Scientia Iranica C (2014) 21(6), 2049–2058

Sharif University of Technology
**Scientia Iranica**
*Transactions C: Chemistry and Chemical Engineering*
www.scientiairanica.com

*Research Note*

# Efficient synthesis of 9-aryl-1,8-dioxo-octahydroxanthenes using melamine trisulfonic acid under thermal, microwave and ultrasound conditions

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Received 2 December 2012; received in revised form 7 April 2013; accepted 12 July 2014

**KEYWORDS**
9-aryl-1,8-dioxo-octahydroxanthene;
1,3-cyclohexanedione;
Arylaldehyde;
Melamine trisulfonic acid (MSTA);
Microwave;
Ultrasound.

**Abstract.** In this work, efficient synthesis of 9-aryl-1,8-dioxo-octahydroxanthene derivatives from 1,3-cyclohexanediones and arylaldehydes in the presence of catalytic amount of melamine trisulfonic acid (MSTA) is described. The reaction is studied under thermal (solvent-free/80°C), microwave (solvent-free/180 W/90°C) and ultrasound (solvent/34-37 kHz/350 W/60°C) conditions.



## 1. Introduction

Xanthene derivatives are essential scaffold of a large number of naturally occurring as well as synthesized biological compounds, and occupy a prominent position in medicinal chemistry [1-3]. They could act as anti-inflammatory [4], antibacterial [5] and antiviral [6] agents. Moreover, xanthenes have been used as sensitizers in photodynamic therapy [7], as inflexible carbon skeletons for the assembly of chiral bidentate phosphine ligands with potential applications in catalytic processes [8,9], and in laser technology [10].

9-aryl-1,8-dioxo-octahydroxanthenes are an important class of xanthene derivatives. The best method for preparation of this kind of xanthenes, involves acid- or base-catalyzed condensation of 1,3-cyclohexanediones with aldehydes [11-20]. Nevertheless, many of the reported methods are associated with the limitations of prolonged reaction times, poor yields, the use of expensive or toxic catalysts, non-availability of catalyst or starting materials for preparation of catalyst, and poor agreement with the green chemistry protocols. Thus, development of new methods, catalysts and conditions for the preparation of 9-aryl-1,8-dioxo-octahydroxanthenes is still in great demand.

Nowadays, the use of $SO_3H$-containing catalysts has received considerable interest in organic synthesis, because of their unique advantages such as efficiency, high reactivity, operational simplicity, environmental compatibility, non-toxicity, low cost, ease of isolation, green nature, easy availability of their starting materials, and ability to promote a wide range of reactions [21-33]. One of the attractive $SO_3H$-containing

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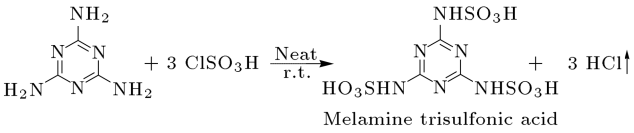


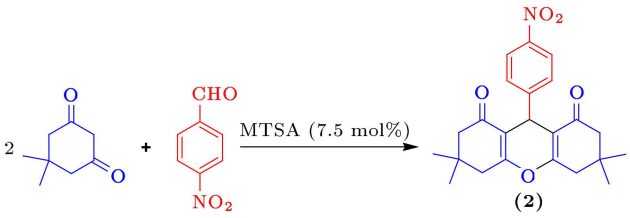

**Scheme 1.** The preparation of melamine trisulfonic acid (MTSA).

catalysts is melamine trisulfonic acid (MTSA), which has been synthesized from melamine and chlorosulfonic acid (Scheme 1), and applied to promote some organic transformations including preparation of 1,3-oxathiolanes of aldehydes [29], coumarins [30], $\beta$-acetamido ketones [31], 3,4-dihydropyrimidin-2(1H)-ones/thiones [32], and acetylated alcohols, phenols as well as amines [33].

Traditionally, organic synthesis is carried out by conductive heating with an oil bath. This is a comparatively slow and inefficient method for transferring energy into the system, since it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. In contrast, microwave irradiation produces efficient internal heating (in-core volumetric heating) by direct coupling of microwave energy with the molecules that are present in the reaction mixture. These effects should be termed "specific microwave effects" and the formation of "molecular radiators" or microscopic hotspots, and the elimination of wall effects caused by inverted temperature gradients [26,34-36]. Thus, microwave-assisted organic reactions have attracted more attention because of their utilities in, generally, providing high yields of pure products, minimizing the use of organic solvents, and allowing for a simplified work-up and shorter reaction times [26,34-36].

