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


Dedicated to Professor Joachim Bargon

Abstract: Tetrahydroxanthenones, which can be easily prepared by a domino oxo-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.

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]

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.

Results and Discussion

At the outset of our synthetic efforts, we realized that tetrahydroxanthenones 5 are easily accessible by means of a domino oxo-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-
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.[5] 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.[6]

Although ketol 10 already possesses the requisite substitution pattern for diversional (1) at C1, C9, and C9a, the corresponding alkyl or carboxymethyl substituent on C4a still had to be introduced.[9] We therefore reasoned that the elimination of water from ketol 10 or a ketol derived from triol 8 would give rise to an $\alpha,\beta$-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

![Scheme 1. Domino oxa-Michael aldol condensation.](image1)

![Scheme 2. Transformations of tetrahydroxanthenone 6: a) NaBH₄, MeOH, RT, 4 h, 77%; b) K₂OsO₄, K₂CO₃, K₃Fe(CN)₆, $t$BuOH/water 5:1, RT, 72 h, 51%; c) Ac₂O, pyridine, 0°C to RT, 4 h, 83%; d) K₂OsO₄, K₂CO₃, NMO (2.2 equiv), acetone/water 5:1, RT, 3 h, 74%; e) K₂OsO₄, K₂CO₃, 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) K₂OsO₄, K₂CO₃, 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.

![Figure 1. Molecular structure of bromohydrine 12.](image2)
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. 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$_2$N$_2'$ reaction (Scheme 4).

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).

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 methylolithium 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-chloroperoxybenzoic 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 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-
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 attributed to hydrogen bonding between the substrate and mCPBA.[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).

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 diastereoselectivity. 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 stereoelectronic 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
syr-ketol 21, the moderate diastereoselectivity 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 syr-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 tetrahydroxanthrenones that are readily available by a domino oxan- Michael aldol condensation. The structure of tetrahydroxanthrenones 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 stereotriadies 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 foil was layered with silica gel with fluorescence indicator (silica gel 60F254). Silica gel 60 (230–400 mesh) under flash conditions. For TLC, aluminum = 0.4 mm thick. TMS = tetramethylsilane. CDCl3: 7.26 ppm (1H, d, J=7.2Hz, H2); 7.16 ppm (1H, d, J=7.2Hz, H3); 5.2 ppm (2H, s, CH2); 4.22 ppm (2H, d, J=10.8Hz, H4); 3.88 ppm (2H, d, J=7.2Hz, H5); 2.29 ppm (2H, d, J=13.4Hz, H6); 1.27 ppm (1H, t, J=7.2Hz, H7).

Highly Functionalized Tetrahydroxanthrenols

2,3,4,4a-Tetrahydroxanthren-1-one (7): Compound 6 (20 mg, 0.10 mmol) was added to a suspension of sodium borohydride (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/Pc 1:1), yielding 7 (23 mg, 77% yield) as colorless crystals. M.p. 129–132°C, [α]D = 11.0 (EtOAc/Pc 1:1); 1H NMR (400 MHz, CDCl3): δ = 1.56–1.68 (m, 1H, cyclohexyl-CH2), 1.88–2.04 (m, 2H, cyclohexyl-CH2), 2.31 (ddd, 3J HH = 18.1, 3J HC = 13.0, 6.1 Hz, 1H, H2 sec), 2.37–2.45 (m, 1H, cyclohexyl-CH2), 2.51 (d pseudo-qui, 3J HH = 17.94, 3J HC = 2.5 Hz, 1H, H3 sec), 4.92 (ddd, 3J HH = 10.9, 6.1, 3J HC = 2.4 Hz, 1H, H4a), 6.80 (d, 3J HH = 7.8 Hz, 1H, H5 sec), 6.87 (ddd, 3J HH = 7.8, 7.6, 3J HC = 1.1 Hz, 1H, H3 sec), 7.12–7.19 (m, 2H, H5 sec). 7.35 ppm (d, 3J HH = 2.4 Hz, 1H, H9); 13C NMR (100 MHz, CDCl3): δ = 18.0, 29.7, 38.8 (cyclohexyl-CH2), 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).

