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Alternative routes to the acylphloroglucinol rhodomyrtone

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ABSTRACT

Two novel routes to the acylphloroglucinol rhodomyrtone (**1**) which has antibiotic properties are presented. In the first route an *ortho*-quinone methide, generated from dioxaborinine **23**, is reacted with syncarpic acid (**10**) leading to xanthenedione **25**. Cleavage of the methyl ether functions led to the known rhodomyrtone precursor **16**. In the second route the bis-ester derivative **28** of trihydroxybenzaldehyde **26** is condensed with syncarpic acid (**10**) to give tricyclic hemiacetal **29**. Acetalization and cuprate addition to the enone function led to bis-ester **32** which gave rhodomyrtone (**1**) by $TiCl_4$-induced regioselective Fries rearrangement.

1. Introduction

The isolation of small molecules from the myrtle family of plants has led to a range of novel biologically active natural products. In Asia and other regions of the planet extracts of Myrtaceae plants have traditionally been used for the treatment of various health problems. Besides terpenoids and flavonoids acylphloroglucinols are quite often found in plants of this family. For example, from *Eucalyptus globulus* Labill, rhodomyrtone (**1**) and eucalyptone G (**2**) were isolated (Fig. 1).[1,2] Both of these acylphloroglucinols display antibiotic activity. Extraction of the leaves of *Callistemon lanceolatus* DC allowed isolation of several acylphloroglucinols with callistenone A (**3**) showing very strong antibacterial activity.[3] From *rhodomyrtus tomentosa* leaves, besides the two isomeric acylphloroglucinols rhodomyrtone (**1**) and rhodomyrtosone B (**4**) several other rhodomyrtosones were isolated.[4] One of them tomentosone A (**6**), illustrates a double coupling of the central acylphloroglucinol part with an aldehyde and syncarpic acid.[5,6] The acylphloroglucinol family of natural products also includes the well-known hyperforin (**7**).[7] Because of the prenyl groups polycyclic structures are quite common within this type of natural products.[8] In particular the antibiotic activity of rhodomyrtone has been studied in more detail[9] but so far the exact mode of action is not known. Quite recently the isolation of a hybrid consisting of a phloroglucinol derivative and the terpene myrcene from *Callistemon viminalis* was described.[10] A new compound rhodomyrtosone E (**5**) was recently found in *Eucalyptus citriodora* Hook leaves.[11]

The retrosynthesis of these acylphloroglucinols is rather obvious. Thus, opening of the heterocyclic ring leads to precursor **9** which can be simplified further to syncarpic acid (**10**), an aldehyde **11**, and an acylated phloroglucinol derivative **12** (Fig. 2). Most likely, similar intermediates are involved in the biosynthesis of acylphloroglucinols.[12] The question is whether aldehyde **11** first reacts with syncarpic acid **10** or with the phloroglucinol derivative **12**. Both **10** and **12** can be prepared from phloroglucinol (**13**).[13]

We recently described the first total synthesis of rhodomyrtone (**1**) and rhodomyrtosone B (**4**) where initially syncarpic acid (**10**) was combined with the aldehyde **14** in a Knoevenagel condensation followed by a Michael addition of the phloroglucinol (**13**) to the enedione **15** (Scheme 1).[13] A similar strategy towards the rhodomyrtones A and B was recently disclosed by Porco et al.[14] The recent synthesis of the calliviminones via a final Diels–Alder reaction of myrcene to a related Knoevenagel intermediate supports this order of events during the biosynthesis.[10] However, the initial reaction of the aldehyde **14** with the phloroglucinol part to form a *ortho*-quinone methide intermediate **20** seems likely as well. Therefore, we set out to investigate this and another option toward rhodomyrtone (**1**).

2. Results and discussion

2.1. Quinone methide strategy

ortho-Quinone methides hold a prominent place as intermediates in synthesis and they are also implicated in many

