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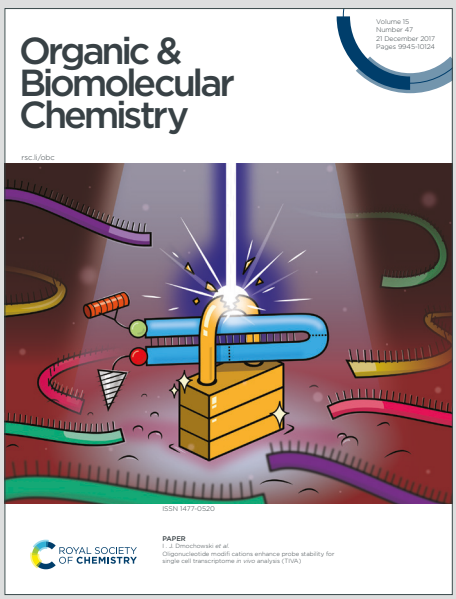

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ARTICLE

Total synthesis and biological evaluation of seven new anti-inflammatory oxacyclododecindione-type macrolactones

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Through variation of our previously published total synthesis of two highly active anti-inflammatory macrolactones from the oxacyclododecindione family (Org. Biomol. Chem., 2015, 7813-7821), seven new representatives of this compound class were prepared. Substitution of the 14-hydroxy group in oxacyclododecindione with a methyl substituent provided a readily accessible non-natural analogue which has similar pharmacological properties as the scarcely available natural product. Since the producible amount of substance is therefore no longer restricted by low fermentation yields, extensive *in vivo* studies become possible for the first time. Based on this finding, further investigations on structure-activity relationships were undertaken by variation of the halogen atom, which showed that exchange or omission of the chloro substituent led to significantly lower binding affinities. Furthermore, it was found that prolongation of the crucial and characteristic aliphatic side chain at C-10 also increased the IC_{50} value in the biological assays of interest.

Introduction

The twelve-membered macrolactones oxacyclododecindione (**1**), 14-deoxyoxacyclododecindione (**2**) and the 13-hydroxy isomer **3** are secondary metabolites of the imperfect fungus *Exserohilum rostratum*.[1-4] Compounds **1** and **2** showed exceptionally high anti-inflammatory activities in reporter gene assays and therefore represent potential lead structures for the development of anti-inflammatory drugs.[3, 5] Indeed, **1** proved to be effective in an *in vivo* mouse model for the chronic autoimmune disease systemic lupus erythematosus (SLE).[6]

With the previously reported synthesis of macrolactone **2**, we disclosed the first total synthesis of an oxacyclododecindione-type macrolactone. Furthermore, its unexpected absolute configuration (14*S*,15*R*) could be deduced from the comparison of the optical rotations of the pure synthetic enantiomers of **2** with the respective value of the natural product.[4, 7]

However, further pharmacological evaluation of **1** and **2** was impeded by low fermentation yields.[1] Accordingly, total synthetic access to either oxacyclododecindione (**1**) itself or a derivative with comparable biological properties is highly desirable.

Herein, the racemic total synthesis of seven new oxacyclododecindione-type macrolactones is presented. To gain a better insight into structure-activity relationships between the macrolactones and their still unknown biological target(s), we investigated the effect of structural variation at C-14. By installing a second methyl group in this position, we aimed to investigate the role of the 14-hydroxy group – a main handicap for the total synthesis of **1**. This would also simplify the molecule by eliminating one of the two stereocenters. Furthermore, the effects of a halogen exchange at C-4 and of the size of the substituent at C-10 should be determined.

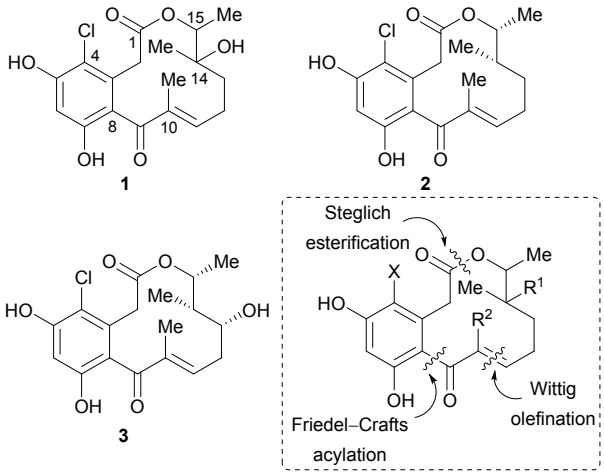

Figure 1 – Structures of the natural macrolactones **1**–**3** and retrosynthetic approach to the derivatives described herein.

