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## AN EFFICIENT CONSTRUCTION OF 9-(GUAIAZULEN-1-YL)-XANTHEN-4(9H)-ONES VIA DOMINO REACTION

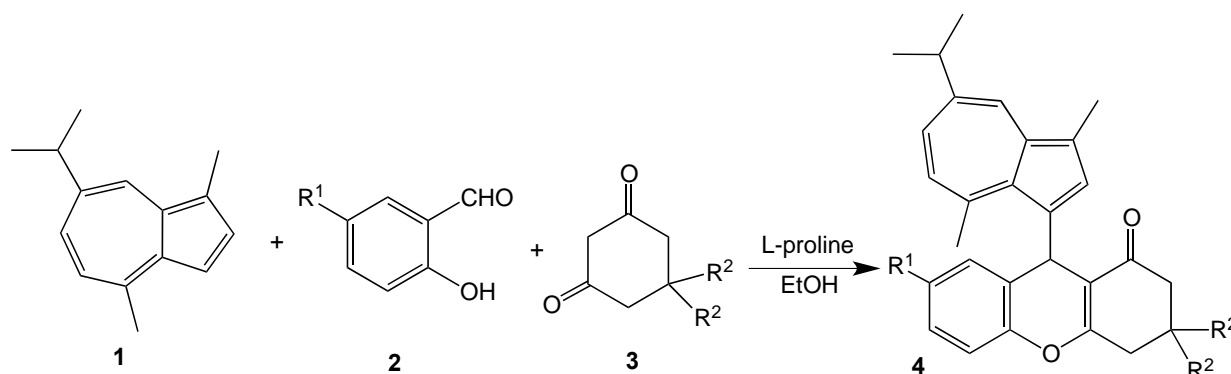
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**Abstract** – A facile, convenient, and efficient synthesis of 9-(guaiazulen-1-yl)-xanthen-4(9H)-one derivatives has been developed by the condensation of guaiazulene with salicylaldehyde, and 1,3-hexanediones in the presence of *L*-proline as the catalyst *via* the tandem Knoevenagel–Michael reaction.

Xanthenes and its derivatives are very important class of heterocyclic compounds and have been extensively used as dyes,<sup>1</sup> fluorescent materials for imagining of biomolecules and in laser technologies.<sup>2</sup> Xanthenes have wide range of biological and therapeutic properties such as antibacterial, antiviral and antiinflammatory actions as good as in photodynamic therapy.<sup>3</sup> Particularly, 1-oxohexahydroxanthene and its derivatives, as oxygen-containing heterocycles, have been reported to exert various biological and pharmacological properties, such as antiestrogenic activity,<sup>4</sup> antimicrobial activity,<sup>5</sup> insulin-sensitizing activities,<sup>6</sup> selective thrombin inhibitory activity,<sup>7</sup> and antibacterial activity.<sup>8</sup> Due to their extensive range of applications, these compounds have usually a great deal of attention in linking with their synthesis. A wide change of methods for the preparation of the xanthenes have been reported in the recent years.<sup>9</sup> On the other hand, azulenes have attracted interest in medicine as antiulcer drugs,<sup>10</sup> anticancer agents,<sup>11</sup> and as antioxidant therapeutics for neurodegenerative conditions.<sup>12</sup> A variety of heterocycle-fused azulenes have attracted the interest owing to their unusual chemical properties.<sup>13</sup> Thus, preparation and reactivities of a number of heterocycle-fused azulenes have already been revealed by many research groups.<sup>14</sup> Recently, our research group has reported the synthesis of new heteroarylazulene derivatives.<sup>15</sup> As part of a continuing effort in our laboratory toward the development of azulene chemistry, we became interested in exploring the reactivity and synthetic applications of guaiazulene<sup>16</sup> to 9-(guaiazulen-yl)-

xanthen-4(9*H*)-ones (**4**) by condensation of guaiiazulene (**1**), salicylaldehyde (**2**), and 1,3-hexanedione (**3**) in the presence *L*-proline via a domino reaction (Scheme 1).

