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TOTAL SYNTHESIS OF (±)-4-DEOXYBLENNOLIDE C VIA SPIROCHROMANONE

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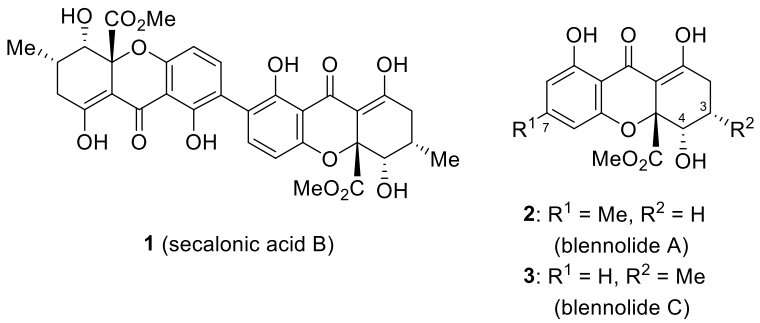
This article is dedicated to Professor Yasuyuki Kita on his 77th birthday.

Abstract – We report the total synthesis of (±)-4-deoxyblennolide C, a deoxy analogue of xanthone antibiotics blennolide C isolated from the fermentation broth of *Blennoria* sp. The synthesis involves construction of a quaternary carbon during the formation of spirochromanone through the aldol reaction of *o*-hydroxyacetophenones and cyclohexenone, oxidative cleavage of the alkene moiety, and the construction of a xanthone framework by Dieckmann condensation.

Xanthones have been isolated from a wide range of plants, bacteria, fungi, and lichens.[1] The blennolides are a class of antibiotic xanthones that were isolated together with secalonic acid B (**1**) from the fermentation broth of *Blennoria* sp., an endophytic fungus from *Carpobrotus edulis*.[2]



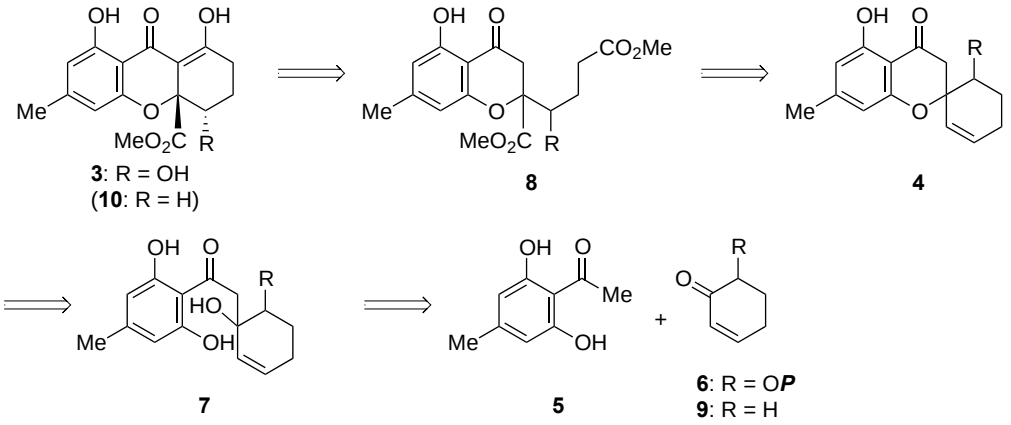
1 (secalonic acid B)

2: R^1 = Me, R^2 = H (blennolide A)
3: R^1 = H, R^2 = Me (blennolide C)

Figure 1. Representative xanthones **1-3** from *Blennoria* sp.

Blennolide A (**2**) is a monomeric part of **1** and blennolide C (**3**) is a regioisomer of **2**, which possesses a methyl group at the 7 position. Compounds **1–3** have shown antibacterial, antifungal, and antialgal activities. A series of synthetic studies toward monomeric blennolides[3] and the corresponding dimers[4] have been reported (Figure 1).

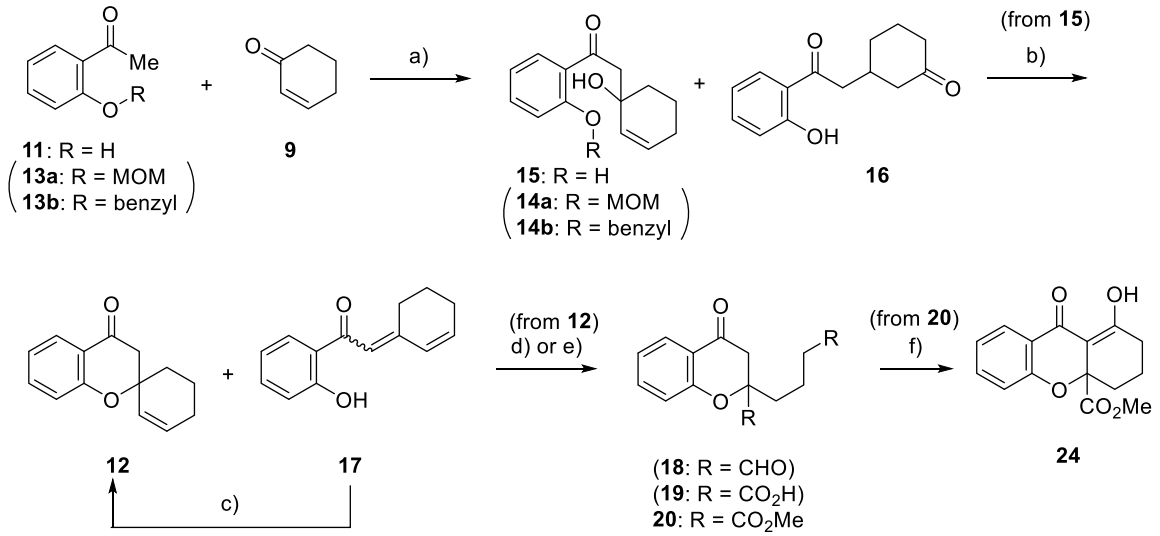
We planned to develop a new methodology for total synthesis of blennolides **2-3** and their derivatives with other ring sizes. A key challenge in the synthesis of xanthones is the construction of the quaternary stereocenter. Spiro compounds are a class of natural products and synthetic intermediates that possess a quaternary carbon center.[5] Blennolides containing a chiral quaternary carbon center can be accessed via spirochromanone intermediates **4** through the aldol reaction of modified acetophenones **5** and α-oxygenated cyclohexenones **6** followed by cyclization of the aldol adduct **7**. The xanthone framework can be constructed by oxidative cleavage of the alkene moiety in spirochromanones **4** and Dieckmann condensation on the chromanone and ester part in the side chain of diester **8**. Application of cycloalkenones other than 6-membered ring will produce the derivatives with another ring size. In this article, we report total synthesis of (±)-4-deoxyblennolide C (**10**) using cyclohexenone (**9**), as a preliminary result of asymmetric total synthesis of blennolide C (**3**)[6] (Scheme 1).



