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Synthesis of 9-Substituted-1,8-Dioxooctahydroxanthenes by an Efficient Iodine-Catalyzed Cyclization

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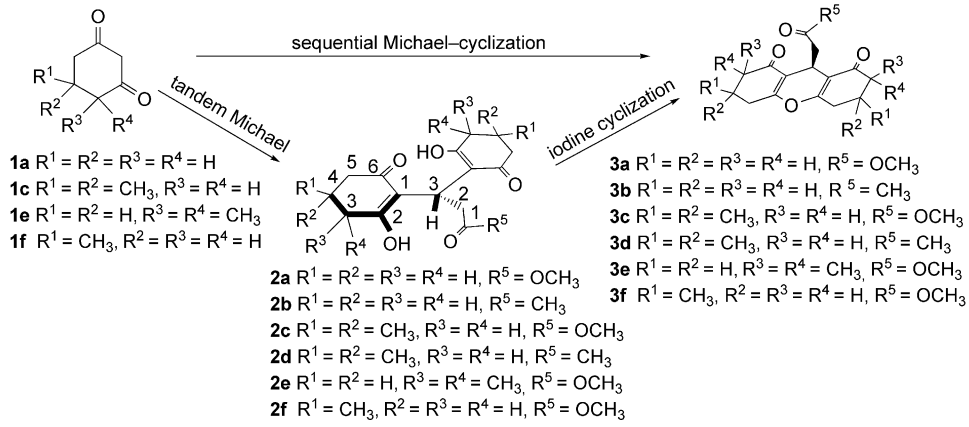
New 1,8-dioxooctahydroxanthenes with substituents in the 2-, 3-, and 9-positions were obtained by cyclization with iodine from tandem Michael/Michael adducts. The X-ray molecular structure of the methyl 2-(1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (**3a**) was solved and shows the parallel laminae packing of these molecules. Furthermore, we reported the structure of intermediate **4** isolated from this reaction.

Introduction

Compounds **2a**–**d** were recently obtained by our research group as products of tandem Michael/Michael additions between 1,3-cyclohexanediones **1a**,**c** with methyl propiolate and butynone.[1] The detailed study of this reaction and structural features of **2** allowed us to discover the performance of 1,3-cyclohexadiones in the intramolecular amino-catalyzed 1,4-additions with acetylenic acceptors. The tautomerism associated with the chirality around the C_{sp^2}–C_{sp^3} bond sets off these atropisomers as a portion present in the antimalarial natural products cordypyridones A and B (Scheme 1).[2]



Scheme 1. Synthesis of octahydroxanthenes **3a**–**f** by sequential tandem Michael–iodine-catalyzed cyclization. Reaction conditions: ≡–C(O)R^5, L-proline, DMSO, room temp., 3 d; then I_2 cat., room temp., 5 h.

A number of synthetic and natural products have the xanthene unit in their molecular structures. The biological activities of many oxoxanthene derivatives have been tested. Some of these derivatives received considerable attention in the bioorganic and medicinal areas, as they exhibited antitumoral, fungicidal, and bactericidal properties.[3–5]

Compounds related to octahydroxanthene have been synthesized from the Knoevenagel reaction between 5,5-di-

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methyl-1,3-cyclohexanedione (dimedone) and aromatic aldehydes, promoted by dodecilbenzenesulfonic acid,[6] PPA/SiO_2,[7] Dowex-50W,[8] and 1-methylimidazolium trifluoroacetate, a Brønsted acidic ionic liquid.[9] The condensation of dimedone with sugars catalyzed by scandium-cation-exchanged montmorillonite has been accomplished in aqueous solution.[10] The NMR spectra of representative examples of the various adducts have been also examined.[11]

The behavior of molecular iodine as a mild Lewis acid and its nontoxic properties are the benefits to its role as a catalyst in many organic transformations. In most cases, the reactions proceed smoothly with good yields and high selectivity.[12] Even though there are many good methods in the literature for the preparation of xanthenes derivatives, there are few reports on the employment of an inexpensive catalyst such as iodine in the sequential synthesis of substituted compounds **3**, with ester and methyl ketone chain functionalities, short reaction times, and excellent yields.

