976, 748 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.03 (m, 2 H), 7.74–7.64 (m, 2 H), 7.31–7.26 (m, 2 H), 6.96–6.90 (m, 3 H), 4.58 (d, *J* = 4.8 Hz, 1 H), 3.91 (d, *J* = 4.8 Hz, 1 H), 1.61 (s, 3 H), 1.44 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{19}NO_4$: 349.1314; found: 349.1316.

38
Mp 165–167 °C.

IR (KBr): 3484, 3401, 1684, 1605, 1574, 1501, 1370, 1335, 1275, 1211, 1138, 965, 750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.03 (m, 2 H), 7.77–7.65 (m, 2 H), 7.27–7.22 (m, 2 H), 6.92–6.79 (m, 3 H), 4.58 (d, *J* = 6.1 Hz, 1 H), 3.95 (d, *J* = 6.1 Hz, 1 H), 1.58 (s, 3 H), 1.46 (s, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{19}NO_4$: 349.1314; found: 349.1315.

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