Results and discussion

Although various ring closure strategies have been extensively studied, intramolecular Friedel–Crafts acylation at low

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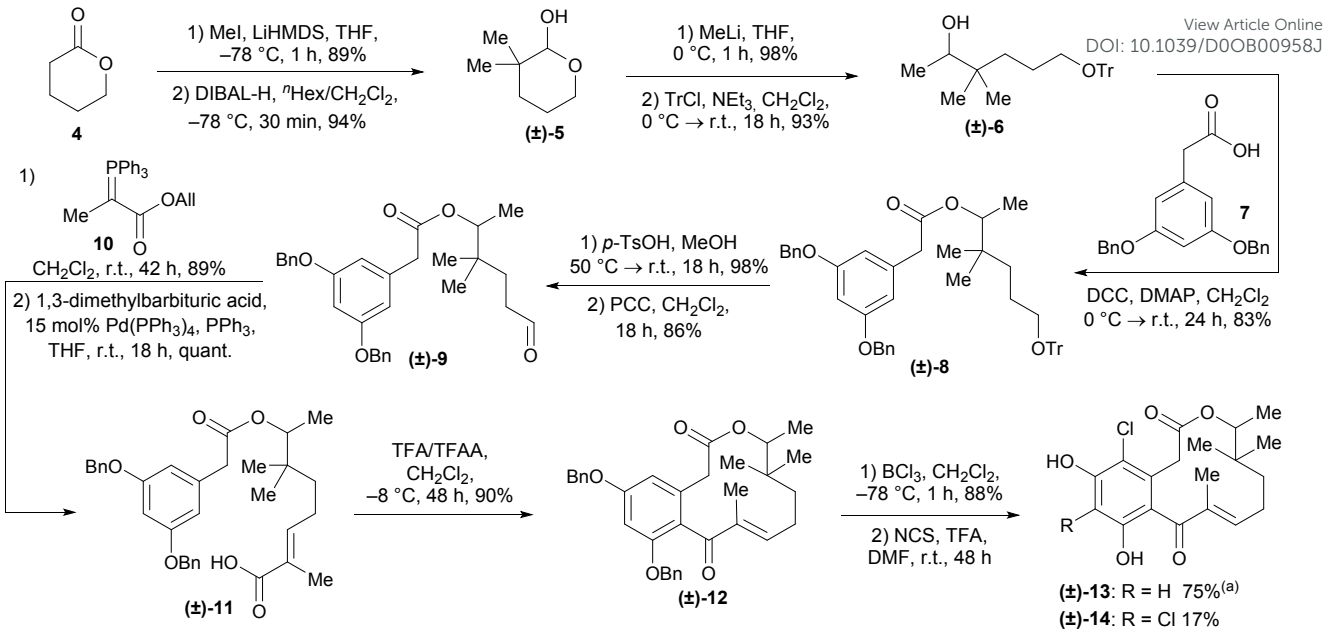
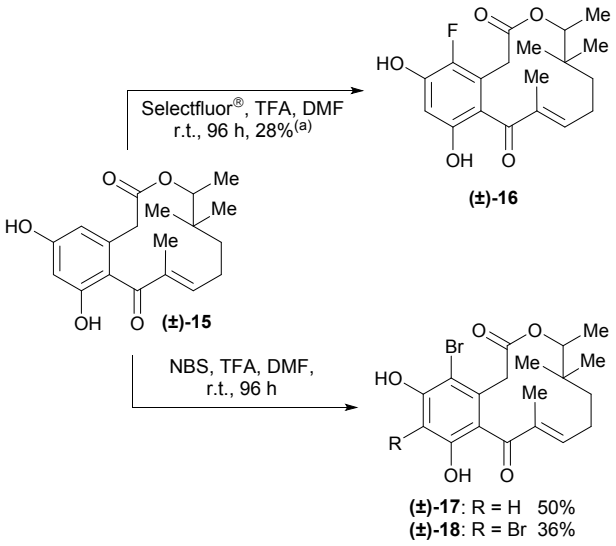


Scheme 1 – Total synthesis of 14-deoxy-14-methyloxacyclododecindionecyclododecindione (±)-**13** and 6-chloro-14-deoxy-14-methyloxacyclododecindionecyclododecindione (±)-**14**. [a] Yield of (±)-**13** varied, the value given is an average for two runs.