(120mg,51%)ascolorlesscrystals.M.p.137–139°C, [α]D = 11.0 (EtOAc/Pc 1:1); 1H NMR (400 MHz, CDCl3): δ = 1.16–1.39 (m, 2H, cyclohexyl-CH2), 1.41–1.53 (m, 1H, cyclohexyl-CH2), 1.61–1.69 (m, 1H, cyclohexyl-CH2), 1.73–1.86 (m, 2H, cyclohexyl-CH2), 3.50 (dd, 3J HH = 11.6, 4.9 Hz, H1a), 3.89 (dd, 3J HH = 12.0, 4.9 Hz, H1), 5.12 (dd, 3J HH = 7.6, 7.6 Hz, H7); 13C NMR (100 MHz, CDCl3): δ = 17.94, 21.7, 32.6, 34.3, 43.5, 51.9, 69.7, 76.7 Hz, 1H, H1a); 13C NMR (100 MHz, CDCl3): δ = 19.6, 27.9, 30.8 (cyclohexyl-CH2), 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): δ = 3516 cm−1 (O–H,O); EI-MS: m/z (%): 256 (90) [M]+, 123 (100) [M–C4H7O]+, 122 (69), [M–C4H7O]+; HR-EIMS: calcd: 236.1049; found: 236.1049; elemental analysis calcd for C13H16O4: C 66.09, H 6.83; found: C 65.91, H 6.74.

O-Acetyl-2,3,4,4a-tetrahydroxanthren-1-ol (9): Acetic anhydride (0.37 mL, 4.0 mmol) was added to an ice-cooled solution of potassium hexacyanoferrate(ii) (988 mg, 3.00 mmol) and potassium osmate(vi) dihydride (17 mg, 50 mmol) in water (5 mL). The mixture was then warmed to room temperature and stirred for 72 h. After this time, sodium sulfate (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/Pc 1:1 as colorless crystals). The diastereoselectivity could be explained by the position of the methyl group. Contrary to the position of the chelating hydroxyl function in place, it seems that it is the steric hindrance of the methyl group which exerts the determining influence in this reaction.
Compound 9 (49 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 7 (29 mg, 80%) as colorless crystals. M.p. 124–127°C; IR (KBr): v = 1742 cm⁻¹ (C=O); EI-MS: m/z (%): 244 (21) [M⁺], 184 (100) [M-HOAc]⁺, 157 (37) [M-H₂OCC₂H₄OH]⁺; HR-EIMS: calc’d: 244.1099; found: 244.1101; elemental analysis calc’d for C₁₉H₂₈O₃: 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-hexahydropyrene-9-one (10): Compound 9 (200 mg, 0.830 mmol) was added to a solution of NMO (280 mg, 1.25 mmol) and potassium osmate(vi) dihydrate (15 mg, 0.42 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 10 (79 mg, 77%), based on recovered starting material) as colorless crystals. M.p. 131–146°C; IR (KBr): v = 1681 cm⁻¹ (C=O), 1731 cm⁻¹; EI-MS: m/z (%): 276 (21) [M⁺], 234 (39) [M-H₂OCC₂H₄OH]⁺, 163 (99) [M-H₂OCC₂H₄OH]⁺, 121 (100) [M-C₆H₄OH]⁺; HR-EIMS: calc’d: 276.0998; found: 276.0996; elemental analysis calc’d for C₁₅H₁₆O₃: C, 75.21; H, 6.29.

1-O-Acetyl-1,9a-trihydroxy-2,3,4,4a,9,9a-hexahydropyrene (11): Compound 9 (200 mg, 0.830 mmol) was added to a solution of NMO (280 mg, 1.25 mmol) and potassium osmate(vi) dihydrate (15 mg, 0.42 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; IR (KBr): v = 1681 cm⁻¹ (C=O), 1731 cm⁻¹; EI-MS: m/z (%): 276 (21) [M⁺], 234 (39) [M-H₂OCC₂H₄OH]⁺, 163 (99) [M-H₂OCC₂H₄OH]⁺, 121 (100) [M-C₆H₄OH]⁺; HR-EIMS: calc’d: 276.0998; found: 276.0996; elemental analysis calc’d for C₁₅H₁₆O₃: C, 75.21; H, 6.29.

9a-Bromo-9-hydroxy-2,3,4,4a,9,9a-hexahydropyrene-1-one (12): Water (15 mL) was slowly added to a solution of 6 (2.00 g, 10.00 mmol) in DMSO (60 mL) until the adduct precipitated. The mixture was then cooled with ice and NBS (3.56 g, 20.00 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, ice 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; IR (KBr): v = 1700 cm⁻¹ (C=O); EI-MS: m/z (%): 244 (21) [M⁺], 184 (100) [M-HOAc]⁺, 157 (37) [M-H₂OCC₂H₄OH]⁺; HR-EIMS: calc’d: 244.1099; found: 244.1101; elemental analysis calc’d for C₁₉H₂₈O₃: C, 73.75; H, 6.60; found: C, 73.52; H, 6.52.