Results and Discussion

With the realization of previous work on the double Michael reaction, compounds **2a**–**d** were obtained from **1a**–**c**, methyl propiolate, and butynone through L-proline-catalyzed addition in DMSO at room temperature.[1] This method could be further developed for the preparation of new compounds **2e**,**f**.

In the presence of a catalytic amount of iodine (3 mol-%), compounds **2a**–**f** (in ethanol, room temperature) can be transformed into new octahydroxanthenes **3a**–**f** by cycloaddition of the ring fragments (Table 1, Entry 5).[13]

This method when applied to the reaction of **2** without catalyst and CH_2Cl_2 as solvent, showed no reaction progress (Table 1, Entry 2), and a long reaction time was necessary to achieve products when the condensation was carried out in a DMSO or EtOAc (Table 1, Entries 3 and 4).

The one-pot transformation of **1**→**3** in DMSO/CH_2Cl_2 with stirring at room temperature for several weeks led to recovery of the starting material (Table 1, Entry 8). However, exposure of a DMSO solution of **2a**,**c** to ultrasonic irradiation at room temperature gave **3a**,**c**, although in low yield (25–45%; Table 1, Entries 6 and 7). Increasing the amount of iodine did not improve the yield. Finally, we discovered the sequential, tandem Michael–iodine-catalyzed cyclization (Table 1, Entry 9).

All products were structurally confirmed by IR and ^1H and ^{13}C NMR spectroscopy, and in particular, adduct **3a** was also studied by X-ray crystallography. In the ^1H NMR spectra of **3a** we observed that the coupling of the triplet for the methine hydrogen at 3.95 ppm with the doublet for the methylene hydrogen of the side chain at 2.61 ppm has a value of ^3J = 4.4 Hz and a torsion angle of 58.11(21)° with a rotation restricted along its bond axis. Therefore, the predominant conformer in solution (alternate conformation) is what situates this methine hydrogen with the ester group in the *anti* position, as we corroborated by X-ray analysis.

Because there is asymmetry in the ring of **2e** as a result of the position of the *gem*-dimethyl group, the ^1H NMR spectrum showed two enol protons. The keto–enol tautomerism is also reflected in the duplicity of the signals of the ring C-3 (34.8, 34.5 ppm), C-5 (35.4, 35.3 ppm), and C-6 (204.1, 203.7 ppm) carbon atoms and the geminal methyl groups (26.2, 26.1 and 24.2, 24.1 ppm). Of all synthesized compounds, **2e** is the only example of this series in which, for the carbonyl group, two chemical shift values appear at 204.1 and 203.7 ppm and a single value appears for *C*=C–OH at 115.1 ppm due to a fast tautomeric equilibrium.

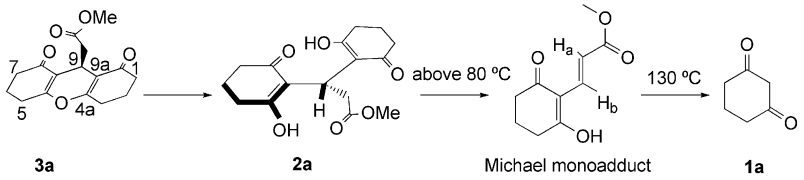
The reverse reaction was investigated by monitoring the transformation of **3a** in [D_6]DMSO by ^1H NMR spectroscopy at temperatures of 50, 80, 100, 110, and 130 °C as proof of the stability of these heterocycles. For the CH_3 group, a downfield chemical shift from 3.58 ppm (50 °C) to 3.63 ppm (100 °C) was observed. Above 80 °C, **3a** suffers spontaneous ring opening followed by the first retro-Michael reaction to generate the corresponding monoadduct, which was confirmed by the two signals for the olefinic protons at 6.73 and 7.67 ppm (d, J = 16.1 Hz, H_a–H_b *trans*; Scheme 2). The second retro reaction occurred at 130 °C leading to starting material **1a**.