substrate concentration (c = 0.65 mM) proved to be the only suitable method for the construction of the twelve-membered lactone ring in the oxacyclododecindione series to date.[7-10] The reason for this counterintuitive observation is probably the steric bulk of the C-10 methyl group and the strain of the macrocyclic ring which lead to a perpendicular arrangement of the arene and the enone moiety. As shown in Figure 1, the required precursors for ring closure are synthesized through Steglich esterification and Wittig olefination of suitable building blocks.[11-13] For the synthesis of 14-deoxy-14-methyl derivative (±)-**13**, trityl protected alcohol (±)-**6** was obtained from commercial δ-valerolactone (**4**) by double α-methylation, subsequent reduction to lactol (±)-**5**,[14] and ring-opening initiated by methyllithium (Scheme 1). Installation of a trityl group allowed selective Steglich esterification of the secondary hydroxyl group with 2-(3,5-bis(benzyloxy)phenyl)acetic acid **7**, which was prepared in five steps from dimethyl 1,3-acetonedicarboxylate using a known procedure.[15-18] The obtained ester (±)-**8** was transformed into aldehyde (±)-**9** by detritylation and subsequent oxidation of the primary alcohol under Corey–Suggs conditions.[19] The aldehyde was reacted with the previously established Wittig ylide allyl 2-(triphenylphosphoranylidene)-propanoate (**10**), prepared in three steps from 2-bromopropionic acid according to Blum.[20] Pd^0-catalysed deallylation furnished carboxylic acid (±)-**11** as precursor for the Friedel–Crafts cyclization. Ring closure using TFA/TFAA in dichloromethane proceeded smoothly, producing lactone (±)-**12** in 90% yield. The reaction sequence was concluded by BCl_3-mediated debenzylation and electrophilic aromatic substitution with *N*-chlorosuccinimide (NCS) providing oxacyclododecindione derivative (±)-**13** in twelve linear steps with an overall yield of 30%. As a byproduct of this last conversion, the dichlorinated compound (±)-**14** was isolated in 17% yield. Target compound (±)-**13** was characterized by X-ray crystallography, revealing an L-shaped conformation with the ester being (*Z*)-configured and the enone unit being nearly perpendicular to the aromatic ring (Figure 2). These three findings also apply to the previously published X-ray structure of natural product **2** and might play a role for their biological properties.[4] As shown in the biological evaluation section below, compound (±)-**13**, bearing a second methyl group at C-14, showed strong inhibitory activity in the transcriptional reporter gene assays of interest which were similar to its natural parent compound **1** and to 14-deoxyoxacyclododecindione (**2**).



Scheme 2 – Variation of the last step in the synthesis of (±)-**13** gave access to the fluorinated and brominated derivatives (±)-**16** and (±)-**17**. [a] Most of (±)-**16** was obtained in a hardly separable mixture with (±)-**15**, the yield stated was calculated based on ^{1}H NMR.

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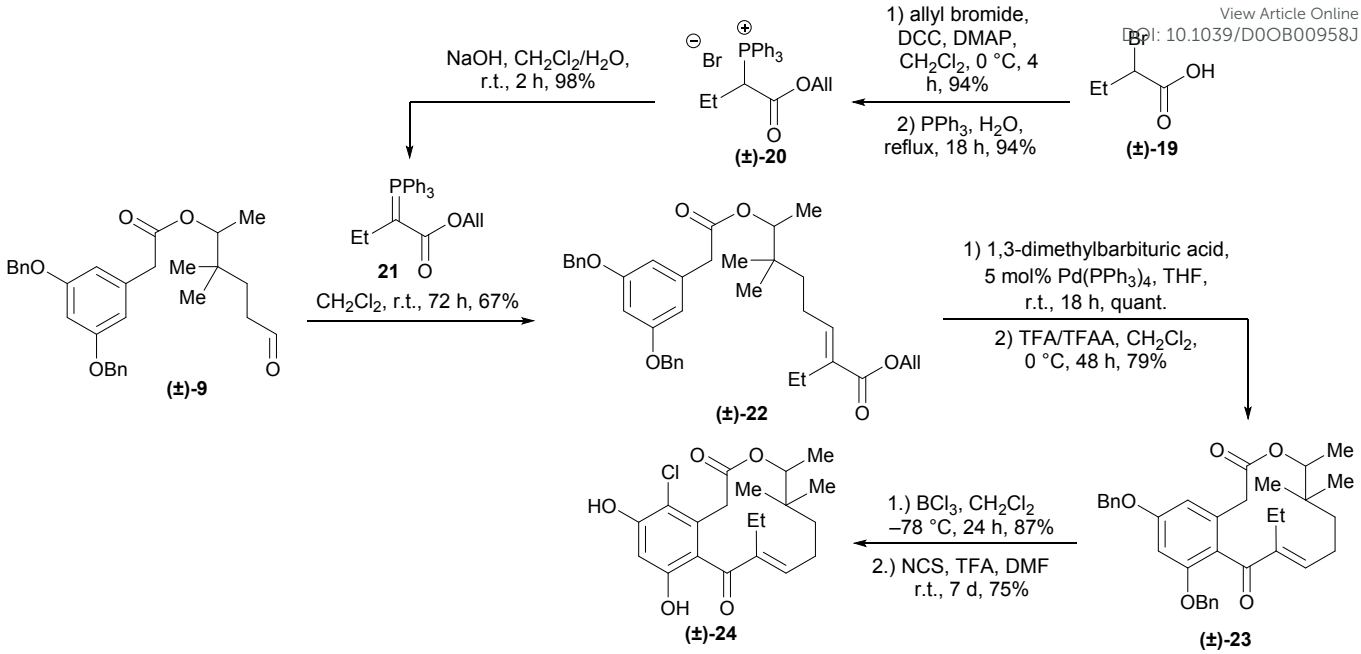

Scheme 3 – Total synthesis of 14-deoxy-10-ethyl-14-methyloxacyclododecindionecyclododecindione (±)-**24**.

