New and General Methods for the Synthesis of Arylmethylene *Bis*(3-Hydroxy-2-Cyclohexene-1-Ones) and Xanthenediones by EDDA and $In(OTf)_3$-Catalyzed One-Pot Domino Knoevenagel/Michael or Koevenagel/Michael/Cyclodehydration Reactions

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Efficient one-pot synthesis of arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-ones) and xanthenediones by EDDA and $In(OTf)_3$-catalyzed reactions was developed starting from dimedone and aryl aldehydes. The key strategies of these reactions involve domino Knoevenagel/Michael reaction or Koevenagel/Michael/Cyclodehydration reactions. The scope and limitation of the two catalysts under various reaction conditions were investigated and described.

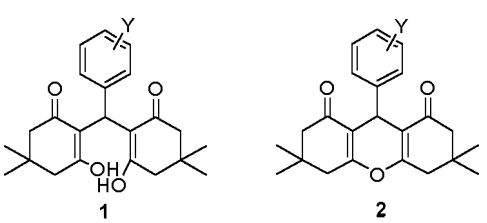
Key Words: Arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-one, Xanthenedione, EDDA, $In(OTf)_3$, Koevenagel/Michael/Cyclodehydration

Introduction

Arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-one) derivatives (**1**) are important substrates extensively used as valuable precursors for the syntheses of xanthenes and acridinediones for laser dye technology (Fig. 1).[1] These compounds have also shown potent activity as antioxidants,[2] lipoxygenase inhibitors,[2] and a new clinical class of tyrosinase inhibitors against very important dermatological disorders including hyperpigmentation and skin melanoma.[3]

Xanthenedione derivatives (**2**) have attracted considerable interest in recent years because of their important biological properties including antibacterial,[4] antiviral,[5] and anti-inflammatory activities,[6] as well as positive allosteric modulators of metabotropic receptors,[7] potent nonpeptide inhibitors of recombinant human calpain I,[8] efficiency in photodynamic therapy,[9] and antagonists for the paralyzing action of zoxazolamine (Fig. 1).[10] In particular, xanthenedione derivatives have been found in nature[11] and used as versatile synthons for biologically active natural products.[12]

A number of synthetic methods for arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-one) derivatives (**1**) have been reported by the condensation of cyclic 1,3-dicarbonyls and aryl aldehydes in the presence of $HClO_4$-SiO_2,[13] Et_4NBr/NH_4Cl,[2] $FeCl_3 \cdot 6H_2O$/TMSCl/[bmim][BF_4],[14] and I_2.[15] The synthesis of xanthenedione derivatives has been also reported by the condensation of cyclic 1,3-dicarbonyls and aryl aldehydes catalyzed by sulfuric acid or hydrochloric acid. Recently, many improved procedures have been reported using silica gel/sulfuric acid,[16] $NaHSO_4/SiO_2$,[17] PPA/SiO_2,[13] $SbCl_3/SiO_2$,[18] $FeCl_3/SiO_2$,[19] TiO_2/SO_4^{-2},[20] Dowex-50W,[21] polyaniline-*p*-toluenesulfonate,[22] *p*-dodecylbenzenesulfonic acid,[23] Amberlyst-15,[24] Fe^{+3}-montmorillonite,[25] diammonium hydrogen phosphate,[26] triethylbenzylammonium chloride,[27] tetrabutylammonium hydrogen sulfate,[28] TMSCl,[29] and [Hmim]TFA[30] as catalysts. Although a variety of methods have been developed and reported, the necessity for development of a simple and efficient methodology for the synthesis of arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-ones) and xanthenediones still remains given their biological importance.



1 2

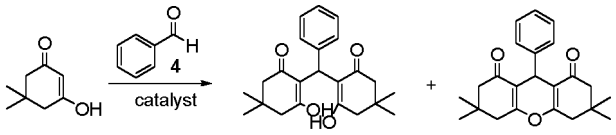
Figure 1

Recently, this lab developed a new and useful methodology for preparing a variety of 2*H*-pyrans using ethylenediamine diacetate (EDDA)[31] or $InCl_3$-catalyzed reactions of 1,3-dicarbonyls with α,β-unsaturated aldehydes.[32] These reactions involve cycloaddition through a domino Knoevenagel condensation/6 π-electrocyclization and provide a rapid route for the synthesis of 2*H*-pyran derivatives with a variety of pyranyl ring substituents. As part of an ongoing study of the efficacy of these catalysts, herein is described a facile and general method for the synthesis of arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-one) derivatives and xanthenediones through a domino Knoevenagel/Michael or Knoevenagel/Michael/Cyclodehydration reaction.

