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Diastereoselective Synthesis of Highly Functionalized Tetrahydroxanthenols—Unprecedented Access to Privileged Structural Motifs

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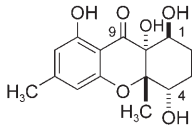
Dedicated to Professor Joachim Bargon

Abstract: Tetrahydroxanthenones, which can be easily prepared by a domino oxa-Michael aldol condensation, offer various possibilities for diastereoselective functionalization, giving access to the stereocontrolled synthesis of stereochemical triades or tetrades, which represent privileged structural motifs. In most cases, the relative stereochemistry was unequivocally established by crystal structure analysis.

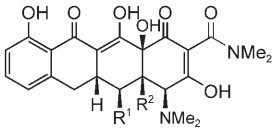
Keywords: domino reactions · oxidation · polyols · tetrahydroxanthenones

Introduction

During our efforts towards the total synthesis of the secalonic acids, we were recently able to complete the first total synthesis of the fungal metabolite diversonol (**1**), which is structurally similar to the secalonic acid monomers.[1,2] An interesting feature of diversonol is the oxidation pattern of the aliphatic moiety. The structural motif of a ketodiol in combination with a fused bicyclic or even oligocyclic system is often found in natural products, especially within the tetracycline class of molecules (basic structure **2**).[3]



diversonol (**1**)



2: R^2=H, Me

However, to the best of our knowledge, there has been no systematic study on the stereocontrolled synthesis of such ketodiols or related systems. In this paper we wish to report on the synthetic modification of readily available tetrahydroxanthenones leading to the synthesis of various tricyclic ketodiols, triols, and related systems which represent privileged stereotriades or tetrades. For most cases, the synthetic transformations could be performed with a high degree of stereocontrol and the products were characterized by X-ray crystal structure analysis.

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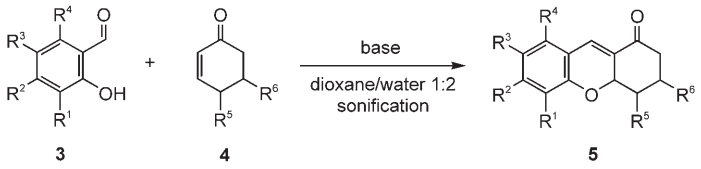
Results and Discussion

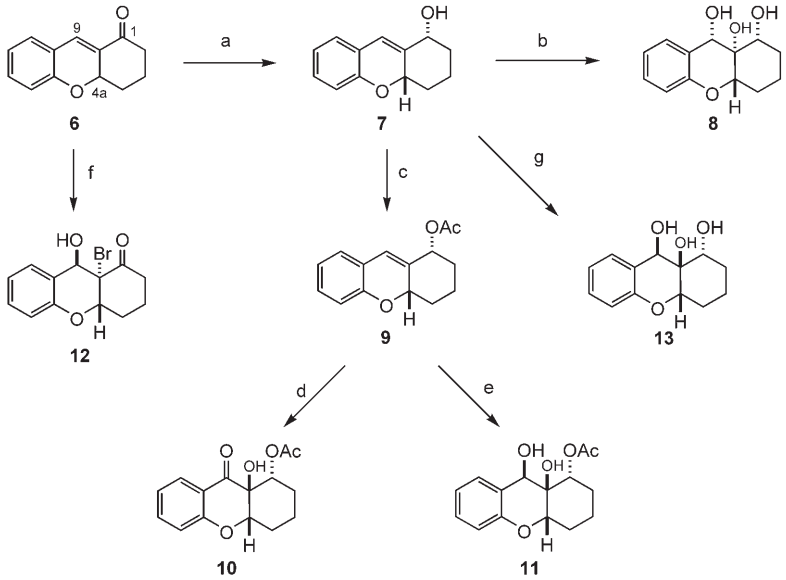
At the outset of our synthetic efforts, we realized that tetrahydroxanthenones **5** are easily accessible by means of a domino oxa-Michael aldol condensation between salicylic aldehydes **3** and cyclohexenones **4** (Scheme 1).[4,5]

Recently, we also reported on the scope and limitations of this reaction, focusing on the substitution pattern of the starting materials.[6] In this paper, with respect to the structural features of our targeted natural product diversonol (**1**), we first concentrated on the C1–C9 oxidation pattern of tetrahydroxanthenones (Scheme 2). Sodium borohydride re-



3 4 5

Scheme 1. Domino oxa-Michael aldol condensation.



6 7 8 9 10 11 12 13

Scheme 2. Transformations of tetrahydroxanthenone **6**: a) $NaBH_4$, MeOH, RT, 4 h, 77%; b) K_2OsO_4, K_2CO_3, $K_3Fe(CN)_6$, *t*BuOH/water 5:1, RT, 72 h, 51%; c) Ac_2O, pyridine, 0°C to RT, 4 h, 83%; d) K_2OsO_4, K_2CO_3, NMO (2.2 equiv), acetone/water 5:1, RT, 3 h, 74%; e) K_2OsO_4, K_2CO_3, NMO (1.1 equiv), acetone/water 5:1, RT, 3 h, 77% (based on recovered starting material); f) NBS, DMSO, RT, 3 h, 80%; g) K_2OsO_4, K_2CO_3, NMO (2.2 equiv), acetone/water 5:1, RT, 3 h, 46% (based on recovered starting material); NMO = *N*-methylmorpholine-*N*-oxide, NBS = *N*-bromosuccinimide.

duction of tetrahydroxanthenone **6** produced allylic alcohol **7** as one single diastereomer in good yield. The relative configuration of this compound was proven by crystal structure analysis and comparison of ^{1}H NMR coupling constants (the crystal structure analysis was performed with a C7-bromo-substituted analogue). The allylic alcohol could then be transformed into the all-*cis* triol **8** by dihydroxylation using potassium cyanoferrate in *t*BuOH/water as the cooxidant in the osmylation reaction (reaction pathway b).

Again, the reaction yielded only one diastereoisomer, the relative configuration of which was determined by comparison of ^{1}H NMR coupling constants. However, by changing the cooxidant from potassium cyanoferrate to *N*-morpholine-*N*-oxide and the solvent from *t*BuOH/water to acetone/water (reaction pathway g), triol **13** with the opposite relative configuration at C9 and C9a (proven by crystal structure analysis) was produced as a single diastereoisomer.[7] Interestingly, acetoxy-protected alcohol **9** could be oxidized under similar conditions yielding either ketol **10** (reaction pathway d) or diol **11** (reaction pathway e), depending on the stoichiometry of the employed cooxidant. If a twofold excess of cooxidant was employed, the intermediate **11** was oxidized in situ to the corresponding ketol **10**. However, the relative configuration at C9a for compounds **10** and **11** was also determined to be the opposite of that of compound **8**. Whether these results arise from the coordination of compound **7** to the osmium reagent during oxidation to triol **8** (depending on the solvent system) or from the influence of the cooxidant is currently under investigation in our laboratory. However, the effect of hydroxyl group directed dihydroxylation has been reported previously for similar osmium-based oxidation protocols.[8] Although ketol **10** already possesses the requisite substitution pattern for diversonol (**1**) at C1, C9, and C9a, the corresponding alkyl or carboxymethyl substituent on C4a still had to be introduced.[1] We therefore reasoned that the elimination of water from ketol **10** or a ketol derived from triol **8** would give rise to an α,β-unsaturated ketone, which in turn should be a suitable substrate for conjugate addition.[9] However, all attempts to perform this reaction by acid- or base-induced elimination or previous activation of the hydroxyl group failed. For ketol **10**, the lack of reactivity could be attributed to the *syn*-relationship between the hydroxyl group and the proton at C4a.