Colorless crystals of **3a** were obtained by slow crystallization from xylene. Single-crystal X-ray diffraction studies revealed an orthorhombic geometry, abnormal for organic compounds with high symmetrical content (Figure 1; Table S1, Supporting Information). They were macroscopically visualized during the crystallization tests with the observation of rhombic shapes 3–4 mm in size. As observed

Table 1. Study on the preparation of octahydroxanthenes **3**.

Entry	Starting material	Reaction conditions[a]	Reaction time	Product	%Yield
1	**2**	EtOH, room temp.	5 h	no reaction	
2	**2**	CH_2Cl_2, room temp.	5 h	no reaction	
3	**2**	DMSO, room temp.	7–15 d	3	< 10
4	**2**	EtOAc	7–15 d	3	< 15
5	**2**	cat. I_2, EtOH, room temp.	5 h	3	quantitative
6	**2a**	cat. I_2, DMSO, room temp.	6 h	3a	30
7	**2c**	cat. I_2, DMSO, room temp.	6 h	3c	40
8	**1** (one-pot reaction)	cat. L-proline, alkyne, cat. I_2, DMSO/CH_2Cl_2 (1:1), room temp.	several weeks	no reaction	
9	**1** (one-pot sequential Michael–cyclization)	cat. L-proline, alkyne, DMSO, 3 d, room temp., then cat. I_2, 5 h, room temp.	77 h	3	85

[a] Entries 1–5, 8, and 9 magnetic stirring; Entries 6 and 7 ultrasonic irradiation.



Scheme 2. Study of the retrocyclization and retro-tandem Michael reactions of **3a** in [D_6]DMSO by ^{1}H NMR spectroscopy at programmed temperatures.

in Figures 1 and 2, this molecule is packed in parallel laminae with an inverted disposition of the side chain on C9 with weak hydrogen-bond interactions through C2–H2···O1^i (symmetry code, i = 1/2 + *x*, *y*, 1/2 – *z*; Tables S2 and S3, Supporting Information).

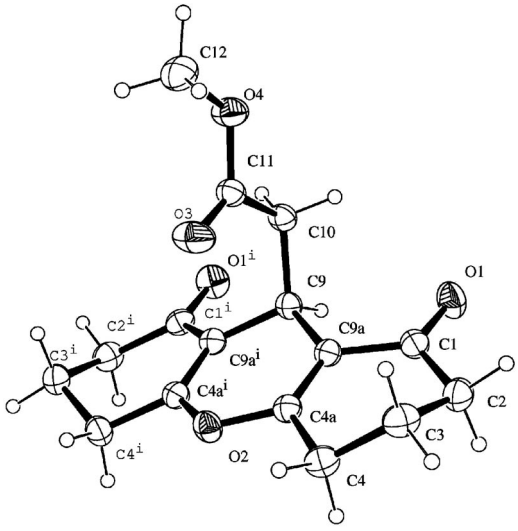


Figure 1. The structure **3a** with the labeling scheme. Displacement ellipsoids are drawn at the 30% probability level. Because a crystallographic mirror plane at the middle of the molecule exists, generated atoms are labeled with i (symmetry code: i = 1/2 + *x*, *y*, 1/2 – *z*]. The relationship between chemical and crystallographic nomenclature is as follows: C1^i = C8, C2^i = C7, C3^i = C6, C4^i = C5, C4a^i = C4b; C9a^i = C8a.

For the formation of the tricycle we propose a plausible mechanism that involves nucleophilic attack of the enol moiety of **2a** to the carbonyl group that is activated by iodine of other moiety. Resulting hemiketal **4** undergoes elimination of a water molecule to form dehydrated octahydroxanthene **3a** (Scheme 3).