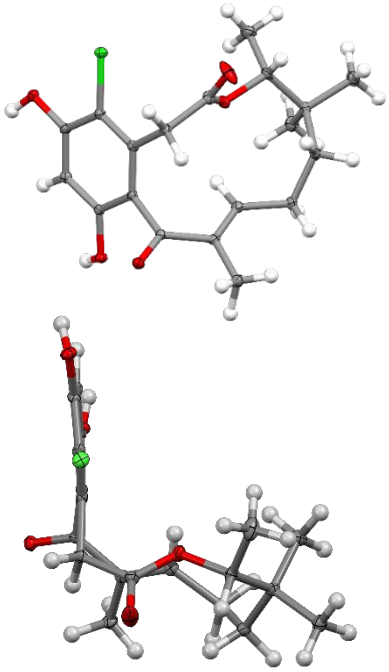

Figure 2 – X-ray crystal structure of ((±)-**13**) as an ORTEP ellipsoid in two different perspectives (30% probability) C: gray, H: white, O: red, Cl: green. For the X-ray molecular structures of compounds (±)-**12** and (±)-**23**, please refer to the Supporting Information.

Considering these results and the lability of the 14-hydroxy group in protected or unprotected form in the Friedel-Crafts reaction (data not shown), (±)-**13** is a useful starting point for further modifications of the macrolactone scaffold. It is known that the absence of the chloro-substituent at C-4 leads to a significant loss of bioactivity for the oxacyclododecindione-type macrolactones.[7] To further evaluate the role of the halogen substituent, chloride was replaced by fluoride and bromide (Scheme **2**). After debenzylation of (±)-**12**, compound (±)-**15** was fluorinated with Selectfluor® to give 4-dechloro-14-deoxy-4-fluoro-14-methyl-oxacyclododecindione ((±)-**16**) in a hardly separable 3:2 mixture with (±)-**15**. Based on ^{1}H NMR, a yield of 28% (±)-**16** was calculated. Nevertheless, the purest fractions of the HPLC run could be isolated to obtain a sample pure enough for biological evaluation. Along the same lines, bromination was performed using *N*-bromosuccinimide (NBS). However, due the limited chemo-selectivity of the latter reaction, a mixture of 4-bromo-4-dechloro-14-deoxy-14-methyloxacyclododecindione ((±)-**17**, 50% yield) and the dibrominated product 4,6-dibromo-4-dechloro-14-deoxy-14-methyloxacyclododecindione ((±)-**18**, 36% yield) was obtained.

In previous studies on oxacyclododecindione- and dehydrocurvularine-type macrolactones, the enone unit on the aromatic ring proved to be associated with the bent three-dimensional structure of this compound class and its biological activity.[5, 7, 8] To evaluate the tolerance for a sterically more demanding group, the methyl substituent at C-10 was replaced by an ethyl group. The latter was introduced using the higher homologue of phosphoranylidene **10** in the Wittig olefination (Scheme **3**). Starting from 2-bromobutyric acid ((±)-**19**), a sequence comprising esterification with allyl alcohol and reaction with triphenylphosphane provided phosphonium salt (±)-**20** which was subsequently deprotonated to provide ylide **21** in three steps with an overall yield of 87%. Wittig

olefination with aldehyde (±)-**9** gave the (*E*)-configured, unsaturated ester (±)-**22** in 67% yield. Following the established route, benzyl-protected macrolactone (±)-**23** was obtained through deallylation and subsequent ring closure. Debenzylation and chlorination led to 14-deoxy-10-ethyl-14-methyloxacyclododecindione (±)-**24** after twelve linear steps with an overall yield of 18%.

Biological evaluation

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As indicated above, macrolactones **1** and **2** are potent inhibitors of TGF-β and IL-4 signalling pathways in mammalian cells.[1, 3, 5] As with the natural compounds and synthetic derivatives investigated previously, the seven new compounds described herein were examined for their inhibitory activity on IL-4-inducible STAT6-dependent and TGF-β-inducible Smad2/3-dependent transcriptional luciferase reporters in transiently

Table 1 – Effect of natural and synthetic macrolactones in two relevant reporter gene assays.[a]

	$(CAGA)_{9x}$-MLP-Luc (Smad2/3) IC_{50} (nM)	pGL3-TK-7xN_4 (STAT6) IC_{50} (nM)
Oxacyclododecindione (**1**)	135.6 ± 13.6	67.8 ± 5.4
(14*S*/15*R*)-14-Deoxyoxacyclododecindione (**2**)	90.1 ± 9.6	20.1 ± 1.4
14-Deoxy-14-methyloxacyclododecindione ((±)-**13**)	30.0 ± 10.9	79.1 ± 27.3
6-Chloro-14-deoxy-14-methyloxacyclododecindione ((±)-**14**)	4623 ± 13	1017 ± 17
4-Dechloro-14-deoxy-14-methyloxacyclododecindione ((±)-**15**)	87.2 ± 30.1	264.7 ± 21.1
4-Dechloro-14-deoxy-4-fluoro-14-methyloxacyclododecindione ((±)-**16**)	1264 ± 11	442.4 ± 28.5
4-Bromo-4-dechloro-14-deoxy-14-methyloxacyclododecindione ((±)-**17**)	381.7 ± 26.7	177.5 ± 4.9
4,6-Dibromo-4-dechloro-14-deoxy-14-methyloxacyclododecindione ((±)-**18**)	852.7 ± 10.2	379.4 ± 12.2
14-Deoxy-10-ethyl-14-methyloxacyclododecindione ((±)-**24**)	519.9 ± 13.1	105.0 ± 23.6