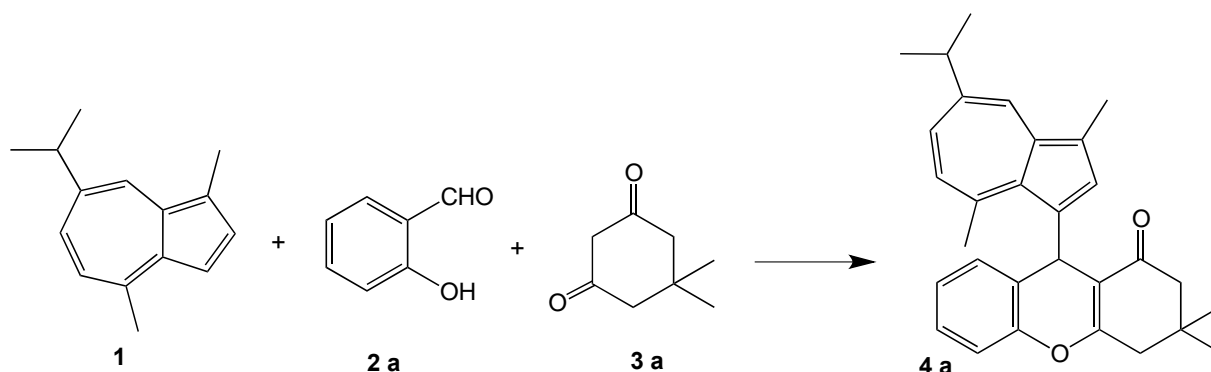


**Scheme 1.** Three-component synthesis of 9-(guaiazulen-1-yl)xanthen-4(9*H*)-ones

First, to optimize the reaction conditions, we studied the effects of catalyst, temperature, reaction time, and solvent. In a typical experiment, a mixture of guaiiazulene (**1**) and salicylaldehyde (**2a**), and dimedone (**3a**) was reacted and monitored by HPLC, and the results are summarized in Table 1.

The initial reaction of guaiiazulene (**1**), salicylaldehyde (**2a**), and dimedone (**3a**) at an ambient temperature in EtOH did not give any product until *L*-proline was added into the reaction mixture and stirred for 12 h. After the reaction was completed, the crude product was recrystallized to give pure product 3,3-dimethyl-9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthen-1-one (**4a**), whose structure was characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR spectra and elemental analysis.

The conditions on the synthesis of **4a** were optimized by screening the solvent such as ethanol, acetonitrile, acetic acid, toluene and tetrahydrofuran, changing the amount of *L*-proline. It was found, when 20 mol% *L*-proline was used, the reaction best proceeded smoothly and gave the product **4a** in 83% yield (Table 1, entry 3). Increasing the amount of *L*-proline to 30 mol%, the yield of **4a** was not further improved (Table 1, entry 8). Furthermore, we also tested the catalytic activity of different catalysts in this reaction, but the desired product **4a** was obtained in lower yields, such as indium chloride, aluminum chloride, zinc chloride, iron chloride, tin (IV) chloride, piperidine and *p*-toluenesulfonic acid.



**Table 1.** Optimization of reaction conditions on the synthesis of 3,3-dimethyl-9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthen-1-one (**4a**)<sup>a</sup>

Entry	Catalyst / (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	none	EtOH	25	12	0
2	<i>L</i> -proline (10)	EtOH	80	9	76
3	<i>L</i> -proline (20)	EtOH	80	7	83
4	<i>L</i> -proline (20)	MeCN	80	10	72
5	<i>L</i> -proline (20)	AcOH	100	7	78
6	<i>L</i> -proline (20)	THF	60	12	64
7	<i>L</i> -proline (20)	toluene	100	14	58
8	<i>L</i> -proline (30)	EtOH	80	6	82
9	InCl <sub>3</sub> (20)	EtOH	80	12	59
10	AlCl <sub>3</sub> (20)	EtOH	80	12	54
11	ZnCl <sub>2</sub> (20)	EtOH	80	12	43
12	FeCl <sub>3</sub> (20)	EtOH	80	12	32
13	SnCl <sub>4</sub> (20)	EtOH	80	12	32
14	piperidine (20)	EtOH	80	12	41
15	<i>p</i> -TsOH (20)	EtOH	80	12	34

<sup>a</sup>All reactions were carried out with guaiazulene (1.0 mmol), salicylaldehyde (1.0 mmol), and dimedone (1.0 mmol); <sup>b</sup>Reaction progress monitored by TLC; <sup>c</sup>Yield of isolated products.