Ultrasonic activation, based on cavitation effects leading to mass transfer improvement, is widely used today to promote numerous organic reactions. A survey of literature shows that synthesis of many heterocyclic compounds has been promoted by ultrasound irradiation. Compared with traditional methods, this technique is more convenient and easily controlled and is more appropriate in the consideration of green chemistry concepts. Moreover, in all cases, the reactions occurred under mild conditions with good to excellent yields [37-39].

In this work, we report efficient synthesis of 9-aryl-1,8-dioxo-octahydroxanthene derivatives via the condensation of 1,3-cyclohexanediones with arylaldehydes using melamine trisulfonic acid (MSTA) as an attractive $SO_3H$-containing catalyst with organic skeleton, under conventional thermal conditions (solvent-free/80°C), microwave irradiation (solvent-free/180 W/90°C) and ultrasound irradiation (solvent/34-37 kHz/350 W/60°C).




**Scheme 2.** The synthesis of 9-aryl-1,8-dioxooctahydroxanthene **2** using MTSA.

**Table 1.** Optimization of the catalyst amount and temperature on the solvent-free reaction of dimedone with 4-nitrobenzaldehyde.

| Entry | Mol% of MTSA | Temperature (°C) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | - | 80 | 240 | 6 |
| 2 | 5 | 80 | 30 | 97 |
| 3 | 7.5 | 80 | 15 | 97 |
| 4 | 10 | 80 | 15 | 97 |
| 5 | 7.5 | 60 | 50 | 90 |
| 6 | 7.5 | 70 | 35 | 93 |
| 7 | 7.5 | 85 | 15 | 97 |

[a]: Isolated yield.

## 2. Results and discussion

At first, as a model reaction, the condensation of dimedone (5,5-dimethylcyclohexane-1,3-dione) (2 mmol) with 4-nitrobenzaldehyde (1 mmol) (Scheme 2) was examined under catalyst-free and solvent-free conditions at 80°C in which trace yield of the desired 9-aryl-1,8-dioxo-octahydroxanthene (**2**) was obtained after long reaction time (Table 1, entry 1). Increasing the reaction time did not improve the yield. Afterward, the reaction was studied in the presence of different molar ratios of MTSA at range of 60-85°C in the absence of solvent. The results are summarized in Table 1.

As Table 1 indicates, the best results were obtained when the reaction was performed using 7.5 mol% of MTSA at 80°C (Table 1, entry 3). Increasing the catalyst amount up to 10 mol% or the temperature up to 85°C did not improve the reaction results.

Considering the high importance of microwave-assisted synthesis (which was mentioned in the Introduction section), the synthesis of 9-aryl-1,8-dioxo-octahydroxanthane derivatives was studied under microwave conditions. For this purpose, firstly the reaction of dimedone (10 mmol) with 4-nitrobenzaldehyde (5 mmol) was checked in the absence of catalyst and solvent under microwave irradiation (180 W, 90°C) wherein the product was obtained in 16% yield within 45 min. Thus, microwave energy (180 W, 90°C) was not sufficient to achieve the reaction efficiently, and there is essential need to promote the reaction using

a catalyst. Afterward, the reaction was examined in the presence of different amounts of MTSA at 180 W of microwave power (90°C). The results showed that the best amount of the catalyst is 7.5 mol%.

As mentioned in the Introduction section, the use of ultrasound energy to promote chemical reactions is associated with different advantages, e.g. milder reaction conditions. This subject encouraged us to examine the efficiency of ultrasound irradiation to promote the synthesis of 9-aryl-1,8-dioxo-octahydroxanthanes. For this purpose, the condensation of dimedone (2 mmol) with 4-nitrobenzaldehyde (1 mmol) in ethyl acetate (3 mL) was tested in the presence of different amounts of MTSA at various temperatures (25-60°C). The reasonable yield (98%) and time (50 min) were obtained when the reaction was carried out using 7.5 mol% of MTSA at 60°C.

