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Total Synthesis of two Potent Anti-Inflammatory Macrolactones of the Oxacyclododecindione Type

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ABSTRACT

An esterification/Friedel-Crafts-cyclization approach permitted the first successful synthetic entry into the oxacyclododecindione subclass of the dihydroxyphenylacetic acid lactone-type natural products. This route allowed the preparation of the two highly active anti-inflammatory fungal secondary metabolites 14-deoxyoxacyclododecindione and 14-deoxy-4-dechlorooxacyclododecindione as well as their 14-desmethyl analogues.

Introduction

The recently reported 12-membered macrolactones 4-dechloro-14-deoxyoxacyclododecindione (**1**) and 14-deoxyoxacyclododecindione (**2**)[1] as well as the previously reported oxacyclododecindione (**3**)[2] are secondary metabolites produced by the imperfect fungus *Exserohilum rostratum*.[1, 2] These compounds exhibit potent anti-inflammatory and anti-fibrotic activities in cell culture experiments and in an in vivo mouse

model of systemic lupus erythematosus (SLE) and may serve as lead structures for therapeutics against chronic inflammatory and/or fibrotic diseases like asthma, rheumatoid arthritis, SLE or cancer.[1] Our previously reported synthetic approaches to biologically active analogues of oxacyclododecindione-type macrolactones, afforded initial structure-activity relationships in this compound class.[3] Since 4-dechloro-14-deoxyoxacyclododecindione (**1**), 14-deoxyoxacyclododecindione (**2**) and oxacyclododecindione (**3**) can only be obtained in minute amounts by fermentation of the producer strain, we herein report the first total synthesis of lactones (±)-**1** and (±)-**2**. To investigate the role of the methyl groups at C10 and C14 for the anti-inflammatory potency, the 14-desmethyl analogues of **1** and **2** were also synthesized and compared with the latter lactones as well as with natural (*S*)-10,11-dehydrocurvularin.

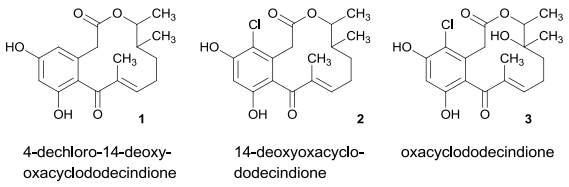
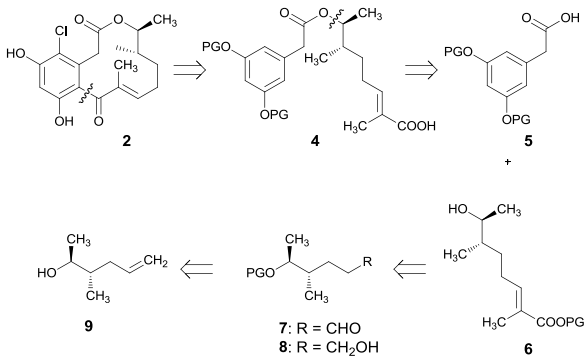


Figure 1. Structures of the natural macrolactones **1**, **2** and **3**.

Results and Discussion

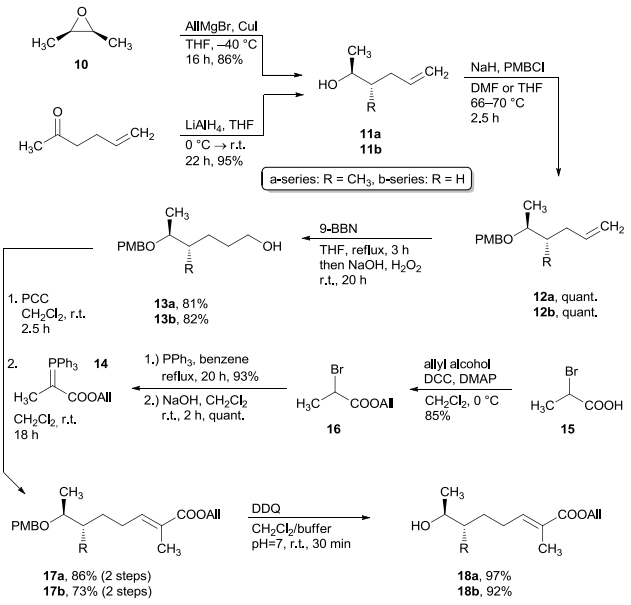
Various strategies such as carbonylative cross-coupling, ring-closing metathesis/isomerization, ring-closing metathesis/hydrogenation/unsaturation as well as hydroacylation to construct the 12-membered core of the oxacyclododecindione-type macrolactones turned out to be unsuccessful,[3] the main reason for this being the steric hindrance imposed by the 10-methyl group. In contrast, an intramolecular Friedel-Crafts acylation at a late stage turned out to be a suitable key step for the synthesis of this compound class. Remarkably, a similar approach only resulted in low yields when applied to the preparation of the less substituted saturated macrolactone (*S*)-curvularin[4-10] or 11-methoxycurvularin[11, 12]. While the elucidation of the relative configuration at C14 and C15

was uncertain,[1] the (*S*)-configuration was tentatively assigned to both stereocenters based on the analogy with other member of the series and NOESY data. The synthetic experiments reported here were performed in the racemic series. The required precursor **4** for the Friedel-Crafts acylation can be synthesized by Steglich esterification of arylacetic acid **5** and alcohol **6** which can be prepared by hydroboration, oxidation and Wittig reaction of hexenol **9** (Scheme 1).



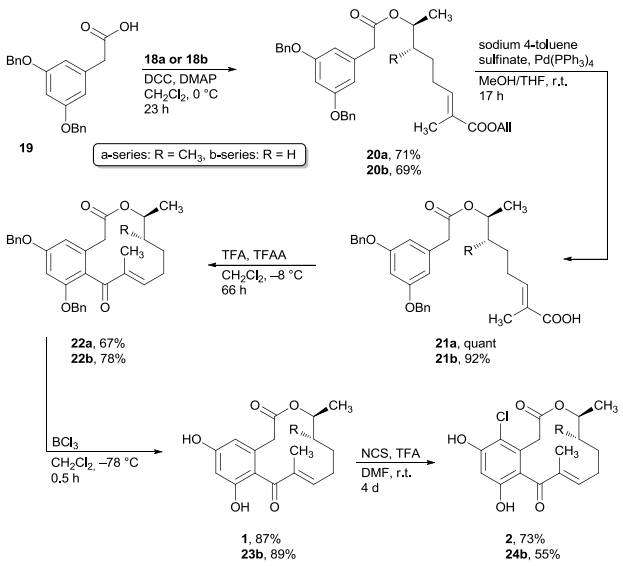
Scheme 1. Retrosynthetic analysis of **2** by an intramolecular Friedel-Crafts acylation.