With this optimized procedure in hand, a range of 9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthen-1-one were synthesized by the one-pot condensation of guaiazulene with substituted salicylaldehyde and 1,3-hexanedione. The reaction proceeded about 6–8 h in good to excellent yields (see Table 2).

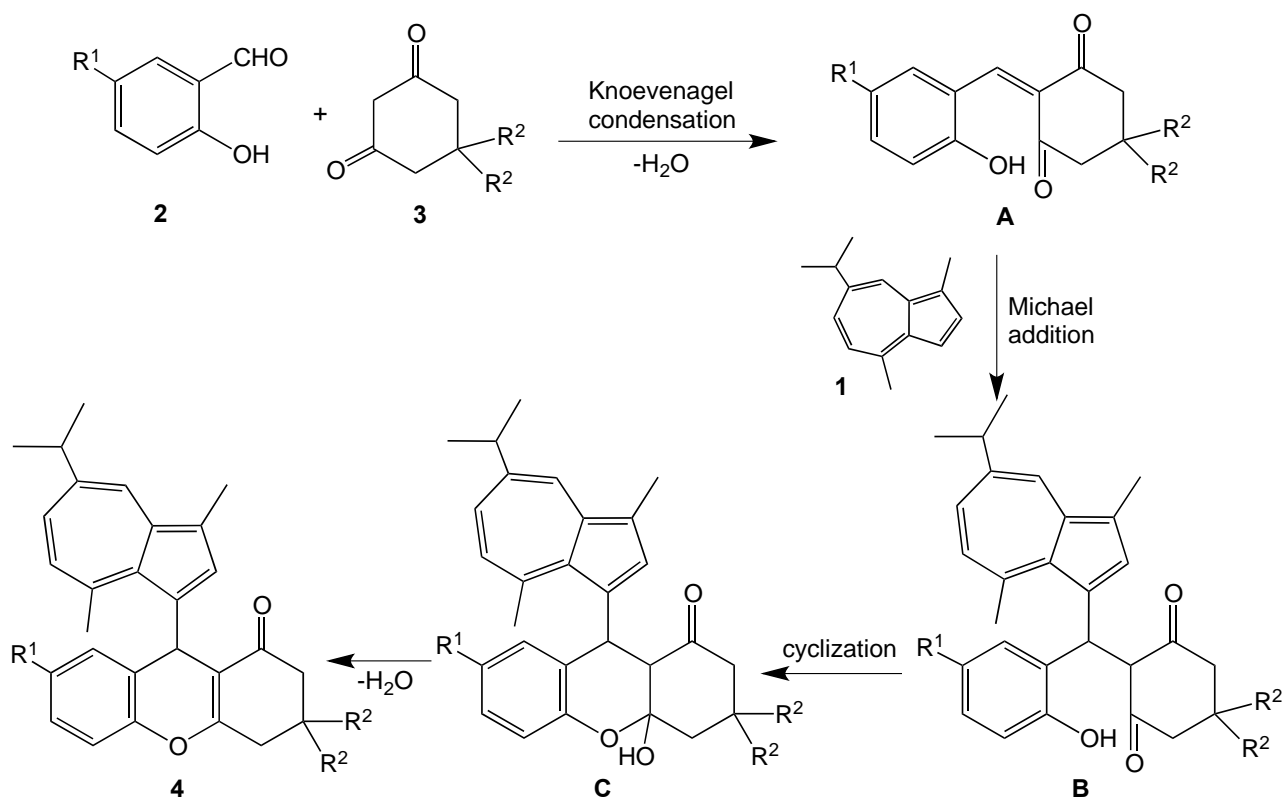
**Table 2.** Synthesis of 9-(guaiazulen-1-yl)xanthen-4(9*H*)-one derivatives **4**

Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Product <b>4</b>	Yield (%)
1	H	Me	7	<b>4a</b>	83
2	Me	Me	6	<b>4b</b>	86
3	Cl	Me	8	<b>4c</b>	80
4	Br	Me	6	<b>4d</b>	75
5	H	H	6	<b>4e</b>	85
6	Me	H	8	<b>4f</b>	88
7	Cl	H	7	<b>4g</b>	79
8	Br	H	8	<b>4h</b>	76