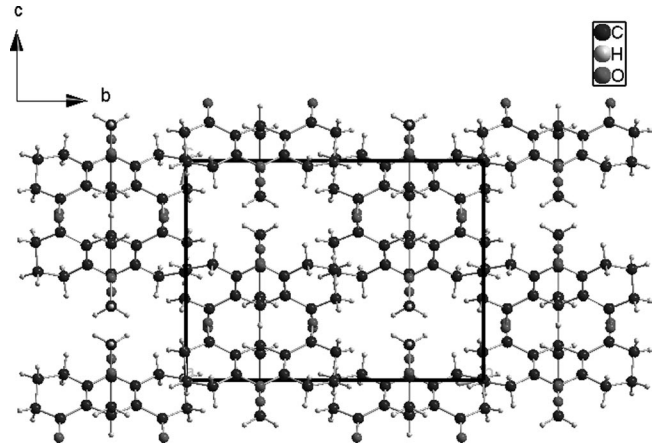
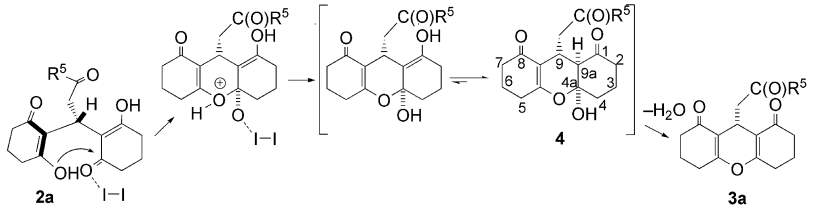


Figure 2. A view of the packing scheme for **3a** normal to the [100] direction (crystalline *a* axis direction).

Intermediate **4** was isolated and characterized by NMR spectroscopy ([D_6]acetone). Examination of its ^{13}C NMR spectrum showed that the signals at 51.8 and 197.1 ppm correspond to the C-9a and C-1 carbon atoms, whereas C-4a (O–C–OH) resonated at 101.8 ppm. All assignments were thus in accord with both the enol and hemiketal portions of **4**. Crystallization from absolute ethanol afforded **4** as crystals suitable for X-ray analysis (Figures 3 and 4).

The molecular structure clearly shows a spatial disposition of the atoms that requires attack of the hydroxy group on the activated carbonyl group from the opposite face of the methyl ester. Intermediate **4** also has a space group that is lower in symmetry than that of **3a** (Table S1, Supporting Information). The location of the H9a hydrogen and the hydroxy group on C4a of **4** is clearly indicative of an annular junction with *syn* stereochemistry (selected bond lengths are given in Table S4, Supporting Information). The packing is stabilized through many hydrogen bonds (Table S5,



Scheme 3. Cyclization pathways for the formation of **3a** through hemiketal **4**.

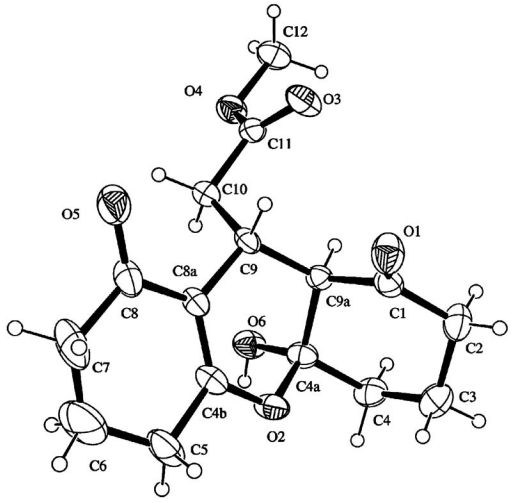


Figure 3. Structure **4** with labeling scheme. Displacement ellipsoids are drawn at the 30% probability level.