Ring-opening of commercial cis-2,3-epoxybutane (**10**) with an allyl cuprate yielded 3-methylhex-5-en-2-ol (**11a**),[13] which was then protected as the PMB-ether[14] (Scheme 2). Subsequent hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) and oxidative work-up afforded alcohol **13a**.[15] Oxidation with pyridinium chlorochromate furnished the corresponding aldehyde which was subjected to a Wittig reaction without further purification. The required phosphonium ylide **14** was prepared from 2-bromopropionic acid (**15**) by esterification with allylic alcohol, phosphonium salt formation and deprotonation with NaOH.[16] The Wittig reaction yielded the PMB-protected *α,β*-unsaturated allyl ester **17a** which was converted to the desired alcohol **18a** by oxidative removal of the PMB group.[17, 18] Similarly, compound **18b** was synthesized in 5 steps from **11b** (protection, hydroboration, oxidation, Wittig reaction and deprotection) in 55% yield.



Scheme 2. Synthesis of alcohol **18**.

Steglich esterification of 3,5-bis(benzyloxy)phenylacetic acid (**19**)[19] with alcohol **18a** yielded ester **20a** in 71% yield.[20] The selective palladium-catalyzed cleavage of the allyl ester with sodium 4-toluenesulfinate[20, 21] afforded the precursor of the Friedel-Crafts acylation. The key step was performed with the catalytic system TFA/TFAA (2:1) at −8 °C and at low concentration (c = 0.65 mM) to avoid polymerization and yielded the desired lactone **22a** in 67% yield. Cleavage of the benzyl ethers with boron trichloride furnished 4-dechloro-14-deoxyoxacyclododecindione (**1**), which was converted to 14-deoxyoxacyclododecindione (**2**) by chlorination with *N*-chlorosuccinimide (Scheme 3). ^{1}H and ^{13}C NMR spectra of both synthetic compounds matched the respective data of the natural products (see supporting information),[1] thus confirming the assumed relative configuration of the two stereocenters. Similarly, the 14-desmethyl analogue **24b** was synthesized in 5 steps in 24% yield.



Scheme 3. Synthesis of 4-dechloro-14-deoxyoxacyclododecindione (**1**) and 14-deoxyoxacyclododecindione (**2**).

Biological evaluation

Lactones **1**–**3** are potent inhibitors of TGF-β and IL-4 signaling in mammalian cells and we therefore investigated the synthetic analogues for their inhibitory activity on IL-4 inducible Stat6-dependent and TGF-β inducible Smad2/3 dependent transcriptional luciferase reporter in transiently transfected HepG2 cells. To exclude unspecific cytotoxic effects, the results were normalized against the constitutive active EF1α-promoter in front of the luciferase gene in order as described previously.[2, 22] The biological activities of the synthetic derivatives in comparison with those of the natural occurring compounds 14-deoxycyclododecindione and 10,11-dehydrocurvularin are shown in table 1.

Table 1. Effect of synthetic and natural macrolactones in two relevant reporter gene assays.

	$(CAGA)_{9x}$-MLP-Luc (Smad2/3) IC_{50} (nM) IC_{90} (nM)	pgl3-TK-7xN_4 (Stat6) IC_{50} (nM) IC_{90} (nM)
10-Methyl-10,11-	377.9 ± 6.68	182 ± 4.34

dehydrocurvularin (±)-**23b**	1365 ± 2.03	379.2 ± 5.32
4-Chloro-10-methyl-10,11-dehydrocurvularin (±)-**24b**	171.2 ± 4.82 590.35 ± 3.56	103.31 ± 4.93 439.81 ± 5.21
4-Dechloro-14-deoxyoxacyclododecindione (±)-**1**	521. 4 ± 15.84 1600 ± 5.45	138.52 ± 8.07 656.18 ± 5.67
14-Deoxyoxacyclododecindione (±)-**2**	137.9 ± 4.8 485.17 ± 5.2	58.4 ± 2.55 214.3 ± 4.68
(14*S*,15*S*)-14-Deoxyoxacyclodedecindione (**2**)	198.2 ± 7.82 402 ± 5.32	140 ± 5.2 396 ± 4.2
(15*S*)-10,11-Dehydrocurvularin	1700 ± 23.5 4300 ± 53.2	3400 ± 43.2 6700 ± 76.4

HepG2 cells were transiently transfected with the indicated reporter gene construct and the constitutively active pRL-EF1α reporter gene and stimulated with 5 ng/mL TGF-β or 5 ng/mL IL-4 with or without test compounds for 16 h as described in Materials and Methods.

The racemic synthetic dehydrocurvularin derivative 4-chloro-10-methyl-10,11-dehydrocurvularin (±)-(**24b**) exhibits a potent inhibiton of TGF-β and IL-4 inducible reporter gene expression with IC_{50}-values of 103 and 172 nM which was comparable to natural **2**. 10-Methyl-10,11-dehydrocurvularin (±)-**23b** which misses the chlorine substituent at C4, was about twofold less active and natural 10,11-dehydrocurvularin which differs from **23b** by the loss of the C10 methyl group was about tenfold less active with respect to TGF-β induced signaling pathway and about 30-fold less active with respect to the IL-4 induced Stat6 signaling pathway. This indicates that the methyl group at C10 and the chlorine substituent at C4 greatly contribute to the biological activity. Synthetic 14-deoxyoxacyclododecindione (±)-(**2**) exhibits a more potent biological activity than the natural optically active counterpart inhibiting TGF-β- and IL-4-inducible reporter gene expression in the nanomolar range. Currently, an asymmetric synthesis of **2** is being developed to investigate this effect. Compared to its chlorinated analogue, compound (±)-**1** exerted a 3-fold reduced inhibitory activity on TGF-β signaling and IL-4 dependent reporter gene expression. Our results indicate that, apart from the $\Delta^{10,11}$-double bond in the lactone ring,[1] the methyl substituent at

C10 and, to a lesser extent, the chlorine atom at C-4 and the 14-methyl group appear to be essential structural features for the high anti-inflammatory and anti-fibrotic activities of this type of fungal 12-membered macrolactones.

Conclusion

In summary, the first racemic total syntheses of the potent anti-inflammatory fungal secondary metabolites 4-dechloro-14-deoxyoxacyclododecindione (24% yield over 10 steps) and 14-deoxyoxacyclododecindione (18% yield over 11 steps) were accomplished by a late-stage intramolecular Friedel-Crafts cyclization and their relative configuration was identified. The compounds inhibit two important pro-inflammatory signaling pathways in the nanomolar concentration range. The 14-desmethyl analogues of the natural products were also prepared to elucidate the impact of this substituent on the biological activity and permitted the establishment of structure activity relationships. The effect of the absolute configuration of the compounds on their biological activity in these pathways is currently being investigated in our labs and the respective results will be reported in due course.