All reactants dissolved well in ethanol in the beginning of the reaction. As the reaction progressed, some insoluble species were gradually precipitated out, and at the end of the reaction, a large amount of solid accumulated in the bottom of the vessel. As a result of this behavior, all the products (**4a-4h**) could be obtained by filtration. Various substituted salicylaldehydes with the both electron donating and withdrawing groups have been used. The electron donating group on salicylaldehydes resulted in excellent yields. However, good yields are obtained for salicylaldehyde with electron withdrawing groups (Table 2). Therefore, the method in Scheme 1 not only expands the synthetic capacity of the three component reaction, but also opens an effective way for accessing some valuable compounds.

To the best of our knowledge, this new procedure provides the first example of an efficient synthesis for the 9-(guaiazulen-yl)xanthen-4(9*H*)-one derivatives. The structures of all the synthesized compounds were established by IR, NMR spectroscopy and elemental analysis.

The proposed mechanism of the process is summarized in Scheme 2. The first step is believed to be the condensation reaction between salicylaldehyde **2** with 1,3-hexanedione **3** to give a Knoevenagel product **A**, which can act as a suitable Michael acceptor.<sup>9,17</sup> Then guaiazulene **1**, as a nucleophile, reacts at the exocyclic benzylidene double bond of the Knoevenagel product **A** to form the intermediate **B**, which further undergoes intramolecular ring-closure reaction followed by dehydration to give the desired title compounds **4**.



**Scheme 2.** Proposed mechanism for the synthesis of compounds **4**

In summary, we have developed an efficient methodology for the synthesis of 9-(guaiazulen-1-yl)-xanthen-4(9*H*)-one derivatives by one-pot three-component condensation of guaiazulene with salicylaldehydes and 1,3-hexanediones in the presence of *L*-proline as the catalyst *via* the integration of Knoevenagel condensation, Michael addition, and intramolecular cyclization reactions.

## EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for <sup>1</sup>H and 100 MHz for <sup>13</sup>C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H, and N analyses were performed by a HP-MOD 1106 microanalyzer.

**General procedure for the synthesis of 9-(guaiazulen-1-yl)xanthen-4(9*H*)-ones.** A mixture of guaiazulene **1** (1.0 mmol), salicylaldehyde **2** (1.0 mmol), 1,3-hexanedione **3** (1.0 mmol), and *L*-proline (0.2 mmol) in EtOH (25 mL) was stirred at 80 °C for the stipulated time mentioned in Table 2. After completion of the reaction (indicated by TLC), the reaction mixture was then cooled to rt, and then diluted with water (20 mL). The solid was filtered and recrystallized from isopropanol to afford the corresponding products. The physical and spectra data of the compounds **4** are as follows:

**3,3-Dimethyl-9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthen-1-one (4a):** Blue scaly crystals. mp 163-165 °C; IR (KBr, cm<sup>-1</sup>): ν 1638 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.12 (s, 3H), 1.18 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 6H), 2.25-2.32 (m, 2H), 2.51 (s, 3H), 2.60-2.67 (m, 2H), 3.03-3.06 (m, 1H), 3.52 (s, 3H), 6.13 (s, 1H), 6.97-7.03 (m, 2H), 7.10-7.14 (m, 3H), 7.30-7.35 (m, 2H), 8.04 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 12.5, 23.9, 26.9, 27.4, 28.5, 30.7, 31.5, 36.9, 40.9, 50.3, 114.4, 115.9, 124.1, 124.6, 126.1, 126.6, 126.9, 128.7, 129.9, 132.2, 133.2, 133.6, 137.6, 138.1, 138.9, 144.7, 147.9, 162.7, 196.8. *Anal.* Calcd for C<sub>30</sub>H<sub>32</sub>O<sub>2</sub>: C 84.87, H 7.60. Found: C 84.94, H 7.64.