Scheme 1. Retrosynthesis for blennolide C (**3**) and 4-deoxyblennolide C (**10**) via spirochromanone intermediates **4**. ***P***: protecting groups

Initially, *o*-hydroxyacetophenone (**11**) was used as a model starting material (Scheme 2). The trials for the synthesis of spirochromanone **12** from **11** and cyclohexenone (**9**) in the presence of a catalytic amount of pyrrolidine, which can be adopted in the reaction with cyclohexanone,[7] gave a complex mixture. Similar results were observed with a stoichiometric amount of pyrrolidine or solvent-free conditions. Next, we next tried a stepwise aldol reaction and cyclization. *o*-Hydroxyacetophenones **13a**[8a] and **13b**[8b] protected by MOM and benzyl groups were subjected to an aldol reaction with **9** mediated by an equimolar amount of LDA[9] to give the corresponding aldol adducts **14a-b** in low yields (38% for **14a**, trace for **14b**). The

aldol adduct yield was improved when unprotected *o*-hydroxyacetophenone (**11**) was used in the presence of 2 equivalents of LDA to give desired product **15** in 81% yield with a small amount of 1,4-adduct **16**. **15** was subjected to acidic conditions (HCl in MeOH)[10] for cyclization to afford spirochromanone **12** with a small amount of dehydrated product **17**. Partial conversion from **17** to **12** was observed in the acidic conditions. Next, oxidative cleavage of the alkene moiety in spirochromanone **12** was examined. Ozonolysis of **12** quenching with dimethyl sulfide to obtain dialdehyde **18**. The crude **18** was subjected to Jones oxidation followed by ester formation with trimethylsilyldiazomethane ($TMSCHN_2$) afforded diester **20** with a small amount of chromone **21**[11] (Figure 2). We speculate that **21** could be generated by decomposition of molozonide **22** to chromone **23** and formic acid on ozonolysis step, followed by Jones oxidation and esterification (Scheme 3). Application of Lemieux-Johnson oxidation gave a better result, providing diester **20** in 84% yield in three steps. Dieckmann condensation of diester **20** with NaH in toluene produced only small amount of desired xanthone **24**[3e,12] (7%) and ring-opened product **25** (9%). The $TiCl_4/Et_3N$ system[3c] at 0 ºC gave **24** (30%) with another Dieckmann product **26** (24%), which was generated by the reaction of chromanecarboxylate and the ester side chain. The reaction at room temperature became messy and lowered the yield of **24** (19%) with byproduct **26** (9%) and ring-opened product **27** (15%) (Figure 2).



Scheme 2. Synthesis of xanthone **24**. Conditions: a) (from **11**) LDA, THF, -78 ºC, 1.5 h, **15** (81%), **16** (8%); b) HCl in MeOH, reflux, 30 min, **12** (67%), **17** (25%); c) HCl in MeOH, reflux, 2 h, **12**:**17** = 3:7; d) 1) O_3, CH_2Cl_2, -60 ºC, 1 h, then Me_2S, 2) Jones reagent, acetone, 0 ºC, 1 h; 3) $TMSCHN_2$, MeOH, CH_2Cl_2, rt, 1 h, **20** (35%), **21** (17%); e) 1) OsO_4 (cat.), $NaIO_4$, THF, H_2O, rt, 24 h; 2) Jones reagent, acetone, 0 ºC, 1 h; 3) $TMSCHN_2$, MeOH, CH_2Cl_2, rt, 2 h, **20** (84%). f) $TiCl_4$, Et_3N, CH_2Cl_2, 0 ºC, 2 h, **24** (30%), **26** (23%).

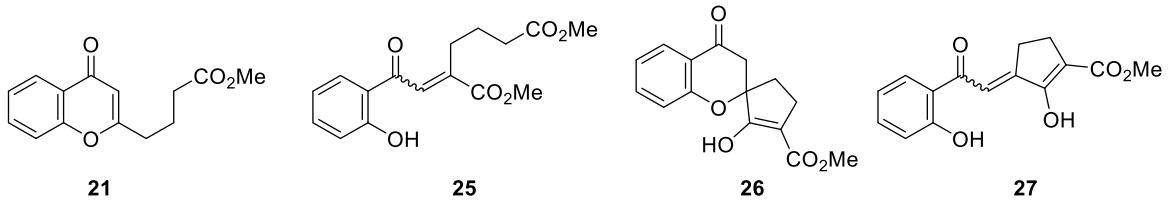
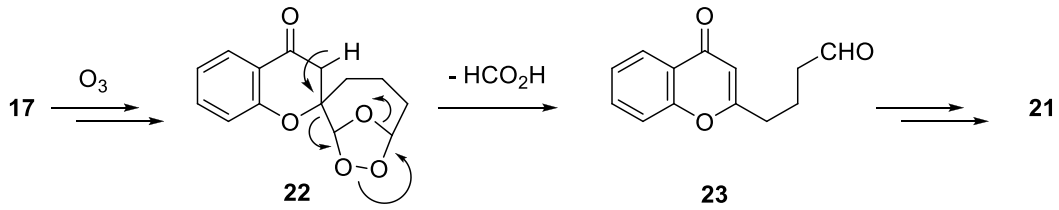


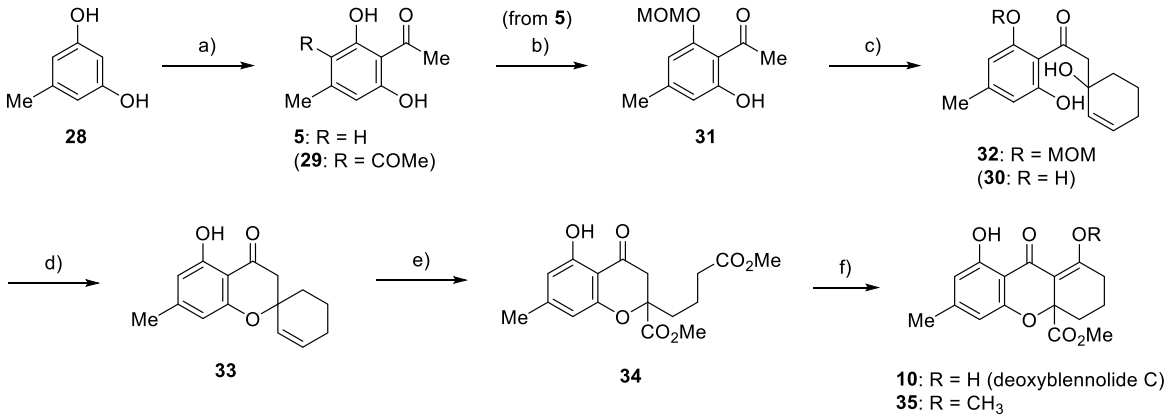
Figure 2. Structures of byproducts during the synthesis of **24**