A straightforward solution to this problem was found by converting tetrahydroxanthenone **6** into the corresponding bromohydrine **12** (Scheme 2). As can be seen from Figure 1, the bromine atom on C9a and the hydrogen on C4a are arranged in a *trans*-relationship which greatly facilitates the base-induced elimination of hydrogen bromide. Consequently, this elimination could be performed at room temperature giving rise to allylic alcohol **14** in very good yield (Scheme 3). However, the following oxidation, which was

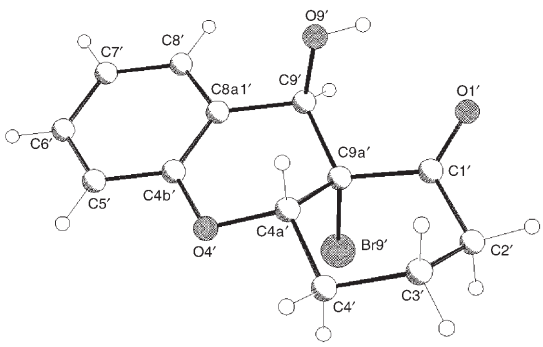
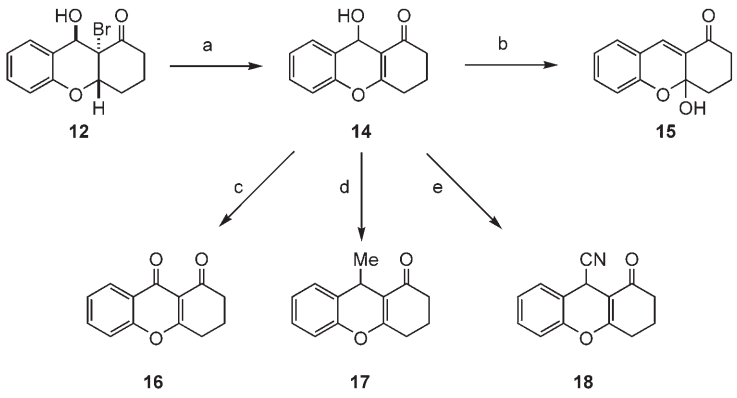


Figure 1. Molecular structure of bromohydrine **12**.



Scheme 3. Transformations of allylic alcohol **14**: a) DABCO, dioxane, RT, 14 h, 74%; b) IBX, DMSO, RT, 1 h, 80%; c) TPAP, NMO, CH_3CN/CH_2Cl_2, sonication, 12 h, 79%; d) $BF_3{\cdot}OEt_2$, $ZnMe_2$, toluene, −78°C, 1 h, 89%; e) $BF_3{\cdot}OEt_2$, Et_2AlCN, toluene, −78°C, 1 h, 60%; DABCO = 1,4-diazabicyclo[2.2.2]octane, IBX = 2-iodoxybenzoic acid, TPAP = tetrapropylammoniumperruthenate, NMO = *N*-methylmorpholine-*N*-oxide.

supposed to give diketone **16** as a suitable acceptor system for attaching a substituent on C4a, turned out to be unexpectedly difficult.

First of all, compound **14** is highly acid- and base-sensitive, so that even mild oxidation protocols, such as manganese dioxide or Parikh–Doering oxidation, failed to produce diketone **16**.[10] Moreover, allylic alcohol **14** displayed unexpected reactivity. Exposure to *o*-iodoxybenzoic acid (IBX) did not produce the expected diketone **16**, but hemiacetal **15**, which was characterized by crystal structure analysis (Figure 2). The formation of this compound could be explained by the coordination of IBX to the hydroxyl function, followed by a S_N2' reaction (Scheme 4).

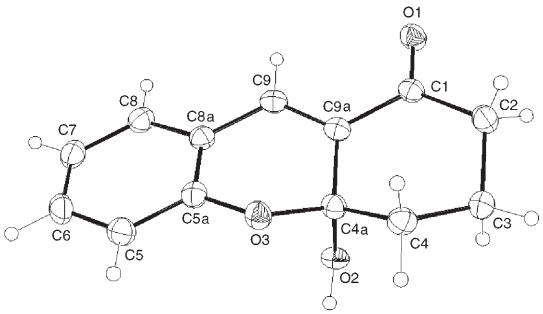
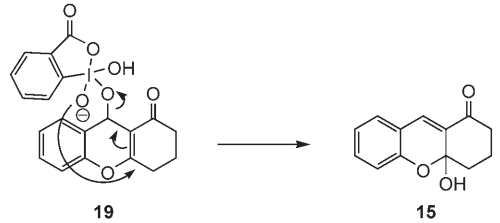


Figure 2. Molecular structure of hemiacetal **15**.

To further corroborate this hypothesis, additional reactions were performed with allylic alcohol **14**. By treating it with boron trifluoride diethyl etherate as a Lewis acid, followed by dimethylzinc or diethylaluminium cyanide as the corresponding nucleophile, compounds **17** and **18** were formed exclusively, indicating that in these cases another mechanistic scenario takes place, presumably involving the formation of an allylic cation followed by nucleophilic attack (Scheme 3).

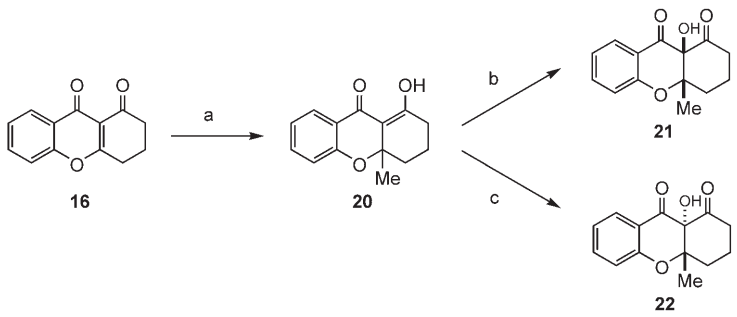


Scheme 4. Proposed mechanism for the formation of **15**.

The intended oxidation to form diketone **16** was finally achieved by applying a modified Ley-oxidation protocol.[11] The accelerating effect of ultrasound in this reaction has been reported previously and turned out to be highly beneficial in our case. With diketone **16** in hand, the introduction of an alkyl group by means of a conjugate addition could be envisaged. Studies on the introduction of substituents by addition of various cuprates on diketone **16** have been performed previously by Gabutt et al.[9] Their results showed that only lower order cyanocuprates are suitable reagents due to their decreased basicity compared to Gilman or Normant cuprates. In accordance with this observation, all our attempts to perform reactions with other types of cuprates only led to the extensive decomposition of diketone **16**. Thus, reacting compound **16** with a cyanocuprate formed from copper cyanide and methyllithium yielded C4a-methylated enol **20** in 79% yield (Scheme 5).

Regarding the substitution pattern of our targeted natural product, the stereoselective introduction of a hydroxyl group possessing a *trans*-relationship to the angular methyl group was the next step to be examined. Interestingly, the diastereoselectivity of the enol hydroxylation could be controlled by varying the reaction protocol. Thus, employing *m*-chloroperbenzoic acid gave rise to a 2:1 mixture of both the *cis*-ketol **21** and *trans*-ketol **22**, from which *cis*-ketol **21** could be isolated in 34% yield, whereas the hydroxylation with magnesium monoperoxophthalate[12] yielded the *trans*-ketol **22** as one single diastereoisomer (Scheme 5). The rather low yields in both cases are not caused by side reactions as clean conversions could be observed on TLC but are rather due to solubility problems during workup. Both diastereoisomers were characterized by crystal structure analysis (Figure 3; in the case of the *trans*-ketol, a brominated derivative was employed). To elucidate the reasons for this reactivity, we also examined enol **20** by crystal structure analysis (Figure 4).

As can be seen from the X-ray structure, the axial methyl group does exert some steric hindrance regarding a cofacial attack. This might explain the complete stereocontrol observed when using magnesium monoperoxophthalate, producing *trans*-diastereoisomer **22**, as the strong steric influ-



Scheme 5. Diastereoselective hydroxylation of enol **20**: a) MeLi, CuCN, Et_2O, −78 °C, 5 h, 79 %; b) *m*CPBA, CH_2Cl_2, RT, 2 h, 34 %; c) magnesium monoperoxophthalate, EtOH, RT, 2 h, 48 %; *m*CPBA = *meta*-chloroperbenzoic acid.