**3,3-Dimethyl-9-(guaiazulen-1-yl)-7-methyl-2,3,4,9-tetrahydroxanthen-1-one (4b):** Blue scaly crystals. mp 207-209 °C; IR (KBr, cm<sup>-1</sup>): ν 1642 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.06 (s, 3H), 1.13 (s, 3H), 1.33 (d, *J* = 7.2 Hz, 6H), 2.14 (s, 3H), 2.19-2.26 (m, 2H), 2.47 (s, 3H), 2.58-2.63 (m, 2H), 2.98-3.02 (m, 1H), 3.45 (s, 3H), 6.04 (s, 1H), 6.86-6.90 (m, 2H), 6.96-6.99 (m, 2H), 7.25-7.28 (m, 2H), 7.99 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 12.4, 20.1, 23.8, 26.8, 27.7, 28.5, 30.6, 31.5, 36.9, 40.9, 50.2, 114.4, 115.5, 124.5, 126.4, 126.8, 130.0, 132.2, 132.6, 133.0, 133.5, 134.1, 135.3, 137.7, 138.0, 138.7, 144.7, 145.9, 162.8, 197.8. *Anal.* Calcd for C<sub>31</sub>H<sub>34</sub>O<sub>2</sub>: C 84.89, H 7.81. Found: C 84.96, H 7.85.

**7-Chloro-3,3-dimethyl-9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthen-1-one (4c):** Blue scaly crystals. mp 188-190 °C; IR (KBr, cm<sup>-1</sup>): ν 1646 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.07 (s, 3H), 1.13 (s, 3H), 1.34 (d, *J* = 7.2 Hz, 6H), 2.14 (s, 3H), 2.16-2.27 (m, 2H), 2.48 (s, 3H), 2.58-2.61 (m, 2H), 3.00-3.04 (m, 1H), 3.45 (s, 3H), 6.04 (s, 1H), 6.99-7.08 (m, 4H), 7.31 (s, 1H), 7.33 (d, *J* = 10.2 Hz, 1H), 8.03 (s, 1H). <sup>13</sup>C NMR

(CDCl<sub>3</sub>):  $\delta$  13.1, 24.6, 27.6, 28.4, 29.2, 31.4, 32.3, 37.7, 41.5, 50.9, 114.8, 118.0, 125.3, 127.0, 127.6, 129.2, 129.5, 129.6, 130.2, 131.8, 134.0, 134.5, 138.1, 138.8, 139.0, 145.4, 147.2, 163.1, 197.3. *Anal.* Calcd for C<sub>30</sub>H<sub>31</sub>ClO<sub>2</sub>: C 78.50, H 6.81. Found: C 78.57, H 6.86.

**7-Bromo-3,3-dimethyl-9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthén-1-one (4d):** Blue scaly crystals. mp 196-198 °C; IR (KBr, cm<sup>-1</sup>):  $\nu$  1635 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.03 (s, 3H), 1.11 (s, 3H), 1.33 (d,  $J$  = 7.2 Hz, 6H), 2.14 (s, 3H), 2.12-2.24 (m, 2H), 2.45 (s, 3H), 2.56-2.58 (m, 2H), 2.97-2.99 (m, 1H), 3.42 (s, 3H), 6.01 (s, 1H), 7.16-7.17 (m, 4H), 7.18 (s, 1H), 7.30 (d,  $J$  = 10.2 Hz, 1H), 7.99 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  13.1, 24.6, 27.5, 28.4, 29.1, 31.3, 32.2, 37.6, 41.5, 50.8, 114.9, 117.1, 118.4, 125.3, 127.1, 127.5, 129.6, 129.9, 131.7, 133.1, 134.0, 134.4, 138.1, 138.7, 139.9, 145.3, 147.7, 163.0, 197.3. *Anal.* Calcd for C<sub>30</sub>H<sub>31</sub>BrO<sub>2</sub>: C 71.57, H 6.21. Found: C 71.64, H 6.25.

**9-(Guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthén-1-one (4e):** Blue scaly crystals. mp 183-185 °C; IR (KBr, cm<sup>-1</sup>):  $\nu$  1641 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.40 (d,  $J$  = 7.2 Hz, 6H), 2.10-2.13 (m, 2H), 2.40-2.42 (m, 2H), 2.48 (s, 3H), 2.83-2.89 (m, 2H), 3.01-3.08 (m, 1H), 3.51 (s, 3H), 6.14 (s, 1H), 6.97-7.04 (m, 2H), 7.10-7.13 (m, 3H), 7.30 (s, 1H), 7.33-7.36 (m, 1H), 8.05 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  12.4, 19.8, 23.8, 23.9, 27.2, 27.7, 30.6, 36.4, 36.9, 115.8, 124.1, 124.5, 126.1, 126.5, 126.9, 128.6, 129.8, 132.2, 133.1, 133.5, 134.1, 137.6, 138.1, 138.8, 144.7, 147.8, 164.4, 196.9. *Anal.* Calcd for C<sub>28</sub>H<sub>28</sub>O<sub>2</sub>: C 84.81, H 7.12. Found: C 84.86, H 7.14.

