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The Domino Oxa-Michael Addition–Aldol Reaction: Access to Variably Substituted Tetrahydroxanthenones

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Tetrahydroxanthenones represent the core of many natural products, most of which exhibit interesting biological activities. In the course of our synthetic efforts towards the total synthesis of the secalonic acids, which contain two of these tricyclic units, we have investigated the influence of substituents on the one-step domino oxa-Michael addition–aldol reaction leading to tetrahydroxanthenones.

Introduction

In the course of our efforts towards the total synthesis of the secalonic acids **1** – secondary metabolites of various fungi (e.g. *Claviceps purpurea*, *Aspergillus aculeatus*, *Phoma terrestris* – see Figure 1) containing a xanthenone unit[1,2] – we have examined a methodology for the one-step formation of tetrahydroxanthenone moieties **2** from a salicylic aldehyde **3** and a cyclohex-2-enone **4** (Scheme 1).[3]

The xanthenone's tricyclic structural feature is found in a wide variety of other fungal metabolites such as diversonol (**5**),[4,5] the beticolins **6**,[6] simaomicins **7**,[7] phomoxanthones[8] **8**, and rugulotrosins **9**,[9] most of which show very interesting biological activities (Figure 1).[10]

So far, only few stereoselective syntheses of natural products containing tetrahydroxanthenone units have been reported.[11,12] The total synthesis of this entire substance class with many more representatives in nature would be within reach if the domino oxa-Michael addition–aldol reaction turned out to be generally applicable to the formation of highly substituted tetrahydroxanthenones. As this domino reaction[13] is based on a modular and efficient synthetic strategy, the substitution pattern in the tetrahydroxanthenone could be varied easily over the choice of the building blocks.

Therefore, our attention focused on the influence of substituents on both building blocks, the salicylic aldehyde and the cyclohexenone, on the condensation reaction. As most of the tetrahydroxanthone natural products carry an oxygen substituent on the methylene group in β-position to the endocyclic oxygen atom (C-5 in numbering of some xanthone natural products;[1,8] C-4 in the cyclohexenone precursor and in tetrahydroxanthone numbering used herein), the application of the condensation reaction to 4-hydroxycyclohexenone derivatives played an important role in our investigations.

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Results and Discussion

Variation of the Salicylic Aldehyde

The examination of the domino oxa-Michael addition–aldol reaction with various substituents on the salicylic aldehyde was carried out with commercially available building blocks[14] and has been reported previously.[3] It was found that the presence of a hydroxy or methoxy group on the salicylic aldehydes **3b**–**e** leads to only moderate alterations of the product yield. Only **3i** with the highly electron-withdrawing nitro moiety furnishes a significantly reduced yield (Table 1, entry 9). Since then we have investigated the condensation reaction of salicylic aldehydes possessing the substitution pattern required for the total synthesis of the secalonic acids (Table 1). This involved the reaction of 5-halogenated salicylic aldehydes **3g** and **3h** allowing a subsequent dimerization[15] and the reaction of 6-methoxysalicylic aldehyde (**3f**) furnishing the future hydroxy group in position 8 (or 1, respectively, see above) of the target natural product.

We found that the 5-halogenated salicylic aldehydes **3g** and **3h** do not convert as easily into the corresponding tetrahydroxanthenones as the electron-rich 5-methoxy compound **3e**, but the yield of 60% is still reasonable (Table 1, entries 7 and 8). However, the yield of the domino oxa-Michael addition–aldol reaction of 6-methoxysalicylic aldehyde (**3f**) (Table 1, entry 6) turned out to be only moderate.

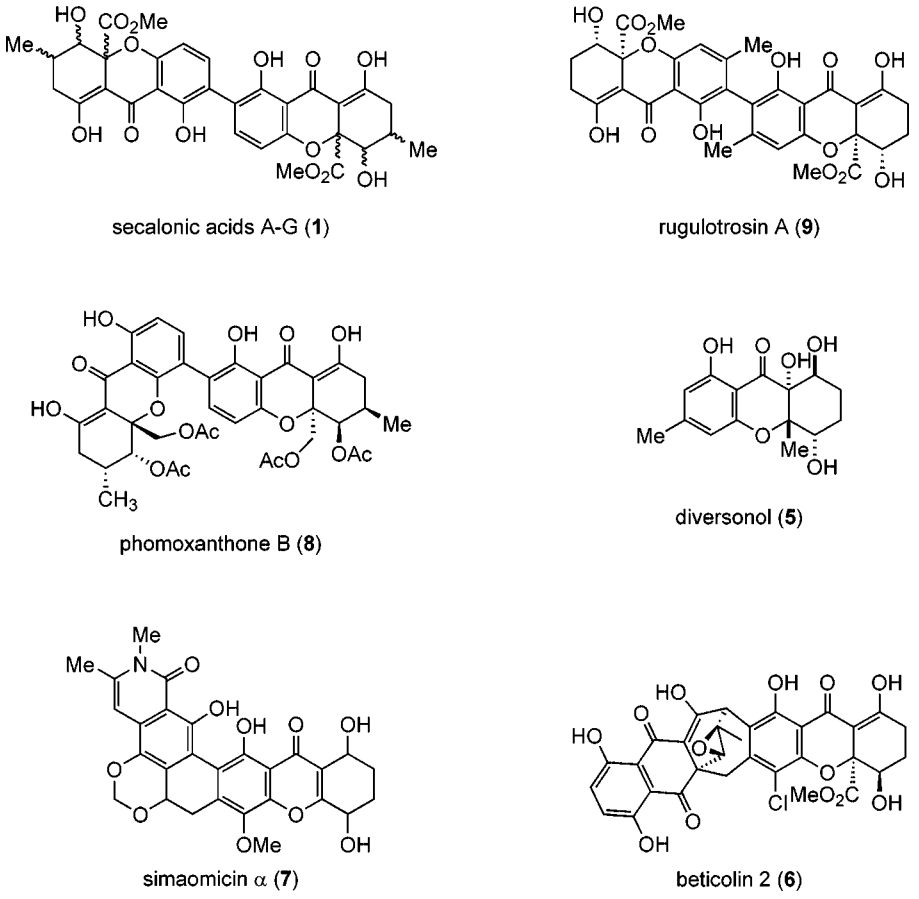
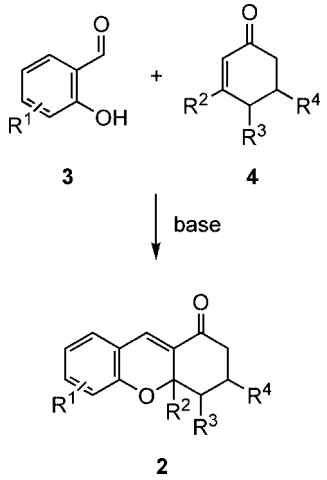


Figure 1. Natural products with tetrahydroxanthenone core.



Scheme 1. The domino oxa-Michael addition–aldol reaction.

Variation of the Cyclohexenone

Having completed the studies concerning the variation of the salicylic aldehyde, we went on to investigate the domino oxa-Michael addition–aldol reaction with substituted cyclohexenones. Aiming at the total synthesis of the secalonic acids **1**, we focused on the exploration of cyclohexenones with substituents in 3-, 4-, and 5-position.

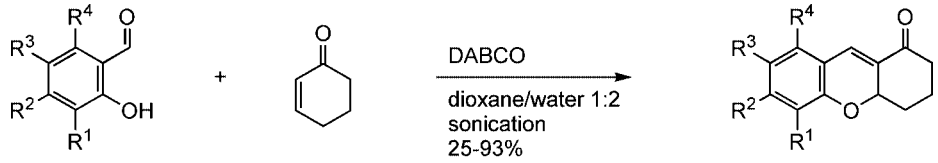
For the investigation of the domino oxa-Michael addition–aldol reaction with 4-substituted cyclohexenones we synthesized various 4-alkylcyclohexenones in moderate to good yields using the protocol described by Nicolaou et al. on a larger scale with toluene as the solvent (Table 2).[16]

4-(Hydroxymethyl)cyclohexenone (**10h**)[19] and 4-hydroxycyclohexenone (**10g**)[20] were synthesized according to literature procedures with slight modifications.[21] We could achieve significant improvement of the last step's yield in the synthesis of **10g**.[5] A procedure for the preparation of the TBDMS-protected (4*S*,5*R*)-4-hydroxy-5-methylcyclohexenone **13a** and unprotected (4*S*,5*R*)-4-hydroxy-5-methylcyclohexenone (**13b**) has also been developed based on an established procedure for the synthesis of (*S*)-4-hydroxycyclohexenone.[22]

To our dismay, there was no possibility to realize the coupling of a 3-substituted cyclohexenone not even with the highly reactive salicylic aldehyde **3e**. 3-Methylcyclohexenone (**14**) as the derivative with the smallest alkyl substituent possible did not yield any tetrahydroxanthenone product **15**, but could be reisolated unchanged (Scheme 2).

As there were no traces at all to be detected of the desired product **15**, we have postponed the introduction of the corresponding substituent to a later stage of our project[23] and went on to the 4-substituted cyclohexenones **10**.

Table 1. Condensation reaction of various salicylic aldehydes.

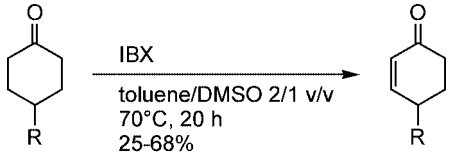


3a–j **10i** **11a–j**

Entry	Starting material	R^1	R^2	R^3	R^4	Product	Yield [%]
1	**3a**	H	H	H	H	**11a**	83[a]
2	**3b**	OH	H	H	H	**11b**	48[a]
3	**3c**	OMe	H	H	H	**11c**	63[a]
4	**3d**	H	OMe	H	H	**11d**	67[a]
5	**3e**	H	H	OMe	H	**11e**	93[a]
6	**3f**	H	H	H	OMe	**11f**	39
7	**3g**	H	H	Br	H	**11g**	60
8	**3h**	H	H	I	H	**11h**	60
9	**3i**	H	H	NO_2	H	**11i**	25[a]
10	**3j**	H	H	–CH=CH–CH=CH–		**11j**	70[a]

[a] Reported previously.[3]

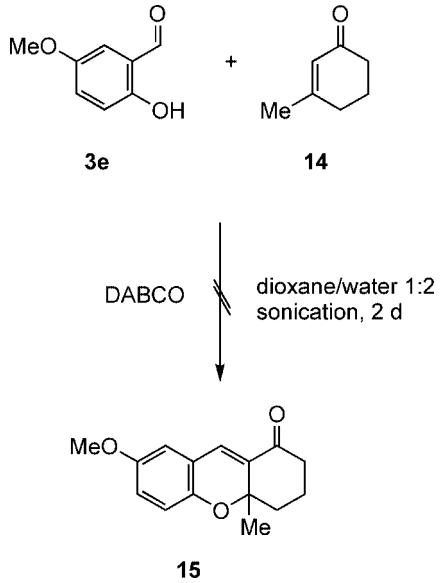
Table 2. Synthesis of 4-alkyl-substituted cyclohexenones **10a**–**e**.