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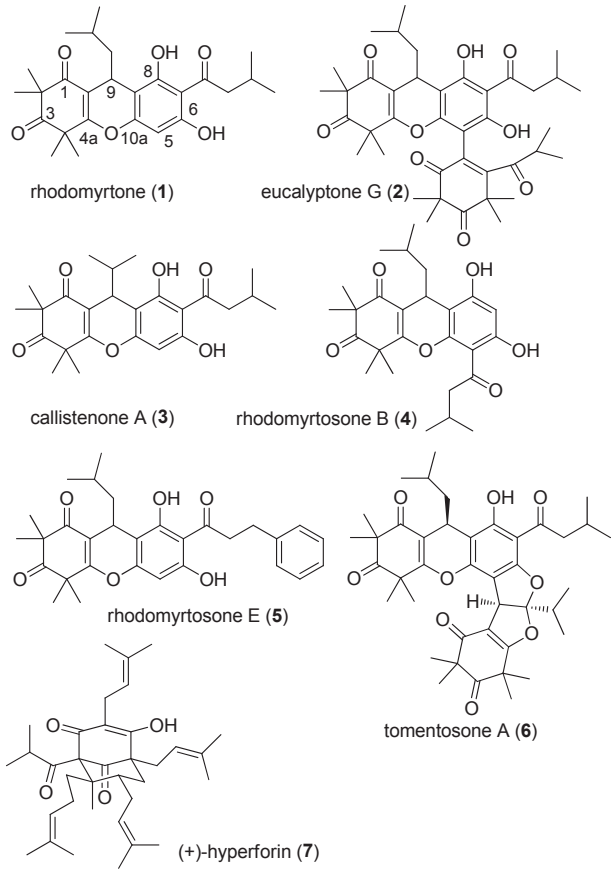


Fig. 1. Structures of some natural acylphloroglucinols.

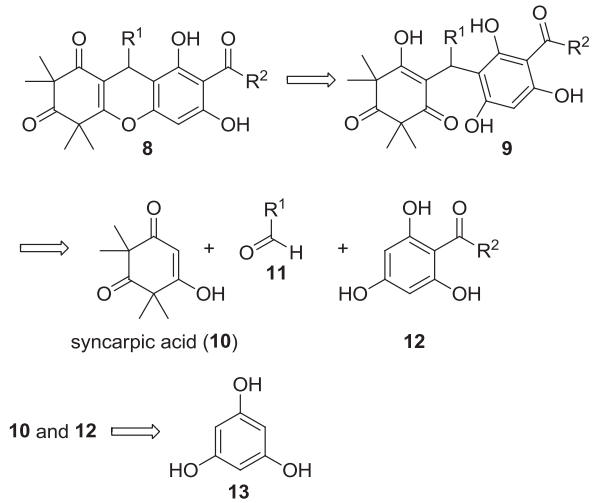
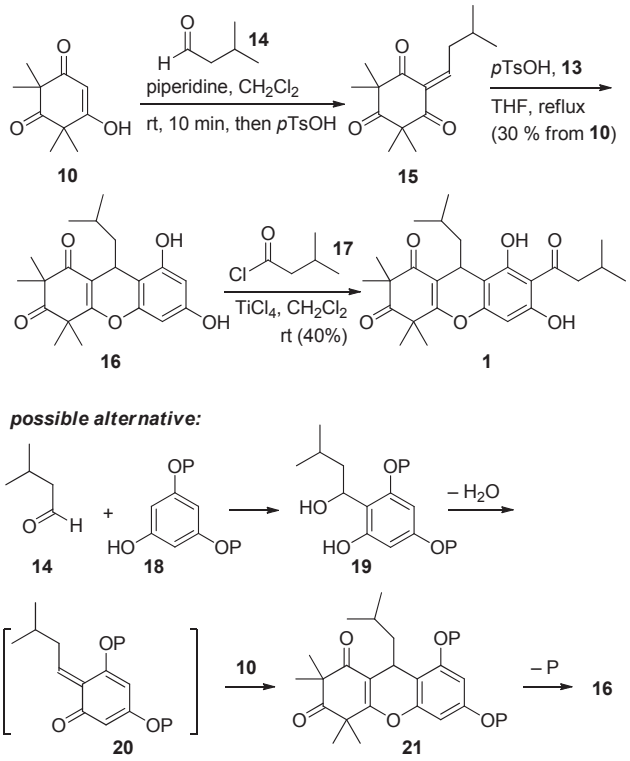
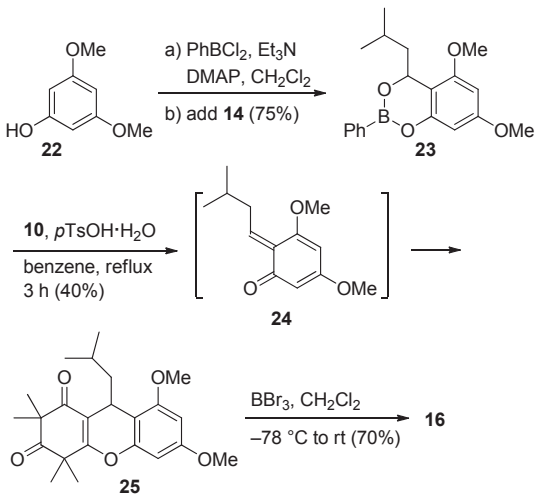


Fig. 2. Retrosynthetic disconnection of acylphloroglucinols of the rhodomyrtone type to the three components **10**, **11**, and **12**.