After optimization of the reaction conditions, dimedone as well as 1,3-cyclohexanedione were condensed with different types of aromatic aldehydes (possessing electron-withdrawing and electron-releasing substituents as well as halogens on their aromatic rings) using MTSA under thermal, microwave irradiation and ultrasound irradiation conditions; the respective results are illustrated in Table 2. As can be seen in Table 2, thermal and microwave conditions afforded the desired 9-aryl-1,8-dioxo-octahydroxanthanes in excellent yields and in short reaction times. Nevertheless, microwave irradiation has advantages relative to thermal conditions; microwave conditions gave shorter reaction times, and could produce the products in larger scale (see the Experimental section). Although the reaction times slightly increased in ultrasound conditions with respect to thermal and microwave cases, the products were produced in high yields under milder reaction conditions using ultrasonic irradiation (60°C). The reaction temperatures in microwave and ultrasonic cases were 90 and 80°C, respectively.

To show the priority of our method for the synthesis of 9-aryl-1,8-dioxo-octahydroxanthanes in comparison with the reported methods, we have tabulated the results of these methods for the preparation of compound 2 in Table 3. As it is clear from Table 3, our method is superior to the previously reported methods in terms of reaction times and yields. Moreover, our method has been performed in three conditions including thermal, microwave and ultrasound; thus, the method has the advantages of the three conditions. In contrast to many reported procedures, in our method, the condensation of both 1,3-cyclohexandione and dimedone with aldehydes has been carried out. The other advantages of the method are given in Conclusion section.

In another study, reusability of the catalyst was investigated upon the reaction of dimedone with 4-nitrobenzaldehyde under thermal conditions to provide compound 2. After completion of the reaction, chloroform was added to the reaction mixture, stirred and heated for 5 min, and filtered to separate the catalyst (the reaction mixture is soluble in warm chloroform, but MTSA is not soluble in this solvent). Then, the recycled catalyst was washed by chloroform, and reused for another run. We observed that the catalytic activity of MTSA was restored for two runs.

## 3. Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by Thin Layer Chromatography (TLC) using silica gel SIL G/UV 254 plates. The reactions were carried out using a laboratory microwave oven (MicroSYNTH, Milestone Company, Italy). The ultrasound apparatus was bath Eurosonic 4D (34-37 kHz/350 W). The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. The $^{1}$H NMR (300, 400 or 500 MHz) and $^{13}$C NMR (75,100 or 125 MHz) were run on a Bruker Avance DPX, FT-NMR spectrometer.

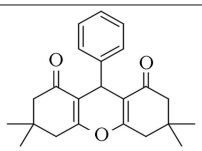
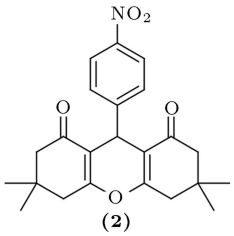
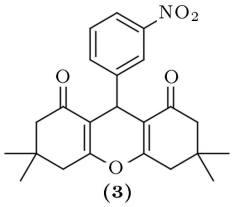
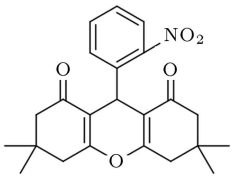
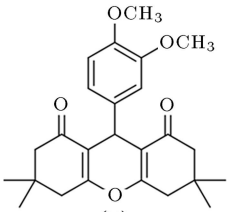
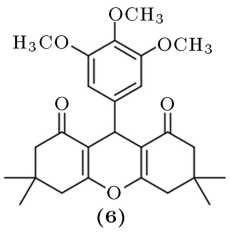
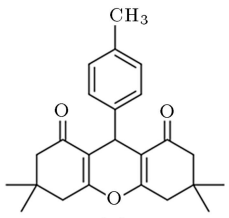
### *3.1. General procedure for the preparation of melamine trisulfonic acid (MTSA)*

A 250 mL suction flask charged with chlorosulfonic acid (5 mL, 75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas overran adsorbing solution, i.e. water. melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas is evolved from reaction vessel immediately. After completion of the addition of melamine, the mixture was shaken for 30 min; meanwhile, the residual HCl was exhausted by suction. The mixture was triturated with $n$-hexane (10 mL) and then filtered. The solid residue was washed with dichloromethane (10 mL) and dried under vacuum. Melamine trisulfonic acid (7.9 g, 87%) was obtained as a white solid, which was stored in a capped bottle; m.p. 140-142°C (lit. [30] 142-144°C).