Results and Discussion

Reaction of dimedone (**3**) with benzaldehyde (**4**) in the presence of several Bronsted acids and bases was first investigated (Table 1). Bronsted acids and bases have demon-

Table 1. Reaction of compound **3** with benzaldehyde (**4**) under several Bronsted acid and base catalysts

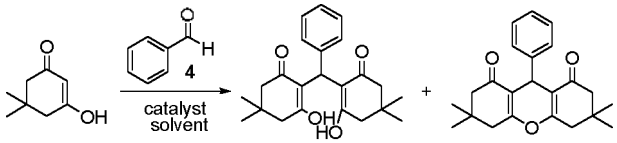


Bronsted acids and bases	solvent	condition	yield (%)	
			1a	**2a**
PPTS (30 mol%)	THF	reflux, 4 h	66	11
DMAT (30 mol%)	CH_3CN	reflux, 4 h	57	22
EDDA (30 mol%)	benzene	reflux, 4 h	70	0
EDDA (30 mol%)	THF	reflux, 4 h	88	0
EDDA (30 mol%)	CH_3CN	reflux, 4 h	75	0
EDDA (30 mol%)	CH_3OH	reflux, 7 h	10	0

strated their potential to serve as active catalysts for a variety of synthetically useful reactions in organic chemistry.[33] With 30 mol% of pyridine *p*-toluenesulfonate (PPTS) in refluxing THF for 4 h, both products **1a** and **2a** were produced in 66 and 11% yields, respectively. Similarly, when 30 mol% diphenylmethylammonium triflate (DMAT) was used as a catalyst in refluxing acetonitrile for 4 h, **1a** and **2a** were also obtained, in 57 and 22% yields, respectively. The two compounds were easily separated by column chromatography and assigned by spectral analysis. The ^{1}H-NMR spectrum of **1a** shows a benzylic methine proton at 5.52 ppm, whereas **2a** a methine proton at 4.69 ppm. Further, clear assignments come from the hydroxyl and carbonyl absorptions at 3400 and 1610 cm^{-1} for **1a** and carbonyl absorption at 1662 cm^{-1} for **2a**. Interestingly, with 30 mol% ethylenediamine diacetate (EDDA) as a catalyst, compound **1a** was produced as the sole compound. The best yield was obtained in refluxing THF (88%) for 4 h. Other solvents included benzene (70%), acetonitrile (75%), and methanol (10%).

In order to study the usefulness and generality of the proposed methodology, additional reactions with a wide range of aryl aldehydes in the presence of 30 mol% EDDA in refluxing THF were examined. The results are summarized in Table 2. One important feature was that aryl aldehydes, both possessing

Table 3. Reaction of compound **3** with benzaldehyde (**4**) under several Lewis acid catalysts



Lewis acid	solvent	condition	yield (%)	
			1a	**2a**
BF_3·OEt_2 (30 mol%)	THF	reflux, 4 h	56	33
$ZnCl_2$ (30 mol%)	THF	reflux, 4 h	87	0
$InCl_3$ (30 mol%)	toluene	reflux, 4 h	0	78
$In(OTf)_3$ (30 mol%)	toluene	reflux, 4 h	0	85

electron-withdrawing and electron-donating groups, afforded the corresponding products in good yields. In particular, aryl aldehydes with substrates at the *para*- and *meta*-positions of the benzene ring gave products in high yield, whereas those at the *ortho*-position gave products in somewhat decreased yields, probably due to steric hindrance. It was also found that EDDA can also efficiently catalyze the reactions of 1-naphthaldehyde and 2-naphthaldehyde to give products **1j** and **2k** in 84 and 86% yields, respectively.

The synthesis of xanthenedione derivatives was next examined using several Lewis acid catalysts, BF_3·OEt_2, $ZnCl_2$, $InCl_3$, and $In(OTf)_3$, as shown in Table 3. In related work, the $InCl_3$·$4H_2O$/[bmin]BF_4-promoted reaction of cyclic dicarbonyls to aryl aldehydes has been reported, but only as a co-catalyst; however, only the $InCl_3$-catalyzed reaction has not been described. Reaction of **3** with benzaldehyde (**4**) in the presence of 30 mol% boron trifluoride diethyl etherate in refluxing tetrahydrofuran for 4 h gave both products **1a** and **2a** in 56 and 33% yields, respectively, whereas zinc chloride (30 mol%) produced uncyclized adduct **1a** in 87% yield. With indium(III) chloride (30 mol%) and indium(III) trifluoromethanesulfonate (30 mol%) as catalysts, cycloadduct **2a** was produced in 78 and 85% yields, respectively. This lab found that indium(III) trifluoromethanesulfonate showed catalytic activity for this reaction superior to that of indium(III) chloride.