[a]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^{-1} TGF-β or 5 ng mL^{-1} IL-4 with or without the test compounds for 16 h as described in Materials and methods. 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.[1, 5]

transfected HepG2 cells (Table 1). The racemate of the synthetic derivative 14-deoxy-14-methyloxa-cyclododecindione ((±)-**13**) exhibits potent inhibition of TGF-β-inducible Smad2/3- as well as IL-4-inducible STAT6-dependent reporter gene expression with IC_{50} values of 30.0 nM (Smad2/3) and 79.1 nM (STAT6), respectively. Therefore, it can be concluded that exchanging the hydroxy group in **1** for a methyl substituent leads to an increase of the inhibitory activity in the signalling pathways of interest. Moreover, only the (14*S*,15*R*)-enantiomer of **2** shows the tabulated IC_{50} values in the lower nanomolar range, while its (14*R*,15*S*)-enantiomer is much less active. Thus, it can be assumed that the activity of enantiopure (15*R*)-**13** is even higher and already the racemate is by far the strongest inhibitor of Smad2/3 signalling in the series.

It has been observed that a dechlorinated derivative of **2** is not as active as the latter.[7] The same trend was found in the newly synthesized series. Furthermore, the fluorinated and brominated derivatives (±)-**16** and (±)-**17** as well as the dihalogenated species (±)-**14** and (±)-**18** show practically no inhibitory activity on TGF-β induced Smad2/3 signalling and very weak inhibitory activity in the IL-4 reporter gene expression, which is in strong contrast to the excellent bioactivity of (±)-**13**. The C-10-ethyl derivative (±)-**24** showed only a weak response in the TGF-β reporter assay but was only a little less active in the IL-4 assay. The significant loss of both kinds of activity upon exchange of the chlorine substituent in (±)-**13** to fluorine appears particularly remarkable. While the introduction of fluorine into the non-halogenated compound (±)-**15** only reduced the inhibitory activity on the STAT6-pathway by a factor of 2, the Smad2/3 dependant transcriptional reporter was reduced by 14.5-fold. On the other hand, the introduction of chlorine into (±)-**15** led to an almost 3-fold increase of the inhibitory activity in the same system.

Conclusion

The general synthetic approach to oxacyclododecindione-type macrolactones through Friedel-Crafts-cyclization provided a broad and reliable access to further derivatives of this compound class through variation of the building blocks. Seven new derivatives were obtained and investigated with respect to their biological activity to gain insight into structure-activity relationships. A convenient and scalable total synthesis of 14-deoxy-14-methyl-oxacyclododecindione ((±)-**13**) with an overall yield of 30% in twelve linear steps could be devised. (±)-**13** proved to be a remarkably potent inhibitor of TGF-β dependent Smad2/3 and IL-4 dependent STAT6 signalling in *in vitro* studies with IC_{50} values comparable to the natural product oxacyclododecindione (**1**). While attempts to synthesize **1** have met with little success so far, this is the first report of a synthetic oxacyclododecindione-type macrolactone which surpasses the impressive biological activity of the most potent natural products of the series known so far in the TGF-β-inducible Smad2/3-dependent reporter gene assay. The synthesis could be performed (up to 100 mg) and makes further *in vivo* experiments independent from fermentation yields.