Experimental Section

Material and Methods

All commercially available reagents were reagent grade and used without further purification. Reactions involving moisture or air sensitive reagents were performed under argon atmosphere in oven-dried glassware. Benzene and tetrahydrofuran were distilled from sodium and benzophenone. Dichloromethane was distilled from calcium hydride. Dimethylformamide (DMF, extra dry) was purchased und used without further purification. Thin-layer chromatography (TLC) was carried out on 0.25 µm silica gel plates ($60F_{254}$) using UV light as visualizing agent and colorized with vanillin reagent (solution of vanillin (1.0 g) in

methanol (100 mL), glacial acetic acid (12 mL) and concentrated sulfuric acid (4 mL)) and heat as developing agent. Flash chromatography was performed on silica gel (35–70 µm) using the indicated solvent system. Melting points were determined in open capillary tubes. NMR spectra were recorded on a 300 MHz spectrometer (300 MHz ^{1}H and 75.5 MHz ^{13}C), a 400 MHz spectrometer (400 MHz ^{1}H and 100.6 MHz ^{13}C) and a 600 MHz spectrometer (600 MHz ^{1}H, 150.9 MHz, ^{13}C). The chemical shifts were referenced to the deuterated solvent (e.g., for $CDCl_3$, δ = 7.26 ppm and 77.16 ppm for ^{1}H and ^{13}C NMR, respectively) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm).[23] Infrared spectra were recorded as FT-IR spectra using a diamond ATR unit. High-resolution masses were recorded on a Q-TOF-Instrument with a dual source and a suitable external calibrant.

Biological Assays

HepG2 cells (DSMZ ACC 180) were maintained in DMEM medium supplemented with 10% fetal calf serum (FCS) and 65 µg/mL penicillin G and 100 µg/mL streptomycin sulfate in a humidified atmosphere.

The STAT6-driven reporter plasmid pGL3-TK-7xN_4 contains the herpes simplex virus thymidine kinase promoter under the control of 7 copies of the palindromic sequence TTC$(N)_4$GAA.[2] The STAT6 expression plasmid (TOPO-Stat6) has been previously described.[24] The reporter plasmid $(AGCCAGACA)_9$MLP-Luc contains nine tandem copies of the CAGA Smad binding element upstream of the adenovirus major late promoter driving luciferase expression.[25] The plasmid was kindly provided by Prof. S. Dooley (University of Mannheim, Germany). The control reporter vector pRL-EF1α for data normalization was purchased from Promega (Dual-Luciferase-Reporter-Assay). Luciferase-based reporter gene expression was thereby normalized for transfection variability and cytotoxicity against renilla expression of the constitutively active control vector (pRL-EF1α) assayed in the same sample.

HepG2 cells were transiently transfected by electroporating (Bio-Rad, Gene-Pulser) $1 \cdot 10^7$ cells/mL in DMEM together with of the indicated constructs (50 µg) and the internal control pRL-EF1α vector at 500 V/cm. After electroporation the cells were seeded at 2 x 10^5 cells/mL and allowed to recover for 16 h. For induction of reporter gene expression, the cells were treated either with 5 ng/mL TGF-β or 5 ng/mL IL-4 with or without test compounds in DMEM containing 5% FCS. Luciferase activity was measured 16 h after induction using the luciferase assay system (Promega, Mannheim, Germany) according to the manufacturer's instructions with a luminometer.

3-Methylhex-5-en-2-ol (11a):[13]

Allylmagnesium bromide (1M in Et_2O, 83 mL, 83.0 mmol, 1.5 equiv) was added at −40 °C to a solution of copper(I) iodide (2.11 g, 11.1 mmol, 0.2 equiv) in dry THF (30 mL). After 30 minutes 2,3-cis-epoxybutane (4.00 g, 55.5 mmol) was added. The reaction mixture was stirred at −40 °C for 6 h and was then allowed to warm up to room temperature over 2.5 days. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (100 mL) and stirred for 1 hour. The organic layer was separated, the aqueous layer extracted with diethyl ether (3 x 100 mL), dried over magnesium sulfate and filtered. Distillation yielded **29a** (5.46 g, 47.8 mmol, 86%, Lit.[13]: 88%) as a colorless liquid. $\mathbf{R_f}$ = 0.20 (cyclohexane/EtOAc 5:1), **b.p.:** 130 °C, **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 5.83–5.73 (m, 1H, C*H*=CH_2), 5.04–4.96 (m, 2H, CH=CH_2), 3.63 (p, 1H, *J* = 6.3 Hz, C*H*-2), 2.26–2.19 (m, 1H, CH_{2A}-4), 1.96–1.85 (m, 2H, CH_{2B}-4, O*H*), 1.61–1.51 (m, 1H, C*H*-3), 1.12 (d, 3H, *J* = 6.3 Hz, CH_3-1), 0.85 (d, 3H, *J* = 6.9 Hz, CH_3-3). The data are in accordance with those reported in the literature.[13] **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ [ppm] = 137.5 (*C*H=CH_2), 116.0 (CH=*C*H_2), 71.5 (*C*-2), 40.1 (*C*-3), 37.5 (*C*-4), 19.8 (*C*-1), 14.9 (*C*H_3-3). The data are in accordance with those reported in the literature.[13]

1-Methoxy-4-((3-methylhex-5-en-2-yloxy)methyl)benzene (12a).

Sodium hydride (95%, 80 mg, 3.17 mmol, 1.5 equiv) was added to a solution of 3-methylhex-5-en-2-ol **11a** (238 mg, 2.08 mmol) in dry DMF (8 mL) and the mixture was stirred for 30 minutes. Then, *p*-methoxybenzyl chloride (423 mg, 2.70 mmol, 1.3 equiv) was added and stirred at 70 °C. After 2 h the reaction mixture was cooled and water was added cautiously. The reaction mixture was diluted with diethyl ether (150 mL), washed with water (3 x 75 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane) yielded **12a** (487 mg, 2.08 mmol, quant) as a colorless liquid.

R_f = 0.72 (cyclohexane/EtOAc 4:1), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.30–7.25 (m, 2H, AA'-part of AA'BB'-spin system, *H*-2, *H*-6, PMB), 6.90–6.85 (m, 2H, BB'-part of AA'BB'-spin system, *H*-3, *H*-5, PMB), 5.77 (dddd, 1H, *J* = 16.9 Hz, *J* = 10.2 Hz, *J* = 7.7 Hz, *J* = 6.5 Hz, C*H*=CH_2), 5.04–4.96 (m, 2H, CH=CH_2), 4.49 (d, 1H, *J* = 11.2 Hz, CH_{2A}, OPMB), 4.38 (d, 1H, *J* = 11.2 Hz, CH_{2B}, OPMB), 3.80 (s, 3H, OCH_3), 3.35 (quint, 1H, *J* = 6.2 Hz, *H*-2), 2.30–2.21 (m, 1H, CH_{2A}-4), 1.96–1.85 (m, 1H, CH_{2B}-4), 1.83–1.71 (m, 1H, C*H*-3), 1.12 (d, 3H, *J* = 6.2 Hz, CH_3-1), 0.87 (d, 3H, *J* = 6.8 Hz, CH_3-3). The data are in accordance with those reported in the literature.[26] **^{13}C-NMR, HSQC** (75.5 MHz, $CDCl_3$): δ [ppm] = 159.1 (C_q-4, PMB), 137.7 (*C*H=CH_2), 131.4 (C_q-1, PMB), 129.3 (*C*H-2, *C*H-6, PMB), 115.8 (CH=*C*H_2), 113.8 (*C*H-3, *C*H-5, PMB), 78.0 (*C*H-2), 70.3 (O*C*H_2, PMB), 55.4 (O*C*H_3), 37.8 (*C*H-3), 37.7 (*C*H_2-4), 15.8 (*C*H_3-1), 14.6 (*C*H_3-3). The data are in accordance with those reported in the literature.[26] **IR** (ATR): ũ [cm^{-1}] = 3074, 2972, 2933, 2907, 2876, 2836, 1512, 1245, 1172, 1096, 1072, 1036, 909, 820.