12a-e **10a-e**

Entry	Starting material	R	Product	Yield [%]
1	**12a**	Me[a]	**10a**	58
2	**12b**	Et[a]	**10c**	48
3	**12c**	Pr[b]	**10d**	25
4	**12d**	*i*Pr[a]	**10e**	60
5	**12e**	*t*Bu[c]	**10f**	68

[a] Ref.[17] [b] See experimental section. [c] Ref.[18]



3e **14** **15**

Scheme 2. Failed condensation with 3-methylcyclohexenone **14**.

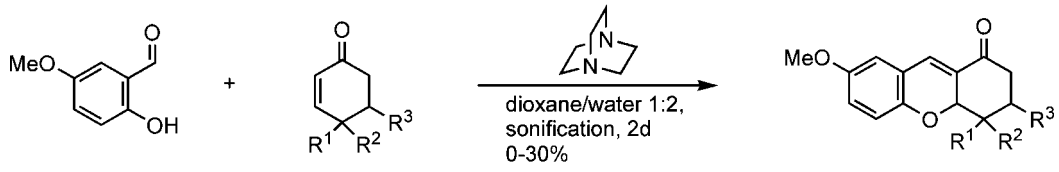
A number of functionalized cyclohexenones were treated with 5-methoxysalicylic aldehyde (**3e**) according to the established procedure employing DABCO (1,4-diazabicyclo[2.2.2]octane) as the base.[3] Under the reaction conditions described in Table 3, the sterically hindered cyclohexenones **10e** and **13a** showed no reactivity at all, even not after prolonged reaction times and could be reisolated unchanged. The 4-hydroxy-substituted cyclohexenone **10g** also did not form the corresponding 4-hydroxytetrahydroxanthenone **16g**, but degraded instead under the given reaction conditions. The condensation of 4,4-dimethylcyclohexenone (**10f**) led to an inseparable mixture of starting materials and product as the reaction proceeded extremely slowly.

However, complete consumption could be observed with 4-methylcyclohexenone (**10a**) after 48 h, showing that the reactivity of the cyclohexenones in the present reaction decreases rapidly with increasing steric demand around the double bond. Obviously, the domino oxa-Michael addition–aldol reaction is more restricted concerning the substitution pattern of the cyclohexenone moiety compared to that of the salicylic aldehyde. We assume that the oxa-Michael addition to C-3 of the cyclohexenone, a supposedly reversible reaction step, is slowed down significantly when the surroundings of C-3 are sterically demanding.

Entry 3 in Table 3 points to another important factor for the success of the reaction: the stability of the cyclohexenone building block towards basic reaction conditions is essential for a successful condensation as the latter requires a long reaction time of two days and more. 4-Hydroxycyclohexenones such as **10g** tend to eliminate water and convert into the corresponding phenol as the most stable compound.

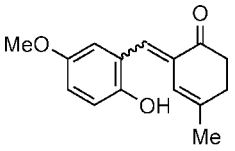
Although we found complete conversion of **10a**, only 30% of the desired tetrahydroxanthenone **16a** could be isolated (Table 3, entry 5). Additionally, a quite large amount of the side product **18** was obtained (Figure 2).

Table 3. Condensation of 4-substituted cyclohexenones using DABCO as the base.



3e **10a, e-g; 13a** **16a, e-g; 17a**

Entry	Starting material	R^1	R^2	R^3	Product	Yield [%]
1	**10e**	*t*Bu	H	H	**16e**	–
2	**10f**	Me	Me	H	**16f**	–
3	**10g**	OH	H	H	**16g**	degradation
4	**13a**	OTBDMS	H	Me	**17a**	–
5	**10a**	Me	H	H	**16a**	30



18

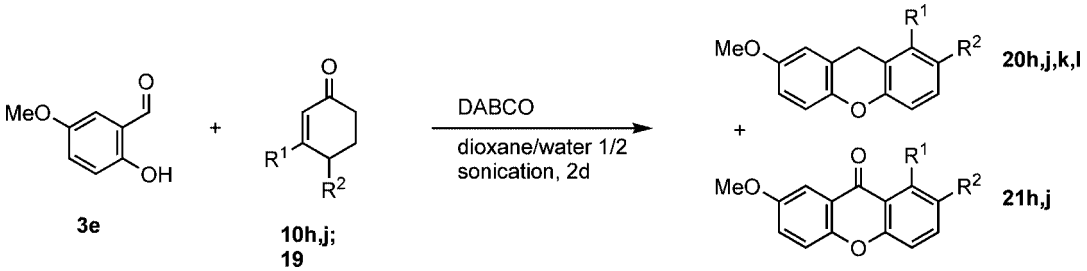
Figure 2. Side product of the reaction of **10a** using DABCO.

We assume its mechanism of formation as follows: deprotonation of the cyclohexenone **10a** in 4-position and subsequent aldol condensation of the resulting enolate leads to **18** (the double bond configuration could not be determined). For further confirmation of the proposed reaction mechanism, we subjected cyclohexenones with an electron withdrawing substituent to the standard reaction conditions for the domino oxa-Michael addition–aldol reaction (Table 4).

These experiments confirmed our mechanistic concept, as the formation of the xanthenes and xanthones (Table 4) must also proceed via an enolate of the α,β-unsaturated ketone. The position of the endocyclic double bond in the aldol condensation product **18** indicates that the intermediate anion is the thermodynamically more stable dienolate **22** as shown in Scheme 3.

These results emphasize the factor that strongly influences the course of the reaction: the basicity of the base employed. Aiming at the efficient synthesis of variably substituted tetrahydroxanthenones the formation of dienolates analogous to **22** has to be suppressed. The choice of the adequate base must therefore depend on two aspects: it should be strong enough to generate the salicylic aldehyde alcoholate needed for the oxa-Michael addition, but not suited for the deprotonation of a substituted cyclohexenone. Similar observations have been reported for the analogous condensation of salicylic aldehydes with prenal.[24] The ratio of the oxa-Michael product to the competitively formed aldol reaction product was shifted in favor of the latter with increasing basicity of the base. Additionally, the usage of a weaker base should also enhance the stability of 4-hydroxycyclohexenones such as **10g** and **13b** during the condensation reaction.

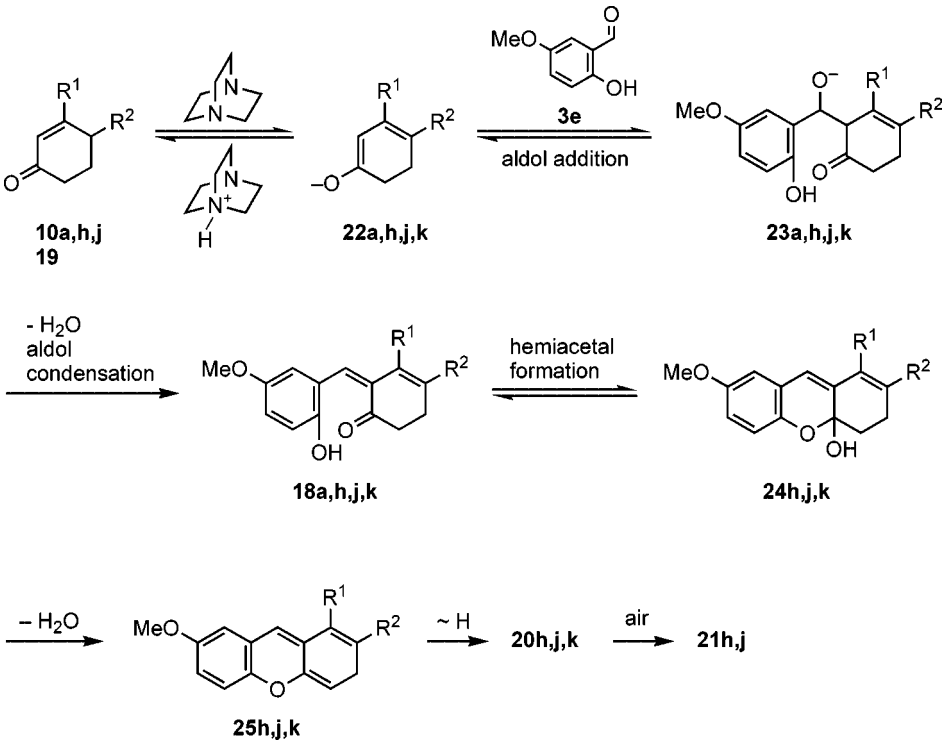
Table 4. Condensation of cyclohexenones with electron-withdrawing substituents in 4-position.



3e **10h,j; 19**

Entry	Cyclohexenone	R^1	R^2	Product[a]	Yield[a] [%] of **20/21**
1	**10h**	H	CH_2OH	**20h** + **21h**	**18**/traces
2	**10j**	H	CO_2Me	**21j**	**4**
3	**19**	Me	CO_2Et	**20k**	**18**
				20l (R^2 = H)	**5**

[a] The xanthenes **20h,j** are formed primarily, but are very sensitive towards oxidation on exposure to air when kept in solution. In contrary, compound **20k** is obviously stable, but undergoes decarboxyethylation to **20l**: The ester moiety is presumably cleaved first, followed by decarboxylation.



Scheme 3. Mechanistic rationale for the formation of xanthenes **20h**,**j**,**k** and xanthones **21h**,**j**.

In consequence, we have examined the domino oxa-Michael addition–aldol reaction on its sensitivity towards the p*K* value of the base. We have employed 4-methylcyclohexenone (**10a**) as the smallest 4-alkyl-substituted compound and 4-hydroxycyclohexenone (**10g**) as starting material tending to degradation by elimination and subsequent aromatization. 4-(Hydroxymethyl)cyclohexenone (**10h**) was chosen as starting material as it is being converted into the corresponding xanthone **21h** instead of the desired tetrahydroxanthenone **16h** when DABCO is used as the base.