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Experimental section

Materials and methods

Unless stated otherwise, all solvents and reagents were obtained from commercial suppliers and used without prior purification. Dichloromethane, chloroform and triethylamine were distilled from calcium hydride right bevor use. Diethyl ether, benzene and toluene were distilled from sodium and benzophenone. Anhydrous tetrahydrofuran was obtained by distillation from potassium. Acetonitrile, *N*,*N*-dimethylformamide and dimethyl sulfoxide were obtained from commercial suppliers as extra dry solvents stored over molecular sieve 3 Å and were used without further purification. Reactions requiring anhydrous conditions were performed under argon atmosphere in flame-dried glassware. Reactions at –78 °C were carried out in a dry ice/acetone cooling bath. For thin-layer chromatography (TLC), 0.25 mm silica plates ($60F_{254}$) from Merck were used. Visualization of the compounds on the TLC-plates was accomplished with UV light (λ = 254 nm) and/or by staining with vanillin reagent (solution of vanillin (1.0 g), methanol (100 mL), glacial acetic acid (12 mL) and conc. sulfuric acid (4 mL)) and heat. Flash-chromatographic purifications (0.2–0.4 bar nitrogen) were performed on silica gel (35–70 µm, Acros Organics). The compositions of all eluents are stated in v/v-ratios. Analytical HPLC separations were carried out on an ACE3-C_{18}-PFP-column (particle size: 3 µm, length: 15 cm, diameter: 4.6 mm, column temperature: 40 °C column, flow rate: 1 mL/min^{-1}) temperature and with UV-DAD detection. Preparative HPLC separations were performed using two high-pressure gradient K-1800 pumps and an *S-260*-UV-DAD detection. The eluents were mixtures given in v/v-ratios of acetonitrile (HPLC grade) and Milli-Q® water. The separations were carried out on an ACE5-C_{18}-PFP-column (particle size: 5 µm, length: 15 cm, diameter: 30 mm, flow rate: 37.5 mL/min^{-1}). NMR spectra were, if not stated otherwise, recorded at 23 °C on a 300 MHz Bruker Avance-III HD (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), a 400 MHz Bruker Avance-II (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) or 600 MHz Bruker Avance-III (^{1}H: 600 MHz, ^{13}C: 151.1 MHz) spectrometer. All chemical shifts were referenced to the signal of the residual solvent ($CDCl_3$: 7.26 ppm & 77.16 ppm, DMSO-d_6: 2.50 ppm & 39.52 ppm, CD_3OD: 3.31 ppm & 49.00 ppm, CD_3CN: 1.94 ppm & 1.32 ppm for ^{1}H NMR and ^{13}C NMR respectively) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS). Infrared spectra were recorded on a FT-IR spectrometer (Bruker Tensor 27) with a diamond ATR unit. Low resolution electron spray ionization (ESI) mass spectra were recorded on a LC/MSD trap XCT spectrometer. HRMS spectra were recorded either on a Waters Q-ToF Ultima III instrument with an ESI source using a suitable external calibrant (reported high resolution masses refer to neutral molecules since the mass of the electron was considered during calibration) or on an Agilent 6545 QTOF-LC/MS with ESI, APCI or APPI source. Unless stated otherwise, spectra were recorded using positive ionization mode. X-ray crystallographic analysis was kindly provided by the Department of Crystal Structure Analysis of the Central Analytical Department of the Department of Chemistry, Mainz.

Biological assays

HepG2 cells (DSMZ ACC 180) were maintained in DMEM medium supplemented with 10% fetal calf serum (FCS) and 65 µg mL^{-1} penicillin G and 100 µg mL^{-1} streptomycin sulfate under a humidified atmosphere. The STAT6-driven reporter plasmid pGL3-TK-7xN4 contains the herpes simplex virus thymidine kinase promoter under the control of seven copies of the palindromic sequence TTC(N)4GAA.[1] The STAT6 expression plasmid (TOPO-STAT6) has been previously described.[21] 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.[22] 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 × 10^7 cells per mL in DMEM together with the indicated constructs (50 µg) and the internal control pRL-EF1α vector at 500 V cm^{-1}. After electroporation the cells were seeded at 2 × 105 cells per mL and allowed to recover for 16 h. For the induction of reporter gene expression, the cells were treated either with 5 ng mL^{-1} TGF-β or 5 ng mL^{-1} IL-4 with or without the 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.

3,3-Dimethyltetrahydro-2*H*-pyran-2-one.[14, 23]

A solution of LiHMDS in anhydrous THF (1 M, 100 mL, 100 mmol, 2.20 eq.) was added dropwise within one hour to a precooled solution (–78 °C) of δ-valerolactone (**4**, 4.55 g, 45.5 mmol, 1.00 eq.) and iodomethane (6.2 mL, 0.10 mmol, 2.20 eq.) in anhydrous THF (80 mL). The mixture was stirred at –40 °C for 2 h before it was warmed to room temperature and acidified with 1 N HCl (aq.). After adding diethyl ether (200 mL), layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 40 mL). The combined organic layers were washed with brine (50 mL), saturated aqueous sodium bicarbonate (20 mL), again with brine (2 x 25 mL) and dried over sodium sulfate. The solvent was removed carefully under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 4:1) yielding 3,3-Dimethyltetrahydro-2*H*-pyran-2-one as a slightly yellow oil (5.13 g, 40.0 mmol, 89%). $\mathbf{R_f}$: 0.26 (cyclohexane/EtOAc 3:1). **^{1}H-NMR, COSY** (300 MHz, $CDCl_3$): δ/ppm = 4.36–4.32 (m, 2H, H-6), 1.92–1.86 (m, 2H, H-5), 1.77–1.73 (m, 2H, H-4), 1.30–1.29

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(m, 6H, 2 x CH_3). **^{13}C-NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$): δ/ppm = 177.1 (C-2), 70.6 (C-6), 38.8 (C-3), 35.1 (C-4), 27.8 (2 x CH_3), 20.6 (C-5). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 2968, 2871, 1726, 1474, 1458, 1400, 1386, 1296, 1276, 1137, 1077, 1016. **HRMS** (ESI): *m*/*z* calcd. for $[C_7H_{12}O_2Na]^+$: 153.0891; found: 153.0898. The analytical data are consistent with those reported in the literature.[14, 23]

3,3-Dimethyltetrahydro-2*H*-pyran-2-ol ((±)-5).[24]