9a-Bromo-9-hydroxy-2,3,4,4a,9,9a-hexahydropyrene-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 (BXX, 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 × 10 mL). After drying over sodium sulfate, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc/Hexa 1:5) to give 15 as an orange solid (174 mg, 80%). M.p. 110–112°C; IR (KBr): v = 1710 cm⁻¹ (C=O); EI-MS: m/z (%): 244 (30) [M⁺], 184 (99) [M-HOAc]⁺, 157 (37) [M-H₂OCC₂H₄OH]⁺; HR-EIMS: calc’d: 244.1099; found: 244.1101; elemental analysis calc’d for C₁₉H₂₈O₃: C, 73.75; H, 6.60; found: C, 73.52; H, 6.52.

9a-Bromo-9-hydroxy-2,3,4,4a,9,9a-hexahydropyrene-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 (BXX, 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 × 10 mL). After drying over sodium sulfate, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc/Hexa 1:5) to give 15 as an orange solid (174 mg, 80%). M.p. 110–112°C; IR (KBr): v = 1710 cm⁻¹ (C=O); EI-MS: m/z (%): 244 (30) [M⁺], 184 (99) [M-HOAc]⁺, 157 (37) [M-H₂OCC₂H₄OH]⁺; HR-EIMS: calc’d: 244.1099; found: 244.1101; elemental analysis calc’d for C₁₉H₂₈O₃: C, 73.75; H, 6.60; found: C, 73.52; H, 6.52.

9a-BrO-9-Hydroxy-2,3,4,4a,9,9a-Hexahydropyrene-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 (BXX, 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 × 10 mL). After drying over sodium sulfate, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc/Hexa 1:5) to give 15 as an orange solid (174 mg, 80%). M.p. 110–112°C; IR (KBr): v = 1710 cm⁻¹ (C=O); EI-MS: m/z (%): 244 (30) [M⁺], 184 (99) [M-HOAc]⁺, 157 (37) [M-H₂OCC₂H₄OH]⁺; HR-EIMS: calc’d: 244.1099; found: 244.1101; elemental analysis calc’d for C₁₉H₂₈O₃: C, 73.75; H, 6.60; found: C, 73.52; H, 6.52.
152.5, 197.5 ppm (C1); IR (KBr): m/z (%): 216 (99), 180 (100); HR-EIMS: calculated 216.0786; found: 216.0783; elemental analysis calculated for C14H18O2: C 72.21, H 5.99; found: C 71.82, H 5.81.

3.4,9-Tetrahydro-1H-xanthene-1,9-dione (16): A solution of NMO (2.0 g, 15.0 mmol), molecular sieves (1.00 g, 4.4 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. TPA (175 mg, 0.50 mmol) was then added and the resulting mixture treated with ultrasonad 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, 77% as a red-brown solid. M.p. 180–183°C; Rf = 0.08 (EtOAc/Chloroform 1:1); 1HNMR (500 MHz, CDCl3): δ = 2.16–2.20 (m, 2H; cyclohexyl-CH2), 2.60–2.63 (2H, 2H; cyclohexyl-CH2); 2.91–3.02 (m, 2H; cyclohexyl-CH2), 7.39–7.42 (2H, 2H; H arom), 7.66 (dd, 1H, J = 8.2, 7.2, 3J = 11 Hz, 1H; H arom), 8.25 ppm (dd, 1H, J = 8.2 Hz, 8J = 1.6 Hz; Hetk); 13C NMR (125 MHz, CDCl3): δ = 33.8, 37.6, 41.6, 50.3, 118.4, 120.3, 121.4, 127.9, 128.1, 129.3, 130.6 ppm; HR-EIMS: calculated 214.0632; found: 214.0632.

9-Methyl-3,4,9-tetrahydroxanthene-1-one (17): Boron trifluoride diethyl etherate (13 mL, 0.100 mol) 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. Dimethylzine (1.00 mL, 2.00 mmol, 2m in toluene) was then added and the solution was stirred at room temperature for 3h. After addition of water, the mixture was extracted with EtOAc (3 x) and dried over sodium sulfate. Column chromatography (EtOAc/Hex 1:5) yielded 17 (191 mg, 89%) as a yellow solid. M.p. 63–65°C; Rf = 0.39 (EtOAc/Ch 5:1); 1HNMR (500 MHz, CDCl3): δ = 0.97 (t, 3J = 6.8 Hz, 3H, CH3), 2.01–2.08 (m, 2H; cyclohexyl-CH2), 2.33–2.42 (m, 1H; cyclohexyl-CH2), 2.47–2.66 (m, 3H; cyclohexyl-CH2), 3.90 (q, 3J = 6.8 Hz, 1H; H-9), 6.98 (dd, 3J = 7.8, 8J = 1.0 Hz, 1H; H arom), 7.10 (dd, 3J = 7.8 Hz, 7.3; 1H = 13.5 Hz; Hetk), 7.14–7.20 ppm (2H, 2H; Hetk); 13C NMR (125 MHz, CDCl3): δ = 20.9 (CH3), 25.7, 26.9, 28.1 (cyclohexyl-CH2), 37.4, 116.4, 116.5, 125.2, 127.6, 127.8, 129.2, 149.5, 167.0, 190.0 ppm; IR (KBr): v ~ 1323, 1640 (C=O), 2946 cm−1; EI-MS: m/z (%): 214 (19) [M]+, 199 (100); HR-EIMS: calculated 214.0993; found: 214.0993.