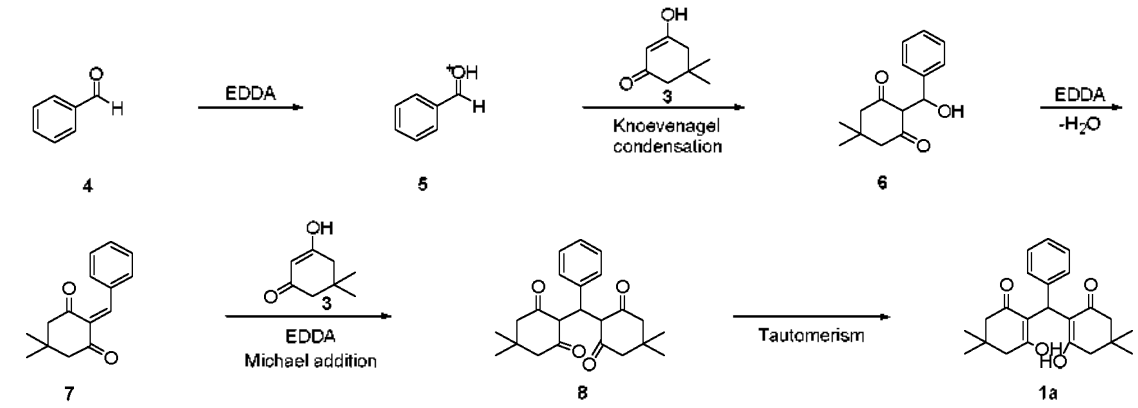
Additional reactions of **3** with a variety of aryl aldehydes in

Table 2. Synthesis of 2,2-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives (**1b-1k**) by EDDA-catalyzed reaction of **3** with aryl aldehydes

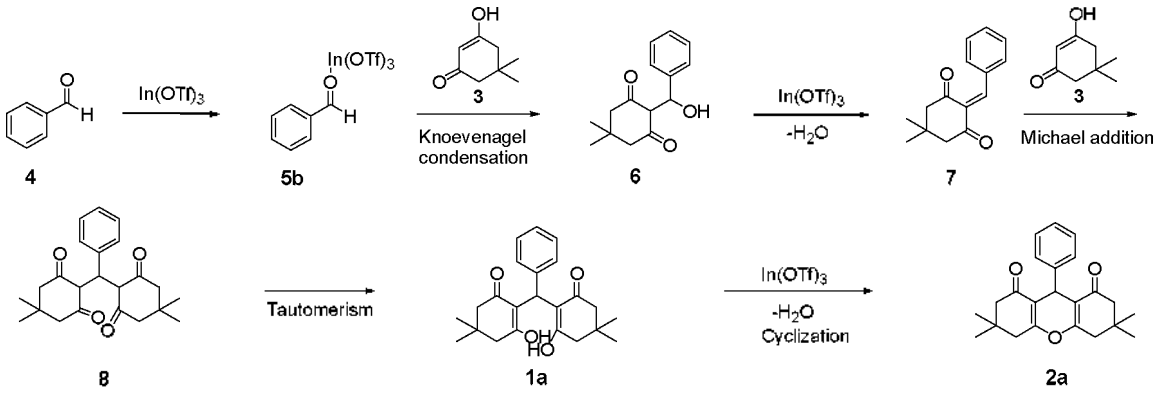
entry	aryl aldehyde	time (h)	product	yield (%)	m.p
1	4-chlorobenzaldehyde	4	**1b**	97	140 - 142
2	4-nitrobenzaldehyde	4	**1c**	92	188 - 190
3	2-nitrobenzaldehyde	6	**1d**	74	249 - 251
4	4-methoxybenzaldehyde	4	**1e**	94	146 - 148
5	2,5-dimethoxybenzaldehyde	6	**1f**	70	146 - 148
6	3,4-dimethoxybenzaldehyde	4	**1g**	84	173 - 175
7	3,5-dimethoxybenzaldehyde	4	**1h**	89	181 - 183
8	2,5-dimethylbenzaldehyde	4	**1i**	76	154 - 156
9	1-naphthaldehyde	4	**1j**	84	233 - 235
10	2-naphthaldehyde	4	**1k**	86	208 - 210