A solution of DIBAL-H in *n*-hexane (1 M, 38.2 mL, 38.2 mmol, 1.10 eq.) was added dropwise at –78 °C within 30 min to a solution of 3,3-dimethyltetrahydro-*2H*-pyran-2-one (4.45 g, 34.7 mmol, 1.00 eq.) in anhydrous dichloromethane (80 mL). After 2 h, the mixture was warmed to room temperature and treated with methanol (15 mL), ethyl acetate (130 mL) and a saturated aqueous potassium sodium tartrate solution (12 mL) until the suspension cleared and a coarse-grained precipitate sedimented (30 min). The suspension was filtered over a pad of celite® and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and the solvents were removed under reduced pressure. 3,3-Dimethyltetrahydro-2*H*-pyran-2-ol ((±)-**5**) was obtained as a colourless oil (4.23 g, 32.5 mmol, 94%). **R$_f$**: 0.29 (cyclohexane/EtOAc 3:1). **^{1}H-NMR, COSY** (300 MHz, $CDCl_3$): δ/ppm = 4.45 (s, 1H, H-2), 4.01–3.93 (m, 1H, H^A-6), 3.54–3.46 (m, 1H, H^B-6), 1.66–1.56 (m, 2H. H^A-4, H^A-5), 1.54–1.43 (m, 1H, H^B-5), 1.37–1.21 (m, 1H, H^B-4), 0.96 (s, 3H, $CH_3{}^A$), 0.93 (s, 3H, $CH_3{}^B$). **^{13}C-NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$): δ/ppm = 100.7 (C-2), 64.2 (C-6), 34.7 (C-4), 34.2 (C-3), 25.8 ($CH_3{}^B$), 22.0 (C-5), 20.4 ($CH_3{}^A$). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3398, 2946, 2927, 2856, 1478, 1453, 1383, 1364, 1274, 1137, 1081, 1028, 978, 950. **HRMS** (ESI): *m*/*z* calcd. for $[C_7H_{14}O_2Na]^+$: 153.0891; found: 153.0898. The analytical data are in accordance with those reported in the literature.[24]

4,4-Dimethylhexane-1,5-diol.

A solution of methyllithium in diethyl ether (1.6 M, 24.6 mL, 39.4 mmol, 1.23 eq.) was added dropwise within 30 min to an ice cold solution of 3,3-dimethyltetrahydro-2*H*-pyran-2-ol ((±)-**5**, 3.01 g, 32.1 mmol, 1.00 eq.) in THF (300 mL). After warming to room temperature, the reaction mixture was quenched with methanol/water (1:1 v/v, 50 mL). The organic solvents were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5 x 20 mL). The organic solution was dried over sodium sulfate before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc 2:1) yielding 4,4-dimethylhexane-1,5-diol as colourless oil (3.32 g, 22.6 mmol, 98%). **R$_f$**: 0.23 (cyclohexane/EtOAc 1:2). **^{1}H-NMR, COSY** (300 MHz, $CDCl_3$): δ/ppm = 3.66–3.61 (m, 2H, H-1), 3.56 (q, 1H, *J* = 6.4 Hz, H-5), 1.64–1.46 (m, 4H, H-2, 2x OH), 1.43–1.34 (m, 1H, H^A-3), 1.30–1.19 (m, 1H, H^B-3), 1.13 (d, 3H, *J* = 6.4 Hz, H-6), 0.87 (s, 3H, $CH_3{}^A$), 0.85 (s, 3H, $CH_3{}^B$). **^{13}C-NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$): δ/ppm = 74.2 (C-5), 63.9 (C-1), 37.2 (C-4), 34.7 (C-3), 27.1 (C-2), 22.8 ($CH_3{}^B$), 22.4 ($CH_3{}^A$), 17.8 (C-6). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3374, 2949, 2872, 1474, 1453, 1386, 1366, 1105, 1068, 1055, 1030, 912. **HRMS** (ESI): *m*/*z* calcd. for $[C_8H_{18}O_2Na]^+$: 169.1204; found: 169.1218.

1-Trityloxy-4,4-dimethylhexan-5-ol ((±)-6).