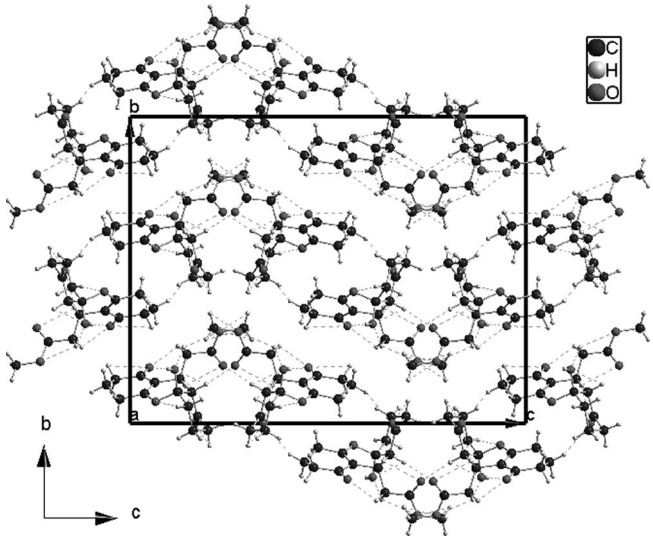


Figure 4. A view of the packing scheme for **4** normal to the [100] direction (crystalline *a* axis direction), indicating the hydrogen bonds.

Supporting Information), establishing infinite chains along the [100] direction (crystalline *a* axis direction) of the crystal.

Conclusions

In conclusion, we have developed a simple, practical, and efficient method for the synthesis of 9-substituted-1,8-dioxooctahydroxanthenes **3a**–**f** in high yields by employing a sequential, tandem Michael–iodine-catalyzed cyclization. The isolation of 4a-hydroxyxanthene intermediate **4** verified the mechanistic pathways for the generation of **3a**.

The functionalities present in **3** provide access to other derivatives of interest. The development of this reaction on solid phase and the preparation of analogs are being investigated.

Experimental Section

General: Melting points (uncorrected) were measured in open capillary tubes with an Electrothermal 9100 apparatus. NMR spectra were recorded with Bruker AC-200E and Bruker Avance 300 MHz spectrometers. FTIR spectra were obtained with a Shimadzu, Prestige 21 Model. X-ray studies were done with a AFC75-Rigaku single-crystal diffractometer over recrystallized samples.

General Procedure for the Synthesis of 3: A solution of L-proline (1.5 mol-%), the corresponding alkyne (2 mmol) in DMSO (4 mL), and dione **1** (2 mmol) was stirred at room temperature for 3 d. Without isolation of **2**, iodine (3 mol-%) was then added to the solution and it was left to stir at room temperature for 5 h. The solution was treated with sodium thiosulfate solution (2 × 10 mL) until it became colorless. The reaction mixture was taken up in CH_2Cl_2 (10 mL) and washed with NH_4Cl solution, brine, and water. The combined organic layer was dried with anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to give **3**.

Preparation of 3 by Iodine Cyclization of 2: A solution of **2** (0.2 mmol) and iodine (3 mol-%) in ethanol (0.5 mL) was stirred at room temperature. The reaction mixture was monitored by TLC and completed in 5 h. The solvent was removed in vacuo, and the residue was taken up in CH_2Cl_2 (10 mL) and washed with sodium thiosulfate solution (2 × 10 mL), brine, and water. The combined organic layer was dried with anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to furnish **3**.

Compounds **2a**–**d** are known and their characterization is listed in ref.[1]

Methyl 3,3-Bis(2-hydroxy-3,3-dimethyl-6-oxocyclohex-1-en-1-yl)-propanoate (2e): Flash chromatography (silica gel; hexane/EtOAc, 60:40) provided **2e** as a pure oil. IR (film): $\tilde{\nu}$ = 3400 (OH), 2925, 2851, 1760 (C=O ester), 1586 (C=C, 1,3-dicarbonyl enol form), 1384 and 1372 (gem dimethyl), 1247 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 13.23, 12.91 (br. s, 1 H), 4.42 (t, J = 7.7 Hz, 1 H), 3.60 (s, 3 H, OMe), 2.99 (d, J = 7.7 Hz, 2 H), 2.46 [br. s, 4 H, -CH_2C(O) keto–enol], 1.73 (m, 4 H, CH_2-CH_2-C), 1.12 and 1.10 (br. s, 12 H, gem-dimethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.1, 203.7 (C=O keto–enol), 172.5 (C=O ester), 115.1 (*C*=C-OH), 51.5 (OCH_3), 35.4, 35.3 (*C*H_2-C=O keto–enol), 34.1 (*C*H_2-C=O side chain), 34.8, 34.5 [*C*(CH_3)$_2$ keto–enol], 24.5 (*C*H), 26.2, 26.1 and 24.2, 24.1 [C(*C*H_3)$_2$ keto–enol], 24.0 (CH_2-*C*H_2-C) ppm.