Table 4. Synthesis of xanthenedione derivatives **2b-2k** by $In(OTf)_3$-catalyzed reaction of 3 with aryl aldehyde

entry	aryl aldehyde	time (h)	product	yield (%)	m.p
1	4-chlorobenzaldehyde	4	**2b**	82	228 - 230
2	4-nitrobenzaldehyde	4	**2c**	86	225 - 227
3	2-nitrobenzaldehyde	6	**2d**	71	259 - 261
4	4-methoxybenzaldehyde	4	**2e**	80	242 - 244
5	2,5-dimethoxybenzaldehyde	6	**2f**	70	200 - 202
6	3,4-dimethoxybenzaldehyde	4	**2g**	92	173 - 175
7	3,5-dimethoxybenzaldehyde	4	**2h**	98	193 - 195
8	2,5-dimethylbenzaldehyde	4	**2i**	91	199 - 201
9	1-naphthaldehyde	4	**2j**	85	232 - 234
10	2-naphthaldehyde	4	**2k**	80	194 - 196



Scheme 1



Scheme 2

the presence of 30 mol% indium(III) trifluoromethanesulfonate were attempted (Table 4). In these reactions, aryl aldehydes with both electron-withdrawing and electron-donating groups on the benzene ring provided the corresponding cycloadducts in good yields. Aryl aldehydes with *para*- and *meta*-substituents on the benzene ring gave products in high yields, but those with *ortho*-substituents afforded adducts in somewhat decreased yields.

The formation of **1a** in the presence of EDDA can be explained by the mechanism presented in Scheme 1. The reaction sequence is a domino Knoevenagel condensation, Michael addition, and tautomerism. Benzaldehyde (**4**) is first protonated by EDDA to give protonated benzaldehyde **5**, which is then attacked by dimedone (**3**) to yield intermediate **6**. Dehydration of **6** in the presence of EDDA gives the other intermediate (**7**) as a Knoevenagel product, which undergoes Michael addition with compound **3**, followed by tautomerization of tetraketone **8** to yield adduct **1a**. Interestingly, in the presence of EDDA as a catalyst, further reaction to cycloadduct **2a** did not occur.

The formation of **2a** in the presence of indium(III) trifluoromethanesulfonate can be explained by the mechanism in Scheme 2. Benzaldehyde (**4**) forms an oxygen-bonded complex through indium(III) trifluoromethanesulfonate to give **5b**, which is attacked by dimedone (**3**) to afford the intermediate

6. Dehydration of **6** in the presence of $In(OTf)_3$ gives another intermediate (**7**), which undergoes further Michael reaction to yield forth tetraketone **8**. Tautomerization of **8** followed by cyclization under $In(OTf)_3$ as a catalyst provides the desired cycloadduct **2a**.

In conclusion, a new and facile method for the synthesis of arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-ones) and xanthenediones by EDDA and $In(OTf)_3$-catalyzed condensation was developed starting from dimedone and aryl aldehydes. The key strategies of these reactions were one-pot domino Knoevenagel/Michael reaction or Koevenagel/Michael/Cyclodehydration reaction.

Experimental Section

All experiments were carried out in a nitrogen atmosphere. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ or acetone-d_6 as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS and MS spectra were carried out at the Korea Basic Science Institute.

Typical procedure for the synthesis of arylmethylene *bis*-(3-hydroxy-2-cyclohexene-1-one) derivatives (1a-1k). To a mixture of dimedone (**3**) (2.0 mmol) and aryl aldehyde (1.0 mmol) in THF (10 mL) was added EDDA (54 mg, 0.3 mmol). The mixture was heated to reflux for 4 - 6 h and the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and evaporated under reduced pressure to give the residues. Purification of the residue by column chromatography on silica gel gave products.

2,2'-Arylmethylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1a).[5] Reaction of **3** (286 mg, 2.0 mmol) and benzaldehyde (106 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1a** (324 mg, 88 %) as a solid: mp 193 - 195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.89 (1H, s), 7.27-7.06 (5H, m), 5.52 (1H, s), 2.41-2.26 (8H, m), 1.21 (6H, s), 1.08 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 189.4, 138.1, 128.2, 126.7, 125.8, 115.5, 47.0, 46.4, 32.7, 31.4, 29.6, 27.4; IR (KBr) 3400, 2962, 1610, 1448, 1373, 1298, 1249, 1163, 1045, 869, 842, 777, 694 cm^{-1}.

4-Chlorophenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1b).[15] Reaction of **3** (286 mg, 2.0 mmol) and 4-chlorobenzaldehyde (141 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1b** (364 mg, 97%) as a solid: mp 140 - 142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.83 (1H, s), 7.21 (2H, d, J = 8.0 Hz), 6.99 (2H, d, J = 8.0 Hz), 5.45 (1H, s), 2.47-2.25 (8H, m), 1.19 (6H, s), 1.08 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 189.3, 136.6, 131.4, 128.2, 128.1, 115.1, 46.9, 46.3, 32.3, 31.3, 29.4, 27.3; IR (KBr) 3427, 2958, 1590, 1489, 1374, 1253, 1158, 1124, 1043, 885, 680, 585, 495 cm^{-1}.