**9-(Guaiazulen-1-yl)-7-methyl-2,3,4,9-tetrahydroxanthén-1-one (4f):** Blue scaly crystals. mp 187-189 °C; IR (KBr, cm<sup>-1</sup>):  $\nu$  1643 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.37 (d,  $J$  = 7.2 Hz, 6H), 2.02-2.05 (m, 2H), 2.14 (s, 3H), 2.32-2.36 (m, 2H), 2.48 (s, 3H), 2.69-2.85 (m, 2H), 3.01-3.03 (m, 1H), 3.51 (s, 3H), 6.05 (s, 1H), 6.86-7.90 (m, 2H), 6.97-7.01 (m, 2H), 7.26 (s, 1H), 7.28-7.29 (m, 1H), 8.01 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  13.2, 20.5, 20.8, 24.5, 24.6, 27.9, 28.5, 37.1, 37.6, 112.7, 116.2, 116.6, 125.1, 125.2, 127.2, 127.6, 130.7, 133.3, 133.8, 134.2, 134.9, 136.1, 138.7, 139.5, 145.5, 146.7, 165.2, 197.7. *Anal.* Calcd for C<sub>29</sub>H<sub>30</sub>O<sub>2</sub>: C 84.84, H 7.37. Found: C 84.93, H 7.40.

**7-Chloro-9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthén-1-one (4g):** Blue scaly crystals. mp 250-252 °C; IR (KBr, cm<sup>-1</sup>):  $\nu$  1646 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.32 (d,  $J$  = 7.2 Hz, 6H), 2.02-2.04 (m, 2H), 2.34-2.35 (m, 2H), 2.48 (s, 3H), 2.76-2.83 (m, 2H), 2.98-3.01 (m, 1H), 3.51 (s, 3H), 6.03 (s, 1H), 7.00-7.03 (m, 4H), 7.20 (s, 1H), 7.31 (d,  $J$  = 10.2 Hz, 1H), 8.02 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  12.4, 19.7, 23.9, 27.1, 27.7, 36.3, 36.9, 115.5, 117.2, 124.6, 126.3, 126.8, 128.5, 128.7, 129.4, 131.2, 133.3, 133.7, 135.3, 137.4, 138.1, 139.2, 144.6, 146.4, 164.1, 196.7. *Anal.* Calcd for C<sub>28</sub>H<sub>27</sub>ClO<sub>2</sub>: C 78.03, H 6.31. Found: C 78.08, H 6.34.

**7-Bromo-9-(guaiazulen-1-yl)-2,3,4,9-tetrahydroxanthén-1-one (4h):** Blue scaly crystals. mp 243-245 °C; IR (KBr, cm<sup>-1</sup>):  $\nu$  1635 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.31 (d,  $J$  = 7.2 Hz, 6H), 2.02-2.03 (m, 2H), 2.32-2.35 (m, 2H), 2.48 (s, 3H), 2.75-2.83 (m, 2H), 2.99-3.03 (m, 1H), 3.51 (s, 3H), 6.03 (s, 1H),

6.95-7.01 (m, 3H), 7.14-7.18 (m, 2H), 7.28 (d,  $J = 10.4$  Hz, 1H), 8.02 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  13.1, 20.4, 24.5, 24.6, 27.8, 28.4, 37.1, 37.7, 112.7, 116.3, 117.1, 118.4, 125.3, 127.6, 129.7, 129.9, 133.1, 134.0, 134.5, 136.0, 138.1, 138.8, 139.9, 145.4, 147.7, 164.7, 197.4. *Anal.* Calcd for  $\text{C}_{28}\text{H}_{27}\text{BrO}_2$ : C 70.74, H 5.72. Found: C 70.79, H 5.74.

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