We have tested tri-*n*-butylphosphane [(*n*Bu)$_3$P], 2,4,6-collidine (Col) and 4-(dimethylamino)pyridine (DMAP), which has been reported to promote the condensation reaction with unsubstituted cyclohexenone in satisfying yields,[25] imidazole (Im) and the non-nucleophilic *N*-methylimidazole (*N*MIm). The pK_a values of their corresponding acids are significantly lower than the pK_a of DABCO (Table 5), but should still enable the deprotonation of salicylic aldehydes. In comparison, the pK_a of 5-methoxysalicylic aldehyde (**3e**) in dioxane/water (1:1 v/v) was determined potentiometrically to be 9.65[26] (calculated 7.79 in water[27]), and the pK_a of unsubstituted salicylic aldehyde **3a** in water was reported to be 8.34 (potentiometric)[28] and 8.37 (spectrophotometric),[29] respectively.

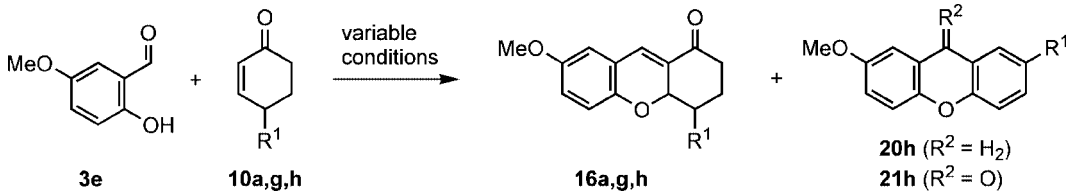
The results are shown in Table 5. We were pleased to see that our perception of the requirements for a successful domino oxa-Michael addition–aldol reaction with structurally more demanding cyclohexenones could be confirmed to full extent.

2,4,6-Collidine did not promote any condensation reaction at all (Table 5, entry 1). Apart from this, the formation of the desired tetrahydroxanthenones is indeed closely linked to the base: obviously, the deprotonation of 4-substituted cyclohexenones is diminished with decreasing basicity, as we have isolated the xanthone byproducts **20h** and **21h** only when using (*n*Bu)$_3$P or DABCO. Interestingly, employing DMAP with a similar pK_a did not lead to the xanthone product, but to small amounts of the desired tetrahydroxanthenone **16h** (1.5%, Table 5, entry 5). The condensation reactions with the two weakest bases, imidazole and *N*-methylimidazole, resulted in significantly better yields for 4-methylcyclohexenone (**10a**) as well as for 4-(hydroxymethyl)cyclohexenone (**10h**).

The deprotonation at C-4 does not pose a problem for the conversion of 4-hydroxycyclohexenone (**10g**). As already mentioned, it is the elimination of water with subsequent aromatization that causes difficulties. Regarding the findings in Table 5, it can be emphasized that utilization of weaker bases leads to formation (Table 5, entries 9 and 10) and rapid increase in the yield of the target molecule **16g** (Table 5, entries 12 and 13).

With these conclusions we turned on investigating the influence of steric hindrance at C-4 on the condensation more thoroughly. Employing the 4- and 4,5-substituted cyclohexenones **10a**–**e**,**g**,**h** and **13a**,**b** we could confirm that bulky residues indeed interfere with the domino oxa-Michael addition–aldol reaction (Table 6). With increasing size of the residue at C-4, the yield of **16** (**17**), is diminished steadily from 65% (63%) [**10a** (**13b**) Table 6, entry 1 (entry 2)] to 0% for 4-*tert*-butylcyclohexenone (**10e**, Table 6, entry 8) and the TBDMS-protected compound **13a** (Table 6, entry 9).

Table 5. Influence of the base on the condensation reaction.

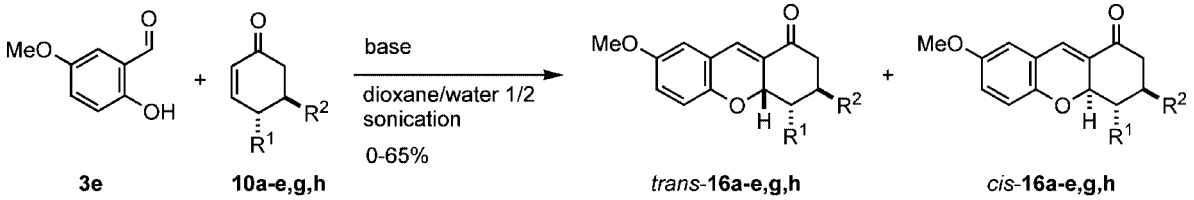


3e **10a,g,h** **16a,g,h** **20h** ($R^2 = H_2$) **21h** ($R^2 = O$)

Entry	Starting material	Base	pK_a	Solvent system	Product	Yield [%]
1	**10a**	Col	7.48[a][b]	A[c]	–	–
2	**10a**	Im	7.18[a][d]	A	**16a**	36
3	**10a**	*N*MIm	7.38[a][d]	A	**16a**	65
4	**10h**	$(n\text{Bu})_3$P	8.43[e]	B	**16h**	4
					21h	1
5	**10h**	DMAP	9.87[a][f]	C	**16h**	1.5
6	**10h**	DABCO	8.72[a][g]	A	**20h**	18
7	**10h**	Im	7.18[a][d]	A	**16h**	38
8	**10h**	*N*MIm	7.38[a][d]	A	**16h**	32
9	**10g**	$(n\text{Bu})_3$P	8.43[e]	B	**16g**	1
10	**10g**	DMAP	9.87[a][f]	C	**16g**	19
11	**10g**	DABCO	8.72[a][g]	A	–	–
12	**10g**	Im	7.18[a][d]	A	**16g**	55
13	**10g**	*N*MIm	7.38[a][d]	A	**16g**	63

[a] Determined potentiometrically in H_2O. [b] Ref.[30] [c] Solvent systems: A) dioxane/H_2O, 1:2 v/v, B) MeCN; C) THF/H_2O 4:1 v/v. [d] Ref.[31] [e] Calculated for H_2O from titration in nitromethane.[32] [f] Ref.[33] [g] Ref.[34]

Table 6. Condensation reactions under improved conditions.



3e **10a-e,g,h** **13a,b** *trans*-**16a-e,g,h** *trans*-**17a,b** *cis*-**16a-e,g,h** *cis*-**17a,b**

Entry	Starting material	R^1	R^2	Product	Yield [%][a] **16**	*cis*/*trans*[c] ratio	Yield [%][b] **16**	*cis*/*trans*[c] ratio
1	**10a**	Me	H	**16a**	36	2:1	65	2:1
2	**10g**	OH	H	**16g**	60	1:2.5	63	1.3:1
3	(4*S*,5*R*)-**13b**	OH	Me	(3*R*,4*S*,4a*R*/*S*)-**17b**	–	–	60	1.5:1
4	**10b**	Et	H	**16b**	27	1.5:1	37	2:1
5	**10h**	CH_2OH	H	**16h**	38	1:1	32	3:1
6	**10c**	Pr	H	**16c**	14	1.5:1	18	1.5:1
7	**10d**	*i*Pr	H	**16d**	traces	–	traces	–
8	**10e**	*t*Bu	H	**16e**	0	–	–	–
9	(4*S*,5*R*)-**13a**	OTBDMS	Me	(3*R*,4*S*,4a*R*/*S*)-**17a**	0	–	–	–

[a] When imidazole (Im) was used as the base. [b] When *N*-methylimidazole (*N*MIm) was used as the base. [c] *cis* and *trans* describe the relative configuration of the substituents on C-4 and C-4a.

We could observe that *N*-methylimidazole gives higher yields than imidazole, even though their basicities do not differ greatly. This might be due to the decreased nucleophilicity of *N*-methylimidazole resulting from greater steric hindrance, which should diminish the aza-Michael addition as a competitive reaction.

The diastereoselectivities of the condensation reactions in Table 6 vary from 1.5:1 to 3:1 in favor of the *cis* product with only one exception, where the *cis*/*trans* ratio is 1:2.5 (Table 6, entry 2). This suggests that the phenolate attacks the cyclohexenone from the side of the double bond that does not contain the substituent, which is also indicated by the X-ray structure of *cis*-**16a** (Figure 3).

The only moderate diastereoselectivity led us to analyze the mechanism of the condensation more thoroughly, as we had expected enhanced selectivity with increasing size of the substituent on the cyclohexenone. Yet, regarding the intermediates formed from the oxa-Michael addition, the cause for the unexpectedly low diastereoselectivity is elucidated: For the formation of the *cis*-tetrahydroxanthenone