4-Nitrophenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1c).[5] Reaction of **3** (286 mg, 2.0 mmol) and 4-nitrobenzaldehyde (151 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1c** (355 mg, 92 %) as a solid: mp 188 - 190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.76 (1H, s), 8.11 (2H, d, J = 8.4 Hz), 7.23 (2H, d, J = 8.4 Hz), 5.53 (1H, s), 2.51-2.28 (8H, m), 1.21 (6H, s), 1.09 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 189.3, 145.9, 127.5, 123.3, 114.8, 46.7, 32.9, 31.3, 29.2, 27.4; IR (KBr) 3422, 2956, 1591, 1513, 1374, 1248, 1157, 1115, 1042, 850, 732, 585, 489 cm^{-1}.

2-Nitrophenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1d).[5] Reaction of **3** (286 mg, 2.0 mmol) and 2-nitrobenzaldehyde (151 mg, 1.0 mmol) in refluxing THF (10 mL) for 6 h afforded **1d** (285 mg, 74 %) as a solid: mp 249 - 251 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.56 (1H, s), 7.49 (1H, d, J = 8.1 Hz), 7.41 (1H, t, J = 7.8 Hz), 7.28 (1H, t, J = 8.1 Hz), 7.19 (1H, d, J = 8.1 Hz), 5.98 (1H, s), 2.39-2.28 (8H, m), 1.07 (6H, s), 0.97 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 149.4, 132.1, 131.2, 129.3, 126.9, 124.0, 114.3, 46.4, 31.6, 29.7, 28.1; IR (KBr) 3261, 2955, 1719, 1616, 1524, 1449, 1388, 1291, 1234, 1071, 985, 839, 747, 696, 570 cm^{-1}.

4-Methoxyphenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1e).[5] Reaction of **3** (286 mg, 2.0 mmol) and 4-methoxybenzaldehyde (136 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1e** (375 mg, 94 %) as a solid: mp 146 - 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (2H, d, J = 8.4 Hz), 6.78 (2H, d, J = 8.4 Hz), 5.46 (1H, s), 3.72 (3H, s), 2.46-2.23 (8H, m), 1.19 (6H, s), 1.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 189.0, 161.8, 157.3, 129.6, 129.0, 127.5, 115.5, 113.4, 54.9, 50.5, 46.8, 46.2, 40.5, 31.8, 31.1, 29.3, 27.0; IR (KBr) 3016, 2959, 1795, 1589, 1510, 1452, 1365, 1246, 1178, 1165, 1033, 918, 829, 661 cm^{-1}.

2,5-Dimethoxyphenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1f). Reaction of **3** (286 mg, 2.0 mmol) and 2,5-dimethoxtbenzaldehyde (166 mg, 1.0 mmol) in refluxing THF (10 mL) for 6 h afforded **1f** (300 mg, 70 %) as a solid: mp 146 - 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (1H, d, J = 1.2 Hz), 6.61 (2H, d, J = 1.2 Hz), 5.46 (1H, s), 3.64 (3H, s), 3.58 (3H, s), 2.30-2.19 (8H, m), 1.17 (6H, s), 1.01 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 153.0, 151.4, 127.9, 116.2, 115.7, 111.1, 110.7, 55.6, 55.5, 46.6, 31.2, 29.3; IR (KBr) 3385, 2957, 1720, 1606, 1496, 1464, 1383, 1350, 1290, 1215, 1141, 1068, 1024, 989, 842, 788, 706 cm^{-1}; FAB HRMS *m/z* ($M+H^-$) calcd for $C_{25}H_{33}O_6$: 429.2277. Found: 429.2281.

3,4-Dimethoxyphenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1g).[5] Reaction of **3** (286 mg, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (166 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1g** (360 mg, 84%) as a solid: mp 173 - 175 °C; ^{1}H NMR (300 MHz, DMSO) δ 6.90-6.58 (3H, m), 5.93 (1H, s), 3.79 (3H, s), 3.73 (3H, s), 2.56-2.30 (8H, m), 1.16 (12H, s); ^{13}C NMR (75 MHz, DMSO) δ 187.5, 148.3, 146.5, 132.9, 118.3, 114.8, 111.5, 110.6, 55.5, 55.2, 46.5, 31.3, 30.6, 27.8; IR (KBr) 2962, 1589, 1514, 1464, 1323, 1240, 1147, 1047, 1028, 869, 804, 761, 663 cm^{-1}.