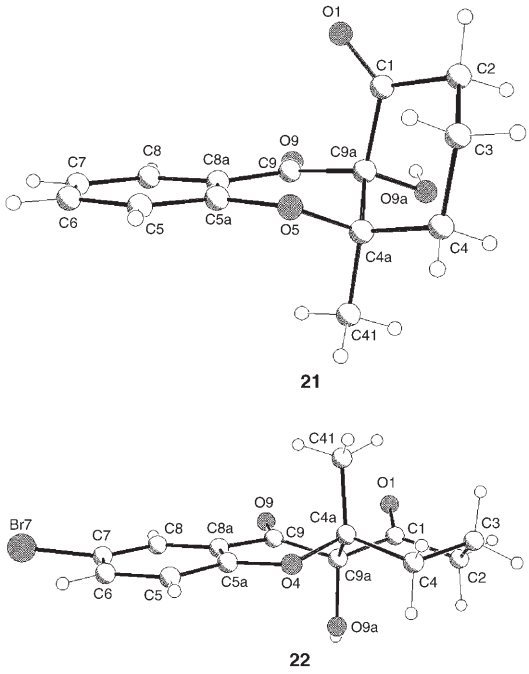


Figure 3. Molecular structures of ketols **21** and **22** (bromo derivative).

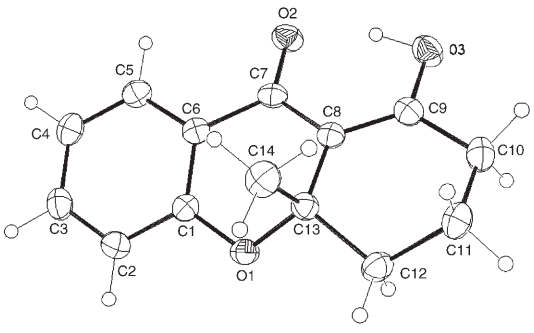
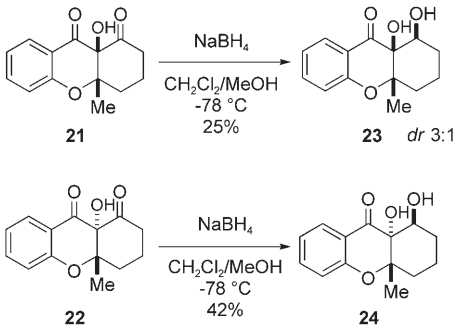


Figure 4. Molecular structure of enol **20**.

ence of axially-positioned angular substituents in fused cyclic systems is a well-known effect.[13] In contrast, it has been established that when *m*-chloroperbenzoic acid is used as an oxidant it is often hardly affected by steric hindrance,[14] and thus it produces a mixture of both diastereoisomers **21** and **22** in the present case. Moreover, the *cis*-selectivity in the epoxidation of allylic alcohols has been described previously by Henbest and coworkers and ascribed to hydrogen bonding between the substrate and *m*CPBA.[15] Whether the solvent does exert any influence on the stereochemical outcome of the reaction or whether a stereoelectronic effect has a decisive influence is currently under investigation in our laboratory.[16]

To establish the complete C1, C9, C9a substitution pattern of diversonol (**1**), the diastereoselective reduction of the unconjugated carbonyl function was envisaged (Scheme 6).



Scheme 6. Diastereoselective reduction of ketols **21** and **22**.

For the *syn*-ketol **21**, the reduction with sodium borohydride gave rise to the all-*syn* diol **23**, although in low yield and with low diasteroselectivity. However, performing the reduction of *trans*-ketol **22** under essentially the same reaction conditions gave rise to the *trans*-diol **24** exclusively. It has been previously observed that the sodium borohydride reduction of fused bicyclic ketols preferentially leads to *trans*-diols, possibly due to the presence of the hydroxyl function, which serves as a chelating agent for the nucleophile.[17] In some cases however, the formation of *syn*-diols is strongly favored, mainly due to sterical or stereoelectronical effects. For example, Marples et al. reported the *syn*-selective reduction of a ketol that is structurally similar to ketol **21**.[18]

Regarding the stereochemical outcome of our reductions, a closer examination of the molecular structures of both ketols **21** and **22** (Figure 3) revealed the possible reasons for the different reactivity. For the *trans*-ketol **22**, the hydroxyl function possibly serves as a chelator for the nucleophile. Besides, the axially-positioned methyl group might also shield one side of the molecule so that a synergistic effect leads to full stereocontrol. Regarding the reduction of the

syn-ketol **21**, the moderate diasteroselectivity could be explained by the position of the methyl group. Contrary to the structure of the *trans*-ketol it does not possess a suitable position for exerting a strong influence on the stereochemistry of the reduction. As the *syn*-diol is favored in this reaction, although a chelating hydroxyl function is in place, it seems that it is the steric hindrance of the methyl group which exerts the determining influence in this reaction.

Conclusion

In summary, we have examined the reactivity of tetrahydroxanthenones that are readily available by a domino oxa-Michael aldol condensation. The structure of tetrahydroxanthenones offers various possibilities for further functionalizations, many of which can be performed with a high degree of diastereoselectivity. By means of this strategy, the structural motifs of bicyclic ketodiols and triols, representing privileged stereotriades and tetrades are easily accessible with full stereocontrol.

Experimental Section

General: Substrates were purchased from commercial sources and were used without further purification (PE = light petroleum, cHex = cyclohexane). Column chromatography was performed by using Macherey-Nagel silica gel 60 (230–400 mesh) under flash conditions. For TLC, aluminum foils layered with silica gel with fluorescence indicator (silica gel 60 F_{254}) produced by Merck were employed. Melting points were determined by using a Laboratory Devices 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 by using $CDCl_3$ as the solvent and residual $CHCl_3$/$CDCl_3$ as shift reference ($CHCl_3$, $\delta = 7.28$ ppm; $CDCl_3$, $\delta = 77.00$ ppm). IR spectra were recorded by using the Bruker FTIR device IFS 88. EI-MS and -HRMS spectra were recorded on a Finnigan MAT 90 instrument; elemental analyses were performed by using a Heraeus CHN-O-Rapid device. X-ray crystallographic analyses were performed by using a Nonius Kappa CCD or a STOE IPDS II diffractometer with $Mo_{K\alpha}$ radiation.

X-ray crystallographic analysis: CCDC-289598 (C7-brominated analogue of **7**), -289599 (**12**), -290027 (**15**), -290026 (**20**), -289600 (**21**), -289601 (**23**), -289602 (C7-brominated derivative of **22**), -289603 (**24**), and -289604 (**13**) 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.

2,3,4,4a-Tetrahydroxanthen-1-one (6): Argon was passed through water (25 mL) for 15 min with simultaneous sonication. DABCO (2.80 g, 25.0 mmol), salicylic aldehyde (6.11 g, 50 mmol), and 2-cyclohexen-1-one (4.81 g, 50 mmol) were then suspended in the degassed solvent and treated with ultrasound for 48 h. After this time, the precipitated product was filtered off, washed with water and a small amount of acetone, and then recrystallized from acetone to give **6** (8.25 g, 83 %) as yellow crystals. M.p. 137–139 °C; $R_f = 0.26$ (EtOAc/PE 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.56$–1.68 (m, 1H; cyclohexyl-CH_2), 1.88–2.04 (m, 2H, cyclohexyl-CH_2), 2.31 (ddd, ^2J(H,H) = 18.1, ^3J(H,H) = 13.0, 6.1 Hz, 1H; $H2_{axial}$), 2.37–2.45 (m, 1H; cyclohexyl-CH_2), 2.51 (d pseudo-qui, ^2J(H,H) = 17.94, ^3J(H,H) = 2.5 Hz, 1H; 3-$H_{equatorial}$), 4.92 (ddd, ^3J(H,H) = 10.9, 6.1, ^4J(H,H) = 2.4 Hz, 1H; H4a), 6.80 (d, ^3J(H,H) = 7.8 Hz, 1H; H_{arom}), 6.87 (ddd, ^3J(H,H) = 7.8, 7.6, ^4J(H,H) = 1.1 Hz, 1H; H_{arom}), 7.12–7.19 (m, 2H; H_{arom}), 7.35 ppm (d, ^4J(H,H) = 2.4 Hz, 1H; H9); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.0$, 29.7, 38.8 (cyclohexyl-CH_2), 74.4 (C4a), 116.0, 122.1, 122.2, 129.8, 130.5, 131.5, 132.0, 155.9 (C5–C9a), 197.4 ppm (C1); IR (KBr): $\tilde{\nu} = 1603$ cm^{-1} (C=O); EI-MS: *m*/*z* (%): 200 (33) $[M]^+$, 144 (100) $[M-C_3H_4O]^+$; HR-EIMS: calcd: 200.0837; found: 200.0840; elemental analysis calcd for $C_{13}H_{12}O_2$: C 77.98, H 6.04; found: C 77.97, H 6.01.