Scheme 1. Summary of our previous synthesis of rhodomyrtone (**1**) and alternative order of assembly; P=protecting group.



Scheme 2. Synthesis of rhodomyrtone precursor **16** via an *ortho*-quinone methide strategy.

biological processes.[15] For example, natural phloroglucinol-terpene adducts are believed to be formed by cycloaddition between an *ortho*-quinone methide as heterodiene, and a double bond of the terpene component.[16]

Since we knew from our previous work that the isovaleryl group would have to be installed in the last step of the synthesis, we started with commercially available 3,5-dimethoxyphenol (**22**). Using the method of Dufresne et al.[17] phenol **22** was reacted with isovaleraldehyde (**14**) in presence of dichlorophenylborane, Et_3N and catalytic amounts of DMAP. This way the 2-phenyl-4*H*-1,3,2-dioxaborinine **23** was produced in 75% yield (Scheme 2). It turned out to be stable towards chromatography. Such dioxaborinines are known to be precursors of *ortho*-quinone methides.[18] Indeed, when a solution of dioxaborinine **23**, syncarpic acid (**10**) and pTsOH·H_2O (3 equiv) in benzene was refluxed for 3 h, xanthenedione **25** was obtained in 40% yield after chromatographic purification. Most likely, syncarpic acid reacts with the intermediate quinone methide **24** in a Michael addition reaction followed by acid-catalyzed cyclization. The alternative would be a Hetero-Diels–Alder reaction with the enol form of syncarpic acid serving as dienophile. In order to reach the known rhodomyrtone precursor **16**,[13] the methyl ethers of **25** had to be cleaved. This was possible with BBr_3 in CH_2Cl_2 at low temperature. It is worth to mention that other methods of generating *ortho*-quinone methide **24** were unsuccessful. For example, the diol precursor of **23** turned out to be unstable in our hands.[19]

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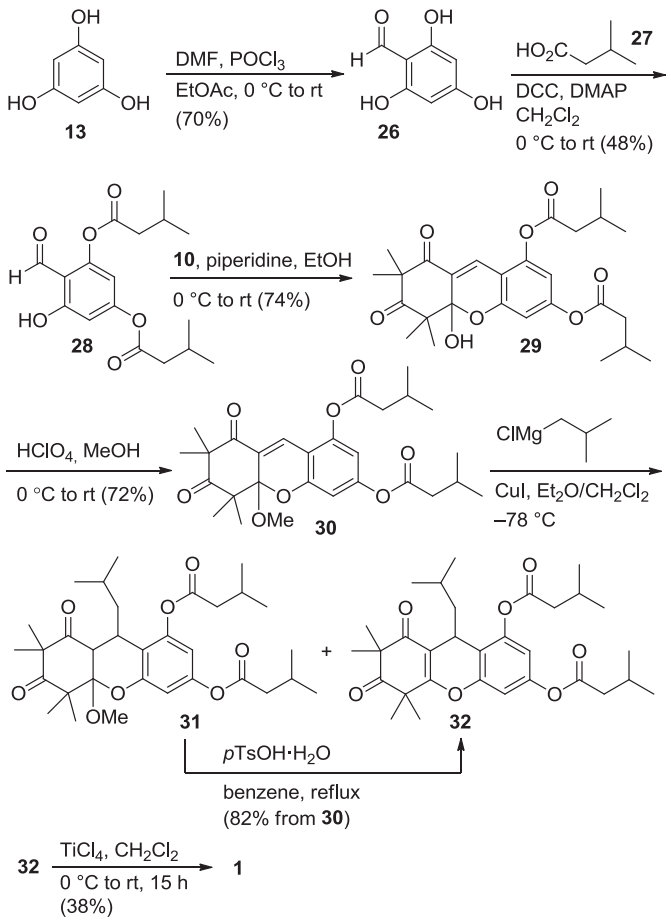
2.2. Knoevenagel strategy