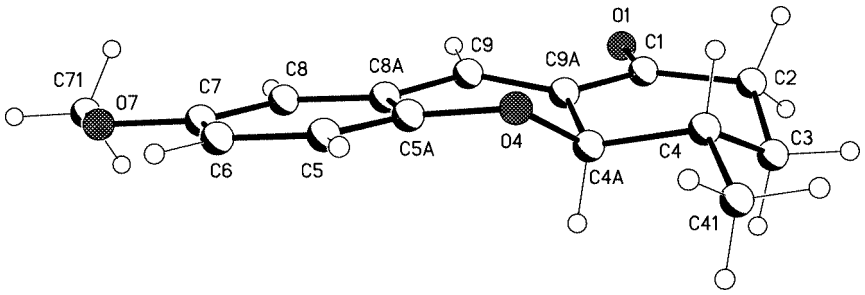
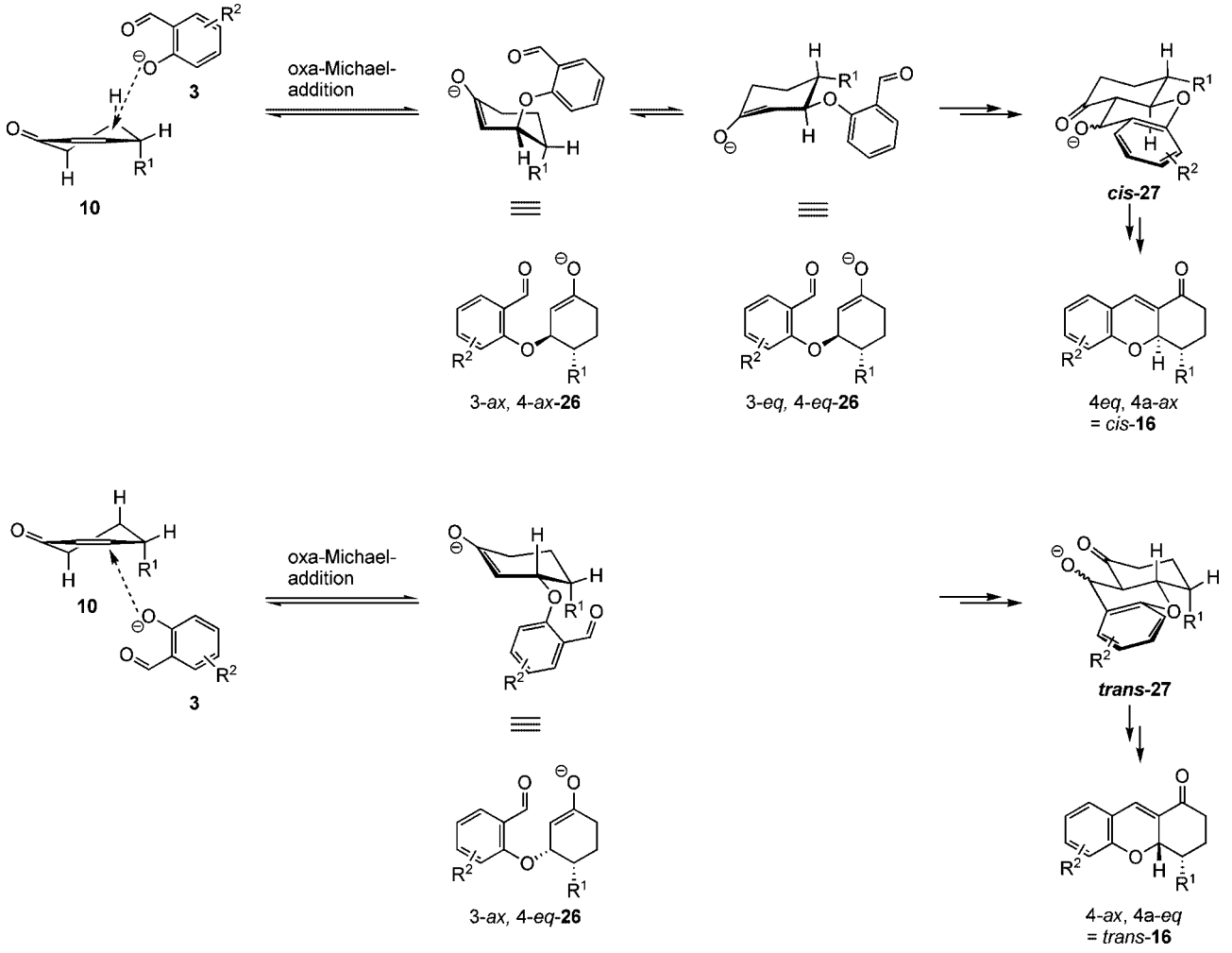


Figure 3. X-ray structure of *cis*-**16a**.

16, the attack of the nucleophilic phenolate must take place from the side of the cyclohexenone double bond that does not contain the substituent and should be kinetically favored. This results inevitably in the prior formation of a cyclohexenone enolate with both substituents in axial position (3*ax*,4*ax*-**26**, Scheme 4). For the formation of the *cis*-annelated heterocycle **16**, an isomerization to the diequatorial conformation 3*eq*,4*eq*-**26** is necessary. Due to the reversibility of the oxa-Michael reaction, the quite unstable primary intermediate 3*ax*,4*ax*-**26** will not completely isomerize to 3*eq*,4*eq*-**26** and undergo the subsequent aldol reaction leading to **16**, but also eliminate the nucleophile to reform the cyclohexenone **10**. This competitive reaction slows down the formation of *cis*-**16** significantly. On the contrary, the kinetically less favored attack of the nucleophile from the side of the cyclohexenone double bond containing the substituent leads to the 3*eq*,4ax-**26** intermediate. For the formation of *trans*-**16** no isomerization is required.



Scheme 4. Mechanistic discussion of the diastereoselectivity for oxa-Michael addition–aldol condensation reactions with 4-substituted cyclohexenones **16**.

Also, the tendency of performing the reverse reaction to cyclohexenone and salicylic aldehyde is smaller than for 3*ax*,4*ax*-**26** as it should be more stable.

In summary, the oxa-Michael addition leading to the tetrahydroxanthenone *cis*-**16** is kinetically favored and therefore faster as the addition leading to *trans*-**16**. However, the reaction pathway shows the tendency of the unstable primary intermediate 3*ax*,4*ax*-**26** to undergo reverse reaction in addition to the need for isomerization to enable formation of *cis*-**16**. On the contrary, the kinetically less favored pathway leading to *trans*-**16** should tend less to undergo the reverse reaction and does not include an isomerization step.

This results in only minor differences in the rate of formation of *cis* and *trans* product **16** and, in consequence, to the moderate diastereoselectivity observed.

However, as we plan on introducing the substituent on C-4a of the secalonic acids **1** by means of a 1,4-addition according to the procedure reported by Gabbutt et al.,[23] we need to create a double bond between C-4a and C-9a. This will eliminate the stereogenic centre on C-4a, so that the moderate diastereoselectivity will not be relevant for our planned total synthesis.

The presence of a small substituent on C-5 of the cyclohexenone does obviously not interfere with the condensation reaction. The yield of tetrahydroxanthenone employing 5-substituted **13b** is comparable to the yield using its unsubstituted analogue **10g** (Table 6, entries 3 and 2). We assume that the additional substituent is distant enough to exert no influence on the oxa-Michael addition as long as it is configured *trans* relative to the residue on C-4. Works on the reactivity of 4,5-*cis* disubstituted cyclohexenones as well as the influence of the 5-substituent's size will be carried out in our research group.

Conclusions

In summary, we have investigated the domino oxa-Michael addition–aldol reaction on its applicability for the synthesis of 4- and 3,4-disubstituted tetrahydroxanthenones. The reaction turned out to be sensitive towards steric hindrance around the cyclohexene C-3 position. A substituent other than hydrogen is not tolerated on C-3, whereas residues at C-4 are tolerated up to a certain size. The development of reaction conditions tolerating 4- and 5-substituents on the cyclohexenone moiety led to a protocol even tolerating the presence of heteroatoms in 4-position as we found that the reaction is strongly depending on the base employed. The key reaction for the synthesis of the secalonic acids, the condensation of a salicylic aldehyde with (4*S*,5*R*)-4-hydroxy-5-methylcyclohexenone (**13b**) could be performed in very satisfying 60% yield. With the optimization of the domino oxa-Michael addition–aldol reaction we have developed a modular synthetic strategy suited for the application in the total synthesis of natural products bearing a tetrahydroxanthenone core.

Experimental Section

General: Substrates were either purchased from commercial sources or donated by BASF (5-bromosalicylic aldehyde, **3g**) and were used without further purification.

Column chromatography was performed using Macherey–Nagel silica gel 60 (230–400 mesh) under flash conditions. For thin-layer chromatography, aluminum foils layered with silica gel with fluorescence indicator (silica gel 60 F_{254}) produced by Merck were employed. Melting points were determined using a Laboratory Devices Inc. MelTemp II device. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AM400 (400 MHz/100 MHz) or Bruker DRX500 (500 MHz/125 MHz) instrument using $CDCl_3$ as the solvent and residual $CHCl_3$/$CDCl_3$ as shift reference [δ($CHCl_3$) = 7.28 ppm/δ($CDCl_3$) = 77.00 ppm]; δ values are given as usual in ppm. The signals are described as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, and combinations thereof. NMR signals that are labeled with an asterisk (*) are interchangeable within their corresponding numbers. ^{13}C signals are labeled with "+" for positive signals in the dept 135 spectrum and with "–" for negative signals, respectively. IR spectra ($\tilde{\nu}$ values, cm^{-1}) were recorded using the Bruker FTIR device IFS 88. EI-MS and EI-HRMS spectra were recorded on a Finnigan MAT 90 instrument; elemental analyses were performed using a Heraeus CHN-O-Rapid device.

X-ray Crystallographic Analysis: CCDC-282602 contains the supplementary crystallographic data for compound *cis*-**16a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Domino Oxa-Michael Addition–Aldol Reaction: Salicylic aldehyde (1.00 mmol, 1.00 equiv.), cyclohexenone (2.00 mmol, 2.00 equiv.) and base (0.50 mmol, 0.50 equiv.) are added to a previously degassed mixture of dioxane and water (1.2 mL, 1:2 v/v). The resulting slurry is treated with ultrasound for 2 d and extracted with ethyl acetate (4 × 5 mL). The organic phase is dried with sodium sulfate, stripped of solvent, and the residue obtained is purified by flash column chromatography.

4-Propyl-2-cyclohexenone (10c): 308 mg (25%) of a colorless oil; R_f = 0.33 (cyclohexane/ethyl acetate, 5:1 v/v) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 6.9 Hz, 3 H, 3′-H), 1.34–1.56 (m, 4 H, 1′-H_2, 2′-H_2), 1.66 (dddd, ^2J = 13.4, ^3J = 12.5, ^3J = 9.4, ^3J = 4.5 Hz, 1 H, 5-H^A), 2.09 (ddddd, ^2J = 13.4, ^3J = 5.0, ^3J = 5.0, ^3J = 5.0, ^4J = 1.3 Hz, 1 H, 5-H^B), 2.33 (ddd, ^2J = 16.7, ^3J = 12.2, ^3J = 4.8 Hz, 1 H, 6-H^A), 2.34–2.44 (m, 1 H, 4-H), 2.48 (dd, ^2J = 16.7, ^3J = 4.8, ^3J = 4.8 Hz, 1 H, 6-H^B), 5.95 (dd, ^3J = 10.2, ^3J = 2.5 Hz, 1 H, 2-H), 6.85 (ddd, ^3J = 10.2, ^3J = 2.6, ^4J = 1.3 Hz, 1 H, 3-H). ^{13}C NMR: δ = 14.0 (+, C-3′), 20.0 (–, C-2′), 28.5 (–, C-1′), 35.7 (+, C-4), 36.7 (–, C-5)*, 36.8 (–, C-6)*,128.7 (+, C-2), 155.3 (+, C-3), 199.9 ($C_{quat.}$, C-1). FTIR (film on KBr): 3027 (vw, νC=C–H), 2957 (w, νC–H), 2930 (w, νC–H), 2872 (w, νC–H), 1681 (s, νC=O). EI-MS: *m*/*z* (%): 138 (26) [M^+], 110 (21) [$(M - CO)^+$], 96 (38) [$(C_6H_8O)^+$], 81 (100), 68 (98). EI-HRMS calcd. for $C_9H_{14}O$ 138.1045, found 138.1044.