Scheme 3. Plausible mechanism for the formation of chromone **21**

Next, we moved to the synthesis using modified acetophenone **5**, which was synthesized from 5-methylresorcinol (**28**) with a slight modification of a reported procedure;[3b] Friedel-Crafts acylation of **28** with acetyl chloride in the presence of $AlCl_3$ gave a 2:3 mixture of acetophenone **5** and diacylated product **29**, which was deacylated with concentrated sulfuric acid to give desired product **5** in 75% yield in two steps. A trial for the aldol reaction of **5** and **9** in the presence of 3 equivalents of LDA did not give desired aldol adduct **30**, and 65% of **5** was recovered. Thus, the reaction was performed after MOM protection of one of the hydroxy groups in **5**. The aldol reaction of MOM ether **31** and **9** gave the desired adduct **32** in 78% yield. Best result was obtained when with 3 equivalents of LDA was used. Treatment of the aldol adduct **32** with HCl in MeOH gave key spirochromanone **33** after the simultaneous removal of the MOM group. Lemieux-Johnson oxidation of **33** followed by sequential Jones oxidation and ester formation gave diester **34**, which was treated with $TiCl_4/Et_3N$ to afford (±)-4-deoxyblennolide C (**10**) in 16% yield with the corresponding enol ether **35** in 12% (Scheme 4).

In conclusion, the total synthesis of (±)-4-deoxyblennolide C (**10**) was achieved via oxidative cleavage of spirochromanone followed by Dieckmann condensation. The spirochromanone was constructed by condensation of the aldol product from *o*-hydroxyacetophenones and cyclohexenone. Further synthetic study toward another xanthones such as blennolides A and B will be developed through this synthetic strategy.



Scheme 4. Synthesis of 4-deoxyblennolide C (**10**). Conditions: a) 1) acetyl chloride, $AlCl_3$, chlorobenzene, 40 ºC, 30 min, 70 ºC, 8 h, 2) conc. H_2SO_4, rt, 5 h, **6** (75%, 2 steps); b) MOMCl, DIPEA, THF-CH_2Cl_2, rt, 5 h, (92%); c) **9**, LDA, THF, -78 ºC, 3.5 h, (78%); d) HCl in MeOH, reflux, 2 h, (98%); e) 1) OsO_4 (cat.), $NaIO_4$, CH_2Cl_2, H_2O, rt, 24 h; 2) Jones reagent, acetone, rt, 1 h; 3) $TMSCHN_2$, MeOH, CH_2Cl_2, rt, 2 h, (60%, 3 steps); f) $TiCl_4$, Et_3N, CH_2Cl_2, rt, 2 h, **10** (16%), **35** (12%).

EXPERIMENTAL

General Commercially available reagents and anhydrous solvents were used without further purification. Anhydrous THF was purchased from Wako Chemicals. Analytical thin layer chromatography was performed on silica gel 60 F254 plate from Merck KGaA. Flash chromatography was carried out with Silica gel 60 (63-210 μm) from Kanto Chemical Co. $TMSCHN_2$ solution (2.0 M in hexane) was purchased from Aldrich.

IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer with Attenuated Total Reflectance Unit ATR PRO450-S. EIMS was recorded on JEOL GC Mate. ESIMS was recorded on a JEOL JMS-T100LP in positive ion mode with DART ion source. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL ECX400 spectrometer and chemical shifts were shown in ppm. Chemical shifts were reported in ppm and *J* in Hz. Abbreviations were used for multiplicity: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublets of doublets, dddd = doublet of doublets of doublets of doublets, m = multiplet.

2-(1-Hydroxy-2-cyclohexenyl)-1-[2-(hydroxy)phenyl]ethenone (15) and 3-[2-(2-hydroxyphenyl)-2-oxoethyl]cyclohexan-1-one (16)

To a solution of diisopropylamine (0.21 mL, 151.6 mg, 1.50 mmol) in THF (0.5 mL), BuLi (1.54 mol/L, 0.96 mL, 1.48 mmol) was added at 0 ºC, and a mixture was stirred at 0 ºC for 30 min. **11** (101.0 mg, 0.74 mmol) in THF (0.7 mL) was added at -78 ºC and the mixture was stirred at -78 ºC for 45 min. **9** (108.7 mg, 1.13 mmol) in THF (0.7 mL) was added and the mixture was stirred at -78 ºC for 1.5 h. H_2O (10 mL)

was added and the whole was extracted with AcOEt (3 x 15 mL). The combined organic layer was washed with H_2O (1 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 2 : 1) to give **15** (a yellow oil, 140 mg, 81%) and **16** (a yellow oil, 13 mg, 8%).

15: IR ν_{max} cm^{-1} : 3503, 2935, 1629. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.61-1.69 (1H, m, CH_2), 1,74 (1H, ddd, *J* = 12.7, 9.9, 2.7 Hz, CH_2), 1.80-1.88 (1H, m, CH_2), 1.90-2.14 (3H, m, CH_2), 3.21 (1H, d, *J* = 16.5 Hz, CH_2), 3.26 (1H, d, *J* = 16.5 Hz, CH_2), 5.77 (1H, dd, *J* = 10.2, 1.7 Hz, CH), 5.85 (1H, ddd, *J* = 10.1, 7.3, 3.7 Hz, CH), 6.90 (1H, ddd, *J* = 8.2, 7.3, 1.2 Hz, Ar-H_4), 6.99 (1H, dd, *J* = 8.2, 1.2 Hz, Ar-H_6), 7.49 (1H, ddd, *J* = 8.2, 7.3, 1.5 Hz, Ar-H_5), 7.76 (1H, dd, *J* = 8.2, 1.5 Hz, Ar-H_3), 12.16 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0, 25.1, 36.2, 47.7, 69.3, 118.7, 119.0, 120.1, 130.3, 130.5, 131.2, 136.9, 162.8, 206.9. HRESIMS *m/z* 215.1078 ($[M-H_2O+H]^+$, calcd. for $C_{14}H_{15}O_2$: 215.1072).