Instead of incorporating the central isobutyl substituent early on, one might construct precursors where this or other groups would be installed in the end, for example, by an organocuprate addition to an enone. This strategy might simplify the synthesis of analogues. With this strategy in mind we started with formylation of phloroglucinol[16,20] (**13**) under Vilsmeier–Haack-conditions (Scheme 3). Thereafter, the resulting trihydroxybenzaldehyde **26** was reacted with isovaleric acid (**27**, 2 equiv) in presence of DCC and a catalytic amount of DMAP. This way a reasonable yield of bis(3-methylbutanoate) **28** could be secured. A piperidine-catalyzed Knoevenagel condensation of syncarpic acid (**10**) with aldehyde **28** led to hydroxyxanthene derivative **29** in good yield. Prior to cuprate addition to the enone function, the hemiacetal of **29** was converted to the mixed acetal **30** by treating a methanol solution of **29** with a catalytic amount of perchloric acid. For the introduction of the isobutyl group, a solution of enone **30** in CH_2Cl_2/Et_2O (1:1) containing CuI (10 mol%) was treated with isobutylmagnesium chloride (2 equiv) at −78 °C. Inspection of the ^1H NMR of the crude product mixture showed only one set of signals for **31**, indicating that the addition reaction was highly diastereoselective (see Supplementary data). However, we could not assign the relative stereochemistry (*cis* or *trans* to the methoxy group at C-4a). Workup led to a mixture of **31** (up to 35%) and **32**. In order to eliminate methanol from **31**, the mixture was refluxed in benzene that contained a small amount of *p*TsOH·H_2O. The total yield for the conversion of **30** to **32** was 82%. The ester functions were not affected by the cuprate reagent. When a solution of bis-(butanoate) **32** in CH_2Cl_2 was treated with $TiCl_4$ (5 equiv) at 0 °C, followed by stirring of the mixture for 15 h at room temperature, rhodomyrtone (**1**) was obtained in 38% yield. An experiment performed in an NMR tube (^1H NMR) using 4 equiv of $TiCl_4$, indicated a mixture of diester **32**, rhodomyrtone (**1**), monoesters, and a trace of rhodomyrtosone B (**4**). Using a larger excess (5 equiv) of $TiCl_4$ drives the reaction towards the desired rhodomyrtone (**1**), however, at the same time the reaction mixture turned dark brown with the formation of some black precipitate (tar).



Scheme 3. Synthesis of rhodomyrtone (**1**) via Knoevenagel condensation between syncarpic acid (**10**) and benzaldehyde **28** followed by late-stage introduction of the isobutyl group at C-9.

3. Conclusion

In this paper we present two novel routes to the antibiotic rhodomyrtone (**1**). The first route relies on reaction of syncarpic acid (**10**) with the quinone methide, generated from dioxaborinine **23**. After cleavage of the aryl methyl ether functions, xanthenedione **16**, which can be converted in one step (40%) to rhodomyrtone,[13] was obtained. The second route was designed with regard to variations at C-9 of rhodomyrtone. Here a Knoevenagel condensation between syncarpic acid (**10**) and benzaldehyde **28** eventually led to xanthene derivative **30**, containing a mixed acetal and isovaleroyl groups on the phenolic hydroxyl functions. The isobutyl substituent could be introduced by cuprate addition to the enone function of **30**. Acid-induced elimination of methanol and Lewis acid-induced Fries rearrangement led to rhodomyrtone as well. All three routes start from syncarpic acid (**10**) which is available in three steps from phloroglucinol (**13**) in an overall yield of 45%.[13,21] Counting from syncarpic acid, route one requires three steps (10% overall yield), route two involves four steps (8.4% overall yield), and route three takes six steps (5.6% overall yield). Both of the routes one and two might correspond to a biomimetic synthesis. The strategies outlined here might be useful for the synthesis of other natural and unnatural acylphloroglucinols.