3,5-Dimethoxyphenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1h). Reaction of **3** (286 mg, 2.0 mmol) and 3,5-dimethoxybenzaldehyde (166 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1h** (381 mg, 89%) as a solid: mp 181 - 183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (2H, s), 6.23 (1H, s), 5.44 (1H, s), 3.68 (3H, s), 3.66 (3H, s), 2.44-2.24 (8H, m), 1.20 (6H, s), 1.06 (6H, s); ^{13}C NMR (75

MHz, $CDCl_3$) δ 190.1, 189.2, 160.5, 140.6, 115.4, 105.2, 97.7, 55.0, 47.0, 46.2, 32.8, 31.1, 29.5, 27.1; IR (KBr) 2966, 1597, 1460, 1323, 1305, 1257, 1195, 1066, 1051, 1018, 866, 773, 686 cm^{-1}; FAB HRMS *m/z* ($M+H^-$) calcd for $C_{25}H_{33}O_6$: 429.2277. Found: 429.2280.

2,5-Dimethylphenyl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1i). Reaction of **3** (286 mg, 2.0 mmol) and 2,5-dimethylbenzaldehyde (134 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1i** (301 mg, 76%) as a solid: mp 154 - 156 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (1H, s), 6.97 (1H, d, *J* = 7.2 Hz), 6.92 (1H, d, *J* = 7.2 Hz), 5.50 (1H, s), 2.46-2.32 (8H, m), 2.29 (3H, s), 2.12 (3H, s), 1.09 (12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 161.9, 142.9, 134.6, 134.3, 129.9, 128.3, 126.9, 116.8, 50.7, 40.9, 32.2, 31.8, 29.1, 28.3, 27.8, 27.1; IR (KBr) 3314, 2959, 1726, 1668, 1502, 1467, 1358, 1197, 1165, 1138, 1001, 933, 912, 812, 731, 652 cm^{-1}; FAB HRMS *m/z* ($M+H^-$) calcd for $C_{25}H_{33}O_4$: 397.2379. Found: 397.2376.

Naphthalen-1-yl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1j). Reaction of **3** (286 mg, 2.0 mmol) and 1-naphthaldehyde (156 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1j** (352 mg, 84%) as a solid: mp 233 - 235 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 11.76 (1H, s), 7.76-7.64 (3H, m), 7.41-7.33 (4H, m), 6.12 (1H, s), 2.40-2.20 (8H, m), 1.03 (12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 161.9, 133.3, 131.5, 127.8, 127.1, 125.5, 125.3, 125.0, 124.6, 117.0, 116.6, 50.4, 40.6, 31.9, 31.1, 29.0, 27.0; IR (KBr) 2959, 1714, 1595, 1386, 1265, 1163, 1068, 1016, 985, 891, 779, 736 cm^{-1}; FAB HRMS *m/z* ($M+H^-$) calcd for $C_{27}H_{31}O_4$: 419.2222. Found: 419.2223.

Naphthalen-2-yl-2,2'-methylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (1k). Reaction of **3** (286 mg, 2.0 mmol) and 2-naphthaldehyde (156 mg, 1.0 mmol) in refluxing THF (10 mL) for 4 h afforded **1k** (360 mg, 86%) as a solid: mp 208 - 210 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78-7.68 (3H, m), 7.51 (1H, s), 7.44-7.37 (2H, m), 7.24-7.21 (1H, m), 5.68 (1H, s), 2.51-2.30 (8H, m), 1.29 (6H, s), 1.11 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 189.4, 135.6, 133.2, 131.8, 127.8, 127.4, 125.8, 125.3, 115.5, 47.1, 46.4, 33.0, 31.4, 29.5, 27.4; IR (KBr) 2961, 1597, 1464, 1377, 1307, 1259, 1153, 1126, 1064, 1043, 925, 817, 752, 727, 626 cm^{-1}; FAB HRMS *m/z* ($M+H^-$) calcd for $C_{27}H_{31}O_4$: 419.2222. Found: 419.2224.

Typical procedure for the synthesis of xanthenedione derivatives (2a-2k). To a mixture of dimedone (**3**) (2.0 mmol) and aryl aldehyde (1.0 mmol) in toluene (10 mL) was added indium(III) trifluoromethanesulfonate (167 mg, 0.3 mmol). The mixture was heated to reflux for 4 - 6 h and the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and evaporated under reduced pressure to give the residues. Purification of the residue by column chromatography on silica gel gave products.

9-Aryl-3,3,6,6-tetramethyltetrahydroxanthene-1,8-dione (2a):[34] Reaction of **3** (286 mg, 2.0 mmol) and benzaldehyde (106 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2a** (298 mg, 85%) as a solid: mp 201 - 203 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.00 (5H, m), 4.69 (1H, s), 2.40 (4H, s), 2.20-2.07 (4H, m), 1.04 (6H, s), 0.93 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 162.1, 143.9, 128.2, 127.8, 126.1, 115.4, 50.5, 40.6, 31.9, 31.6, 29.0, 27.1; IR (KBr) 2959, 1662, 1467, 1361, 1199, 1165, 1141, 1003, 891, 798, 742, 700, 661 cm^{-1}.