16: IR ν_{max} cm^{-1} : 2936, 1709, 1636. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.42-1.52 (1H, m, CH_2), 1.64-1.80 (1H, m, CH_2), 1.90-2.10 (1H, m, CH_2), 2.15 (2H, ddd, *J* = 14.6, 12.7, 1.1 Hz, CH_2), 2.25-2.34 (1H, m, CH_2), 2.38-2.45 (1H, m, CH_2), 2.47-2.57 (2H, m, CH_2), 2.97 (1H, dd, *J* = 16.2, 6.0 Hz, CH_2), 3.04 (1H, dd, *J* = 16.2, 7.0 Hz, CH_2), 6.90 (1H, ddd, *J* = 7.9, 7.3, 1.2 Hz, Ar-H5), 6.99 (1H, dd, *J* = 8.4, 1.0 Hz, Ar-H_3), 7.48 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, Ar-H4), 7.72 (1H, dd, *J* = 7.9, 1.5 Hz, Ar-H6), 12.28 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.85, 31.12, 35.00, 41.17, 44.34, 47.71, 118.69, 118.95, 119.32, 129.80, 136.59, 162.61, 204.59, 210.38. HRESIMS *m/z* 233.1176 ($[M+H]^+$, calcd. for $C_{14}H_{17}O_3$: 233.1178).

3-[2-[2-(Methoxymethoxy)phenyl]-2-oxoethyl]cyclohexan-1-one (14a)

IR ν_{max} cm^{-1}: 1707, 1672. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38-1.48 (1H, m, CH_2), 1.66-1.76 (1H, m, CH_2), 1.94-2.06 (2H, m, CH_2), 2.12 (1H, ddd, *J* = 14.7, 12.4, 1.3 Hz, CH_2), 2.25 (1H, dddd, *J* = 14.8, 11.4, 6.0, 1.2 Hz, CH_2), 2.34-2.42 (1H, m, CH_2), 2.44-2.54 (2H, m, CH_2), 2.98 (1H, dd, *J* = 17.2, 7.1 Hz, CH_2), 3.03 (1H, dd, *J* = 17.2, 7.1 Hz, CH_2), 3.51 (3H, s, CH_3), 5.27 (2H, s, CH_2), 7.05 (1H, ddd, *J* = 7.3, 7.3, 0.9 Hz, Ar-H_4), 7.17 (1H, d, *J* = 8.8 Hz, Ar-H_6), 7.43 (1H, ddd, *J* = 8.8, 7.3, 1.8 Hz, Ar-H_5), 7.61 (1H, dd, *J* = 7.8, 1.8 Hz, Ar-H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 31.1, 35.0, 41.3, 47.9, 50.0, 56.5, 94.6, 114.8, 122.0, 129.3, 123.0, 133.4, 155.8, 201.1, 210.9. HREIMS *m/z* 276.1362 (M^+, calcd. for $C_{16}H_{20}O_4$: 276.1362).

Spiro[chromane-2,1'-cyclohexan]-2'-en-4-one (12) and 2-(2-cyclohexen-1-ylidene)-1-(2-hydroxyphenyl)ethenone (*E* and *Z* mixture) (17)

A mixture of **15** (1.57 g, 6.79 mmol) in MeOH-HCl (0.5 M, 16.0 mL, 8.00 mmol, 1.2 eq) was refluxed for 30 min. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by column

chromatography (hexane – AcOEt = 20 : 1) to give **12** (colorless solids, 968 mg, 67%) and **17** (a yellow oil, 363 mg, 25%).

12: mp 61.5-62.5 ºC. IR ν_{max} cm^{-1}: 1685. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.60-1.72 (2H, m, CH_2), 1.81-1.91 (1H, m, CH_2), 1.95-2.08 (1H, m, CH_2), 2.11-2.21 (2H, m, CH_2), 2.74 (1H, d, *J* = 16.5 Hz, CH_2), 2.87 (1H, d, *J* = 16.5 Hz, CH_2), 5.81-5.85 (1H, diffused d, *J* = 9.2 Hz, CH), 6.02 (1H, ddd, *J* = 10.1, 4.0, 3.4 Hz, CH), 6.93-6.70 (2H, m, Ar-$H_{4,6}$), 7.46 (1H, ddd, *J* = 8.6 , 6.8, 1.8 Hz, Ar-H_5), 7.86 (1H, dd, *J* = 8.2, 1.8 Hz, Ar-H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.3, 25.0, 32.4, 48.1, 78.0, 118.5, 120.6, 120.7, 126.4, 127.6, 133.4, 136.2, 159.8, 192.3. HREIMS *m/z* 214.0993 (M^+, calcd. for $C_{14}H_{14}O_2$: 214.0994)

17: IR ν_{max} cm^{-1} : 3500-2800, 1626. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.77 (2H, quint, J = 6.1 Hz, CH_2)*, 1.87 (2H, quint, *J* = 6.1 Hz, CH_2)‡, 2.13-2.32 (2H, m, CH_2)*‡, 2.54 (2H, ddd, *J* = 8.0, 4.6, 1.5 Hz, CH_2)‡, 3.01-3.05 (2H, ddd, *J* = 7.3, 5.8, 1.5 Hz, CH_2)*, 6.27 (1H, ddd, *J* = 9.4, 1.7, 1.7 Hz, 2'C-H)*, 6.35-6.40 (1H, m, 3'C-H)*‡, 6.60 (1H, s, 2C-H)‡, 6.70 (1H, s, 2C-H)*, 6.85-6.91 (1H, m, Ar-H)*‡, 6.96-7.00 (1H, m, Ar-H)*‡, 7.41-7.46 (1H*, 2H‡, m, Ar-H)*‡, 7.78-7.81 (1H, m, Ar-H)*‡, 12.26 (1H, s, OH)‡, 12.91 (1H, s, OH)* * : ‡ a mixture of *ca.* 2 : 1 of diastereoisomers. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 22.7, 25.7, 26.4, 27.5, 33.2, 116.7, 118.5, 118.5, 118.5, 120.9, 121.1, 126.1, 129.6, 129.7, 130.8, 135.6, 135.7, 140.2, 140.6, 153.9, 155.6, 163.2, 163.3, 195.8, 196.1 (2×1 C missing). HREIMS *m/z* 214.0997 (M^+, calcd. for $C_{14}H_{14}O_2$: 214.0994)

Synthesis of methyl 2-(4-methoxy-4-oxobutyl)-4-oxo-3,4-dihydro-2*H*-1-benzopyran-2-carboxylate (20) and methyl 4-(4-oxo-4*H*-chromen-2-yl)butanoate (21) via ozonolysis of 12

To a solution of **12** (101 mg, 0.47 mmol) in CH_2Cl_2 (5 mL), O_3 was bubbled at -60 ºC for 1 h. The excess O_3 was purged by bubbling with N_2 for 10 min, and dimethyl sulfide (0.18 mL, 2.46 mmol) was added at -60 ºC. The mixture was stirred at rt for 30 min. Another 2 sets of reaction mixture were combined. After addition of brine (5 mL), the whole was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with brine (1 x 40 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and an aliquot (193 mg) of the residue (a colorless oil, 389 mg) was used further used to next step without purification.