Methyl 3,3-Bis(2-hydroxy-4-methyl-6-oxocyclohex-1-en-1-yl)propanoate (2f): Flash chromatography (silica gel; hexane/EtOAc, 50:50) provided **2f** as a pure oil. IR (film): $\tilde{\nu}$ = 3390 (OH), 2950, 2925, 2875, 1741 (C=O ester), 1590, 1247 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 12.90 (br. s, 1 H), 4.50 (t, J = 7.7 Hz, 1 H), 3.62 (s, 3 H, OMe), 3.04 (d, J = 7.7 Hz, 2 H), 2.80 [d, 4 H, -CH_2C(O)], 2.50 (m, 4 H, -CH_2C=), 1.22 (m, 2 H, -CH-Me), 1.05 (br. s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 207.7 (α,β-unsaturated C=O), 172.0 (C=O ester), 163.5 (C=*C*-O), 117.5 (*C*=C-O), 51.6 (OCH_3), 45.8 (*C*H_2-C=C), 41.1 (*C*H_2-C=O ketone), 34.1 (*C*H_2-C=O ester), 26.3 (*C*H), 20.7 (CH*C*H_3), 10.0 (CH_3*C*H-CH_2) ppm.

Methyl (1,8-Dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (3a): Flash chromatography (hexane/EtOAc, 70:30) provided **3a** as a white solid in quantitative yield. M.p. 155–156 °C. IR (film): $\tilde{\nu}$ = 2925, 2853, 1732 (C=O ester), 1660 (α,β-unsaturated C=O), 1622 (C=C), 1471, 1175 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.94 (t, J = 4.7 Hz, 1 H, CH), 3.57 (s, 3 H, OCH_3), 2.62 (d, J

= 4.5 Hz, 2 H, CH_2 α-ester), 2.42 [m, 8 H, -CH_2C(O), -CH_2C=], 2.05 (m, 4 H, CH_2-CH_2-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 197.1 (α,β-unsaturated C=O), 172.2 (C=O ester), 166.0 (C=*C*-O), 114.2 (*C*=C-O), 51.2 (OCH_3), 37.0 and 36.9 (*C*H_2-C=O ketone and ester), 27.1 (*C*H_2-C-O), 23.7 (CH), 20.4 (CH_2-*C*H_2-CH_2) ppm. HRMS: calcd. for $C_{16}H_{18}O_5$ 290.1154 $[M + H]^+$; found 291.1241.

9-(2-Oxopropyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3b): Flash chromatography (hexane/EtOAc, 60:40) provided **3b** as a white solid in quantitative yield. M.p. 95–96 °C. IR (film): $\tilde{\nu}$ = 2950, 1711 (C=O ketone), 1654 (α,β-unsaturated ketone), 1615 (C=C), 1379, 1175 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.87 (t, *J* = 4.7 Hz, 1 H, CH), 2.67 (d, *J* = 4.5 Hz, 2 H, CH_2 side chain), 2.48 [m, 8 H, -CH_2C(O) and -CH_2C=], 2.10 (s, 3 H, OCH_3), 2.00 (m, 4 H, CH_2-CH_2-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 208.3 (C=O ketone), 197.5 (α,β-unsaturated *C*=O, ketone), 166.1 (C=*C*-O), 114.8 (*C*=C-O), 46.9 (*C*H_2-C=O side chain), 36.9 (*C*H_2-C=O), 30.3 [C(O)*C*H_3], 27.1 (*C*H_2-C-O), 23.4 (*C*H), 20.3 (CH_2-*C*H_2-CH_2) ppm. HRMS: calcd. for $C_{16}H_{18}O_4$ [M + H]$^+$ 274.1205; found 275.1284.