5-((4-Methoxybenzyl)oxy)-4-methylhexan-1-ol (13a)[15]

A solution of 9-BBN (0.5M in THF, 22.4 mL, 11.2 mmol, 1.2 equiv) was added to hexenol **12a** (2.18 g, 9.30 mmol) and refluxed. After 3 h the reaction mixture was cooled in an ice bath and 2N sodium hydroxide solution (12.7 mL) and hydrogen peroxide (35%, 12.7 mL) were added cautiously. The reaction mixture was stirred at 0 °C for 1 h and 19 h at room temperature. Then saturated aqueous ammonium chloride solution (200 mL) was added,

extracted with diethyl ether (4 x 200 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane/EtOAc 3:1) yielded **13a** (1.90 g, 7.53 mmol, 81%) as a colorless oil.

R_f = 0.11 (cyclohexane/EtOAc 5:1), **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ [ppm] = 7.30–7.24 (m, 2H, AA'-part of AA'BB'-spin system, *H*-2, *H*-6, PMB), 6.90–6.85 (m, 2H, BB'-part of AA'BB'-spin system, *H*-3, *H*-5, PMB), 4.48 (d, 1H, *J* = 11.4 Hz, OCH_{2A}, PMB), 4.38 (d, 1H, *J* = 11.4 Hz, OCH_{2B}, PMB), 3.79 (s, 3H, CH_3, PMB), 3.59 (t, 2H, *J* = 6.4 Hz, CH_2-1), 3.34 (quint, 1H, *J* = 6.2 Hz, C*H*-5), 1.84 (s_{br}, 1H, O*H*), 1.74–1.64 (m, 1H, C*H*-4), 1.64–1.42 (m, 3H, CH_2-2, CH_{2A}-3), 1.19–1.09 (m, 1H, CH_{2B}-3), 1.11 (d, 3H, *J* = 6.2 Hz, CH_3-6), 0.89 (d, 3H, *J* = 6.8 Hz, CH_3-4). **^{13}C-NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): δ [ppm] = 159.1 (C_q-4, PMB), 131.2 (C_q-1, PMB), 129.3 (*C*H-2, *C*H-6, PMB), 113.8 (*C*H-3, *C*H-5, PMB), 78.3 (*C*H-5), 70.2 (O*C*H_2, PMB), 63.2 (*C*H_2OH), 55.4 (O*C*H_3), 37.5 (*C*H-4), 30.6 (*C*H_2-2), 29.1 (*C*H_2-3), 15.6 (*C*H_3-6), 14.7 (*C*H_3-4). **IR** (ATR): ũ [cm^{-1}] = 3365, 2935, 2872, 2837, 1612, 1512, 1245, 1174, 1105, 1059, 1034, 819. **HRMS** (ESI): calcd for [$C_{15}H_{24}O_3$ + Na]$^+$: 275.1623, found: 275.1629.

5-((4-Methoxybenzyl)oxy)-4-methylhexanal

Pyridinium chlorochromate (961 mg, 4.46 mmol, 1.5 equiv) was added to a solution of hexanol **13a** (750 mg, 2.97 mmol) in dichloromethane (40 mL). The reaction mixture was stirred for 2.5 h and then filtered through a short plug of silica/hyflo (cyclohexane/EtOAc 4:1). Removing the solvent in vacuo yielded the crude aldehyde (699 mg, 2.79 mmol, 94%) as a colorless oil.

R_f = 0.39 (cyclohexane/EtOAc 4:1), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.74 (t, 1H, *J* = 1.8 Hz, C*H*O), 7.28–7.23 (m, 2H, AA'-part of AA'BB'-spin system, *H*-2, *H*-6, PMB), 6.89–6.84 (m, 2H, BB'-part of AA'BB'-spin system, *H*-3, *H*-5, PMB), 4.50 (d, 1H, *J* = 11.3 Hz, OCH_{2A}), 4.35 (d, 1H, *J* = 11.3 Hz, OCH_{2B}), 3.79 (s, 3H, OCH_3, PMB), 3.32 (quint, 1H, *J* = 6.2 Hz, C*H*-5), 2.51–2.31 (m, 2H, CH_2-2), 1.88–1.78 (m, 1H, CH_{2A}-3), 1.71–1.60 (m, 1H, C*H*-4), 1.51–1.37 (m, 1H, CH_{2B}-3), 1.13 (d, 3H, *J* = 6.2 Hz, CH_3-6), 0.88 (d, 3H, *J* = 6.8 Hz,

C*H*$_3$-4). **^{13}C-NMR, HSQC** (75.5 MHz, $CDCl_3$): δ [ppm] = 203.0 (*C*HO), 159.2 (*C*-4, PMB), 131.1 (*C*-1, PMB), 129.3 (*C*-2, *C*-6, PMB), 113.8 (*C*-3, *C*-5, PMB), 78.1 (*C*H-5), 70.3 (O*C*H$_2$, PMB), 55.4 (O*C*H$_3$), 42.0 (*C*H$_2$-2), 37.6 (*C*H-4), 25.2 (*C*H$_2$-3), 15.9 (*C*H$_3$-6), 14.8 (*C*H$_3$-4). **IR** (ATR): ũ [cm^{-1}] = 2965, 2934, 2876, 2837, 1723, 1513, 1246, 1172, 1104, 1070, 1034, 822. **HRMS** (ESI): calcd for $[C_{15}H_{22}O_3 + Na]^+$: 273.1467, found: 273.1457.

Allyl 2-bromopropionate (16)

A solution of 2-bromopropionic acid (30.00 g, 196 mmol), allyl alcohol (16.4 mL, 240 mmol, 1.2 equiv) and DMAP (1.22 g, 10 mmol, 0.05 equiv.) in dry dichloromethane (120 mL) was cooled to 0 °C. *N,N'*-Dicyclohexylcarbodiimide (40.20 g, 196 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (30 mL) and added. After stirring for 4 h, the reaction mixture was filtered through a short plug of silica (CH_2Cl_2). The solvent was carefully removed in vacuo. Distillation yielded **16** (31.95 g, 166 mmol, 85%) as a colorless oil.