To a solution of crude **18** (193 mg, 0.70 mmol as pure) in acetone (9 mL), Jones reagent (2.7 M, 0.64 mL, 1.73 mmol) was added at 0 ºC and the whole was stirred at 0 ºC for 1 h. 2-Propanol (1 mL) and H_2O (10 mL) were added and the whole was extracted with AcOEt (4 x 60 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue (199 mg) was used to next step without purification.

To a solution of crude **19** (199 mg) in CH_2Cl_2 (20 mL) and MeOH (5.7 mL), $TMSCHN_2$ (2.0 M in hexane,

0.79 mL, 1.58 mmol) was added at 0 ºC and the whole was stirred at rt for 1 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 4 : 1) to give **20** (a yellow oil, 74 mg, 35% in 3 steps) and **21** (a colorless oil, 30 mg, 17%).

20: IR ν_{max} cm^{-1} : 1733, 1692, 1607. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70-1.79 (1H, m, CH_2), 1.84-1.95 (1H, m, CH_2), 2.01-2.09 (2H, m, CH_2), 2.40 (2H, t, *J* = 7.4 Hz, CH_2), 2.93 (1H, d, *J* = 16.7 Hz, CH_2), 3.15 (1H, d, *J* = 16.7 Hz, CH_2), 3.678 (3H, s, COOMe), 3.684 (3H, s, COOMe), 7.05 (1H, ddd, *J* = 7.8, 7.1, 0.9 Hz, Ar-H_6), 7.08 (1H, dd, *J* = 8.2, 0.9 Hz, Ar-H_8), 7.52 (1H, ddd, *J* = 8.2, 7.1, 1.4 Hz, Ar-H_7), 7.82-7.85 (1H, dd, *J* = 7.8, 1.4 Hz, Ar-H_5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9, 33.5, 37.2, 44.2, 51.6, 52.9, 83.8, 118.1, 120.4, 121.8, 126.7, 136.5, 160.1, 171.4, 173.2, 189.9. HREIMS *m/z* 306.1101 (M^+, calcd. for $C_{16}H_{18}O_6$: 306.1103)

21: IR ν_{max} cm^{-1} : 1733, 1649. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06-2.13 (2H, quint, *J* = 7.4 Hz, CH_2), 2.44 (2H, t, *J* = 7.3 Hz, CH_2), 2.70 (2H, t, *J* = 7.6 Hz, CH_2), 3.69 (3H, s, COOMe), 6.19 (1H, s, CH), 7.38 (1H, ddd, *J* = 8.0 , 7.1, 0.9 Hz, Ar-H_8), 7.43 (1H, d, *J* = 8.5 Hz, Ar-H_6), 7.65 (1H, ddd, *J* = 8.5, 7.1, 1.8 Hz, Ar-H_7), 8.18 (1H, dd, *J* = 8.0, 1.6 Hz, Ar-H_5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 32.8, 33.5, 51.7, 110.2, 117.8, 123.6, 125.0, 125.6, 133.5, 156.4, 168.3, 173.1, 178.2. LREIMS *m/z* 246 (M^+, 81.9%), 187 (24.2%), 173 (100%), 121 (43.1%).

Synthesis of methyl 2-(4-methoxy-4-oxobutyl)-4-oxo-3,4-dihydro-2*H*-1-benzopyran-2-carboxylate (20) via Lemieux-Johnson oxidation of 12

To a solution of **12** (1.026 g, 4.79 mmol) in THF (10 mL), H_2O (20 mL), and *t*-BuOH (4.7 mL), OsO_4 (61 mg, 0.24 mmol) was added and the whole was stirred with shielding from light. $NaIO_4$ (3.01 g, 14.09 mmol) was added portionwise in each 10 seconds within 10 min. The whole was stirred at rt for 24 h. H_2O (20 mL) was added and the whole was extracted with AcOEt (3 x 140 mL). The combined organic layer s was washed with H_2O (1 x 50 mL) and brine (1 x 30 mL). The solvent was evaporated *in vacuo* and the residue (a yellow oil, 1.435 g) was used to next step without purification.

18: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.69-2.03 (4H, m, 2 x CH_2), 2.42 (1H, t, *J* = 7.1 Hz, CH_2), 2.53 (1H, m, CH_2), 2.84 (1H, ddd, *J* = 16.9, 3.3, 1.0 Hz, CH_2), 3.05 (1H, d, *J* = 16.9 Hz, CH_2), 7.06 (1H, diffused t, *J* = 7.5 Hz, Ar-H_6), 7.12 (1H, d, *J* = 8.5 Hz, Ar-H_8), 7.54 (1H, ddd, *J* = 8.5, 7.2, 1.5 Hz, Ar-H_7), 7.85 (1H, diffused dd, *J* = 7.8, 1.5 Hz, Ar-H_5), 9.68-9.69 (1H, m, CHO), 9.77 (1H, s, CHO).

To a solution of crude **18** (1.435 g, 4.79 mmol as pure) in acetone (60 mL), Jones reagent (2.7 M, 4.3 mL, 11.65 mmol) was added at 0 ºC and the mixture was stirred at 0 ºC for 1 h. 2-Propanol (2.5 mL) and H_2O (35 mL) were added, and the whole was extracted with AcOEt (4 x 150 mL). The combined organic layer was washed with H_2O (1 x 20 mL) and brine (1 x 15 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue (gray solid, 1.41 g) was used to next step without purification.

19: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73-1.84 (1H, m, CH_2-H), 1.86-1.97 (1H, m, CH_2-H), 2.02-2.12 (2H, m, CH_2), 2.40 (2H, t, *J* = 7.3 Hz, CH_2), 2.93 (1H, d, *J* = 16.7 Hz, CH_2), 3.16 (1H, d, *J* = 16.7 Hz, CH_2), 3.44 (2H, brs, 2 x COOH), 7.02 (1H, dd, *J* = 7.7 Hz, 7.3 Hz, Ar-H_6), 7.08 (1H, d, *J* = 8.2 Hz, Ar-H_8), 7.51 (1H, ddd, *J* = 8.2, 7.3, 1.6 Hz, Ar-H_7), 7.83 (1H, dd, *J* = 7.7, 1.6 Hz, Ar-H_5).