2,3,4,4a-Tetrahydroxanthen-1-ol (7): Compound **6** (300 mg, 1.50 mmol) was added to a suspension of sodiumborohydride (23 mg, 0.60 mmol) in methanol (2 mL) at 0 °C. The suspension was warmed to room temperature and stirred for 4 h. After this time, diluted hydrochloric acid (2 mL) was added and the mixture was extracted with dichloromethane (3 × 5 mL). After drying over sodium sulfate and evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc/PE 1:5), yielding **7** (233 mg, 77 %) as colorless crystals. M.p. 129–132 °C; $R_f = 0.13$ (EtOAc/PE 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$–1.41 (m, 1H; cyclohexyl-CH_2), 1.63–1.73 (m, 1H; cyclohexyl-CH_2), 1.76–1.89 (m, 1H; cyclohexyl-CH_2), 2.02–2.11 (m, 2H; cyclohexyl-CH_2), 3.98 (dd, ^3J(H,H) = 10.9, 4.0 Hz, 1H; H1), 4.83 (dd, ^3J(H,H) = 11.2, 5.3 Hz, 1H; H4a), 6.27 (s, 1H; H9), 6.60 (d, ^3J(H,H) = 8.1 Hz, 1H; H8), 6.72 (ddd, ^3J(H,H) = 7.4, 7.3, ^4J(H,H) = 1.01 Hz, 1H; H6), 6.83 (dd, ^3J(H,H) = 7.4, ^4J(H,H) = 1.6 Hz, 1H; H5), 6.95 ppm (ddd, ^3J(H,H) = 8.1, ^3J(H,H) = 7.4, ^4J(H,H) = 1.6 Hz, 1H; H7); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.9$, 34.5, 36.3 (cyclohexyl-CH_2), 70.5 (C1), 76.2 (C4a), 113.5, 114.8, 120.8, 120.9, 126.4, 128.7, 139.7, 152.7 ppm (C5–C9a); IR (KBr): $\tilde{\nu} = 2940$ (C–H), 3319 cm^{-1} (O–H); EI-MS: *m*/*z* (%): 202 (79) $[M]^+$, 157 $[M-C_2H_5O]^+$, 131 ppm (100) $[M-C_4H_7O]^+$; HR-EIMS: calcd: 202.0994; found: 202.0999; elemental analysis calcd for $C_{13}H_{14}O_Z$: C 77.20, H 6.98; found: C 76.91, H 6.96.

1,9,9a-*cis*-Trihydroxy-2,3,4,4a,9,9a-hexahydroxanthene (8): A solution of 2,3,4,4a-tetrahydroxanthen-1-ol (**7**) (202 mg, 1.00 mmol) in *tert*-butanol (5 mL) was added to an ice-cooled solution of potassium hexacyanoferrate(III) (988 mg, 3.00 mmol) and potassium osmate(VI) dihydrate (17 mg, 50 μmol) in water (5 mL). The mixture was then warmed to room temperature and stirred for 72 h. After this time, sodium sulfite (ca. 1 g) was added and the mixture was stirred for 1 h before being extracted with EtOAc (3 × 10 mL). Finally, after drying and evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc/PE 1:1) to give **8** (120 mg, 51 %) as colorless crystals. M.p. 137–138 °C; $R_f = 0.15$ (EtOAc/PE 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.16$–1.39 (m, 2H; cyclohexyl-CH_2), 1.41–1.53 (m, 1H; cyclohexyl-CH_2), 1.61–1.69 (m, 1H; cyclohexyl-CH_2), 1.73–1.86 (m, 2H; cyclohexyl-CH_2), 3.50 (dd, ^3J(H,H) = 11.6, 4.9 Hz, 1H; H4a), 3.89 (dd, ^3J(H,H) = 12.00, 4.9 Hz, 1H; H1), 5.04 (s, 1H; H9), 6.73 (dd, ^3J(H,H) = 7.6, ^4J(H,H) = 0.9 Hz, 1H; H_{arom}), 6.86 (td, ^3J(H,H) = 7.6, ^4J(H,H) = 1.0 Hz, 1H; H_{arom}), 7.10 (td, ^3J(H,H) = 7.6, ^4J(H,H) = 1.3 Hz, 1H; H_{arom}), 7.39 ppm (d, ^3J(H,H) = 7.6 Hz, 1H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.6$, 27.9, 30.8 (cyclohexyl-CH_2), 63.9, 70.4, 77.2, 78.6 (C1, C4a, C9, C9a), 116.5, 120.9, 121.1, 128.3, 129.1, 151.6 ppm (C5–C9a); IR (KBr): $\tilde{\nu} = 3516$ cm^{-1} (O–H···O); EI-MS: *m*/*z* (%): 236 (90) $[M]^+$, 123 (100) $[M-C_6H_9O_2]^+$, 122 (69), $[M-C_7H_6O_2]^+$; HR-EIMS: calcd: 236.1049; found: 236.1049; elemental analysis calcd for $C_{13}H_{16}O_4$: C 66.09, H 6.83; found: C 65.91, H 6.74.

***O*-Acetyl-2,3,4,4a-tetrahydroxanthen-1-ol (9)**: Acetic anhydride (0.37 mL, 0.41 g, 4.0 mmol) was added to an ice-cooled solution of 2,3,4,4a-tetrahydroxanthen-1-ol (**7**) (404 mg, 2.00 mmol) in pyridine (5 mL). The mixture was then warmed to room temperature and stirred for 4 h. After this time, the mixture was diluted with sodium carbonate solution (0.1 mol L^{-1}, 10 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were washed with saturated ammonium chloride, dried over sodium sulfate, evaporated, and purified by flash column chromatography (EtOAc/PE 1:5), giving **9** (402 mg, 83 %) as colorless crystals. M.p. 91–93 °C; $R_f = 0.68$ (EtOAc/PE 1:5); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$–1.50 (m, 2H; cyclohexyl-CH_2), 1.64–1.87 (m, 1H; cyclohexyl-CH_2), 2.00–2.16 (m, 2H; cyclohexyl-CH_2), 2.11 (s, 3H; acetyl-CH_3), 4.88 (dd, ^3J(H,H) = 11.1, 5.5 Hz, 1H; H1), 5.12 (dd, ^3J(H,H) = 9.4, 5.3 Hz, 1H; H4a), 6.05 (s, 1H; H9), 6.60 (d, ^3J(H,H) = 7.4 Hz, 1H; H8), 6.71 (ddd, ^3J(H,H) = 7.9, 7.4, ^4J(H,H) = 1.1 Hz, 1H; H6), 6.82 (dd, ^3J(H,H) = 7.4, ^4J(H,H) = 1.7 Hz, 1H; H5), 6.96 ppm (ddd, ^3J(H,H) = 7.4, 7.3, ^4J(H,H) = 1.7 Hz, 1H; H7); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.7$, 21.1, 32.6, 34.3, (cyclohexyl-CH_2 and acetyl CH_3), 71.5 (C1), 75.9 (C4a), 114.2, 114.9, 120.4, 120.9, 126.4, 128.8, 135.5, 152.6 (C5a–C9a), 169.9 ppm (acetyl-

H_3CCO_2); IR (KBr): $\tilde{\nu}=1742\ cm^{-1}$ (C=O); EI-MS: *m/z* (%): 244 (21) $[M]^+$, 184 (100) $[M-HOAc]^+$, 157 (37) $[M-H_3CCO_2C_2H_3]^+$; HR-EIMS: calcd: 244.1099; found: 244.1101; elemental analysis calcd for $C_{15}H_{16}O_3$: C 73.75, H 6.60; found: C 73.52, H 6.52.