4. Experimental section

4.1. General section

*4.1.1. 4-Isobutyl-5,7-dimethoxy-2-phenyl-4H-benzo[d][1,3,2]dioxaborinine (**23**).* To a cooled (0 °C) solution of 3,5-dimethoxyphenol (**22**) (4.6 g, 29.84 mmol), Et_3N (4.16 mL, 29.84 mmol), and DMAP (365 mg, 2.99 mmol) in CH_2Cl_2 (100 mL), dichlorophenylborane (97%, 3.8 mL, 28.41 mmol) was added in a dropwise fashion. After 15 min, isovaleraldehyde (**14**) (3.15 mL, 28.71 mmol) was slowly added and stirring of the mixture was continued for 1 h at room temperature until full conversion was achieved (TLC control). The yellowish reaction mixture was quenched with satd. NH_4Cl solution (300 mL) and extracted with CH_2Cl_2 (3×400 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 30:1 to 25:1) provided the title compound as a colorless oil (6.98 g, 75%). R_f=0.46 (petroleum ether/EtOAc, 10:1); ^1H NMR (400 MHz, $CDCl_3$): δ=0.93 (d, J=6.7 Hz, 3H, 3′-H), 1.05 (d, J=6.7 Hz, 3H, 3′-H), 1.63 (dt, J=14.0, 6.7, Hz, 2H, 1′-H), 2.05 (qqt, J=6.7, 6.7, 6.7 Hz, 1H, 2′-H), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.34 (t, J=6.7 Hz, 1H, 4-H), 6.19 (d, J=2.3 Hz, 1H, 6- or 8-H), 6.29 (d, J=2.3 Hz, 1H, 6- or 8-H), 7.39–7.43 (m, 2H, 3″-H), 7.46–7.51 (m, 1H, 4″-H), 7.95–7.99 (m, 2H, 2″-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.6 (C-3′), 23.7 (C-3′), 24.5 (C-2′), 47.9 (C-1′), 55.4 (OCH_3), 55.5 (OCH_3), 68.1 (C-4), 93.7, 94.9 (C-6, C-8), 108.4 (C-4a), C-1″ is obscured, 127.7 (C-2″), 131.3 (C-4″), 134.4 (C-3″), 150.2, 156.2, 160.3 (C-5, C-7, C-8a).

*4.1.2. 9-Isobutyl-6,8-dimethoxy-2,2,4,4-tetramethyl-4,9-dihydro-1H-xanthene-1,3(2H)-dione (**25**).* A mixture of benzodioxaborinine **23** (6.80 g, 20.85 mmol), syncarpic acid (**10**) (4.2 g, 23.05 mmol) and *p*-toluenesulfonic acid monohydrate (11.9 g, 62.56 mmol) in benzene

(180 mL) was refluxed for 3 h. Thereafter, the resulting dark-red solution was cooled down to room temperature, partitioned between water (500 mL) and Et_2O (500 mL). The aqueous layer was extracted with Et_2O (3×500 mL). The combined organic layers were washed with satd. NaCl solution (1×400 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 15:1) provided xanthenedione **25** (3.22 g, 40%) as a yellowish oil. R_f=0.34 (petroleum ether/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.82 (d, J=6.2 Hz, 6H, 3′-H), 1.34 (s, 3H, 2-CH_3), ~1.35 (obscured, 1H, 2′-H), ~1.35 (obscured, 2H, 1′-H), 1.38 (s, 3H, 2-CH_3), 1.44 (s, 3H, 4-CH_3), 1.54 (s, 3H, 4-CH_3), 3.80 (s, 6H, OCH_3), 4.22 (dd, J=6.4, 5.4 Hz, 1H, 9-H), 6.24 (d, J=2.3 Hz, 1H, Ar), 6.26 (d, J=2.3 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.8 (C-3′), 23.6 (C-3′), 24.3 (CH_3), 24.5 (CH_3), 24.6 (CH_3), 24.8 (CH_3), 25.1 (C-2′), 25.4 (C-9), 46.6 (C-1′), 47.2 (C-4), 55.4 (OCH_3), 55.5 (OCH_3), 55.9 (C-2), 92.9, 95.1 (C-5, C-7), 107.8 (C-8a), 113.8 (C-9a), 152.3 (C-10a), 157.9, 159.5 (C-6, C-8), 167.7 (C-4a), 197.5 (C-1), 212.7 (C-3); HRMS (ESI/TOF): $[M+Na]^+$ calcd for $C_{23}H_{30}O_5Na$ 409.19854, found 409.19848.