### *3.2. General procedure for the synthesis of 9-aryl-1,8-dioxo-octahydroxanthenes in thermal conditions*

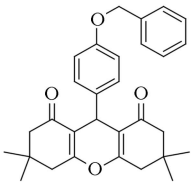
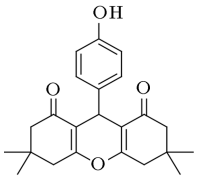
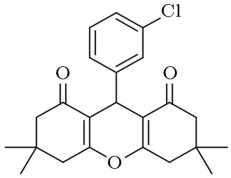
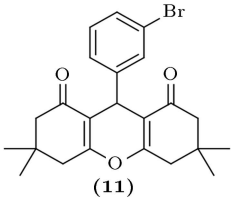
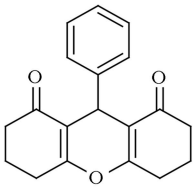
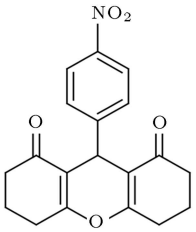
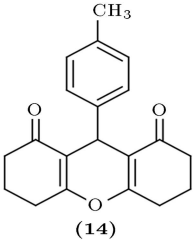
To a mixture of 1,3-cyclohexanedione (2 mmol) and arylaldehyde (1 mmol) in a test tube, MTSA (0.027 g, 7.5 mol%) was added. The resulting mixture was firstly stirred magnetically at 80°C for about 8 min (during this time, the mixture was solidified). Then, the solid mixture was stirred with a small rod at this temperature. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled

**Table 2.** The MTSA-catalyzed preparation of 9-aryl-1,8-dioxo-octahydroxanthenes via the condensation of dimedone with arylaldehydes under thermal, microwave and ultrasound conditions.

| Product | Thermal | Microwave | Ultrasound | M.p. (°C) |
|---|---|---|---|---|
| | Time[a]/Yield[b] (%) | Time[a]/Yield[b] (%) | Time[a]/Yield[b] (%) | (Lit.) |
|  **(1)** | 20/94 | 14/97 | 110/86 | 201-203 (205-206) [15] |
|  **(2)** | 15/97 | 11/96 | 50/98 | 228-230 (226-227) [16] |
|  **(3)** | 20/98 | 13/97 | 85/94 | 165-167 (170-171) [18] |
|  **(4)** | 25/96 | 13/97 | 170/83 | 260-262 (259-261) [18] |
|  **(5)** | 25/94 | 16/96 | 150/84 | 178-180 (178-180) [17] |
|  **(6)** | 30/98 | 20/98 | 110/80 | 190-192 (187-189) [15] |
|  **(7)** | 20/95 | 15/97 | 190/85 | 217-219 (216-218) [17] |

[a]: Reaction time in min; [b]: Isolated yield in %.

**Table 2.** The MTSA-catalyzed preparation of 9-aryl-1,8-dioxo-octahydroxanthenes via the condensation of dimedone with arylaldehydes under thermal, microwave and ultrasound conditions (continued).

| Product | Thermal | Microwave | Ultrasound | M.p. (°C) |
|---|---|---|---|---|
| | Time[a]/Yield[b] (%) | Time[a]/Yield[b] (%) | Time[a]/Yield[b] (%) | (Lit.) |
|  **(8)** | 20/98 | 16/95 | 100/89 | 153-155 (145-147) [15] |
|  **(9)** | 20/98 | 15/96 | 150/87 | 249-251 (246-248) [15] |
|  **(10)** | 30/92 | 13/97 | 110/80 | 186-188 (186-187) [17] |
|  **(11)** | 20/97 | 13/95 | 220/86 | 188-190 (190-192) [15] |
|  **(12)** | 25/94 | 18/95 | 120/86 | 268-270 (271-273) [20] |
|  **(13)** | 15/95 | 13/93 | 75/96 | 226-228 (224-227) [20] |
|  **(14)** | 25/94 | 17/91 | 160/82 | 258-260 (260-262) [20] |

[a]: Reaction time in min; [b]: Isolated yield in %.