Methyl 2-(3,3,6,6-Tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (3c): Flash chromatography (hexane/EtOAc, 80:20) provided **3c** as white solid in quantitative yield. M.p. 151–152 °C. IR (film): $\tilde{\nu}$ = 2955, 2872, 1732 (C=O ester), 1660 (α,β-unsaturated C=O), 1624 (C=C), 1381, 1138 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.91 (t, *J* = 4.2 Hz, 1 H, CH), 3.55 (s, 3 H, OCH_3), 2.72 (d, *J* = 4.3 Hz, 2 H, CH_2 α-ester), 2.39 [s, 4 H, -CH_2C(O)], 2.29 (s, 4 H, -CH_2C-O), 1.11 [s, 12 H, C(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 197.1 (α,β-unsaturated C=O), 172.5 (C=O ester), 164.5 (C=*C*-O), 113.1 (*C*=C-O), 51.2 (O*C*H_3), 50.8 (*C*H_2-C=O ketone), 36.3 (*C*H_2-C=O ester), 40.9 (*C*H_2-C-O), 32.0 [*C*(CH$_3$)$_2$], 29.5 and 26.9 [C(*C*H_3)$_2$], 23.8 (*C*H) ppm. HRMS: calcd. for $C_{20}H_{26}O_5$ $[M + H]^+$ 346.1780; found 347.1852.

3,3,6,6-Tetramethyl-9-(2-oxopropyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3d): Flash chromatography (hexane/EtOAc, 70:30) provided **3d** as a white solid in 99% yield. M.p. 98–99 °C. IR (film): $\tilde{\nu}$ = 2950, 1712 (C=O ketone), 1655 (α,β-unsaturated C=O), 1610 (C=C), 1379, 1175 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.83 (t, *J* = 4.4 Hz, 1 H, CH), 2.79 (d, *J* = 4.7 Hz, 2 H, CH_2 side chain), 2.38 [s, 4 H, -CH_2C(O)], 2.25 (s, 4 H, -CH_2C-O), 2.08 (s, 3 H, CH_3), 1.09 and 1.05 [s, 12 H, C(CH$_3$)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 208.4 (C=O ketone), 197.4 (α,β-unsaturated C=O), 164.7 (C=*C*-O), 113.6 (*C*=C-O), 50.9 (*C*H_2-C=O ring), 45.7 (*C*H_2-C=O side chain), 40.9 (*C*H_2-C-O), 32.0 [*C*(CH$_3$)$_2$], 30.4 [C(O)*C*H_3], 29.3 and 27.1 [C(*C*H_3)$_2$], 23.3 (*C*H) ppm. HRMS: calcd. for $C_{20}H_{26}O_4$ [M + H]$^+$ 330.1831; found 331.1897.

Methyl 2-(2,2,7,7-Tetramethyl-1,8-dioxo-3,4,5,6,8,9-hexahydro-1*H*-xanthen-9-yl)acetate (3e): Flash chromatography (hexane/EtOAc, 85:15) provided **3e** as a white solid in quantitative yield. M.p. 149–151 °C. IR (film): $\tilde{\nu}$ = 2965, 2869, 1733 (C=O ester), 1661 (α,β-unsaturated C=O), 1627 (C=C), 1377, 1166 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.92 (t, *J* = 4.2 Hz, 1 H, CH), 3.55 (s, 3 H, OCH_3), 2.57 (d, *J* = 4.3 Hz, 2 H, CH_2 α-ester), 2.50 (m, 4 H, -CH_2C-O), 1.85 (dd, 4 H, CH_2-CH_2-C), 1.14 and 1.11 [s, 12 H, C(CH$_3$)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 201.9 (α,β-unsaturated C=O), 172.4 (C=O ester), 163.8 (C=*C*-O), 112.1 (*C*=C-O), 51.1 (OCH_3), 40.5 [(CH$_3$)$_2$*C*-C=O ketone], 36.8 and 34.1 (*C*H_2-C=O ester, *C*H_2-C=C), 24.6 and 24.0 [C(*C*H_3)$_2$], 24.4 (CH), 24.1 (CH_2-*C*H_2-C) ppm. HRMS: calcd. for $C_{20}H_{26}O_5$ 346.1780 [M + H]$^+$ found; 347.1822.