*4.1.3. 6,8-Dihydroxy-9-isobutyl-2,2,4,4-tetramethyl-4,9-dihydro-1H-xanthene-1,3(2H)-dione (**16**).* To a solution of dimethyl ether **25** (400 mg, 1.03 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of BBr_3 in CH_2Cl_2 (1 M, 5.2 mL, 5.2 mmol) at −78 °C. After complete addition, the dark-red reaction mixture was left to reach room temperature overnight while stirring. It was quenched with water (50 mL) and extracted with EtOAc (4×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give the dihydroxy-xanthene-1,3(2*H*)-dione **16** (260 mg, 70%) as a brownish solid. Its spectral data matched with the reported ones.[13]

*4.1.4. 2,4,6-Trihydroxybenzaldehyde (**26**).* To a cooled (0 °C) solution of phloroglucinol (**13**) (20.0 g, 0.159 mol) and DMF (12.2 mL, 0.159 mol) in EtOAc (300 mL), $POCl_3$ (14.83 mL, 0.159 mol) was added dropwise within 60 min. After complete addition the resulting suspension was left to stir at room temperature for 6 h. When full consumption was achieved, the yellow suspension was poured on ice-water (500 mL), and the two-phase mixture was stirred vigorously while adding satd. NaOAc solution to it until a pH of 5–6 was reached. During the addition the solution became dark-red, then it was extracted with EtOAc (4×600 mL). The combined organic layers were washed with satd. NaCl solution (1×500 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was recrystallized from water (200 mL) to provide benzaldehyde **26** (17.18 g, 70%) as red crystals. ^{1}H NMR (400 MHz, DMSO-d_6): δ=5.78 (s, 2H, 3-H), 9.92 (s, 1H, CHO), 10.64 (s, 1H, OH), 11.45 (s, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ=94.1 (C-3), 104.5 (C-1), 164.1 (C-2), 167.2 (C-4), 190.9 (CHO).

*4.1.5. 4-Formyl-5-hydroxy-1,3-phenylene bis(3-methylbutanoate) (**28**).* To a cooled solution (0 °C) of isovaleric acid (**27**) (11.75 mL, 0.106 mol) in CH_2Cl_2 (500 mL) was added DMAP (650 mg, 5.32 mmol), followed by the addition of aldehyde **26** (8.2 g, 0.053 mol) in one portion. Subsequently, a solution of DCC (22.5 g, 0.109 mol) in CH_2Cl_2 (150 mL) was added dropwise over 30 min at 0 °C. The resulting suspension was allowed to stir at room temperature for 6 h. All precipitates were filtered-off and the filtrate was transferred to a separation funnel together with water (650 mL). After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3×500 mL). The combined organic layers were washed with satd. NaCl solution (1×500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 18:1) to give bis-ester **28** (8.22 g, 48%) as a white solid. R_f=0.5 (petroleum ether/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (d, J=6.7 Hz, 6H, 4-H), 1.05 (d, J=6.7 Hz, 6H, 4-H), 2.20 (qqt, J=6.8, 6.8, 6.8 Hz, 1H, 3-H), 2.23 (qqt, J=6.8, 6.8, 6.8 Hz, 1H, 3-H), 2.42 (d, J=7.1 Hz, 2H, 2-H), 2.49 (d, J=7.1 Hz, 2H, 2-H), 6.56 (d, J=2.0 Hz, 1H, Ar), 6.63 (d, J=2.0 Hz, 1H, Ar), 10.02 (s, 1H, CHO), 11.76 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.3 (2×C-4), 22.4 (2×C-4), 25.7 (2×C-3), 43.0 (C-2), 43.2 (C-2), 107.7 (C-2′), 108.2 (C-6′), 111.2 (C-4′), 153.8 (C-3′), 157.5 (C-1′), 164.1 (C-5′), 170.0 (C-1), 170.4 (C-1), 191.9 (CHO); HRMS (ESI/TOF): $[M+Na]^+$ calcd for $C_{17}H_{22}O_6Na$ 345.13086, found 345.13110.