**Table 3.** Comparison of the results of the preparation of compound **2** from 4-nitrobenzaldehyde (1 mmol) and dimedone (2 mmol) using our method with those obtained by the reported methods.

| Catalyst, reaction conditions | Time (min) | Yield (%) | Ref. |
|---|---|---|---|
| MTSA (7.5 mol%), Solvent-free, 80°C | 15 | 97 | Our method |
| MTSA (7.5 mol%), Solvent-free, MW (180 W, 90°C) | 11 | 96 | Our method |
| MTSA (7.5 mol%), EtOAc, Ultrasound (60°C) | 50 | 98 | Our method |
| [Hmim]TFA[a] (50 mol%), Solvent-free, 80°C | 210 | 82 | [13] |
| $NaHSO_4.SiO_2$ (0.1 g), $CH_3CN$, Reflux | 390 | 93 | [14] |
| Silica chloride (0.1 g), $CH_3CN$, Reflux | 360 | 90 | [14] |
| [Hbim]$BF_4$[b] (2 mL), MeOH, Ultrasound (30°C) | 60 | 88 | [15] |
| *p*-Toluenesulfonic acid (5 mol%), MeOH/$H_2O$, 50°C | 30 | 85 | [15] |
| $SiO_2$-R-$SO_3H$ (0.1 g), solvent-free, 80°C | 270 | 60 | [16] |
| [$Et_3N$-$SO_3H$]Cl (25 mol%), solvent-free, 80°C | 35 | 97 | [17] |
| Selectfluor$^{TM}$ (10 mol%), solvent-free, 120°C | 150 | 96 | [18] |
| Nano-MCM-41-$SO_3H$ (5 mol%), $H_2O$, ultrasound (60°C) | 60 | 95 | [20] |
| SBSSA[c] (0.3 g), EtOH, Reflux | 120 | 95 | [40] |
| Dowex-50W (0.4 g), solvent-free, 100°C | 120 | 84 | [41] |
| Amberlyst-15 (0.2 g), $CH_3CN$, Reflux | 300 | 94 | [42] |
| CAN[d] (5 mol%), 2-propanol, ultrasound (50°C) | 50 | 91 | [43] |
| [Bmim]$BF_4$[e] (1 mL)-$Mg(BF_4)_2$ (0.5 mol%), solvent-free, 80°C | 15 | 86 | [44] |
| [Cmmim]$BF_4$[f] (88 mol%), MeOH, ultrasound (30°C) | 60 | 85 | [45] |

[a]: 1-Methylimidazolium triflouroacetate; [b]: 1-Butylimidazolium tetraflouroborate;
[c]: Silica-bonded S-sulfonic acid; [d]: Ceric ammonium nitrate;
[e]: 1-Butyl-3-methylimidazolium tetraflouroborate; [f]: 1-Carboxymethyl-3-methylimidazolium tetrafluoroborate.

to room temperature, and recrystallized from EtOH (96%) to give the pure product.

### *3.3. General procedure for the preparation of 9-aryl-1,8-dioxo-octahydroxanthenes promoted by microwave irradiation*

A mixture of compounds, consisting of 1,3-cyclohexanedione (10 mmol), arylaldehyde (5 mmol) and MTSA (0.137 g, 7.5 mol%) in a microwave vessel, was irradiated in a microwave oven at 180 W of microwave power (90°C). After completion of the reaction, the reaction mixture was cooled to room temperature, and recrystallized from EtOH (96%) to give the pure product.

### *3.4. General procedure for the synthesis of 9-aryl-1,8-dioxo-octahydroxanthenes under ultrasound irradiation*

A mixture of 1,3-cyclohexanedione (2 mmol), arylaldehyde (1 mmol) and MTSA (0.027 g, 7.5 mol%) in ethyl acetate (3 mL) was irradiated and stirred in an ultrasound bath at 60°C. The reaction progress was monitored by TLC. After completion of the reaction, the solvent was evaporated, and the resulting solid was recrystallized from EtOH (96%) to give the pure product.

## 4. Conclusions

In summary, we have developed new efficient procedures for the synthesis of 9-aryl-1,8-dioxo-octahydroxanthenes under conventional thermal, microwave and ultrasound conditions. The advantages of our work include efficiency, generality, high product yield, short reaction times, simple and clean procedure, easy work-up, easy availability of the starting material for the catalyst synthesis, performing transformation under three conditions, and good agreement with the green chemistry protocols (in the case of thermal and microwave methods).

## Acknowledgment

The authors gratefully acknowledge financial support of this work by Research Council of Payame Noor University.