1-*O*-Acetyl-1,9a-dihydroxy-2,3,4,4a,9,9a-hexahydroxanthen-9-one (10): Compound **9** (94 mg, 0.39 mmol) was added to a solution of NMO (101 mg, 0.860 mmol) and potassium osmate(VI) dihydrate (7 mg, 20 μmol) in acetone/water 5:1 (2.5 mL) at 0 °C, and the resulting mixture was warmed to room temperature and stirred for 3 h. After this time, sodium sulfite (ca. 1 g) was added and the mixture stirred for a further 1 h. The mixture was then extracted with EtOAc (3×5 mL). After drying over sodium sulfate and evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc/PE 1:5) to give **10** (79 mg, 74%) as colorless crystals. M.p. 121–124 °C; $R_f=0.50$ (EtOAc/PE 1:5); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.27$ (s, 3H; acetyl-CH_3), 1.44–1.54 (m, 1H; cyclohexyl-CH_2), 1.68–1.77, (m, 1H; cyclohexyl-CH_2), 1.90–2.08 (m, 4H; cyclohexyl-CH_2), 3.77 (s, 1H; C9a-HOH), 4.31 (d, ^3J(H,H)=1.3 Hz; H1), 4.80 (d, ^3J(H,H)=1.7 Hz, 1H; H4a), 6.91–6.97 (m, 2H; H_{arom}), 7.45 (ddd, ^3J(H,H)=8.3, 7.2, ^4J(H,H)=1.9 Hz, 1H; H_{arom}), 7.75 ppm (dd, ^3J(H,H)=8.3, ^4J(H,H)=1.9 Hz, 1H; H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=13.4$, 18.8, 24.5, 25.0 (cyclohexyl-CH_2, acetyl-CH_3), 68.7 (C9a), 71.2 (C1), 77.2 (C4a), 116.7, 118.4, 120.1, 126.1, 152.7, 161.7 (C5a–C8a), 168.5 (acetyl-H_3CCO_2), 194.4 ppm (C9); IR (KBr): $\tilde{\nu}=1681$ (C=O), 1731 cm^{-1}; EI-MS: *m/z* (%): 276 (21) $[M]^+$, 234 (39) $[M-H_3CCO]^+$, 163 (99), $[M-H_3CCO_2C_4H_6]^+$, 121 ppm (100) $[M-C_8H_{11}O_3]^+$; HR-EIMS: calcd: 276.0998; found: 276.0990; elemental analysis calcd for $C_{15}H_{16}O_5$: C 65.21, H 5.84; found: C 64.94, H 5.89.

1-*O*-Acetyl-1,9,9a-trihydroxy-2,3,4,4a,9,9a-hexahydroxanthene (11): Compound **9** (200 mg, 0.830 mmol) was added to a solution of NMO (146 mg, 1.25 mmol) and potassium-(VI)-osmatdihydrate (15 mg, 42 μmol) in acetone/water 5:1 (10 mL) at 0 °C, and the mixture was then warmed to room temperature and stirred for 72 h. After this time, sodium sulfite (ca. 1 g) was added and the resulting mixture was stirred for a further 1 h. The mixture was then extracted with EtOAc (3×10 mL). After drying over sodium sulfate and evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc/PE 1:5) to give **11** (94 mg, 77%, based on recovered starting material) as colorless crystals. M.p. 131–146 °C; $R_f=0.19$ (EtOAc/PE 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.36$–1.43 (m, 1H; cyclohexyl-CH_2), 1.45 (s, 3H; acetyl-CH_3), 1.51–1.61 (m, 1H; cyclohexyl-CH_2), 1.71–1.88 (m, 2H; cyclohexyl-CH_2), 1.92–2.50 (m, 2H; cyclohexyl-CH_2), 2.47 (d, ^3J(H,H)=4.2 Hz, 1H; cyclohexyl-CH_2), 3.42 (s, 1H; OH-9a), 4.03 (dd, ^3J(H,H)=6.6, 3.7 Hz, 1H; H1), 4.60 (s, 1H; 9-CHOH), 4.93 (dd, ^3J(H,H)=6.1, 3.7 Hz, 1H; H4a), 6.79 (d, ^3J(H,H)=8.3 Hz, 1H; H_{arom}), 6.85 (ddd, ^3J(H,H)=8.3, 7.6, ^4J(H,H)=1.1 Hz, 1H; H_{arom}), 7.14 (ddd, ^3J(H,H)=8.3, 7.6, ^4J(H,H)=1.6 Hz, 1H; H_{arom}), 7.25 ppm (dd, ^3J(H,H)=7.6, ^4J(H,H)=1.1 Hz, 1H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.5$, 19.3, 25.5, 26.3 (cyclohexyl-CH_2, acetyl-CH_3), 65.6 (C9), 67.4 (C9a), 73.3 (C1), 74.0 (C4a), 115.6, 119.7, 121.1, 128.7, 128.8, 152.8 (C5–C9a), 169.4 ppm (acetyl-H_3CCO_2); IR (KBr): $\tilde{\nu}=1702$, 1736 (C=O, C=O···H), 3321 cm^{-1} (O–H); EI-MS: *m/z* (%): 278 (11) $[M]^+$, 200 (54) $[M-C_6H_6]^+$, 121 (51) $[M-C_8H_{13}O_3]^+$, 96 (100); HR-EIMS: calcd: 278.1154; found: 278.1151; elemental analysis calcd for $C_{15}H_{18}O_5$: C 64.74, H 6.52; found: C 64.72, H 6.52.

9a-Bromo-9-hydroxy-2,3,4,4a,9,9a-hexahydroxanthen-1-one (12): Water (ca. 15 mL) was slowly added to a solution of **6** (2.00 g, 10.0 mmol) in DMSO (60 mL), until the adduct precipitated. The mixture was then cooled with ice and NBS (3.56 g, 20.0 mmol) was slowly added. After all of the NBS had been added, the mixture was warmed to room temperature and stirred for 2 h. After this time, brine was added, the mixture was extracted with diethyl ether (5×15 mL), the organic layers were dried over sodium sulfate, and the solvent was evaporated. Column chromatography over silica gel (EtOAc/PE 1:5) produced **12** (2.39 g, 80%) as a yellow solid. M.p. 124–127 °C; $R_f=0.30$ (EtOAc/PE 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.55$–1.70 (m, 1H; cyclohexyl-CH_2), 1.94–2.06 (m, 1H; cyclohexyl-CH_2), 2.17–2.27 (m, 2H; cyclohexyl-CH_2), 2.34–2.44 (m, 1H; cyclohexyl-CH_2), 3.20 (td, ^3J(H,H)=14.8, 6.7 Hz, 1H; cyclohexyl-CH_2), 3.83 (s, 1H; OH), 4.22–4.30 (m, 1H; H4a), 5.12 (s, 1H; H9), 6.89–7.00 (m, 2H; H_{arom}), 7.21–7.32 ppm (m, 2H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.5$, 26.9, 36.2 (cyclohexyl-CH_2), 66.7 (C9a), 68.7 (C9), 72.2 (C4a), 116.6, 120.8, 121.6, 130.2, 131.5, 152.9 (C_{arom}), 203.8 ppm (C1); IR (KBr): $\tilde{\nu}=1719$ (C=O), 2873, 2951, 3386 cm^{-1} (br, O–H); EI-MS: *m/z* (%): 298/296 (46/47) $[M]^+$, 199 (100) $[M-HOBr]^+$; HR-EIMS: calcd: 296.0048; found: 296.0052; elemental analysis calcd for $C_{13}H_{13}O_3Br$: C 52.55, H 4.41; found: C 52.31, H 4.42.