*4.1.6. 4a-Hydroxy-2,2,4,4-tetramethyl-1,3-dioxo-2,3,4,4a-tetrahydro-1H-xanthene-6,8-diyl bis(3-methylbutanoate) (**29**).* To a 0 °C cooled suspension of aldehyde **28** (7.0 g, 21.7 mmol) and syncarpic acid (**10**) (4.15 g, 22.77 mmol) in EtOH (200 mL), piperidine (0.1 mL, 1.01 mmol) was added. The ice-bath was removed and stirring was continued for 10 h at room temperature until the reaction mixture turned to a clear-yellow solution. All volatiles were removed using a rotavapor. Purification of the resulting yellow oil by flash chromatography (petroleum ether/EtOAc, 6:1) provided of xanthene derivative **29** (7.86 g, 74%) as a yellowish solid. R_f=0.51 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (d, J=6.7 Hz, 6H, 4-H), 1.08 (d, J=6.7 Hz, 6H, 4-H), 1.10 (s, 3H, 4′-CH_3), 1.37 (s, 3H, 2′-CH_3), 1.40 (s, 3H, 2′-CH_3), 1.46 (s, 3H, 4′-CH_3), 2.23 (qqdd, J=6.8, 6.8, 6.8, 6.8 Hz, 1H, 3-H), 2.24 (qqdd, J=6.8, 6.8, 6.8, 6.8 Hz, 1H, 3-H), 2.42 (d, J=7.1 Hz, 2H, 2-H), 2.53 (d, J=7.1 Hz, 2H, 2-H), 3.70 (br s, 1H, OH), 6.69 (d, J=2.1 Hz, 1H, Ar), 6.80 (d, J=2.0 Hz, 1H, Ar), 7.78 (s, 1H, 9′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.3 (2×C-4), 22.4 (2×C-4), 23.2 (4′-CH_3), 24.0 (2′-CH_3), 25.8 (2′-CH_3), 25.8 (2×C-3), 26.7 (4′-CH_3), 43.1 (C-2), 43.2 (C-2), 53.8 (C-4′), 54.6 (C-2′), 97.8 (C-4a'), 108.6, 110.1 (C-5′, C-7′), 110.6 (C-8a'), 125.8 (C-9′), 126.1 (C-9a'), 149.2 (C-8′), 153.3 (C-6′), 153.5 (C-10a'), 170.7 (C-1), 171.0 (C-1), 198.2 (C-1′), 211.5 (C-3′); HRMS (ESI/TOF): $[M+Na]^+$ calcd for $C_{27}H_{34}O_8Na$ 509.21459, found 509.21506.

*4.1.7. 4a-Methoxy-2,2,4,4-tetramethyl-1,3-dioxo-2,3,4,4a-tetrahydro-1H-xanthene-6,8-diyl bis(3-methylbutanoate) (**30**).* To a 0 °C cooled solution of hemiacetal **29** (50 mg, 0.1 mmol) in MeOH (3 mL) perchloric acid (60%, one drop, catalytic amount) was added. The ice-bath was removed and stirring was continued for 4 h at room temperature until full conversion was observed (TLC control). The mixture was partitioned between water (10 mL) and Et_2O (10 mL). After separation of the layers, the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with satd. NaCl solution (1×20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. On this scale purification was done by preparative TLC (petroleum ether/EtOAc, 6:1) giving methyl acetal **30** (37 mg, 72%) as an amorphous solid. R_f=0.61 (petroleum ether/EtOAc, 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (d, J=6.7 Hz, 6H, 4-H), 1.04 (s, 3H, 4′-CH_3), 1.08 (d, J=6.7 Hz, 6H, 4-H), 1.30, 1.36 (2 s, 3H, 2′-CH_3), 1.40 (s, 3H, 4′-CH_3), 2.20 (qqdd, J=6.8, 6.8, 6.7, 6.7 Hz, 1H, 3-H), 2.27 (qqdd, J=6.8, 6.8, 6.7, 6.7 Hz, 1H, 3-H), 2.41 (d, J=7.1 Hz, 2H, 2-H), 2.53 (d, J=7.1 Hz, 2H, 2-H), 3.03 (s, 3H, OCH_3), 6.65 (d, J=2.1 Hz, 1H, Ar), 6.77 (dd, J=2.1, 0.8 Hz, 1H, Ar), 8.00 (d, J=0.8 Hz, 1H, 9′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.3 (2×C-4), 22.4 (2×C-4), 22.5 (4′-CH_3), 24.5 (2′-CH_3), 25.8 (2′-CH_3), 25.8 (2×C-3), 26.4 (4′-CH_3), 43.1 (C-2), 43.2 (C-2), 50.9 (OCH_3), 54.3 (C-4′), 54.8 (C-2′), 101.9 (C-4a′), 106.5 (C-7′), 109.5 (C-8a′), 109.7 (C-5′), 121.6 (C-9a′), 128.0 (C-9′), 149.3 (C-8′), 153.8 (C-6′), 155.9 (C-10a′), 170.5 (C-1), 170.6 (C-1), 198.6 (C-1′), 211.0 (C-3′); HRMS (ESI/TOF): $[M+Na]^+$ calcd for $C_{28}H_{36}O_8Na$ 523.23024, found 523.23083.