R$_f$ = 0.73 (cyclohexane/EtOAc 4:1), **b.p.:** 90 °C (50 mbar), b.p. (Lit.):[27] 91–93 °C (40 Torr), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 5.93 (ddt, 1H, *J* = 17.2 Hz, *J* = 10.4 Hz, *J* = 5.7 Hz, C*H*=CH$_2$), 5.37 (dq, 1H, *J* = 17.2 Hz, *J* = 1.5 Hz, CH=C*H*$_{2A}$), 5.28 (dq, 1H, *J* = 10.4 Hz, *J* = 1.3 Hz, CH=C*H*$_{2B}$), 4.73–4.60 (m, 2H, OC*H*$_2$), 4.39 (t, 1H, *J* = 6.9 Hz, C*H*), 1.84 (d, 3H, *J* = 6.9 Hz, C*H*$_3$). The data are in accordance with those reported in the literature.[27] **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ [ppm] = 170.0 (*C*OO), 131.4 (*C*H=CH$_2$), 119.0 (CH=*C*H$_2$), 66.5 (O*C*H$_2$), 40.1 (*C*H), 21.8 (*C*H$_3$). The data are in accordance with those reported in the literature.[28]

(1-Allyloxy-1-oxopropan-2-yl)triphenylphosphonium bromide[16]

A solution of allyl 2-bromopropionate (**16**) (1.00 g, 5.18 mmol) and triphenylphosphine (1.36 g, 5.18 mmol, 1.0 equiv) in benzene (2.6 mL) was stirred at 70 °C. After 20 h, the solvent was removed in vacuo and the residue was washed with pentane to yield the product as a colorless solid (2.20 g, 4.83 mmol, 93%).

m.p.: 145.0–145.5 °C (pentane), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.01–7.93 (m, 6H, Ph), 7.78–7.72 (m, 3H, Ph), 7.69–7.62 (m, 6H, Ph), 6.97 (dq, 1H, *J* = 15.7 Hz, *J* = 7.1 Hz,

C*H*), 5.54 (ddt, 1H, *J* = 17.2 Hz, *J* = 10.3 Hz, *J* = 5.9 Hz, C*H*=CH_2), 5.15–5.06 (m, 2H, CH=CH_2), 4.47–4.34 (m, 2H, OCH_2), 1.67 (dd, 3H, *J* = 18.4 Hz, *J* = 7.1 Hz, CH_3). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ [ppm] = 167.8 (d, *J* = 1.6 Hz, *C*OO), 135.0 (d, *J* = 3.1 Hz, 3 x *C*-4, Ph), 134.4 (d, *J* = 9.9 Hz, 3 x *C*-3, 3 x *C*-5, Ph), 130.4 (*C*H=CH_2), 130.3 (d, *J* = 12.7 Hz, 3 x *C*-2, 3 x *C*-6, Ph), 117.8 (d, *J* = 86.4 Hz, 3 x *C*-1, Ph), 120.0 (CH=*C*H_2), 67.3 (O*C*H_2), 36.8 (d, *J* = 50.6 Hz, *C*H), 13.0 (d, *J* = 2.8 Hz, *C*H_3). **IR** (ATR): ũ [cm^{-1}] = 3081, 3058, 3016, 2991, 2920, 1735, 1439, 1238, 1186, 1109, 741, 724, 689, 659. **HRMS** (ESI): calcd for $[C_{24}H_{24}O_2P]^+$: 375.1514, found: 375.1524.

Allyl 2-(triphenylphosphoranylidene)propionate (14)

A solution of sodium hydroxide (367 mg, 9.18 mmol, 2.0 equiv) in water (100 mL) was added to a solution of (1-allyloxy-1-oxopropan-2-yl)triphenylphosphonium bromide (2.09 g, 4.59 mmol) and strongly stirred at room temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed in vacuo to yield **14** (1.72 g, 4.59 mmol, quant) as a yellow oil.

m.p.: 121.8–123.4 °C (CH_2Cl_2), **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.63–7.57 (m, 6H, 3 x *H*-2, 3 x *H*-6, Ph), 7.55–7.50 (m, 3H, 3 x *H*-4, Ph), 7.47–7.42 (m, 6H, 3 x *H*-3, 3 x *H*-5, Ph), 5.28 (s_{br}, 1H, C*H*=CH_2), 4.69 (s_{br}, 2H, CH=C*H*$_2$), 4.29 (s_{br}, 2H, OC*H*$_2$), 1.63 (d, 3H, *J* = 13.9 Hz, C*H*$_3$). **^{13}C-NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): δ [ppm] = 170.4 (br, *C*OO), 133.7 (d, *J* = 9.6 Hz, 3 x *C*H-2, 3 x *C*H-6, Ph), 132.2 (d, *J* = 10.3 Hz, 3 x C_q-1, Ph), 131.7 (d, *J* = 2.9 Hz, 3 x *C*H-4, Ph), 128.6 (d, *J* = 12.3 Hz, 3 x *C*H-3, 3 x *C*H-5, Ph), 134.8 (*C*H=CH_2), 115.3 (CH=*C*H_2), 63.0 (O*C*H_2), 32.4 (br, C_q-2), 12.8 (br, *C*H_3). **IR** (ATR): ũ [cm^{-1}] = 3058, 2980, 2926, 2858, 1598, 1300, 1100, 1081, 1068, 743, 713, 691. **HRMS** (ESI): calcd for $[C_{24}H_{23}O_2P + H]^+$: 375.1514, found: 375.1511.

(*E*)-Allyl 7-((4-methoxybenzyl)oxy)-2,6-dimethyloct-2-enoate (17a)

5-((4-Methoxybenzyl)oxy)-4-methylhexanal (670 mg, 2.68 mmol) was dissolved in dichloromethane (50 mL) and phosphonium ylide **14** (1.30 g, 3.48 mmol, 1.3 equiv) was added. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane/EtOAc 20:1) yielded **17a** (851 mg, 2.46 mmol, 92%) as a colorless oil.

R_f = 0.13 (cyclohexane/EtOAc 50:1), **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.27–7.24 (m, 2H, AA'-part of AA'BB'-spin system, *H*-2, *H*-6, PMB), 6.88–6.85 (m, 2H, BB'-part of AA'BB'-spin system, *H*-3, *H*-5, PMB), 6.79 (tq, 1H, *J* = 7.4 Hz, *J* = 1.2 Hz, *H*-3), 5.96 (ddt, 1H, *J* = 17.2 Hz, *J* = 10.5 Hz, *J* = 5.6 Hz, C*H*=CH_2), 5.33 (dq, 1H, *J* = 17.2 Hz, *J* = 1.5 Hz, CH=CH_{2A}), 5.23 (dq, 1H, *J* = 10.5 Hz, *J* = 1.5 Hz, CH=CH_{2B}), 4.64 (dt, 2H, *J* = 5.6 Hz, *J* = 1.5 Hz, CH_2CH=CH_2), 4.48 (d, 1H, *J* = 11.4 Hz, CH_{2A}, PMB), 4.37 (d, 1H, *J* = 11.4 Hz, CH_{2B}, PMB), 3.79 (s, 3H, OCH_3, PMB), 3.34 (quint, 1H, *J* = 6.2 Hz, *H*-7), 2.27–2.07 (m, 2H, CH_2-4), 1.84 (q, 3H, *J* = 1.2 Hz, CH_3-2), 1.74–1.65 (m, 1H, C*H*-6), 1.64–1.55 (m, 1H, CH_{2A}-5), 1.31–1.22 (m, 1H, CH_{2B}-5), 1.11 (d, 3H, *J* = 6.2 Hz, CH_3-8), 0.90 (d, 3H, *J* = 6.8 Hz, CH_3-6). **^{13}C-NMR, HSQC** (100.6 MHz, $CDCl_3$): δ [ppm] = 167.9 (*C*O), 159.1 (C_q-4, PMB), 143.0 (*C*H-3), 132.7 (*C*H=CH_2), 131.1 (C_q-1, PMB), 129.2 (*C*H-2, *C*H-6, PMB), 127.5 (C_q-2), 117.8 (CH=*C*H_2), 113.8 (*C*H-3, *C*H-5, PMB), 78.1 (*C*H-7), 70.2 (O*C*H_2, PMB), 65.2 (*C*H_2CH=CH_2), 55.4 (O*C*H_3), 37.5 (*C*H-6), 31.8 (*C*H_2-5), 26.6 (*C*H_2-4), 15.7 (*C*H_3-8), 14.6 (*C*H_3-6), 12.5 (*C*H_3-2). **IR** (ATR): ũ [cm^{-1}] = 2961, 2934, 2875, 2837, 1709, 1513, 1246, 1171, 1099, 1070, 1035, 821. **HRMS** (ESI): calcd for [$C_{21}H_{30}O_4$ + Na]$^+$: 369.2042, found: 369.2040.