To a solution of crude **19** (1.41 g, 4.79 mmol as pure) in CH_2Cl_2 (140 mL) and MeOH (45 mL), $TMSCHN_2$ (2.0 M in hexane, 5.1 mL, 10.20 mmol) was added at 0 °C and the mixture was stirred at rt for 2 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 4 : 1) to give **20** (a colorless oil, 1.235 g, 3 steps 84%).

Methyl 1-hydroxy-9-oxo-3,4,4a,9-tetrahydro-2*H*-xanthene-4a-carboxylate (24) and methyl 2'-hydroxy-4-oxo-3,4-dihydrospiro[1-benzopyran-2,1'-cyclopentan]-2'-ene-3'-carboxylate (26)

To a solution of **20** (101.9 mg, 0.33 mmol) in CH_2Cl_2 (1 mL), $TiCl_4$ (0.08 mL, 138.4 mg, 0.73 mmol) and Et_3N (0.05 mL, 36.3 mg, 0.36 mmol) were added successively at rt. The mixture was stirred at rt for 2 h. Saturated aqueous NH_4Cl (3 mL) and H_2O (3 mL) were added and the whole was extracted with AcOEt (3 x 30 mL). The combined organic layer was dried over Na_2SO_4. Solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 4 : 1) to give **24** (yellow solids, 28 mg, 30%) and **26** (orange solids, 21 mg, 23%).

24: mp 121.0-126.0 °C (lit[12] 123-129 °C). IR ν_{max} cm^{-1} : 2931, 1742, 1600. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81-2.01 (2H, m, CH_2), 2.20 (1H, dt, *J* = 13.5, 3.9 Hz, CH_2), 2.43 (1H, dt, *J* = 9.3, 3.9 Hz, CH_2), 2.51-2.55 (2H, m, CH_2), 3.64 (3H, s, COOMe), 7.02 (1H, d, *J* = 8.4 Hz, Ar-H_5), 7.07 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 1.2 Hz, Ar-H_7), 7.46 (1H, ddd, *J* = 8.4 Hz, 8.0 Hz, 1.9 Hz, Ar-H_6), 7.84 (1H, dd, *J* = 7.8, 1.9 Hz, Ar-H_8), 15.33 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4, 30.3, 32.5, 52.9, 81.0, 104.6, 117.6, 120.5, 122.4, 126.6, 135.4, 158.4, 172.8, 179.6, 185.1. HREIMS *m/z* 274.0849 (M^+, calcd. for $C_{15}H_{14}O_5$: 274.0841).

26: IR ν_{max} cm^{-1} : 3300-3000, 1733, 1689. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (1H, ddd, *J* = 15.3, 7.9, 4.3 Hz, CH_2), 2.22 (1H, ddd, *J* = 14.0, 8.5, 4.3 Hz, CH_2), 2.45 (1H, ddd, *J* = 14.8, 8.5, 4.1 Hz, CH_2), 2.63 (1H, ddd, *J* = 15.0, 8.5, 4.9 Hz, CH_2), 2.77 (1H, d, *J* = 16.5 Hz, CH_2), 3.24 (1H, d, *J* = 16.5 Hz, CH_2), 3.81 (3H, s, COOMe), 6.97 (1H, dd, *J* = 8.2, 0.6 Hz, Ar-H_8), 7.02 (1H, ddd, *J* = 7.9, 7.3, 0.9 Hz, Ar-H_6), 7.48 (1H, ddd, *J* = 8.2, 7.3, 1.8 Hz, Ar-H_7), 7.88 (1H, dd, *J* = 7.9, 1.8 Hz, Ar-H_5), 9.97 (1H, brs, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.4, 32.8, 43.9, 51.7, 88.3, 103.4, 118.2, 120.6, 121.4, 126.5, 136.2, 159.8, 168.9, 169.6, 190.8. HREIMS *m/z* 274.0837 (M^+, calcd. for $C_{15}H_{14}O_5$: 274.0841).

Dimethyl 2-[2-(2-hydroxyphenyl)-2-oxoethylidene]hexanedioate (25)

A yellow oil. IR ν_{max} cm^{-1} : 3800-3000, 1723, 1636. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88 (quint, *J* = 7.6

Hz, CH_2), 2.37 (2H, t, *J* = 7.6 Hz, CH_2), 2.67 (2H, t, *J* = 7.6 Hz, CH_2), 3.65 (3H, s, COOMe), 3.87 (3H, s, COOMe), 6.93 (1H, diffused dd, *J* = 8.3, 8.3 Hz, Ar-H_5), 7.02 (1H, d, *J* = 8.2 Hz, Ar-H_3), 7.52 (1H, ddd, *J* = 8.7, 8.4, 1.5 Hz, Ar-H_4), 7.73 (1H, dd, *J* = 8.2, 1.5 Hz, Ar-H_6), 7.76 (1H, s, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 27.8, 33.6, 51.5, 52.7, 118.6, 119.2, 120.1, 130.6, 131/7, 137.2, 144.3, 163.1, 167.1, 144.3, 163.1, 167.1, 173.5, 197.0. HRESIMS *m/z* 307.1192 ([M+H]$^+$, calcd. for $C_{16}H_{19}O_6$: 307.1182)

Methyl 2-hydroxy-3-[2-(2-hydroxyphenyl)-2-oxoethylidene]cyclopent-1-ene-1-carboxylate (27)

Yellow solids. mp 141.5-145.5 ºC. IR ν_{max} cm^{-1} : 3300, 1661, 1631. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.69 (2H, t, *J* = 4.6 Hz, CH_2), 3.18 (2H, m, CH_2), 3.86 (3H, s, COOMe), 6.92 (1H, diffused d, *J* = 7.2 Hz, Ar-H_3), 7.00 (1H, diffused d, *J* = 7.3 Hz, Ar-H_5), 7.41 (1H, t, *J* = 2.7 Hz, CH-CO), 7.47 (1H, diffused t, *J* = 8.5 Hz, Ar-H_4), 7.90 (1H, dd, *J* = 8.1, 1.4 Hz, Ar-H_6), 9.92 (1H, s, OH), 12.87 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0, 28.0, 51.9, 114.1, 114.6, 118.5, 118.8, 120.8, 129.5, 136.2, 158.3, 163.4, 166.8, 169.6, 194.9. HREIMS *m/z* 274.0832 ([M+H]$^+$, calcd. for $C_{15}H_{14}O_5$: 274.0841)

1-(2,6-Dihydroxy-4-methylphenyl)ethan-1-one (5)