*4.1.8. 9-Isobutyl-2,2,4,4-tetramethyl-1,3-dioxo-2,3,4,9-tetrahydro-1H-xanthene-6,8-diyl bis(3-methylbutanoate) (**32**).* A solution of compound **30** (222 mg, 0.44 mmol) in Et_2O (2 mL) and CH_2Cl_2 (2 mL) was treated with CuI (8 mg, 0.04 mmol) at −78 °C. The

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resulting suspension was stirred for 30 min before isobutyl magnesium chloride (2 M in THF, 0.44 mL, 0.88 mmol) was added within a 10 min period. Stirring was continued for 1.5 h at the same temperature before the reaction mixture was quenched with satd. NH_4Cl solution, and extracted with Et_2O (3×30 mL). The combined organic layers were washed with satd. NaCl solution (1×50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 16:1) to provide the desired xanthene **32** (200 mg) as colorless oil, which contains up to 35% of byproduct **31**. This mixture was dissolved in benzene (5 mL) and *p*TsOH·H_2O (7 mg, 0.04 mmol) was added. The resulting solution was refluxed for 1 h and then cooled to room temperature. After addition of water, the mixture was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 16:1) to give pure xanthene **32** (192 mg, 82%) as colorless oil, which slowly solidified in the freezer. R_f=0.38 (petroleum ether/EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (d, J=6.3 Hz, 3H, 3″-H), 0.87 (d, J=6.2 Hz, 3H, 3″-H), 1.04 (d, J=6.7 Hz, 6H, 4-H), 1.06 (d, J=6.7 Hz, 3H, 4-H), 1.07 (d, J=6.7 Hz, 3H, 4-H), 1.34 (s, 3H, 2′-CH_3), 1.37 (s, 3H, 2′-CH_3), 1.44 (s, 3H, 4′-CH_3), 1.53 (s, 3H, 4′-CH_3), ~1.35 (obscured, 1H, 2″-H), ~1.35 (obscured, 2H, 1″-H), 2.21 (qqdd, J=6.8, 6.8, 6.7, 6.7 Hz, 1H, 3-H), 2.24 (qqdd, J=6.8, 6.8, 6.7, 6.7 Hz, 1H, 3-H), 2.41 (d, J=7.1 Hz, 2H, 2-H), 2.48 (dd, J=15.3, 7.1 Hz, 2H, 2-H), 4.11 (t, J=5.9 Hz, 1H, 9′-H), 6.76 (d, J=2.2 Hz, 1H, Ar), 6.82 (d, J=2.2 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.4 (2×C-4), 22.4 (C-4), 22.5 (C-4), 23.1 (C-3″), 23.2 (C-3″), 24.2 (2′-CH_3), 24.5 (2′-CH_3), 24.7 (4′-CH_3), 24.8 (4′-CH_3), 24.8 (C-2″), 25.7 (C-3), 25.8 (C-3), 26.2 (C-9′), 43.1 (C-2), 43.2 (C-2), 46.9 (C-4′), 47.2 (C-1″), 55.9 (C-2′), 107.5 (C-7′), 112.7 (C-5′), 112.9 (C-8a'), 117.0 (C-9a'), 148.2 (C-8′), 149.2 (C-6′), 151.8 (C-10a'), 167.8 (C-4a'), 170.8 (C-1), 170.9 (C-1), 197.4 (C-1′), 212.0 (C-3′); HRMS (ESI/TOF): $[M+Na]^+$ calcd for $C_{31}H_{42}O_7Na$ 549.28227, found 549.28266.

*4.1.9. Rhodomyrtone (**1**).* To a solution of bis-ester **32** (100 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) a solution of $TiCl_4$ in CH_2Cl_2 (1 M, 0.95 mL, 0.95 mmol) was added slowly. Thereafter, the dark-red solution was stirred for 15 h at room temperature before it was treated with water (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with satd. NaCl solution (1×50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 5:1) to give rhodomyrtone (**1**) (32 mg, 38%) as a yellowish solid.

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Supplementary data

General information and copies of NMR spectra. Supplementary data associated with this article (copies of ^{1}H and ^{13}C NMR spectra) can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.10.063.

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