(*E*)-Allyl 7-hydroxy-2,6-dimethyloct-2-enoate (18a)[17, 18]

To a vigorously stirred solution of PMB-ether **17a** (818 mg, 2.36 mmol) in dichloromethane (20 mL) and phosphate buffer (pH = 7, 63 mM) (1.0 mL) was added DDQ (642 mg, 2.83 mmol, 1.2 equiv) at room temperature. After 30 minutes, saturated aqueous sodium hydrogen carbonate solution (100 mL) was added, extracted with dichloromethane (4 x 100 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo.

Purification by flash chromatography on silica (cyclohexane/EtOAc 6:1) yielded **18a** (519 mg, 2.29 mmol, 97%) as a colorless oil.

R_f = 0.21 (cyclohexane/EtOAc 4:1), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 6.79 (tq, 1H, *J* = 7.4 Hz, *J* = 1.2 Hz, *H*-3), 5.95 (ddt, 1H, *J* = 17.2 Hz, *J* = 10.4 Hz, *J* = 5.6 Hz, C*H*=CH_2), 5.32 (dq, 1H, *J* = 17.2 Hz, *J* = 1.5 Hz, CH=CH_{2A}), 5.22 (dq, 1H, *J* = 10.4 Hz, *J* = 1.5 Hz, CH=CH_{2B}), 4.63 (dt, 2H, *J* = 5.6 Hz, *J* = 1.5 Hz, CH_2CH=CH_2), 3.65 (quint, 1H, *J* = 6.3 Hz, *H*-7), 2.33–2.06 (m, 2H, CH_2-4), 1.85 (q, 3H, *J* = 1.2 Hz, CH_3-2), 1.68–1.54 (m, 1H, CH_{2A}-5), 1.54–1.41 (m, 1H, C*H*-6), 1.30–1.18 (m, 1H, CH_{2B}-5), 1.13 (d, 3H, *J* = 6.3 Hz, CH_3-8), 0.90 (d, 3H, *J* = 6.8 Hz, CH_3-6). **^{13}C-NMR, HSQC** (75.5 MHz, $CDCl_3$): δ [ppm] = 167.9 (*C*O), 142.8 (*C*H-3), 132.7 (*C*H=CH_2), 127.7 (C_q-2), 117.9 (CH=*C*H_2), 71.7 (*C*H-7), 65.2 (*C*H_2CH=CH_2), 39.8 (*C*H-6), 31.4 (*C*H_2-5), 26.5 (*C*H_2-4), 19.7 (*C*H_3-8), 14.6 (*C*H_3-6), 12.5 (*C*H_3-2). **IR** (ATR): ũ [cm^{-1}] = 3428, 2967, 2930, 2877, 1709, 1262, 1201, 1140, 1097, 1069, 992, 926. **HRMS** (ESI): calcd for $[C_{13}H_{22}O_3 + Na]^+$: 249.1467, found: 249.1475.

(*E*)-Allyl 7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (20a)[20]

A solution of 3,5-bis(benzyloxy)phenylacetic acid (**19**) (429 mg, 1.23 mmol), (*E*)-allyl 7-hydroxy-2,6-dimethyloct-2-enoate (**18a**) (279 mg, 1.23 mmol, 1.0 equiv) and DMAP (15 mg, 0.12 mmol, 0.1 equiv) in dry dichloromethane (25 mL) was cooled to 0 °C. *N,N'*-Dicyclohexylcarbodiimide (279 mg, 1.35 mmol, 1.1 equiv) was dissolved in dry dichloromethane (5 mL) and added. After 7 h, another portion of *N,N'*-dicyclohexylcarbodiimide (56 mg, 0.27 mmol, 0.2 equiv) was dissolved in dry dichloromethane (5 mL) and added. The reaction mixture was stirred for 16 h and was allowed to warm up to room temperature. The reaction mixture was filtered through a short plug of silica (CH_2Cl_2). The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane/EtOAc 20:1) yielded **20a** (485 mg, 0.87 mmol, 71%) as a colorless oil.

R_f = 0.26 (cyclohexane/EtOAc 10:1), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.44–7.30 (m, 10H, 2 x Ph), 6.75 (tq, 1H, *J* = 7.3 Hz, *J* = 1.3 Hz, *H*-3'), 6.56 (d, 2H, *J* = 2.2 Hz, *H*-2, *H*-6),