9,9a-*cis*-1,9,9a-Trihydroxy-2,3,4,4a,9,9a-hexahydroxanthene (13): 2,3,4,4a-Tetrahydroxanthen-1-ol (**7**) (404 mg, 2.00 mmol) was added to a ice-cooled solution of NMO (468 mg, 4.00 mmol) and potassium-(VI)-osmate-dihydrate (36 mg, 100 μmol) in acetone/water 5:1 (18 mL). The mixture was then warmed to room temperature and stirred for 72 h. After this time, sodium sulfite (ca. 1 g) was added and the mixture was stirred for a further 1 h, before being extracted with EtOAc (3×10 mL). After drying and evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc/PE 1:1) to give **13** as colorless crystals (110 mg, 46%; based on recovered starting material). $R_f=0.21$ (EtOAc/CH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.35$–1.73 (m, 3H; cyclohexyl-CH_2), 1.77–1.83 (m, 1H; cyclohexyl-CH_2), 1.89–1.94 (m, 1H; cyclohexyl-CH_2), 1.99–2.03 (m, 1H; cyclohexyl-CH_2), 3.04 (s, 1H; OH), 3.52 (s, 2H; OH), 3.80 (dd, ^3J(H,H)=11.4, 4.8 Hz, 1H; H4a), 4.07 (dd, ^3J(H,H)=12.1, 5.1 Hz, 1H; H1), 5.21 (s, 1H; H9), 6.83 (dd, ^3J(H,H)=8.3, ^4J(H,H)=1.3 Hz, 1H; H_{arom}), 6.97 (td, ^3J(H,H)=7.6, ^4J(H,H)=1.3 Hz, 1H; H_{arom}), 7.20 (td, ^3J(H,H)=8.1, ^4J(H,H)=1.5 Hz, 1H; H_{arom}), 7.51 ppm (d, ^3J(H,H)=7.6 Hz, 1H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.9$, 28.2, 31.3 (cyclohexyl-CH_2), 64.4, 70.5, 77.6, 78.7 (C-1, C-4a, C-9, C-9a), 78.7, 116.9, 121.4, 128.6, 129.6, 151.9 ppm (C5a–C9a); IR (KBr): $\tilde{\nu}=3481$ cm^{-1} (O–H···O); EI-MS: *m/z* (%): 236 (20) $[M]^+$, 123 (100) $[M-C_6H_9O_2]^+$; HR-EIMS: calcd: 236.1049; found: 236.1046.

9-Hydroxy-2,3,4,9-tetrahydroxanthen-1-one (14): DABCO (1.13 g, 10.1 mmol) was added to a solution of **12** (1.00 g, 3.37 mmol) dissolved in dioxane (15 mL). The initially clear solution was stirred for 18 h whilst DABCO hydrobromide precipitated. After this time, the reaction mixture was diluted with water (50 mL) and extracted with diethyl ether (3×15 mL). The combined organic layers were then dried over sodium sulfate, the solvent was evaporated, and the residue was filtered over silica gel (EtOAc/PE 1:5+5% triethylamine) to give **14** (529 mg, 73%) as an orange oil, which was pure enough for synthetic purposes. To obtain an analytically pure sample of **14**, a sample was purified by flash column chromatography (EtOAc/PE 1:5+5% triethylamine), yielding the title compound as colorless crystals. M.p. 99–101 °C; $R_f=0.14$ (EtOAc/PE 1:5+5% NEt_3); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.94$–2.06 (m, 2H; cyclohexyl-CH_2), 2.35–2.43 (m, 2H; cyclohexyl-CH_2), 2.53–2.60 (m, 2H; cyclohexyl-CH_2), 5.65 (s, 1H; H9), 6.98 (dd, ^3J(H,H)=7.8, ^4J(H,H)=1.1 Hz, 1H; H_{arom}), 7.10 (ddd, ^3J(H,H)=7.9, 7.8, ^4J(H,H)=1.1 Hz, 1H; H_{arom}), 7.20 (ddd, ^3J(H,H)=7.8, 7.8, ^4J(H,H)=1.6 Hz, 1H; H_{arom}), 7.46 ppm (dd, ^3J(H,H)=7.8, ^4J(H,H)=1.6 Hz, 1H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.5$, 26.6, 35.7 (cyclohexyl-CH_2), 57.0 (C9), 112.6, 115.4 (C_{arom}), 121.6 (C9a), 124.1, 128.2, 129.1, 129.3, 148.5 (C_{arom}), 166.3 (C4a), 198.5 ppm (C1); IR (KBr): $\tilde{\nu}=1638$ (C=O), 2945, 3416 cm^{-1} (O–H); EI-MS: *m/z* (%): 216 (37) $[M]^+$, 215 (100) $[M-H]^+$, 198 (80) $[M-H_2O]^+$; HR-EIMS: calcd: 216.0786; found: 216.0791; elemental analysis calcd for $C_{13}H_{12}O_3$: C 72.21, H 5.59; found: C 71.64, H 5.54.

4a-Hydroxy-2,3,4,4a-tetrahydroxanthen-1-one (15): A solution of **14** (216 mg, 1.00 mmol) in THF (2 mL) was added to an ice-cooled solution of *o*-iodoxybenzoic acid (IBX, 560 mg, 2.00 mmol) in DMSO (2 mL). The solution was then warmed to room temperature and the conversion was controlled by TLC. After complete consumption of the starting material (ca. 1 h), water (10 mL) was added and the mixture extracted with EtOAc (×3). After drying over sodium sulfate, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc/cHex 1:5) to give **15** as an orange solid (174 mg, 80%). M.p. 110–112 °C; $R_f=0.17$ (EtOAc/CH 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.97–2.01 (m, 1H; cyclohexyl-CH_2), 2.09–2.23 (m, 2H; cyclohexyl-CH_2), 2.31–2.38 (m, 1H; cyclohexyl-CH_2), 2.46–2.49 (m, 1H; cyclohexyl-CH_2), 2.62–2.66 (m, 1H; cyclohexyl-CH_2), 3.32 (s, 1H; OH), 7.03 (d, 2H ^3J(H,H)=7.8 Hz; H_{arom}), 7.33 (d, 2H, ^3J(H,H)=7.5 Hz; H_{arom}), 7.51 ppm (s, 1H; H9); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=18.0$, 35.7, 38.8 (cyclohexyl-CH_2), 96.3 (C4a), 117.1, 119.5, 122.1, 129.7, 130.1, 130.3, 132.2,

152.5, 197.5 ppm (C1); IR (KBr): $\tilde{\nu}$ = 1603, 1557, 1664 (C=O), 3335 cm^{-1} (O−H); EI-MS: *m/z* (%): 216 (99) $[M]^+$, 188 (100); HR-EIMS: calcd: 216.0786; found: 216.0783; elemental analysis calcd for $C_{13}H_{12}O_3$: C 72.21, H 5.59; found: C 71.82, H 5.81.