9-(4-Chloro-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2b):[34] Reaction of **3** (286 mg, 2.0 mmol) and 4-chlorobenzaldehyde (141 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2b** (312 mg, 82%) as a solid: mp 228 - 230 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.14 (4H, m), 4.69 (1H, s), 2.44 (4H, s), 2.25-2.11 (4H, m), 1.08 (6H, s), 0.97 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 162.4, 142.7, 132.0, 129.8, 128.2, 115.3, 50.7, 40.9, 32.2, 31.5, 29.2, 27.3; IR (KBr) 2955, 1660, 1467, 1362, 1197, 1163, 1008, 846, 713, 666, 565 cm^{-1}.

3,3,6,6-Tetramethyl-9-(4-nitro-phenyl)-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2c):[34] Reaction of **3** (286 mg, 2.0 mmol) and 4-nitrobenzaldehyde (151 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2c** (340 mg, 86%) as a solid: mp 225 - 227 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (2H, d, *J* = 8.4 Hz), 7.45 (2H, d, *J* = 8.4 Hz), 4.81 (1H, s), 2.47 (4H, s), 2.27-2.11 (4H, m), 1.10 (6H, s), 0.97 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 162.9, 151.4, 146.5, 129.3, 123.4, 114.5, 50.6, 40.8, 32.3, 32.2, 29.6, 29.2, 27.2; IR (KBr) 2957, 1660, 1515, 1465, 1357, 1199, 1164, 1005, 864, 734, 564 cm^{-1}.

3,3,6,6-Tetramethyl-9-(2-nitro-phenyl)-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2d):[34] Reaction of **3** (286 mg, 2.0 mmol) and 2-nitrobenzaldehyde (151 mg, 1.0 mmol) in refluxing toluene (10 mL) for 6 h afforded **2d** (281 mg, 71%) as a solid: mp 259 - 261 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* = 8.1 Hz), 7.40-7.06 (3H, m), 5.48 (1H, s), 2.43 (4H, s), 2.21-2.06 (4H, m), 1.07 (6H, s), 1.04 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 162.9, 150.8, 149.7, 131.9, 127.9, 127.3, 124.5, 115.6, 50.4, 40.7, 32.1, 31.9, 29.0, 28.8, 27.4; IR (KBr) 2956, 1640, 1531, 1463, 1377, 1235, 1196, 1024, 914, 732, 653, 575 cm^{-1}.

9-(4-Methoxy-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2e):[34] Reaction of **3** (286 mg, 2.0 mmol) and 4-methoxybenzaldehyde (136 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2e** (304 mg, 80%) as a solid: mp 242 - 244 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, d, *J* = 8.0 Hz), 6.73 (1H, d, *J* = 8.0 Hz), 4.67 (1H, s), 3.71 (3H, s), 2.43 (4H, s), 2.24-2.11 (4H, m), 1.07 (6H, s), 0.97 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 162.0, 157.9, 136.4, 126.2, 115.7, 113.4, 55.0, 50.7, 40.8, 32.1, 30.9, 29.2, 27.3; IR (KBr) 3460, 2956, 1667, 1511, 1462, 1359, 1259, 1194, 1032, 841, 729, 568 cm^{-1}.

9-(2,5-Dimethoxy-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2f): Reaction of **3** (286 mg, 2.0 mmol) and 2,5-dimethoxybenzaldehyde (166 mg, 1.0 mmol) in refluxing toluene (10 mL) for 6 h afforded **2f** (287 mg, 70%) as a solid: mp 200 - 202 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (1H, d, *J* = 2.0 Hz), 6.68-6.62 (2H, m), 4.80 (1H, s), 3.73 (6H, s), 2.47-2.30 (4H, m), 2.21-2.08 (4H, m), 1.06 (6H, s), 0.93 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 162.7, 153.2, 152.0, 131.7, 117.3, 113.7, 112.6, 111.5, 55.7, 55.5, 50.7, 40.8, 32.0, 29.3, 29.1, 26.8; IR (KBr) 3200, 2962, 1657, 1502, 1462, 1358, 1226, 1199, 1138, 1045, 814, 731, 686 cm^{-1}; HRMS *m/z* (M^-) calcd for $C_{25}H_{30}O_5$: 410.2093. Found: 410.2096.