Methyl 2-(3,6-Dimethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (3f): Flash chromatography (hexane/EtOAc, 70:30) provided **3f** as a white crystalline solid in 99% yield. M.p. 151–152 °C. IR (film): $\tilde{\nu}$ = 2956, 2925, 2851, 1733 (C=O ester), 1668 (α,β-unsaturated C=O), 1622 (C=C), 1383, 1190 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.92 (br. s, 1 H), 3.62 (s, 3 H, OMe), 2.64 (m, *J* = 4.3 Hz, 2 H, CH_2 α-ester), 2.51 (d, 4 H, CH_2-C=O ketone), 2.18 (m, CH_2C-O), 1.22 (m, 2 H, -C*H*-Me), 1.11 (br. s, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 197.1 (α,β-unsaturated C=O), 172.3 (C=O ester), 165.7 (C=*C*-O), 113.9 (*C*=C-O), 51.2 (OCH_3), 45.3 (*C*H_2-C-O), 36.5 (*C*H_2-C=O ester), 35.3 (*C*H_2-C=O ketone), 23.8 (CH), 20.8 (CH*C*H_3), 14.1 (CH_3*C*H-CH_2) ppm. HRMS: calcd. for $C_{20}H_{26}O_5$ $[M + H]^+$ 346.1780; found 347.1822.

Methyl 2-[(4a*R*,9*R*,9a*S*)-4a-hydroxy-1,8-dioxo-2,3,4,4a,5,6,7,8,9,9a-decahydro-1*H*-xanthen-9-yl]acetate (4): A solution of ester **2a** (60 mg, 0.2 mmol) in EtOH (or EtOH/H_2O, 9:1) (5 mL) was kept at 50 °C for a period of 15 min and then it was slowly left to cool until crystals were formed. The crystals were filtered and dried to give compound **4**. M.p. 118–119 °C. IR (film): $\tilde{\nu}$ = 3383 (OH), 2949, 1734 (C=O ester), 1715 (C=O ketone), 1589 (O=C-CH=CH), 1387, 1195 cm^{-1}. ^{1}H NMR [300 MHz, $(CD_3)_2CO$, 25 °C]: δ = 4.48 (t, *J* = 7.7 Hz, 1 H, H-9), 3.60 (m, 1 H, H-9a), 3.57 (s, 3 H, OCH_3), 3.01 (d, *J* = 7.7 Hz, 2 H, CH_2 α-ester), 2.79 [m, 6 H, CH_2C(O) and *C*H_2-C-OH], 2.39 (m, 2 H, CH_2C=), 1.85 (m, 4 H, CH_2-CH_2-CH_2) ppm. ^{13}C NMR [75 MHz, $(CD_3)_2CO$, 25 °C]: δ = 197.1 (C=O ketone), 192.1 (α,β-unsaturated C=O), 173.0 (C=O ester), 168.4 (C=*C*-O), 117.6 (*C*=C-O), 101.8 (O-C-OH), 51.8 and 51.4 (C-9a and OCH_3), 40.6 and 37.9 (*C*H_2-C=O), 35.6 and 33.6 (*C*H_2-C-O-C and *C*H_2-C-OH), 29.4 (CH_2 α-ester), 27.4 (C-9), 21.4 and 20.8 (CH_2-*C*H_2-CH_2) ppm.

CCDC-708841 (for **3a**) and -708845 (for **4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Crystallographic data and selected bond lengths and angles.

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