To a mixture of **28** (105 mg, 0.84 mmol) and $AlCl_3$ (323 mg, 2.43 mmol) in chlorobenzene (1 mL), acetyl chloride (0.12 mL, 1.69 mmol) was added at 40 ºC. The mixture was stirred at 40 ºC for 30 min and at 70 ºC for 8 h. After ice-cooling, conc. HCl (3 mL) and H_2O (2 mL) were added successively, and the mixture was extracted with AcOEt (3 x 20 mL). The combined organic layer was washed with H_2O (1 x 5 mL) and brine (1 x 5 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give a mixture of **5** and **29** (a yellow oil, 270 mg). The residue was treated with 85% H_2SO_4 (1.5 mL) at 0 ºC, and the mixture was stirred at rt for 5 h. Ice-H_2O (3 mL) was added and the mixture was extracted with AcOEt (1 x 30 mL). The organic layer was washed with H_2O (1 x 5 mL) and brine (1 x 5 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 10 : 1) to give **5** (yellow solids, 104 mg, 75%, 2 steps).

mp 144.5-147.0 ºC (lit[13] 145.5-149 ºC). IR ν_{max} cm^{-1} : 3280, 1637. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 2.17 (3H, s, CH_3), 2.61 (3H, s, $COCH_3$), 6.20 (2H, s, Ar-H), 11.90 (2H, brs, OH). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 21.6, 33.0, 107.8, 108.1, 147.5, 161.9, 204.5. HRESIMS *m/z* 167.0656 ([M+H]$^+$, calcd. for $C_9H_{11}O_3$: 167.0708).

1-[2-Hydroxy-6-(methoxymethoxy)-4-methylphenyl]ethan-1-one (31)

To a solution of **6** (2.50 g, 15.1 mmol) in THF (10 mL) and CH_2Cl_2 (40 mL), DIPEA (3.65 mL, 21.2 mmol) and MOMCl (1.50 mL, 19.8 mmol) were added, and the whole was stirred at rt for 5 h. H_2O (75 mL) was added and the whole was extracted with AcOEt (3 x 150 mL). The combined organic layer was

washed with H_2O (1 x 100 mL) and brine (1 x 100 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – Et_2O = 4 : 1) to give **31** (yellow solids, 2.92 g, 92%).

mp 36.5-37.5 ºC. IR ν_{max} cm^{-1} : 3005, 1622. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.29 (3H, s, CH_3), 2.68 (3H, s, $COCH_3$), 3.52 (3H, s, OCH_3), 5.27 (2H, s, CH_2), 6.41 (1H, s, Ar-H), 6.43 (1H, s, Ar-H), 13.22 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.3, 33.4, 56.6, 94.3, 105.1, 109.5, 111.9, 147.8, 158.7, 164.4, 204.3. HRESIMS *m/z* 211.0975 ($[M+H]^+$, calcd. for $C_{11}H_{15}O_4$: 211.0970).

1-[2-Hydroxy-6-(methoxymethoxy)-4-methylphenyl]-2-(hydroxycyclohex-2-en-1-yl)ethan-1-one (32)

To a solution of diisopropylamine (0.16 mL, 1.14 mmol) in THF (0.5 mL), *n*-BuLi (1.51 M in hexane, 0.69 mL, 1.04 mmol) was added at 0 ºC. The mixture was stirred at 0 ºC for 30 min. After cooling at -78 ºC, a solution of **31** (102 mg, 0.48 mmol) in THF (0.7 mL) was added and the mixture was stirred at -78 ºC for 40 min. A solution of **9** (72 mg, 0.34 mmol) in THF (0.7 mL) was added at -78 ºC and the mixture was stirred at -78 ºC for 3.5 h. Saturated aqueous NH_4Cl (5 mL) was added and the whole was extracted with AcOEt (3 x 30 mL). The combined organic layer was washed with H_2O (1 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – Et_2O = 4 : 1) to give **32** (yellow solids, 116 mg, 78%).

IR ν_{max} cm^{-1} : 2921, 1625. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.57-1.65 (1H, m, CH_2), 1.70 (1H, ddd, *J* = 12.8, 9.8, 3.1 Hz, CH_2), 1.81-1.99 (3H, m, CH_2), 2.04-2.12 (1H, m, CH_2), 2.29 (3H, s, CH_3), 3.30 (1H, d, CH_2), 3.40 (1H, d, CH_2), 3.52 (3H, s, CH_3), 4.07 (1H, s, OH), 5.25 (2H, s, CH_2), 5.76-5.82 (2H, m, 2 x CH), 6.40 (1H, s, Ar-H), 6.45 (1H, s, Ar-H), 12.80 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0, 22.3, 25.2, 36.2, 53.7, 56.8, 69. 5, 94.5, 105.4, 110.3, 112.2, 129.6, 131.7, 148.4, 158.6, 164.4, 207.0. HRESIMS *m/z* 329.1360 ($[M+H]^+$, calcd. for $C_{17}H_{22}NaO_5$: 329.1365)

5-Hydroxy-7-methylspiro[chromane-2,1'-cyclohexan]-2'-en-4-one (33)

A solution of **32** (102 mg, 0.33 mmol) in HCl-MeOH (0.5 M, 1 mL, 0.50 mmol) was refluxed for 2 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 3 : 1) to give **33** (colorless solids, 79 mg, 98%).

mp 93.5-97.5 ºC. IR ν_{max} cm^{-1} : 2968, 1647. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.60-1.72 (2H, m, CH_2), 1.81-1.91 (1H, m, CH_2), 1.98-2.07 (1H, m, CH_2), 2.11-2.23 (2H, m, CH_2), 2.66 (3H, s, CH_3), 2.73 (1H, d, *J* = 16.5 Hz, CH_2), 2.83 (1H, d, *J* = 16.5 Hz, CH_2), 5.82 (1H, diffused d, *J* = 9.8 Hz, CH=), 6.02 (1H, ddd, *J* = 9.8, 4.3, 3.1 Hz, CH=), 6.24 (1H, s, Ar-H), 6.30 (1H, s, Ar-H), 11.62 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.2, 22.5, 25.0, 43.7, 47.3 77.5, 105.7, 108.7, 109.4, 127.3, 133.6, 150.5, 159.6, 161.6, 197.2. HRESIMS *m/z* 245.1202 ($[M+H]^+$, calcd. for $C_{15}H_{17}O_3$: 245.1178).