9-(3,4-Dimethoxy-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2g):[34] Reaction of **3** (286 mg, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (166 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2g** (378 mg, 92%) as a solid: mp 173 - 175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (1H, s), 6.74-6.60 (2H, m), 4.67 (1H, s), 3.82 (3H, s), 3.76 (3H, s), 2.43 (4H, s), 2.23-2.11 (4H, m), 1.07 (6H, s), 0.97 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 162.0, 148.4, 147.4, 136.9, 120.0, 115.6, 112.3, 110.8, 55.8, 55.6, 50.7, 40.8, 32.0, 31.1, 29.6, 29.2, 27.1; IR (KBr) 2957, 1666, 1514, 1464, 1359, 1263, 1228, 1195, 1138, 1028, 916, 854, 729, 646 cm^{-1}.

9-(3,5-Dimethoxy-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2h): Reaction of **3** (286 mg, 2.0 mmol) and 3,5-dimethoxybenzaldehyde (166 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2h** (402 mg, 98%) as a solid: mp 193 - 195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (2H, m), 6.21 (1H, s), 4.67 (1H, s), 3.73 (3H, s), 3.71 (3H, s), 2.42 (4H, s), 2.19 (4H, s), 1.07 (6H, s), 1.00 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 162.2, 160.13, 146.3, 115.2, 106.5, 98.4, 54.9, 50.5, 40.6, 31.9, 31.6, 28.9, 27.2; IR (KBr) 3439, 2961, 1664, 1597, 1469, 1361, 1195, 1147, 1060, 999, 856, 694, 669 cm^{-1}; HRMS *m/z* (M^-) calcd for $C_{25}H_{30}O_5$: 410.2093. Found: 410.2091.

9-(2,5-Dimethyl-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2i): Reaction of **3** (286 mg, 2.0 mmol) and 2,5-dimethylbenzaldehyde (134 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2i** (344 mg, 91%) as a solid: mp 199 - 201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (1H, d, J = 7.8 Hz), 6.76 (1H, d, J = 7.8 Hz), 6.67 (1H, s), 4.79 (1H, s), 2.76 (3H, s), 2.46 (3H, s), 2.21-2.04 (8H, m), 1.07 (6H, s), 1.00 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 161.8, 142.83, 134.4, 134.0, 129.8, 128.2, 126.7, 116.5, 50.6, 40.7, 32.0, 29.0, 27.6, 26.9, 20.8, 19.1; IR (KBr) 3441, 2957, 1662, 1467, 1356, 1199, 1165, 1138, 1003, 914, 727, 655 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{30}O_3$: 378.2195. Found: 378.2194.

3,3,6,6-Tetramethyl-9-naphthalen-1-yl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2j): Reaction of **3** (286 mg, 2.0 mmol) and 1-naphthaldehyde (156 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2j** (340 mg, 85%) as a solid: mp 232 - 234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, d, J = 7.0 Hz), 7.74 (1H, d, J = 7.8 Hz), 7.65-7.60 (2H, m), 7.44 (1H, t, J = 7.8 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.21 (1H, d, J = 7.0 Hz), 5.53 (1H, s), 2.51 (4H, s), 2.22-2.05 (4H, m), 1.08 (6H, s), 0.94 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 161.9, 142.23, 133.4, 131.5, 127.9, 127.1, 126.0, 125.6, 125.3, 125.0, 124.7, 116.7, 50.4, 40.7, 31.9, 29.1, 27.1; IR (KBr) 3043, 2959, 1666, 1626, 1512, 1467, 1358, 1195, 1163, 1138, 1001, 912, 783, 729, 652 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{27}H_{28}O_3$: 400.2038. Found: 400.2042.

3,6-Dimethyl-9-naphthalen-2-yl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (2k): Reaction of **3** (286 mg, 2.0 mmol) and 2-naphthaldehyde (156 mg, 1.0 mmol) in refluxing toluene (10 mL) for 4 h afforded **2k** (320 mg, 80%) as a solid: mp 194 - 196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.68 (4H, m), 7.49-7.33 (3H, m), 4.90 (1H, s), 2.48 (4H, s), 2.25-2.10 (4H, m), 1.09 (6H, s), 0.97 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 162.3, 141.63, 133.3, 132.3, 127.9, 127.6, 127.4, 127.1, 126.8, 125.5, 125.2, 115.5, 50.7, 40.8, 32.1, 31.9, 29.6, 29.2, 27.2; IR (KBr) 3061, 2959, 1662, 1626, 1462, 1361, 1195, 1163, 1138, 1003, 912, 783, 729, 652 cm^{-1}; HRMS *m/z* (M^-) calcd for $C_{27}H_{28}O_3$: 400.2038. Found: 400.2036.

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