8-Methoxy-2,3,4,4a-tetrahydroxanthen-1-one (11f): 91 mg (39%) of a yellow solid; m.p. 109 °C; R_f = 0.38 (cyclohexane/ethyl acetate, 5:1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60–1.75 (m, 1 H, cyclohexyl-CH_2), 1.92–2.15 (m, 2 H, cyclohexyl-CH_2), 2.35–2.60 (m, 3 H, cyclohexyl-CH_2), 4.85 (ddd, ^3J = 10.5, ^3J = 6.3, ^4J = 2.1 Hz, 1 H, H-4a), 6.41–6.59 (m, 2 H, H_{ar}), 7.15–7.21 (m, 1 H, H_{ar}), 7.82 (d, ^4J = 2.1 Hz, 1 H, H-9). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 (–, CH_2), 29.8 (–, CH_2), 39.1 (–, CH_2), 56.1 (+, OCH_3), 74.6 (+,

C-4a), 104.0 (+, C_{ar}), 108.9 (+, C_{ar}), 112.6 ($C_{quat.}$, C_{ar}), 127.9 (+, C_{ar}), 128.3 ($C_{quat.}$, C_{ar}), 132.9 (+, C-9), 157.1 ($C_{quat.}$, C-9a), 158.4 ($C_{quat.}$, C_{ar}), 197.6 ($C_{quat.}$, C-1). FTIR (KBr): 2945 (w, νC_{ar}-H), 1675 (m, νC=O), 1603 (m), 1481 (w), 1202 (w). EI-MS: *m*/*z* (%): 230 (37) [M^+], 174 (100) [$(M - C_3H_4O)^+$]. EI-HRMS calcd. for $C_{14}H_{14}O_3$ 230.0942, found 230.0940.

7-Bromo-2,3,4,4a-tetrahydroxanthen-1-one (11g): 167 mg (60%) of a yellow solid; m.p. 137 °C; R_f = 0.33 (cyclohexane/ethyl acetate, 5:1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63–1.76 (m, 1 H, cyclohexyl-CH_2), 1.94–2.17 (m, 2 H, cyclohexyl-CH_2), 2.33–2.63 (m, 3 H, cyclohexyl-CH_2), 4.99 (ddd, ^3J = 10.7, ^3J = 6.1, ^4J = 2.1 Hz, 1 H, H-4a), 6.76 (d, ^3J = 9.2 Hz, 1 H, H-5), 7.31–7.34 (m, 3 H, H-6,8,9). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (–, CH_2), 29.9 (–, CH_2), 39.2 (–, CH_2), 75.2 (+, C-4a), 114.4 ($C_{quat.}$, C_{ar}), 118.2 (+, C_{ar}), 124.2 ($C_{quat.}$, C_{ar}), 130.3 (+, C_{ar}), 131.7 ($C_{quat.}$, C_{ar}), 132.1 (+, C-9), 134.8 (+, C-9a), 155.1 ($C_{quat.}$, C_{ar}), 197.5 ($C_{quat.}$, C-1). FTIR (KBr): 2949 (w, νC_{ar}-H), 1677 (m, νC=O), 1614 (m), 1474 (w), 1409 (w). EI-MS: *m*/*z* (%): 280/278 (21/21) [M^+], 224/222 (100/100) [$(M - C_3H_4O)^+$]. EI-HRMS calcd. for $C_{13}H_{11}BrO_2$ 277.9942, found 277.9946. $C_{13}H_{11}BrO_2$ (279 g/mol): calcd. C 55.94, H 3.97; found: C 55.78, H 4.35.

7-Iodo-2,3,4,4a-tetrahydroxanthen-1-one (11h): 195 mg (60%) of a yellow solid; m.p. 123 °C; R_f = 0.48 (cyclohexane/ethyl acetate, 5:1 v/v). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.64–1.78 (m, 1 H, cyclohexyl-CH_2), 1.90–2.14 (m, 2 H, cyclohexyl-CH_2), 2.29–2.64 (m, 3 H, cyclohexyl-CH_2), 4.97 (ddd, ^3J = 8.2, ^3J = 5.8, ^4J = 2.4 Hz, 1 H, H-4a), 6.64 (d, ^3J = 9.5 Hz, 1 H, H_{ar}), 7.28–7.30 (m, 1 H, H_{ar}), 7.48–7.51 (m, 2 H, H_{ar}, H-9). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.2 (–, CH_2), 29.9 (–, CH_2), 39.1 (–, CH_2), 75.1 (+, C-4a), 84.2 ($C_{quat.}$, C_{ar}), 118.6 (+, C_{ar}), 124.8 ($C_{quat.}$, C_{ar}), 130.2 (+, C_{ar}), 131.4 ($C_{quat.}$, C-9a), 138.1 (+, C-9), 140.7 (+, C_{ar}), 155.8 ($C_{quat.}$, C_{ar}), 197.5 ($C_{quat.}$, C-1). FTIR (KBr): 2946 (w, νC_{ar}-H), 1679 (m, νC=O), 1606 (m), 1474 (w), 1199 (w). EI-MS: *m*/*z* (%): 326 (1) [M^+], 43 (100). EI-HRMS calcd. for $C_{13}H_{11}IO_2$ 325.9802, found 325.9805. $C_{13}H_{11}IO_2$ (326 g/mol): calcd. C 47.88, H 3.40; found: C 47.83,H 3.80.

***cis*/*trans*-7-Methoxy-4-methyl-2,3,4,4a-tetrahydroxanthen-1-one (*cis*/*trans*-16a):** 158 mg (65%) of an orange yellow oil, 2:1 mixture of diastereoisomers; R_f = 0.28 (cyclohexane/ethyl acetate, 5:1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, ^3J = 7.1 Hz, 3 H, *trans*-CH_3), δ = 1.27 (d, ^3J = 6.3 Hz, 3 H, *cis*-CH_3), 1.43–1.54 (m, 2 H, *trans*-3-H_2), 1.82–1.98 (m, 2 H, *cis*-3-H_2), 2.10–2.21 (m, 2 H, *trans*-2-H_2), 2.38–2.61 (m, 4 H, *cis*/*trans*-4-H, *cis*-2-H_2), 3.75–3.76 (m, 6 H, *cis*/*trans*-OCH_3), 4.44 (dd, ^3J = 10.1, ^4J = 2.3 Hz, 1 H, *cis*-4a-H), 5.09 (dd, ^3J = 5.6, ^4J = 2.5 Hz, 1 H, *trans*-4a-H), 6.70–6.83 (m, 6 H, *cis*/*trans*-H_{ar}), 7.39 (d, ^4J = 2.3 Hz, 1 H, *cis*-9-H), 7.41 (d, ^4J = 2.3 Hz, 1 H, *trans*-9-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (+, *trans*-CH_3), 19.0 (+, *cis*-CH_3), 24.4 (–, *trans*-CH_2), 27.1 (–, *cis*-CH_2), 30.8 (+, *trans*-C-4), 33.6 (–, *trans*-CH_2), 35.9 (+, *cis*-C-4), 39.1 (–, *cis*-CH_2), 56.0 (+, *cis*-OCH_3), 56.1 (+, *trans*-OCH_3), 77.8 (+, *trans*-C-4a), 80.4 (+, *cis*-C-4a), 113.6 (+, *cis*-C_{ar}), 113.9 (+, *trans*-C_{ar}), 117.0 (+, *trans*-C_{ar}), 117.1 (+, *cis*-C_{ar}), 118.4 (+, *trans*-C_{ar}), 118.5 (+, *cis*-C_{ar}), 122.3 ($C_{quat.}$, *trans*-C_{ar}), 122.8 ($C_{quat.}$, *cis*-C_{ar}), 129.9 ($C_{quat.}$, *trans*-C_{ar}), 130.7 ($C_{quat.}$, *cis*-C_{ar}), 132.1 (+, *cis*-C-9), 133.0 (+, *trans*-C-9), 150.0 ($C_{quat.}$, *trans*-C-9a), 150.4 ($C_{quat.}$, *cis*-C-9a), 154.6 ($C_{quat.}$, *trans*-C_{ar}), 154.7 ($C_{quat.}$, *cis*-C_{ar}), 197.8 ($C_{quat.}$, *cis*-C-1), 197.9 ($C_{quat.}$, *trans*-C-1). FTIR (KBr): 2949 (m), 1677 (m, νC=O), 1566 (m, νC_{ar}=C_{ar}). EI-MS: *m*/*z* (%): 244 (100) [M^+]. EI-HRMS calcd. for $C_{15}H_{16}O_3$ 244.1099, found 244.1102.

***cis*/*trans*-7-Methoxy-4-ethyl-2,3,4,4a-tetrahydroxanthen-1-one (*cis*/*trans*-16b):** 95 mg (37%) of an orange yellow oil, 1.5:1 mixture of diastereoisomers; R_f = 0.27 (cyclohexane/ethyl acetate, 5:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00–1.06 (m, 6 H, CH_3), 1.32–1.43 (m, 4 H, *cis*/*trans*-CH_2), 1.69–1.77 (m, 2 H, *trans*-CH_2), 1.87–2.12 (m, 4 H, *cis*/*trans*-CH_2), 2.24–2.28 (m, 1 H, *trans*-4-H), 2.37–2.46 (m, 2 H, *cis*-CH_2), 2.59–2.64 (m, 1 H, *cis*-4-H), 3.76–3.78 (m, 6 H, *cis*/*trans*-OCH_3), 4.53 (dd, ^3J = 10.1, ^4J = 2.2 Hz, 1 H, *cis*-4a-H), 5.09 (dd, ^3J = 5.3, ^4J = 2.3 Hz, 1 H, *trans*-4a-H), 6.71–6.83 (m, 6 H, *cis*/*trans*-H_{ar}), 7.39 (d, ^4J = 2.2 Hz, 1 H, *trans*-9-H), 7.41 (d, ^4J = 2.2 Hz, 1 H, *cis*-9-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.2 (+, *cis*-CH_3), 11.9 (+, *trans*-CH_3), 19.0 (–, *cis*-CH_2), 20.7 (–, *trans*-CH_2), 23.5 (–, *cis*-CH_2), 25.4 (–, *trans*-CH_2), 33.7 (–, *trans*-CH_2), 37.9 (+, *trans*-C-4), 39.1 (–, *cis*-CH_2), 42.1 (+, *cis*-C-4), 56.1 (+, *cis*-OCH_3), 56.1 (+, *trans*-OCH_3), 77.7 (+, *trans*-C-4a), 78.6 (+, *cis*-C-4a), 113.6 (+, *cis*-C_{ar}), 113.9 (+, *trans*-C_{ar}), 117.0 (+, *trans*-C_{ar}), 117.1 (+, *cis*-C_{ar}), 118.5 (+, *cis*-C_{ar}), 118.5 (+, *trans*-C_{ar}), 122.4 ($C_{quat.}$, *trans*-C_{ar}), 122.9 ($C_{quat.}$, *cis*-C_{ar}), 130.3 ($C_{quat.}$, *trans*-C_{ar}), 130.8 ($C_{quat.}$, *cis*-C_{ar}), 132.2 (+, *cis*-C-9), 132.7 (+, *trans*-C-9), 150.1 ($C_{quat.}$, *trans*-C-9a), 150.5 ($C_{quat.}$, *cis*-C-9a), 154.6 ($C_{quat.}$, *trans*-C_{ar}), 154.8 ($C_{quat.}$, *cis*-C_{ar}), 197.9 ($C_{quat.}$, *cis*-C-1), 198.2 ($C_{quat.}$, *trans*-C-1). FTIR (KBr): 2959 (m), 1679 (m, νC=O), 1565 (m, νC_{ar}=C_{ar}). EI-MS: *m*/*z* (%): 258 (100) [M^+]. EI-HRMS calcd. for $C_{16}H_{18}O_3$ 258.1255, found 258.1258.