6.54 (t, 1H, *J* = 2.2 Hz, *H*-4), 5.96 (ddt, 1H, *J* = 17.2 Hz, *J* = 10.4 Hz, *J* = 5.6 Hz, C*H*=CH_2), 5.33 (dq, 1H, *J* = 17.2 Hz, *J* = 1.5 Hz, CH=CH_{2A}), 5.23 (dq, 1H, *J* = 10.4 Hz, *J* = 1.5 Hz, CH=CH_{2B}), 5.03 (s, 4H, 2 x OCH_2Ph), 4.83 (quint, 1H, *J* = 6.4 Hz, *H*-7'), 4.63 (dt, 2H, *J* = 5.6 Hz, *J* = 1.5 Hz, CH_2CH=CH_2), 3.54 (s, 2H, CH_2COO), 2.28–2.04 (m, 2H, CH_2-4'), 1.84 (q, 3H, *J* = 1.3 Hz, CH_3-2'), 1.76–1.63 (m, 1H, C*H*-6'), 1.56–1.44 (m, 1H, CH_{2A}-5'), 1.28–1.17 (m, 1H, CH_{2B}-5'), 1.15 (d, 3H, *J* = 6.4 Hz, CH_3-8'), 0.89 (d, 3H, *J* = 6.9 Hz, CH_3-6'). **^{13}C-NMR, HSQC** (75.5 MHz, $CDCl_3$): δ [ppm] = 171.0 (*C*OO), 167.8 (*C*OOAll), 160.1 (C_q-3, C_q-5), 142.4 (*C*H-3'), 136.6 (2 x C_q-1, Ph), 136.5 (C_q-1), 132.7 (*C*H=CH_2), 128.7 (2 x *C*H-3, 2 x *C*H-5, Ph), 128.1 (2 x *C*H-4, Ph), 127.8 (C_q-2'), 127.6 (2 x *C*H-2, 2 x *C*H-6, Ph), 117.9 (CH=*C*H_2), 108.6 (*C*H-2, *C*H-6), 100.9 (*C*H-4), 74.6 (*C*H-7'), 70.1 (2 x O*C*H_2Ph), 65.2 (*C*HCH=CH_2), 42.1 (*C*H_2COO), 37.2 (*C*H-6'), 31.3 (*C*H_2-5'), 26.3 (*C*H_2-4'), 16.2 (*C*H_3-8'), 14.7 (*C*H_3-6), 12.5 (*C*H_3-2'). **IR** (ATR): ũ [cm^{-1}] = 3089, 3065, 3033, 2977, 2935, 2876, 1710, 1594, 1498, 1263, 1149, 1103, 1057, 735, 697. **HRMS** (ESI): calcd for [$C_{35}H_{40}O_6$ + Na]$^+$: 579.2723, found: 579.2717.

(*E*)-7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoic acid (21a)[20, 21]

(*E*)-Allyl 7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (**20a**) (462 mg, 0.83 mmol) was dissolved in methanol (20 mL) and THF (20 mL). $Pd(PPh_3)_4$ (96 mg, 83 µmol, 0.1 equiv) and sodium 4-toluenesulfinate (223 mg, 1.25 mmol, 1.5 equiv) were added. After 17 h stirring at room temperature, the solvent was removed in vacuo. Hydrochloric acid (2N, 50 mL) was added to the residue, extracted with dichloromethane (4 x 50 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane/EtOAc 4:1 + 1% NEt_3 → cyclohexane/EtOAc 4:1 + 1% HOAc) afforded a yellow oil, which was dissolved in ethyl acetate (30 mL), washed with 2N HCl (3 x 30 mL), dried over magnesium sulfate and filtered. Removing the solvent in vacuo yielded **21a** (429 mg, 0.83 mmol, quant.) as a yellow oil.

R_f = 0.11 (cyclohexane/EtOAc 4:1), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.45–7.29 (m, 10H, 2 x Ph), 6.82 (tq, 1H, *J* = 7.4 Hz, *J* = 1.3 Hz, *H*-3'), 6.57 (d, 2H, *J* = 2.0 Hz, *H*-2, *H*-6),

6.55 (t, 1H, *J* = 2.0 Hz, *H*-4), 5.02 (s, 4H, 2 x OC*H*$_2$Ph), 4.81 (quint, 1H, *J* = 6.4 Hz, *H*-7‘), 3.53 (s, 2H, C*H*$_2$COO), 2.28–2.02 (m, 2H, C*H*$_2$-4’), 1.81 (q, 3H, *J* = 1.3 Hz, C*H*$_3$-2‘), 1.72–1.61 (m, 1H, C*H*-6‘), 1.55–1.44 (m, 1H, C*H*$_{2A}$-5‘), 1.29–1.16 (m, 1H, C*H*$_{2B}$-5‘), 1.14 (d, 3H, *J* = 6.4 Hz, C*H*$_3$-8‘), 0.88 (d, 3H, *J* = 6.9 Hz, C*H*$_3$-6). **^{13}C-NMR, HSQC** (75.5 MHz, $CDCl_3$): δ [ppm] = 172.9 (*C*OOH), 171.0 (*C*OO), 160.1 (*C*$_q$-3, *C*$_q$-5), 144.7 (*C*H-3’), 137.0 (2 x *C*$_q$-1, Ph), 136.5 (*C*$_q$-1), 128.7 (2 x *C*H-3, 2 x *C*H-5, Ph), 128.1 (2 x *C*H-4), 127.6 (2 x *C*H-2, 2 x *C*H-6, Ph), 127.3 (*C*$_q$-2’), 108.6 (*C*H-2, *C*H-6), 100.9 (*C*H-4), 74.6 (*C*H-7’), 70.2 (2 x OCH_2Ph), 42.2 (*C*H_2COO), 37.3 (*C*H-6’), 31.1 (*C*H_2-5’), 26.5 (*C*H_2-4’), 16.3 (*C*H_3-8’), 14.8 (*C*H_3-6’), 12.2 (*C*H_3-2’). **IR** (ATR): ũ [cm^{-1}] = 3063, 3033, 2975, 2931, 2875, 1724, 1684, 1594, 1452, 1290, 1154, 1058, 697. **HRMS** (ESI): calcd for $[C_{32}H_{36}O_6 + Na]^+$: 539.2410, found: 539.2414.

5,7-Di-*O*-benzyl-4-dechloro-14-deoxyoxacylododecindione (22a)

Dichloromethane (155 mL), trifluoroacetic acid (12 mL) and trifluoroacetic anhydride (6 mL) was cooled to −8 °C. Acid **21a** (60 mg, 116 µmol) was dissolved in dichloromethane (5 mL) and added. The reaction mixture stood at −8 °C for 66 h. The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane/EtOAc 15:1) yielded **22a** (39 mg, 78 µmol, 67%) as a colorless oil.

R$_f$ = 0.37 (cyclohexane/EtOAc 4:1), **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ [ppm] = 7.42–7.24 (m, 10H, 2 x Ph), 6.61–6.41 (m, 3H, *H*-4, *H*-6, *H*-11), 5.07–4.98 (m, 4H, 2 x OC*H*$_2$Ph), 4.59 (dq, 1H, *J* = 8.5 Hz, *J* = 6.2 Hz, *H*-15), 3.40–3.29 (m, 2H, C*H*$_2$-2), 2.50–2.32 (m, 1H, C*H*$_{2A}$-12), 2.23–2.04 (m, 1H, C*H*$_{2B}$-12), 1.93 (s, 3H, C*H*$_3$-10), 1.70–1.63 (m, 1H, C*H*$_{2A}$-13), 1.55–1.47 (m, 1H, C*H*-14), 1.46–1.37 (m, 1H, C*H*$_{2B}$-13), 1.09 (d, 3H, *J* = 6.2 Hz, C*H*$_3$-15), 0.92 (d, 3H, *J* = 7.1 Hz, C*H*$_3$-14). **^{13}C-NMR, HSQC, HMBC** (100.6 MHz, $CDCl_3$): δ [ppm] = 199.3 (*C*O), 170.4 (*C*OO), 159.8 (*C*$_q$-5), 156.6 (*C*$_q$-7), 152.9 (*C*H-11), 137.1 (br, *C*$_q$-10), 136.8 (*C*$_q$-1, Ph), 136.6 (*C*$_q$-1, Ph), 133.2 (br, *C*$_q$-3), 128.7 (*C*H-3, *C*H-5, Ph), 128.5 (*C*H-3, *C*H-5, Ph), 128.2 (*C*H-4, Ph), 127.8 (*C*H-4, Ph), 127.6 (*C*H-2, *C*H-6, Ph), 126.9 (*C*H-2, *C*H-6, Ph), 124.2 (br, *C*$_q$-8), 107.6 (*C*H-4), 100.4 (*C*H-6), 77.4 (*C*H-15), 70.3 (O*C*H_2Ph), 70.3 (O*C*H_2Ph), 39.7 (*C*H_2-2), 38.9 (br, *C*H-14), 28.9 (br, *C*H_2-12), 33.2 (br, *C*H_2-13), 19.2 (br, *C*H_3-14,