Methyl

5-hydroxy-2-(4-methoxy-4-oxobutyl)-1-methyl-4-oxo-3,4-dihydro-2*H*-1-benzopyran-2-carboxylate (34)

To a solution of **33** (101 mg, 0.41 mmol) in CH_2Cl_2 (1 mL), H_2O (2 mL) and *t*-BuOH (0.4 mL), OsO_4 (6.3 mg, 0.03 mmol) was added. $NaIO_4$ (269 mg, 1.26 mmol) was added portionwise in each 10 sec within 5 min. The mixture was stirred at rt for 24 h. H_2O (5 mL) was added, and the mixture was extracted with AcOEt (3 x 30 mL). The combined organic layer was washed with H_2O (1 x 10 mL) and brine (1 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the crude dialdehyde (127 mg) was used to next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.69-1.97 (4H, m, 2 x CH_2), 2.31 (3H, s, CH_3), 2.54 (2H, ddd, J = 7.0 6.8, 0.9 Hz, CH_2), 2.85 (1H, ddd, J = 17.1, 3.4, 0.9 Hz, CH_2), 3.02 (1H, d, J = 17.1 Hz, CH_2), 6.37 (1H, diffused s, Ar-H), 6.41 (1H, diffused s, Ar-H), 9.65 (1H, diffused s, CHO), 9.78 (1H, diffused s, CHO), 11.51 (1H, s, OH).

To a solution of crude diacid (127 mg, 0.41 mmol as pure) in acetone (1 mL), Jones reagent (2.7 M, 0.31 mL, 0.83 mmol) was added at 0 ºC, and the mixture was stirred at rt for 1 h. 2-Propanol (0.3 mL) and H_2O (10 mL) were added, and the whole was extracted with AcOEt (6 x 30 mL). The combined organic layer was washed with H_2O (1 x 10 mL) and brine (1 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue (a brown oil, 124 mg) was used to next step without purification.

Diacid: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70-2.10 (4H, m, CH_2), 2.30 (3H, s, CH_3), 2.38-2.52 (2H, m, CH_2), 2.94 (1H, *d*, J = 17.1 Hz, CH_2), 3.14 (1H, *d*, J = 17.1 Hz, CH_2), 4.30 (2H, brs, COOH), 6.36 (1H, s, Ar-H), 6.37 (1H, s, Ar-H), 11.48 (1H, s, OH).

To a solution of crude diacid (124 mg, 0.41 mmol as pure) in CH_2Cl_2 (9 mL) and MeOH (3 mL), $TMSCHN_2$ (2.0 M in hexane, 0.42 mL, 0.84 mmol) was added at 0 ºC. The mixture was stirred at rt for 2 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 5 : 1) to give **34** (a colorless oil, 83 mg, 3 steps 60%).

IR (ATR) ν_{max} cm^{-1} : 2954, 1733, 1644. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.66-1.77 (1H, m, CH_2), 1.81-1.93 (1H, m, CH_2), 1.97-2.08 (2H, m, CH_2), 2.29 (3H, s, CH_3), 2.39 (2H, t, J = 7.3 Hz, CH_2), 2.93 (1H, d, J = 16.5 Hz, CH_2), 3.12 (1H, d, J = 16.5 Hz, CH_2), 3.68 (3H, s, COOMe), 3.71 (3H, s, COOMe), 6.34 (1H, s, Ar-H), 6.38 (1H, s, Ar-H), 11.50 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.8, 22.6, 33.4, 37.2, 43.2, 51.6, 53.1, 83.3, 105.6, 108.4, 110.5, 151.0, 159.6, 161.7, 171.3, 173.2, 195.0. HRESIMS *m/z* 337.1295 ([M+H]$^+$, calcd. for $C_{17}H_{21}O_7$: 337.1287).

Methyl 1,8-dihydroxy-6-methyl-9-oxo-3,4,4a,9-tetrahydro-2*H*-xanthene-4a-carboxylate (10) and methyl 8-hydroxy-1-methoxy-6-methyl-9-oxo-3,4,4a,9-tetrahydro-2*H*-xanthene-4a-carboxylate (35)

To a solution of **34** (206 mg, 0.61 mmol) in CH_2Cl_2 (2 mL), $TiCl_4$ (0.15 mL, 1.37 mmol) and Et_3N (0.09 mL, 0.65 mmol) were added successively at 0 ºC. After 10 min, Et_3N (0.04 mL, 0.5 eq) was added. After further 30 min Et_3N (0.10 mL, 0.72 mmol) and the mixture was stirred at rt for 2 h. Saturated aqueous NH_4Cl (6 mL) and H_2O (5 mL) were added and the whole was extracted with AcOEt (3 x 30 mL). The combined organic layer was washed with H_2O (1 x 5 mL) and brine (1 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane – AcOEt = 10 : 1) to give **10** (colorless solids, 29.0 mg, 16%) and **35** (a yellow oil, 21 mg, 11%).

10: mp 133-135 ºC. IR ν_{max} cm^{-1} : 2935, 1731, 1646. ^1H NMR (400 MHz, $CDCl_3$) δ : 1.78-1.98 (2H, m, CH_2), 2.13 (1H, ddd, *J* = 13.4, 13.4, 4.3 Hz, CH_2), 2.28 (3H, s, CH_3), 2.37 (1H, ddd, *J* = 13.4, 3.7, 3.7 Hz, CH_2), 2.46 (1H, ddd, *J* = 19.2, 6.1, 2.4 Hz, CH_2), 2.55 (1H, ddd, *J* = 19.2, 11.0, 6.7 Hz, CH_2), 3.69 (3H, s, COOMe), 6.32 (1H, s, Ar-H), 6.34 (1H, s, Ar-H), 11.24 (1H, s, OH), 13.91 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.3, 22.5, 28.5, 32.3, 53.1, 80.9, 103.6, 105.2, 108.7, 111.1, 149.9, 158.5, 161.8, 172.5, 178.1, 187.1. HRESIMS *m/z* 305.1020 ($[M+H]^+$, calcd. for $C_{16}H_{17}O_6$: 305.1025).

35: IR ν_{max} cm^{-1} : 2952, 1733, 1634. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.77-1.88 (1H, m, CH_2), 1.90-1.99 (1H, m, CH_2), 2.13 (1H, ddd, *J* = 13.4, 11.6, 3.7 Hz, CH_2), 2.24-2.30 (4H, m, CH_2 + Me), 2.55-2.59 (2H, m, CH_2), 3.66 (3H, s, OMe), 3.92 (3H, s, COOMe), 6.28 (1H, s, Ar-H), 6.31 (1H, s, Ar-H), 12,57 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.6, 22.4, 26.1, 32.3, 53.1, 56.1, 82.6, 106.6, 107.5, 107.7, 110.8, 149.0, 158.4, 162.8, 168.6, 172.8, 185.8. HRESIMS *m/z* 319.1175 ($[M+H]^+$, calcd. for $C_{17}H_{19}O_6$: 319.1182).

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