***cis*/*trans*-7-Methoxy-4-propyl-2,3,4,4a-tetrahydroxanthen-1-one (*cis*/*trans*-16c):** 49 mg (18%) of an orange yellow oil, 1.5:1 mixture of diastereoisomers; R_f = 0.29 (cyclohexane/ethyl acetate, 5:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96–1.01 (m, 6 H, CH_3), 1.28–1.60 (m, 8 H, CH_2), 1.70–1.83 (m, 2 H, CH_2), 1.97–2.11 (m, 5 H, *cis*/*trans*-CH_2), 2.36–2.51 (m, 2 H, CH_2, *trans*-4-H), 2.58–2.63 (m, 1 H, *cis*-4 H), 3.77 (m, 6 H, *cis*/*trans*-OCH_3), 4.51 (dd, ^3J = 9.8, ^4J = 2.2 Hz, 1 H, *cis*-4a-H), 5.09 (dd, ^3J = 5.3, ^4J = 2.2 Hz, 1 H, *trans*-4a-H), 6.72–6.87 (m, 6 H, *cis*/*trans*-H_{ar}), 7.40 (d, ^4J = 2.5 Hz, 1 H, *trans*-9-H), 7.42 (d, ^4J = 2.2 Hz, 1 H, *cis*-9-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6 (+, *trans*-CH_3), 14.8 (+, *cis*-CH_3), 20.1 (–, *cis*-CH_2), 20.7 (–, *trans*-CH_2), 21.1 (–, *trans*-CH_2), 24.0 (–, *cis*-CH_2), 28.2 (–, *trans*-CH_2), 33.8 (–, *trans*-CH_2), 35.1 (–, *cis*-CH_2), 35.9 (+, *trans*-C-4), 39.1 (–, *cis*-CH_2), 40.6 (+, *cis*-C-4), 56.1 (+, *cis*-OCH_3), 56.1 (+, *trans*-OCH_3), 77.7 (+, *trans*-C-4a), 79.1 (+, *cis*-C-4a), 113.6 (+, *cis*-C_{ar}), 113.9 (+, *trans*-C_{ar}), 117.0 (+, *trans*-C_{ar}), 117.1 (+, *cis*-C_{ar}), 118.5 (+, *cis*-C_{ar}), 118.5 (+, *trans*-C_{ar}), 122.4 ($C_{quat.}$, *trans*-C_{ar}), 122.9 ($C_{quat.}$, *cis*-C_{ar}), 130.3 ($C_{quat.}$, *trans*-C_{ar}), 130.8 ($C_{quat.}$, *cis*-C_{ar}), 132.2 (+, *cis*-C-9), 132.7 (+, *trans*-C-9), 150.1 ($C_{quat.}$, *trans*-C-9a), 150.5 ($C_{quat.}$, *cis*-C-9a), 154.6 ($C_{quat.}$, *trans*-C_{ar}), 154.8 ($C_{quat.}$, *cis*-C_{ar}), 197.9 ($C_{quat.}$, *cis*-C-1), 198.2 ($C_{quat.}$, *trans*-C-1). FTIR (KBr): 2959 (m), 1678 (m, νC=O), 1568 (m, νC_{ar}=C_{ar}). EI-MS: *m*/*z* (%): 272 (100) [M^+]. EI-HRMS calcd. for $C_{17}H_{20}O_3$ 272.1412, found 272.1409.

(4*R,4a*R**)-4-Hydroxy-7-methoxy-1,2,3,4-tetrahydroxanthen-1-one (*cis*-16g):** 46 mg (36%) of an orange yellow solid [the compound undergoes isomerization to the (4*R**,4a*S**)-diastereomer very fast]; R_f = 0.27 (cyclohexane/ethyl acetate, 1:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$, determined from a 2:1 mixture with diastereomer *trans*-**16g**): δ = 1.87 (dddd, ^2J = 13.9, ^3J = 13.9, ^3J = 12.1, ^3J = 4.8 Hz, 1 H, H-3^A), 2.20–2.27 (m, 1 H, H-3^B), 2.53 (ddd, ^2J = 18.4 Hz ^3J = 13.9, ^3J = 6.0 Hz, 1 H, H-2^A), 2.68 (ddd, ^2J = 18.4, ^3J = 4.8, ^3J = 2.1 Hz, 1 H, H-2^B), 2.78 (br. s, 1 H, OH), 3.80 (s, 3 H, OCH_3), 4.32 (ddd, ^3J = 12.1, ^3J = 8.6, ^3J = 3.8 Hz, 1 H, H-4), 4.80 (dd, ^3J = 8.6, ^4J = 2.1 Hz, 1 H, H-4a), 6.75–6.78 (m, 1 H, H_{ar}), 6.84–6.91 (m, 2 H, H_{ar}), 7.41 (d, ^4J = 2.1 Hz, 1 H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$, determined from a 2:1 mixture with diastereomer *trans*-**16g**): δ = 25.8 (–, C-3), 36.8 (–, C-2), 55.8 (+, OCH_3), 71.3 (+, C-4), 80.2 (+, C-4a), 113.7 (+, C_{ar}), 116.8 (+, C_{ar}), 118.5 (+, C_{ar}), 122.1 ($C_{quat.}$, C-8a), 128.1 ($C_{quat.}$, C-9a), 133.0 (+, C-9), 149.1 ($C_{quat.}$, C-5a*), 154.7 ($C_{quat.}$, C-7*), 195.7 ($C_{quat.}$, C-1).

(4*R,4a*S**)-4-Hydroxy-7-methoxy-1,2,3,4-tetrahydroxanthen-1-one (*trans*-16g):** 36 mg (27%) of an orange yellow solid; m.p. 158 °C; R_f = 0.43 (cyclohexane/ethyl acetate, 1:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (ddd, ^2J = 14.3, ^3J = 13.8, ^3J = 5.8 Hz, 1 H, H-3^A), 2.37 (dddd, ^2J = 14.3, ^3J = 6.8, ^3J = 4.9, ^3J = 1.6 Hz, 1 H, H-3^B), 2.44 (ddd, ^2J = 18.2, ^3J = 5.8, ^3J = 1.6 Hz, 1 H, H-2^A), 2.66 (br. s, 1 H, OH), 2.88 (ddd, ^2J = 18.2, ^3J = 13.8, ^3J = 6.8 Hz, 1 H H-2^B), 3.80 (s, 3 H, OCH_3), 4.47–4.51 (m, 1 H, H-4), 5.01 (dd, ^3J = 2.8, ^4J = 2.6 Hz, 1 H, H-4a), 6.75–6.78 (m, 1 H, H_{ar}), 6.84–6.87 (m, 2 H, H_{ar}), 7.45 (d, ^4J = 2.6 Hz, 1 H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6 (–, C-3), 32.3 (–, C-2), 55.8 (+, O*C*H$_3$), 65.2 (+, C-4), 77.4 (+, C-4a), 113.7 (+, C_{ar}), 116.9 (+, C_{ar}), 118.0 (+, C_{ar}), 122.1 ($C_{quat.}$, C-8a), 128.6 ($C_{quat.}$, C-9a), 132.5 (+, C-9), 148.7 ($C_{quat.}$, C-5a*), 154.8 ($C_{quat.}$, C-7*), 197.1 ($C_{quat.}$, C-1). FTIR (film on KBr): 3528 (m, νO–H), 2916 (w, νC–H), 2840 (w, νCH$_3$),1679 (m, νC=O), 1611 (m, νC=C), 1572 (m, νC$_{ar}$=C$_{ar}$). EI-MS: *m*/*z* (%): 246 (100) [M$^+$], 203 (73) [(M – C_2H_3O)$^+$], 174 (26) [($C_{11}H_{10}O_2$)$^+$]. EI-HRMS calcd. for $C_{14}H_{14}O_4$ 246.0892, found 246.0890.