CH_3-15), 10.4 (br, *C*H_3-10). **IR** (ATR): ũ [cm^{-1}] = 3090, 3064, 3033, 2927, 2875, 1724, 1637, 1603, 1584, 1498, 1281, 1154, 1145, 736. **HRMS** (ESI): calcd for $[C_{32}H_{34}O_5 + Na]^+$: 521.2304, found: 521.2317.

4-Dechloro-14-deoxyoxacylododecindione (±1)

A solution of **22a** (84 mg, 168 µmol) in dry dichloromethane (25 mL) was cooled to −78 °C. Boron trichloride (1M in hexane, 1.68 mL, 1.68 mmol, 10.0 equiv) was added and the mixture was stirred at that temperature. After 30 min the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution (50 mL) and warmed up to room temperature. The organic layer was separated and the aqueous layer extracted with dichloromethane (4 x 70 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane/EtOAc 2:1) yielded **1** (46 mg, 144 µmol, 87%) as a colorless oil.

R_f = 0.27 (cyclohexane/EtOAc 2:1), **^{1}H-NMR, COSY, NOESY** (400 MHz, Methanol-d_4): δ [ppm] = 6.53 (s_{br}, 1H, *H*-11), 6.28 (s_{br}, 1H, *H*-4), 6.25 (d, 1H, *J* = 2.2 Hz, *H*-6), 4.59 (dq, 1H, *J* = 8.5 Hz, *J* = 6.2 Hz, *H*-15), 3.29 (d, 1H, *J* = 15.1 Hz, CH_{2A}-2), 3.20 (d, 1H, *J* = 15.1 Hz, CH_{2B}-2), 2.51–2.43 (m, 1H, CH_{2A}-12), 2.27–2.17 (m, 1H, CH_{2B}-12), 1.88 (s, 3H, CH_3-10), 1.75–1.68 (m, 1H, CH_{2A}-13), 1.62–1.52 (m, 1H, C*H*-14), 1.48–1.40 (m, 1H, CH_{2B}-13), 1.13 (d, 3H, *J* = 6.2 Hz, CH_3-15), 0.94 (d, 3H, *J* = 7.1 Hz, CH_3-14). The data are in accordance with those reported in the literature.[1] **^{13}C-NMR, HSQC, HMBC** (100.6 MHz, Methanol-d_4): δ [ppm] = 203.1 (*C*O), 172.1 (*C*OO), 160.2 (C_q-7), 157.4 (C_q-5), 154.3 (*C*H-11), 138.0 (C_q-10), 134.7 (C_q-3), 121.0 (C_q-8), 109.4 (*C*H-4), 102.5 (*C*H-6), 78.2 (*C*H-15), 40.8 (br, *C*H-14), 40.4 (*C*H_2-2), 34.3 (br, *C*H_2-13), 29.8 (br, *C*H_2-12), 19.5 (*C*H_3-14), 19.4 (*C*H_3-15), 10.5 (*C*H_3-10). The data are in accordance with those reported in the literature.[1] **IR** (ATR): ũ [cm^{-1}] = 3364, 2977, 2932, 2877, 1727, 1701, 1618, 1454, 1327, 1304, 1264, 1154. **HRMS** (ESI): calcd for $[C_{18}H_{22}O_5 + Na]^+$: 341.1365, found: 341.1362.

14-Deoxyoxacylododecindione (±2)

Lactone (±)-**1** (32 mg, 100 µmol) and *N*-chlorosuccinimide (13.4 mg, 100 µmol, 1.0 equiv) were dissolved in dry DMF (4 mL) and trifluoroacetic acid (11 µL, 150 µmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 4 days. The solvent was removed in vacuo. Purification by flash chromatography on silica (cyclohexane/EtOAc 2:1) yielded **2** (26 mg, 73 µmol, 73%) as a colorless oil.

R_f = 0.15 (cyclohexane/EtOAc 2:1), **^{1}H-NMR, COSY, NOESY** (600 MHz, Acetonitrile-d_3, 333K): δ [ppm] = 7.37 (s_{br}, 2H, O*H*), 6.61 (dd, 1H, *J* = 11.1 Hz, *J* = 4.6 Hz, *H*-11), 6.52 (s, 1H, *H*-6), 4.64 (dq, 1H, *J* = 9.1 Hz, *J* = 6.3 Hz, *H*-15), 3.56 (d, 1H, *J* = 17.1 Hz, CH_{2A}-2), 3.28 (d, 1H, *J* = 17.1 Hz, CH_{2B}-2), 2.53 (dddd, 1H, *J* = 13.7 Hz, *J* = 11.1 Hz, *J* = 6.6 Hz, *J* = 2.4 Hz, CH_{2A}-12), 2.04–1.97 (m, 1H, CH_{2B}-12), 1.85 (s, 3H, CH_3-10), 1.67–1.63 (m, 1H, CH_{2A}-13), 1.58–1.52 (m, 1H, C*H*-14), 1.34–1.28 (m, 1H, CH_{2B}-13), 1.10 (d, 3H, *J* = 6.3 Hz, CH_3-15), 0.92 (d, 3H, *J* = 7.2 Hz, CH_3-14). The data are in accordance with those reported in the literature.[1] **^{13}C-NMR, HSQC, HMBC** (150.9 MHz, Acetonitrile-d_3, 333K): δ [ppm] = 200.0 (*C*O), 169.4 (*C*OO), 155.1 (C_q-5), 154.8 (C_q-7), 152.3 (*C*H-11), 137.7 (C_q-10), 133.4 (C_q-3), 123.2 (C_q-8), 114.3 (C_q-4), 104.0 (*C*H-6), 77.5 (*C*H-15), 39.4 (CH_2-2), 40.0 (*C*H-14), 29.5 (CH_2-12), 34.6 (CH_2-13), 19.5 (CH_3-14), 19.4 (CH_3-15), 10.6 (CH_3-10). The data are in accordance with those reported in the literature.[1] **IR** (ATR): ũ [cm^{-1}] = 3338, 2977, 2934, 2876, 1723, 1707, 1610, 1438, 1290, 1251, 1233, 1162. **HRMS** (ESI): calcd for [$C_{18}H_{21}ClO_5$ + Na]$^+$: 375.0975, found: 375.0976.

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