2,3,4,9-Tetrahydro-1*H*-xanthene-1,9-dione (16): A solution of NMO (2.03 g, 15.0 mmol), molecular sieves (1.00 g, 4 Å), and **15** (1.08 g, 5.00 mmol) in a mixture of dichloromethane (25 mL) and acetonitrile (5 mL) was stirred under argon for 15 min. TPAP (175 mg, 0.500 mmol) was then added and the resulting mixture treated with ultrasound for 12 h. After this time, the solvent was evaporated and the residue was directly purified by column chromatography (EtOAc/chloroform 1:1) to give **16** (0.854 g, 79%) as a red-brown solid. M.p. 180–183 °C; R_f = 0.08 (EtOAc/Chloroform 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.16–2.21 (m, 2H; cyclohexyl-CH_2), 2.60–2.63 (m, 2H; cyclohexyl-CH_2), 2.99–3.02 (m, 2H; cyclohexyl-CH_2), 7.39–7.42 (m, 2H; H_{arom}), 7.66 (ddd, 1H, ^3J(H,H) = 8.2, 7.2, ^4J(H,H) = 1.9 Hz; H_{arom}), 8.25 ppm (dd, 1H, ^3J(H,H) = 8.2, ^4J(H,H) = 1.6 Hz; H_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 30.2, 39.1 (cyclohexyl-CH_2), 117.6, 118.2, 125.8, 126.5, 127.5, 134.5, 155.3, 174.3, 178.4, 194.4 ppm; IR (KBr): $\tilde{\nu}$ = 1400, 1616, 1696 cm^{-1} (C=O); EI-MS: *m/z* (%): 214 (53) $[M]^+$, 186 (100); HR-EIMS: calcd: 214.0629; found: 214.0632.

9-Methyl-2,3,4,9-tetrahydroxanthene-1-one (17): Boron trifluoride diethyl etherate (13 μL, 0.100 mmol) was added to a pre-cooled (−78 °C) solution of **14** (216 mg, 1.00 mmol) in toluene (10 mL) under argon. The resulting dark yellow solution was stirred at −78 °C for 5 min. Dimethylzinc (1.00 mL, 2.00 mmol, 2 M in toluene) was then added and the solution was slowly warmed to room temperature. After the addition of water, the mixture was extracted with EtOAc (3×) and dried over sodium sulfate. Column chromatography (EtOAc/cHex 1:5) yielded **17** (191 mg, 89%) as a yellow solid. M.p. 63–65 °C; R_f = 0.39 (EtOAc/CH 1:5); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (d, ^3J(H,H) = 6.8 Hz, 3H; CH_3), 2.01–2.08 (m, 2H; cyclohexyl-CH_2), 2.33–2.42 (m, 1H; cyclohexyl-CH_2), 2.47–2.66 (m, 3H; cyclohexyl-CH_2), 3.90 (q, ^3J(H,H) = 6.8 Hz, 1H; H-9), 6.98 (dd, ^3J(H,H) = 7.8, ^4J(H,H) = 1.0 Hz, 1H; H_{arom}), 7.10 (ddd, ^3J(H,H) = 7.6, 7.3, ^4J(H,H) = 1.3 Hz; H_{arom}), 7.14–7.20 ppm (m, 2H; H_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9 (CH_3), 25.7, 26.9, 28.1 (cyclohexyl-CH_2), 37.4, 116.1, 116.5, 125.2, 127.6, 127.8, 129.2, 149.9, 167.0, 198.0 ppm; IR (KBr): $\tilde{\nu}$ = 1232, 1640 (C=O), 2946 cm^{-1}; EI-MS: *m/z* (%): 214 (19) $[M]^+$, 199 (100); HR-EIMS: calcd: 214.0993; found: 214.0999.

9-Cyano-2,3,4,9-tetrahydroxanthene-1-one (18): Boron trifluoride diethyl etherate (13 μL, 0.100 mmol) was added to a pre-cooled solution (−78 °C) of **14** (216 mg, 1.00 mmol) in toluene (10 mL) under argon. The resulting dark yellow solution was stirred at −78 °C for 5 min. Diethylaluminium cyanide (2.00 mL, 2.00 mmol, 1 M in toluene) was then added and the solution was slowly warmed to room temperature. After the addition of water, the mixture was extracted with EtOAc (×3) and dried over sodium sulfate. Column chromatography (EtOAc/cHex 1:5) yielded **18** (135 mg, 60%) as an orange solid. M.p. 141–142 °C; R_f = 0.06 (EtOAc/CH 1:5); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.09–2.16 (m, 2H; cyclohexyl-CH_2), 2.43–2.76 (m, 4H; cyclohexyl-CH_2), 4.96 (s, 1H; 9-H), 7.10 (dd, ^3J(H,H) = 8.3, ^4J(H,H) = 1.0 Hz, 1H; H_{arom}), 7.23 (ddd, ^3J(H,H) = 8.3, 7.6, ^4J(H,H) = 1.0 Hz; H_{arom}), 7.35 (ddd, ^3J(H,H) = 8.6, 8.5, ^4J(H,H) = 1.5 Hz; H_{arom}), 7.43 ppm (d, ^3J(H,H) = 7.6 Hz, 1H; H_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2 (cyclohexyl-CH_2), 24.1 (CH), 26.9, 28.1 (cyclohexyl-CH_2), 105.9, 115.3, 117.4, 118.9, 126.0, 129.8, 130.2, 148.8, 168.2, 198.6 ppm; IR (KBr): $\tilde{\nu}$ = 1644 (C=O), 2242 (CN), 2960 cm^{-1}; EI-MS: *m/z* (%): 225 (100) $[M]^+$, 198 (24); HR-EIMS: calcd: 225.0789; found: 225.0793.

1-Hydroxy-4a-methyl-2,3,4,4a-tetrahydroxanthene-9-one (20): Methyllithium (6.25 mL, 10.0 mmol; 1.6 M in ether) was slowly added to a solution of copper cyanide (896 mg, 10.0 mmol) in diethyl ether (15 mL) under argon at −50 °C. After the copper cyanide had dissolved, the solution was cooled to −78 °C and **16** (428 mg, 2.00 mmol) was added. The resulting deep-red solution was stirred at −78 °C for 5 h and then poured into an HCl solution (10%). This mixture was filtered through Celite, the filter cake washed with EtOAc, and the organic layer separated. After drying over sodium sulfate, evaporation of the solvent, and column chromatography (EtOAc/cHex 1:5), **20** (363 mg, 79%) was isolated as a yellow solid. M.p. 95–96 °C; R_f = 0.62 (EtOAc/CH 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 3H; CH_3), 1.73–2.13 (m, 4H; cyclohexyl-CH_2), 2.35–2.59 (m, 2H; cyclohexyl-CH_2), 6.88 (d, ^3J(H,H) = 8.2 Hz, 1H; H_{arom}), 7.01 (ddd, ^3J(H,H) = 7.6, 7.3, ^4J(H,H) = 0.9 Hz; H_{arom}), 7.43 (td, ^3J(H,H) = 7.3, ^4J(H,H) = 1.8 Hz; H_{arom}), 7.84 (dd, ^3J(H,H) = 7.9, ^4J(H,H) = 1.8 Hz, 1H; H_{arom}), 15.26 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6 (CH_3), 26.6, 30.8, 36.0 (cyclohexyl-CH_2), 78.8, 109.1, 118.2, 120.6, 121.6, 126.7, 135.5, 158.7, 180.5, 182.9 ppm; IR (KBr): $\tilde{\nu}$ = 1610 (C=O), 2953 cm^{-1}; EI-MS: *m/z* (%): 230 (7) $[M]^+$, 215 (100); HR-EIMS: calcd: 230.0942; found: 230.0947.

4a,9a-*cis*-9a-Hydroxy-4a-methyl-3,4,4a,9a-tetrahydro-2*H*-xanthene-1,9-dione (21): *m*-Chloroperbenzoic acid (322 mg, 1.30 mmol, 70%) was added to a solution of **20** (200 mg, 0.870 mmol) in dichloromethane (10 mL) and the mixture was stirred at room temperature for 4 h. After this time, saturated $NaHCO_3$ solution was added and the mixture was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate, and after evaporation of the solvent the crude mixture of **21** and **22** was purified by column chromatography (EtOAc/cHex 1:5) to give **21** (73 mg, 34%) as a white solid. R_f = 0.31 (EtOAc/CH 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3H; CH_3), 1.88–2.25 (m, 4H; cyclohexyl-CH_2), 2.31–2.40 (m, 1H; cyclohexyl-CH_2), 2.80–2.93 (m, 1H; cyclohexyl-CH_2), 4.49 (s, 1H; OH), 6.92 (d, ^3J(H,H) = 8.2 Hz, 1H; H_{arom}), 7.04 (ddd, ^3J(H,H) = 8.2, 7.9, ^4J(H,H) = 0.9 Hz; H_{arom}), 7.51 (ddd, ^3J(H,H) = 7.9, 7.3, ^4J(H,H) = 1.8 Hz; H_{arom}), 7.86 ppm (dd, ^3J(H,H) = 7.6, ^4J(H,H) = 1.5 Hz, 1H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (CH_3), 20.7, 32.7, 36.6 (cyclohexyl-CH_2), 80.7, 86.9, 118.9, 119.1, 122.0, 127.2, 128.2, 137.3, 192.6, 208.2 ppm; IR (KBr): $\tilde{\nu}$ = 1682 (C=O), 2959, 3443 cm^{-1} (OH); EI-MS: *m/z* (%): 246 (52) $[M]^+$, 121 (100); HR-EIMS: calcd: 246.0892; found: 246.0897.