***cis*/*trans*-4-(Hydroxymethyl)-7-methoxy-2,3,4,4a-tetrahydroxanthen-1-one (*cis*/*trans*-16h):** 27 mg (38%) of an orange yellow solid; m.p. 111–114 °C (1:8 mixture of diastereomers); R_f = 0.36 (cyclohexane/ethyl acetate, 1:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): *cis*-diastereoisomer: δ = 1.60 (dddd, ^2J = 13.8, ^3J = 13.8, ^3J = 13.8, ^3J = 4.6 Hz, 1 H, 3-H^A), 2.09 (dddd, ^2J = 13.9, ^3J = 6.1, ^3J = 3.0, ^3J = 2.3 Hz, 1 H, 3-H^B), 2.21 (m, 1 H, OH), 2.29–2.38 (m, 1 H, 4-H), 2.48 (ddd, ^2J = 18.1, ^3J = 13.9, ^3J = 6.1 Hz, 1 H, 2-H^A), 2.66 (ddd, ^2J = 18.1, ^3J = 4.4, ^3J = 1.9 Hz, 1 H, 2-H^B), 3.79 (s, 3 H, OCH_3), 3.88 (ddd, ^2J = 10.9, ^3J = 7.2, ^3J = 5.3 Hz, 1 H, CH_2OH), 4.01 (ddd, ^2J = 10.9, ^3J = 4.7, ^3J = 3.6 Hz, 1 H, CH_2OH), 4.84 (dd, ^3J = 10.4, ^4J = 2.1 Hz, 1 H, 4a-H), 6.77 (br. s, 1 H, H_{ar}), 6.83–6.85 (m, 2 H, H_{ar}), 7.44 (d, ^4J = 2.1 Hz, 1 H, H-9); *trans*-diastereoisomer: δ = 1.72 (br. s, 1 H, OH), 1.84 (dddd, ^2J = 15.0, ^3J = 12.0, ^3J = 6.1, ^3J = 2.3 Hz, 1 H, 3-H^A), 2.17–2.25 (m, 1 H, 3-H^B), 2.42–2.57 (m, 2 H, 2-H$_2$), 2.63–2.70 (m, 1 H, 4-H), 3.79 (s, 3 H, OCH_3), 3.86 (dd, ^2J = 11.3, ^3J = 5.4 Hz, 1 H, CH_2OH), 4.19 (dd, ^2J = 11.3, ^3J = 6.9 Hz, 1 H, CH_2OH), 5.18 (dd, ^3J = 5.8, ^4J = 2.1 Hz, 1 H, 4a-H), 6.77 (br. s, 1 H, H_{ar}), 6.84–6.87 (m, 2 H, H_{ar}), 7.47 (d, ^4J = 2.1 Hz, 1 H, 9-H). ^{13}C NMR (125 MHz, $CDCl_3$): *cis*-diastereoisomer: δ = 21.4 (–, C-3), 38.3 (–, C-2), 42.6 (+, C-4), 55.79 (+, O*C*H$_3$), 65.2 (+, 4-*C*H$_2$OH), 76.9 (+, C-4a), 113.5 (+, C_{ar}), 116.8 (+, C_{ar}), 118.3 (+, C_{ar}), 122.4 ($C_{quat.}$, C_{ar}), 129.9 ($C_{quat.}$, C_{ar}), 132.1 (+, C-9), 149.4 ($C_{quat.}$, C-9a), 154.7 ($C_{quat.}$, C_{ar}), 196.9 ($C_{quat.}$, C-1); *trans*-diastereoisomer: δ = 20.7 (–, C-3), 34.4 (–, C-2), 38.2 (+, C-4), 55.81 (+, O*C*H$_3$), 62.1 (–, 4-*C*H$_2$OH), 77.0 (+, C-4a), 113.6 (+, C_{ar}), 116.9 (+, C_{ar}), 118.4 (+, C_{ar}), 119.4 ($C_{quat.}$, C_{ar}), 129.7 ($C_{quat.}$, C_{ar}), 132.7 (+, C-9), 148.9 ($C_{quat.}$, C-9a), 154.8 ($C_{quat.}$, C_{ar}), 197.2 ($C_{quat.}$, C-1). FTIR (KBr): 3457 (s, νO–H), 3065 (w, νC$_{ar}$–H), 2999 (m, νC–H), 2958 (m, νC–H), 2840 (m, νOCH$_3$), 1667 (s, νC=O), 1604 (s, νC=C), 1567 (s, νC$_{ar}$=C$_{ar}$). EI-MS: *m*/*z* (%): 260 (100) [M$^+$], 242 (27) [(M – H_2O)$^+$], 229 (16) [(M – OCH$_3$)$^+$], 174 (66) [(M – C_3H_4O)$^+$]. EI-HRMS calcd. for $C_{15}H_{16}O_4$ 260.1049, found 260.1047.

(3*R*,4*S*,4a*S*)-4-Hydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroxanthen-1-one (*cis*-17b): 29 mg (11%) of a yellow solid and 75 mg (28%) of a 8.5:1 *cis*/*trans*-diastereomeric mixture; m.p. 123–126 °C; R_f = 0.27 (cyclohexane/ethyl acetate, 2:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (d, ^3J = 6.4 Hz, 3 H, 3-CH_3), 1.96–2.09 (m, 1 H, 3-H), 2.24 (dd, ^2J = 18.0, ^3J = 13.2 Hz, 1 H, 2-H^A), 2.70 (br. s, 1 H, OH), 2.67 (dd, ^2J = 18.0, ^3J = 4.5 Hz, 1 H, 2-H^B), 3.80 (s, 3 H, OCH_3), 3.93 (dd, ^3J = 10.8, ^3J = 8.7 Hz, 1 H, 4-H), 4.79 (dd, ^3J = 8.7, ^4J = 2.5 Hz, 1 H, 4a-H), 6.77 (d, ^4J = 2.7 Hz, 1 H, 8-H), 6.87 (dd, ^3J = 8.9, ^4J = 2.76 Hz, 1 H, 6-H), 6.90 (d, ^3J = 8.9 Hz, 1 H, 5-H), 7.45 (d, ^4J = 2.62 Hz, 1 H, 9-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3 (+, 3-*C*H$_3$), 30.9 (–, C-3), 45.7 (+, C-2), 55.8 (+, O*C*H$_3$), 76.1 (+, C-4), 79.9 (+, C-4a), 113.7 (+, C-8), 116.8 (+, C-5), 118.5 (+, C-6), 122.0 ($C_{quat.}$, C_{ar}), 128.5 ($C_{quat.}$, C_{ar}), 132.6 (+, C-9), 149.1 ($C_{quat.}$, C-9a), 154.7 ($C_{quat.}$, C_{ar}), 195.4 ($C_{quat.}$, C-1). FTIR (KBr): 3398 (s, νO–H), 2965 (m, νC–H), 2878 (m, νOCH$_3$), 1658 (s, νC=O), 1598 (s, νC=C). EI-MS: *m*/*z* (%): 260 (28) [M$^+$], 203 (100) [($C_{13}H_{15}O_2$)$^+$]. EI-HRMS calcd. for $C_{15}H_{16}O_4$ 260.1049, found 260.1042. $[\alpha]_D^{20}$ –135.33 ($CHCl_3$, *c* = 2.03).

(3*R*,4*S*,4a*R*)-4-Hydroxy-7-methoxy-5-methyl-1,2,3,4-tetrahydroxanthen-1-one (*trans*-17b): 61 mg (23%) of a yellow oil; R_f = 0.34 (cyclohexane/ethyl acetate, 2:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, ^3J = 7.6 Hz, 3 H, 3-CH_3), 2.28 (dd, ^2J = 17.7, ^3J = 1.6 Hz, 1 H, 2-H^A), 2.55–2.63 (m, 1 H, 3-H), 2.75 (br. s, 1 H, OH), 3.04 (dd, ^2J = 17.7, ^3J = 6.2 Hz, 1 H, 2-H^B), 3.80 (s, 3 H, OCH_3), 4.30 (dd, ^3J = 3.7, ^3J = 3.3 Hz, 1 H, 4-H), 5.09 (dd, ^3J = 3.3, ^4J = 2.6 Hz, 1 H, 4a-H), 6.78 (d, ^4J = 2.6 Hz, 1 H, 8-H), 6.85 (dd, ^3J = 8.9, ^4J = 2.6 Hz, 1 H, 6-H), 6.88 (d, ^3J = 8.9 Hz, 1 H, 5-H), 7.45 (d, ^4J = 2.62 Hz, 1 H, 9-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.0 (+, 3-*C*H$_3$), 30.6 (+, C-3), 39.8 (–, C-2), 55.8 (+, O*C*H$_3$), 69.6 (+, C-4), 74.8 (+, C-4a), 113.7 (+, C-8), 117.0 (+, C-5), 118.1 (+, C-6), 122.2 ($C_{quat.}$, C_{ar}), 128.4 ($C_{quat.}$, C_{ar}), 132.3 (+, C-9), 149.0 ($C_{quat.}$, C-9a), 154.8 ($C_{quat.}$, C_{ar}), 197.4 ($C_{quat.}$, C-1). FTIR (KBr): 3467 (w, νO–H), 3039 (vw, νC$_{ar}$–H), 2958 (w, νC–H), 2909 (w, νC–H), 2839 (w, νOCH$_3$), 1681 (m, νC=O), 1614 (m, νC=C), 1570 (m, νC=C). EI-MS: *m*/*z* (%): 260 (14) [M$^+$], 243 (1) [(M – OH)$^+$], 203 (16) [($C_{13}H_{15}O_2$)$^+$], 84 (38) [(C_4H_4O)$^+$], 56 (100) [(C_3H_4O)$^+$]. EI-HRMS calcd. for $C_{14}H_{14}O_4$ 260.1049, found 260.1052. $[\alpha]_D^{20}$ = +105.02 ($CHCl_3$, *c* = 1.45).

2-(2-Hydroxy-5-methoxybenzylidene)-4-methylcyclohex-3-enone (18): 54 mg (22%) of an orange oil; R_f = 0.33 (cyclohexane/ethyl acetate, 1:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.91 (s, 3 H, CH_3), δ = 2.49 (dd, ^3J = 6.9 Hz, 2 H, CH_2), 2.66 (dd, ^3J = 6.9, 6.6 Hz, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 6.50 (s, 1 H, 3-H), 6.77–6.85 (m, 3 H, H_{ar}), 7.33 (s, 1 H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4 (+, *C*H$_3$), 29.8 (–, *C*H$_2$), 38.3 (–, *C*H$_2$), 56.1 (+, O*C*H$_3$), 115.2 (+, C_{ar}), 116.1 (+, C_{ar}), 117.2 (+, C_{ar}), 121.1 (+, CH), 123.2 ($C_{quat.}$, C_{ar}), 125.4 (+, CH), 132.3 ($C_{quat.}$, C_{ar}), 141.5 ($C_{quat.}$), 149.1 ($C_{quat.}$), 153.2 ($C_{quat.}$), 201.0 ($C_{quat.}$, C-1). FTIR (KBr): 3382 (m, νO–H), 2930 (m), 1670 (m, νC=O), 1495 (m, νC$_{ar}$=C$_{ar}$). EI-MS: *m*/*z* (%): 244 (15) [M$^+$], 227 (17) [M$^+$-OH], 43 (100) [C_2H_3O]$^+$. EI-HRMS calcd. for $C_{15}H_{16}O_3$ 244.1099, found 244.1097.