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## Appendix

***Selected spectral data of the products***

**3,3,6,6-Tetramethyl-9-phenyl-1,8-dioxo-octahydroxanthene (1):** $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.90 (s, 6H), 1.04 (s, 6H), 2.09 (d,

$J$=16.1 Hz, 2H), 2.27 (d, $J$=16.2 Hz, 2H), 2.53 (d, $J$=17.1 Hz, 2H), 2.58 (d, $J$=17.7 Hz, 2H), 4.53 (s, 1H), 7.10 (t, $J$=7.0 Hz, 1H), 7.18 (d, $J$=7.0 Hz, 2H), 7.21 (t, $J$=7.20 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 27.3, 29.3, 31.8, 32.2, 40.9, 50.7, 115.6, 126.4, 128.0, 128.4, 144.1, 162.3, 196.4.

**3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-1,8-dioxo-octahydroxanthene (3):** $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.01 (s, 6H), 1.13 (s, 6H), 2.18 (d, $J$=16.3 Hz, 2H), 2.27 (d, $J$=16.3 Hz, 2H), 2.53 (t, $J$=18.5 Hz, 4H), 4.85 (s, 1H), 7.41 (t, $J$=7.9 Hz, 1H), 7.81 (d, $J$=7.5 Hz, 1H), 7.99 (d, $J$=8.2 Hz, 1H), 8.06 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 27.7, 29.6, 32.5, 32.7, 41.2, 51.0, 114, 9, 122.0, 123.1, 129.2, 136.0, 146.8, 148.7, 163.5, 196.8.

**3,3,6,6-Tetramethyl-9-(3,4,5-trimethoxyphenyl)-1,8-dioxo-octahydroxanthene (6):** $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.96 (s, 6H), 1.05 (s, 6H), 2.14 (d, $J$=16.2 Hz, 2H), 2.29 (d, $J$=16.2 Hz, 2H), 2.50-2.54 (Distorted AB system, 4H), 3.32 (s, 3H), 3.60 (s, 3H), 3.69 (s, 3H), 4.50 (s, 1H), 6.42 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 27.2, 29.4, 31.8, 32.2, 40.9, 50.7, 56.1, 60.7, 105.6, 115.5, 136.5, 139.7, 152.8, 162.4, 196.5.

**3,3,6,6-Tetramethyl-9-(4-benzyloxyphenyl)-1,8-dioxo-octahydroxanthene (8):** $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.01 (s, 6H), 1.09 (s, 6H), 2.13-2.27 (m, 4H), 2.45 (s, 4H), 4.69 (s, 1H), 4.82 (s, 2H), 6.80 (d, $J$=8.7 Hz, 2H), 7.22 (d, $J$=8.7 Hz, 2H), 7.29-7.43 (m, 5H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 27.2, 29.4, 31.8, 32.2, 40.9, 50.7, 69.0, 114.8, 115.6, 126.9, 127.3, 128.4, 129.3, 136.5, 139.7, 152.8, 162.4, 196.5.

**3,3,6,6-Tetramethyl-9-(4-hydroxyphenyl)-1,8-dioxo-octahydroxanthene (9):** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.97 (s, 6H), 1.07 (s, 6H), 2.09-2.25 (m, 4H), 2.44 (s, 4H), 4.64 (s, 1H), 6.51 (d, $J$=7.4 Hz, 2H), 7.04 (d, $J$=7.4 Hz, 2H), 7.17 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 27.4, 29.2, 30.9, 32.3, 40.8, 50.7, 115.3, 115.9, 129.3, 135.4, 154.8, 162.5, 197.4.

**3,3,6,6-Tetramethyl-9-(3-chlorophenyl)-1,8-dioxo-octahydroxanthene (10):** $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.02 (s, 6H), 1.12 (s, 6H), 2.18-2.27 (Distorted AB system, 4H), 2.52 (t, $J$=14.0 Hz, 4H), 4.74 (s, 1H), 7.09 (d, $J$=7.6 Hz, 1H), 7.16 (t, $J$=7.9 Hz, 2H), 7.25 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 27.8, 29.6, 32.2, 32.6, 41.2, 51.1, 115.5, 127.0, 127.4, 128.8, 129.6, 134.3, 146.6, 163.1, 196.7.

**9-(p-Tolyl)-1,8-dioxo-octahydroxanthene (14):** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.98 (m, 4H), 2.29 (s, 3H), 2.28 (m, 4H), 2.57 (m, 4H), 4.76 (s, 1H), 7.04 (d, $J$=7.3 Hz, 2H), 7.18 (d, $J$=7.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 20.7, 22.1, 29.9, 32.3, 36.7, 116.2, 128.1, 128.6, 135.4, 140.9, 163.5, 196.6.

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