4a,9a-*trans*-9a-Hydroxy-4a-methyl-3,4,4a,9a-tetrahydro-2*H*-xanthene-1,9-dione (22): Magnesiummonoperoxophthalate (192 mg, 0.310 mmol; 80%) was added to a solution of **20** (143 mg, 0.620 mmol) in ethanol (20 mL). The mixture was stirred at room temperature for 2 h and then the solvent was evaporated. The residue was directly purified by column chromatography (EtOAc/cHex 1:2) to give **22** (74 mg, 48%) as a white solid. R_f = 0.23 (EtOAc/CH 1:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 3H; CH_3), 1.65–1.73 (m, 1H; cyclohexyl-CH_2), 1.89–1.93 (m, 1H; cyclohexyl-CH_2), 2.04–2.10 (m, 1H; cyclohexyl-CH_2), 2.27–2.30 (m, 1H; cyclohexyl-CH_2), 2.67–2.74 (m, 1H; cyclohexyl-CH_2), 3.29–3.36 (m, 1H; cyclohexyl-CH_2), 3.54 (s, 1H; OH), 6.96 (dd, ^3J(H,H) = 8.5, ^4J(H,H) = 0.6 Hz, 1H; H_{arom}), 7.06 (ddd, ^3J(H,H) = 8.2, 7.9, ^4J(H,H) = 0.9 Hz; H_{arom}), 7.52 (ddd, ^3J(H,H) = 8.5, 7.2, ^4J(H,H) = 1.9 Hz; H_{arom}), 7.92 ppm (dd, ^3J(H,H) = 8.2, ^4J(H,H) = 1.9 Hz, 1H; H_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.7 (CH_3), 20.7, 31.5, 37.5 (cyclohexyl-CH_2), 77.9, 84.7, 118.5, 119.7, 122.2, 128.1, 136.6, 157.4, 186.8, 206.0 ppm; IR (KBr): $\tilde{\nu}$ = 1464, 1606, 1728 (C=O), 2979, 3377 cm^{-1} (OH); EI-MS: *m/z* (%): 246 (29) $[M]^+$, 121 (100); HR-EIMS: calcd: 246.0892; found: 246.0895.

4a,9a-*cis*-1,9a-Dihydroxy-4a-methyl-1,2,3,4,4a,9a-hexahydroxanthene-9-one (23, mixture of diastereoisomers): Sodium borohydride (5 mg, 0.130 mmol) was added in portions to a solution of **21** (33 mg, 0.130 mmol) in dichloromethane/methanol (1:1, 1 mL) under argon at −78 °C. The conversion was monitored by TLC. After complete consumption of the starting material (ca. 1 h), the mixture was warmed to room temperature and the solvent was evaporated. The residue was directly purified by column chromatography (EtOAc/cHex 1:5) to give **23** (8 mg, 25%) as an inseparable mixture of two diasteroisomers (*cis*-1,9a/*trans*-1,9a 3:1) as a white solid. R_f = 0.16 (EtOAc/CH 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 3H; CH_3 *trans*), 1.33 (s, 3H; CH_3 *cis*), 1.55–2.09 (m, 12H; cyclohexyl-CH_2), 2.56 (s, 2H; OH), 3.69–3.74 (ddd, ^3J(H,H) = 10.1, 5.0, 3.5 Hz, 1H; H1 *cis*), 3.78 (s, 1H; OH *cis*), 3.89–3.96 (ddd, ^3J(H,H) = 14.9, 10.4, 4.6 Hz, 1H; H1 *trans*), 3.97 (s, 1H; OH *trans*), 6.92–6.95 (m, 2H; H_{arom}), 7.00–7.04 (m, 2H; H_{arom}), 7.48–7.54 (m, 2H; H_{arom}), 7.84–7.87 ppm (m, 2H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3 *trans*), 18.8 (CH_3 *cis*), 19.6 (CH_2 *trans*), 20.7 (CH_2 *cis*), 26.9 (CH_2 *cis*), 28.8 (CH_2 *trans*), 32.9 (CH_2 *trans*), 33.5 (CH_2 *cis*), 70.4 (*trans*), 74.4 (*cis*), 74.6 (*trans*), 77.2 (*cis*), 77.6 (*trans*), 83.3 (*cis*), 83.4 (*cis*), 85.0 (*trans*), 118.4 (*trans*), 118.6 (*cis*), 121.3 (*trans*), 121.3 (*cis*), 126.7 (*cis*), 127.4 (*trans*), 136.8 (*cis*), 136.9 (*trans*), 159.2 (*trans*), 160.2 (*cis*), 195.9

(*trans*), 197.3 ppm (*cis*); IR (KBr): $\tilde{\nu}$ = 1677 (C=O), 2932, 3410 cm^{-1} (OH); EI-MS: *m*/*z* (%): 248 (16) $[M]^+$, 177 (100); HR-EIMS: calcd: 248.1048; found: 248.1046.

1,9a-*trans*-4a,9a-*trans*-1,9a-Dihydroxy-4a-methyl-1,2,3,4,4a,9a-hexahydroxanthene-9-one (24): Sodium borohydride (7 mg, 0.180 mmol) was added in portions to a solution of **22** (44 mg, 0.180 mmol) in dichloromethane/methanol 1:1 (2 mL) under argon at −78 °C. The conversion was monitored by TLC. After complete consumption of the starting material (ca. 1 h), the mixture was warmed to room temperature and the solvent was evaporated. The residue was directly purified by column chromatography (EtOAc/cHex 1:2) to give **24** (17 mg, 42%) as a white solid. R_f = 0.44 (EtOAc/CH 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3H; CH_3), 1.65–1.73 (m, 1H; cyclohexyl-CH_2), 1.89–1.93 (m, 1H; cyclohexyl-CH_2), 2.04–2.10 (m, 1H; cyclohexyl-CH_2), 2.27–2.30 (m, 1H; cyclohexyl-CH_2), 2.67–2.74 (m, 1H; cyclohexyl-CH_2), 3.29–3.36 (m, 1H; cyclohexyl-CH_2), 3.54 (s, 1H; OH), 6.96 (dd, ^3J(H,H) = 8.5, ^4J(H,H) = 0.6 Hz, 1H; H_{arom}), 7.06 (ddd, ^3J(H,H) = 8.2, 7.9, ^4J(H,H) = 0.9 Hz; H_{arom}), 7.52 (ddd, ^3J(H,H) = 8.5, 7.2, ^4J(H,H) = 1.9 Hz; H_{arom}), 7.92 ppm (dd, ^3J(H,H) = 8.2, ^4J(H,H) = 1.9 Hz, 1H; H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (CH_3), 20.3, 28.6, 33.4 (cyclohexyl-CH_2), 68.9, 75.0, 83.9, 119.4, 121.6, 121.8, 128.0, 136.9, 160.1, 193.9 ppm; IR (KBr): $\tilde{\nu}$ = 1463, 1608, 1658 (C=O), 2948, 3437 cm^{-1} (OH); EI-MS: *m*/*z* (%): 248 (30) $[M]^+$, 121 (100); HR-EIMS: calcd: 248.1048; found: 248.1047.

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