7-(Hydroxymethyl)-2-methoxy-9*H*-xanthene (20h): 43 mg (18%) of a white solid; m.p. 154 °C; R_f = 0.18 (cyclohexane/ethyl acetate, 2:1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (br. s, 1 H, OH), 3.81 (s, 3 H, OCH_3), 4.05 (s, 2 H, H-9), 4.66 (s, 2 H, CH_2OH), 6.71 (d, ^3J = 2.9 Hz, 1 H, H_{ar}), 6.78 (dd, ^3J = 8.8, ^4J = 2.9 Hz, 1 H, H_{ar}), 7.00 (d, ^3J = 8.8 Hz, 1 H, H_{ar}), 7.03 (d, ^3J = 8.9 Hz, 1 H, H_{ar}), 7.17–7.27 (m, 2 H, H_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 (–, C-9), 55.7 (+, O*C*H$_3$), 65.0 (–, *C*H$_2$OH), 113.3 (+, C_{ar}), 113.4 (+, C_{ar}), 116.4 (+, C_{ar}), 117.1 (+, C_{ar}), 120.1 ($C_{quat.}$, C_{ar}), 121.0 ($C_{quat.}$, C_{ar}), 126.7 (+, C_{ar}), 127.8 (+, C_{ar}), 135.2 ($C_{quat.}$, C_{ar}), 145.9 ($C_{quat.}$, C_{ar}), 151.7 ($C_{quat.}$, C_{ar}), 155.3 ($C_{quat.}$, C-2). EI-MS: *m*/*z* (%): 242 (95) [M$^+$], 241 (56) [(M – H)$^+$], 211 (32) [(M – OCH$_3$)$^+$], 43 [(C_2H_3O)$^+$]. EI-HRMS calcd. for $C_{15}H_{14}O_3$: 242.0943, found 242.0945.

2-(Carboxyethyl)-7-methoxy-1-methyl-9*H*-xanthene (20k): 54 mg (18%) of an off-white solid; m.p. 138–139 °C; R_f = 0.69 (cyclohexane/ethyl acetate, 2:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$CH_3), 2.56 (s, 3 H, Ar-CH_3), 3.81 (s, 3 H, OCH_3), 3.99 (s, 2 H, 9-H$_2$), 4.36 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH$_3$), 6.73 (d, ^4J = 2.9 Hz, 1 H, 8-H), 6.77 (dd, ^3J = 8.8, ^4J

= 2.9 Hz, 1 H, 6-H), 6.89 (d, ^3J = 8.7 Hz, 1 H, 4-H), 6.97 (d, ^3J = 8.8 Hz, 1 H, 5-H), 7.76 (d, ^3J = 8.7 Hz, 1 H, 3-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5 (+, OCH_2CH_3), 16.3 (+, Ar-CH_3), 26.5 (–, C-9), 55.7 (+, OCH_3), 60.6 (–, OCH_2CH_3), 113.4 (+, C-8), 113.73 (+, C-6)*, 113.75 (+, C-4)*, 116.9 (+, C-5), 119.3 ($C_{quat.}$, C_{ar}), 120.2 ($C_{quat.}$, C_{ar}), 125.0 ($C_{quat.}$, C_{ar}), 130.1 (+, C-3), 139.9 ($C_{quat.}$, C_{ar}), 144.7 ($C_{quat.}$, C_{ar}), 154.2 ($C_{quat.}$, C_{ar}), 155.5 ($C_{quat.}$, C_{ar}), 167.7 ($C_{quat.}$, CO_2Et). FTIR (KBr): 3054 (w, νC_{ar}-H), 2996 (w, νC–H), 2936 (w, νC–H), 2902 (w, νC–H), 2838 (w, νO–CH_3), 1707 (m, νC=O). EI-MS: *m*/*z* (%): 298 (1) [M^+], 283 (1) [$(M - CH_3)^+$], 269 (1) [$(M - C_2H_5)^+$], 225 (1) [$(M - C_3H_5O_2)^+$], 58 (39) [$(C_3H_6O)^+$], 43 (100) [$(C_2H_3O)^+$]. EI-HRMS calcd. for $C_{18}H_{18}O_4$: 298.1205, found 298.1202. $C_{18}H_{18}O_4$ (298.3331 g/mol): calcd. C 72.47%, H 6.08, found C 72,15, H 5.88.

7-Methoxy-1-methyl-9*H*-xanthene (20l): 11 mg (5%) of a colorless solid; m.p. 120 °C, R_f = 0.79 (cyclohexane/ethyl acetate, 2:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, 1-CH_3), 3.81 (s, 3 H, OCH_3), 4.01 (s, 2 H, 9-H_2), 6.71 (d, ^4J = 3.0 Hz, 1 H, 8-H), 6.77 (dd, ^3J = 8.8, ^4J = 3.0 Hz, 1 H, 6-H), 6.83–6.89 (m, 2 H, H_{ar}), 6.99 (d, ^3J = 8.8 Hz, 1 H, 5-H), 7.06 (d, ^3J = 7.6 Hz, 1 H, H_{ar}). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (+, 1-CH_3), 28.0 (–, C-9), 55.7 (+, OCH_3), 113.3 (+, C_{ar}), 113.4 (+, C_{ar}), 116.8 (+, C_{ar}), 116.9 ($C_{quat.}$, C_{ar}), 117.1 (+, C_{ar}), 121.4 ($C_{quat.}$, C_{ar}), 123.6 (+, C_{ar}), 128.6 (+, C_{ar}), 137.6 ($C_{quat.}$, C_{ar}), 146.1 ($C_{quat.}$, C_{ar}), 152.0 ($C_{quat.}$, C_{ar}), 155.1 ($C_{quat.}$, C_{ar}). FTIR (KBr): 3029 (m, νC_{ar}–H), 2918 (m, νC–H), 2855 (m, νOCH_3), 1582 (m, νC_{ar}=C_{ar}), 1499 (m, νC_{ar}=C_{ar}). EI-MS: *m*/*z* (%): 226 (100) [M^+], 225 (86) [$(M - H)^+$], 211 (30) [$(M - CH_3)^+$], 195 (13) [$(M - OCH_3)^+$]. EI-HRMS calcd. for $C_{15}H_{14}O_2$: 226.0994, found 226.0992.

7-(Hydroxymethyl)-2-methoxyxanthone (21h): 10 mg (4%) of a light yellow solid; m.p. 129–131 °C; R_f = 0.35 (cyclohexane/ethyl acetate, 1:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.20 (br. s, OH), 3.94 (s, 3 H, OCH_3), 4.83 (s, 2 H, CH_2OH), 7.35 (dd, ^3J = 9.1, ^4J = 3.1 Hz, 1 H, 3-H*), 7.45 (d, ^3J = 9.1 Hz, 1 H, 4-H**), 7.49 (d, ^3J = 8.7 Hz, 1 H, 5-H**), 7.71 (d, ^4J = 3.1 Hz, 1 H, 1-H***), 7.75 (dd, ^3J = 8.7, ^4J = 2.0 Hz, 1 H, 6-H*), 8.30 (d, ^4J = 2.0 Hz, 1 H, 8-H***). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.9 (+, OCH_3), 64.5 (–, CH_2OH), 105.7 (+, C_{ar}), 118.3 (+, C_{ar}), 119.4 (+, C_{ar}), 120.9 ($C_{quat.}$, C_{ar}), 122.0 ($C_{quat.}$, C_{ar}), 124.5 (+, C_{ar}), 125.0 (+, C_{ar}), 133.7 (+, C_{ar}), 136.6 ($C_{quat.}$, C_{ar}), 151.0 ($C_{quat.}$, C_{ar}), 155.5 ($C_{quat.}$, C_{ar}), 156.0 ($C_{quat.}$, C_{ar}), 177.0 ($C_{quat.}$, C-9). FTIR (KBr): 3418 (m, νO–H), 3030 (vw, νC_{ar}–H), 2932 (w, νC–H), 1642 (s, νC=O), 1619 (s, νC_{ar}=C_{ar}), 1484 (s, νC_{ar}=C_{ar}). EI-MS: *m*/*z* (%): 256 (100) [M^+], 239 (14) [$(M - OH)^+$], 227 (47) [$(M - CHO)^+$]. EI-HRMS calcd. for $C_{15}H_{12}O_4$: 256.0736, found 256.0738.

7-(Carboxymethyl)-2-methoxyxanthone (21j): 12 mg (4%) of a colorless solid; R_f = 0.47 (cyclohexane/ethyl acetate, 3:1 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, 2-OCH_3)*, 4.00 (s, 3 H, CO_2CH_3)*, 7.38 (dd, ^3J = 9.1, ^4J = 3.1 Hz, 1 H, 3-H)**, 7.48 (d, ^3J = 9.1 Hz, 1 H, 4-H)***, 7.55 (d, ^3J = 8.8 Hz, 1 H, 5-H)***, 7.73 (d, ^4J = 3.1 Hz, 1 H, 1-H)****, 8.38 (dd, ^3J = 8.8, ^4J = 2.2 Hz, 1 H, 6-H)**, 9.05 (d, ^4J = 2.2 Hz, 1 H, 8-H)****. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.4 (+, OCH_3), 56.0 (+, OCH_3), 106.0 (+, C-1)*, 118.4 (+, C-5)**, 119.5 (+, C-4)**, 120.8 ($C_{quat.}$), 122.1 ($C_{quat.}$), 125.3 (+, C-3)***, 125.8 ($C_{quat.}$, C_{ar}), 129.3 (+, C.-8)*, 135.1 (+, C-6)***, 150.8 ($C_{quat.}$, C_{ar}), 156.4 ($C_{quat.}$, C_{ar}), 158.6 ($C_{quat.}$, C_{ar}), 165.8 ($C_{quat.}$, C_{ar}), 176.5 ($C_{quat.}$, C-9). FTIR (KBr): 3092 (vw, νC_{ar}–H), 2955 (vw, νC–H), 2844 (vw, νC–H), 1724 (m, νCO_2Me), 1663 (m, νC=O), 1621 (m, νC_{ar}=C_{ar}), 1482 (m, νC_{ar}=C_{ar}), 1029 (m, νC–O). EI-MS: *m*/*z* (%): 284 (59) [M^+], 253 (34) [$(M - OCH_3)^+$], 225 (13) [$(M - CO_2CH_3)^+$], 43 (100) [$(C_2H_3O)^+$]. EI-HRMS calcd. for $C_{16}H_{12}O_5$: 284.0685, found 284.0682.

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