2-1H,9a-2H-Dihydro-4a-methyl-3,4a,9a-tetrahydro-2H-xanthene-1,9-dione (21): Magnesiummonooxonopropylxanthenol (192 mg, 0.310 mmol; 80%) 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 4h. After this time, saturated NaHCO3 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/Hex 1:5) to give 21 (73 mg, 34%) as a white solid. Rf = 0.31 (EtOAc/Ch 1:5); 1HNMR (400 MHz, CDCl3): δ = 1.31 (s, 3H, CH3), 1.65–1.73 (1H; cyclohexyl-CH2), 1.89–1.93 (1H; cyclohexyl-CH2), 2.04–2.10 (1H, 1H; cyclohexyl-CH2), 2.27–2.30 (1H, 1H; cyclohexyl-CH2), 2.67–2.74 (1H, 1H; cyclohexyl-CH2), 3.29–3.36 (1H, 1H; cyclohexyl-CH2), 3.54 (s, 1H; OH), 6.96 (dd, 3J = 8.5, 8J = 0.6 Hz, 1H; Hetk), 7.06 (dd, 3J = 8.2, 7.9, 7.9; 1H = 1.8 Hz; Hetk), 7.86 ppm (dd, 3J = 7.6, 1.5 Hz 1H; H arom); 13C NMR (100 MHz, CDCl3): δ = 19.2 (CH2), 20.7, 20.7, 21.4 ppm (2H, 2H; cyclohexyl-CH2), 78.3, 80.0, 88.6, 118.3, 121.9, 127.5, 138.3, 144.4, 156.1 ppm; HR-EIMS: calculated 246.0892; found: 246.0897.

4a,9a-1H,9a-Dihydro-4a-methyl-3,4a,9a-tetrahydro-2H-xanthene-1,9-dione (22): Magnesumpimonopropylxanthanethiol (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 2h then the solvent was evaporated. The residue was directly purified by column chromatography (EtOAc/Hex 1:2) to give 22 (74 mg, 48%) as a white solid. Rf = 0.74 (EtOAc/Ch 1:2); 1HNMR (500 MHz, CDCl3): δ = 0.31 (s, 3H, CH3), 1.65–1.73 (1H; cyclohexyl-CH2), 1.89–1.93 (1H; cyclohexyl-CH2), 2.04–2.10 (1H, 1H; cyclohexyl-CH2), 2.27–2.30 (1H, 1H; cyclohexyl-CH2), 2.67–2.74 (1H, 1H; cyclohexyl-CH2), 3.29–3.36 (1H, 1H; cyclohexyl-CH2), 3.54 (s, 1H; OH), 6.96 (dd, 3J = 8.5, 8J = 0.6 Hz, 1H; Hetk), 7.06 (dd, 3J = 8.2, 7.9, 7.9; 1H = 1.8 Hz; Hetk), 7.86 ppm (dd, 3J = 7.6, 1.5 Hz 1H; H arom); 13C NMR (100 MHz, CDCl3): δ = 17.7 (CH2), 20.7, 31.5, 37.5 (cyclohexyl-CH2), 77.9, 84.7, 118.5, 119.7, 122.2, 128.1, 136.6, 157.4, 186.8, 206.0 ppm; IR (KBr): v ~ 1464, 1606, 1728 (C=O), 2979, 3377 cm−1 (OH); EI-MS: m/z (%): 246 (29) [M]+, 121 (100); HR-EIMS: calculated 246.0892; found: 246.0895.
1,9a-trans-4a,9a-trans-1,9a-Dihydroxy-4a-methyl-1,2,3,4,4a,9a-hexahydro- 
drostan-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 dichloro-
ethane/methanol 1:1 (2 mL) under argon at −78 °C. The conversion was 
monitored by TLC. After complete consumption of the starting material 
(1 h), the mixture was warmed to room temperature and the solvent 
was removed in vacuo.

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