Compound (±)-**6** was prepared according to a procedure by Yasukouchi and Kanematsu.[25] A solution of 4,4-dimethylhexane-1,5-diol (3.12 g, 21.3 mmol, 1.0 eq.) in dichloromethane (80 mL) was treated with triethylamine, which was freshly distilled from calcium hydride (7.4 mL, 53.2 mmol, 2.5 eq.). The solution was cooled to 0 °C before a solution of trityl chloride (6.53 g, 23.4 mmol, 1.1 eq.) in dichloromethane (30 mL) was added dropwise. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 10:1) yielding trityl ether (±)-**6** as colourless, highly viscous oil (7.73 g, 19.9 mmol, 93%). **R$_f$**: 0.51 (cyclohexane/EtOAc 2:1). **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ/ppm = 7.48–7.44 (m, 6H, *o*-H^{Tr}), 7.33–7.29 (m, 6H, *m*-H^{Tr}), 7.26–7.22 (m, 3H, *p*-H^{Tr}), 3.55 (q, 1H, *J* = 6.4 Hz, H-5), 3.06 (t, 2H, *J* = 6.8 Hz, H-1), 1.67–1.55 (m, 2H, H-2), 1.34–1.18 (m, 3H, H-3, OH), 1.12 (d, 3H, *J* = 6.4 Hz, H-6), 0.87 (s, 3H, $CH_3{}^A$), 0.84 (s, 3H, $CH_3{}^B$). **^{13}C-NMR, HSQC, HMBC** (101 MHz, $CDCl_3$): 144.5 (*ipso*-C^{Tr}), 128.7 (*o*-C^{Tr}), 127.7 (*m*-C^{Tr}), 126.8 (*p*-C^{Tr}), 86.4 (*C*Ph$_3$), 74.3 (C-5), 64.6 (C-1), 37.1 (C-4), 34.9 (C-2), 24.5 (C-3), 22.5 ($CH_3{}^B$), 22.4 ($CH_3{}^A$), 17.7 (C-6). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3407, 3086, 3058, 3032, 2963, 2872, 1491, 1448, 1386, 1220, 1183, 1155, 1072, 912, 900, 746, 705, 633. **HRMS** (ESI): *m*/*z* calcd. for $[C_{27}H_{32}O_2Na]^+$: 411.2305; found: 411.2300.

3,3-Dimethyl-6-(trityloxy)hexan-2-yl [3,5-bis(benzyloxy)-phenyl]-acetate ((±)-8).

According to a previously published procedure,[7] to an ice cold solution of 1-trityloxy-4,4-dimethylhexan-5-ol ((±)-**6**, 940 mg, 2.42 mmol, 1.00 eq.), (3,5-bis(benzyloxy)-phenyl)acetic acid (**7**, 843 mg, 2.42 mmol, 1.00 eq.) and 4-(dimethylamino)pyridine (58.9 mg, 482 µmol, 20.0 mol%) in dichloromethane (80 mL) was slowly added a solution of *N,N'*-dicyclohexylcarbodiimide (598 mg, 2.90 mmol, 1.20 eq.) in dichloromethane (15 mL). The mixture was stirred for 3 h at 0 °C and for 16 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 20:1) yielding ester (±)-**8** as colourless oil (1.44 g, 2.00 mmol, 83%). **R$_f$**: 0.51 (cyclohexane/EtOAc 4:1). **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ/ppm = 7.47–7.22 (m, 25H, H^{Tr}, H^{Bn}), 6.56–6.55 (m, 2H, H-2', H-6'), 6.53–6.52 (m, 1H, H-4'), 4.99 (s, 4H, PhCH_2), 4.78 (q, 1H, *J* = 6.4 Hz, H-2''), 3.59–3.51 (m, 2H, H-2), 3.08–2.99 (m, 2H, H-6''), 1.59–1.53 (m, 2H, H-5''), 1.31–1.23 (m, 2H, H-4''), 1.13 (d, 3H, *J* = 6.4 Hz, H-1''), 0.85 (s, 6H, 2 x CH_3). **^{13}C-NMR, HSQC, HMBC** (101 MHz, $CDCl_3$): δ/ppm = 170.9 (C-1), 159.9 (C-3', C-5'), 144.5 (*ipso*-C^{Tr}), 136.9 (*ipso*-C^{Bn}), 136.4 (C-1'), 128.7 (*o*-C^{Tr}), 128.6 (*m*-C^{Bn}), 128.0 (*p*-C^{Bn}), 127.8 (*m*-C^{Tr}), 127.5 (*o*-C^{Bn}), 126.9 (*p*-C^{Tr}), 108.5 (C-2', C-6'), 100.9 (C-4'), 86.4 (*C*Ph$_3$), 77.1 (C-2''), 70.0 (PhCH_2), 64.4 (C-6''), 42.1 (C-2), 36.5 (C-3''), 35.2 (C-4''), 24.5 (C-5''), 23.2 ($CH_3{}^A$), 22.7 ($CH_3{}^B$), 14.6 (C-1''). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3087, 3061, 3033, 2964, 2945,

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2872, 1727, 1595, 1491, 1449, 1378, 1291, 1156, 1116, 1061, 1030, 745, 736, 698. **HRMS** (ESI): *m*/*z* calcd. for $[C_{49}H_{50}O_5Na]^+$: 741.3556; found: 741.3585.

6-Hydroxy-3,3-dimethylhexan-2-yl [3,5-bis(benzyloxy)-phenyl]-acetate.

p-Toluenesulfonic acid monohydrate (19 mg, 0.10 mmol, 5.0 mol%) was added to a suspension of trityl ether (±)-**8** (1.40 g, 1.95 mmol, 1.0 eq.) in methanol (250 mL). The mixture was warmed to 50 °C for 2 h, whereas the starting material dissolved completely within a few minutes. After stirring overnight at room temperature, the solvent volume was decreased to 1/3 of the initial volume by evaporation under reduced pressure. Saturated aqueous sodium bicarbonate (100 mL) was added and the aqueous layer was extracted with ethyl acetate (4 x 50 mL). The organic solution was washed with brine (50 mL), dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 3:1) yielding 6-Hydroxy-3,3-dimethylhexan-2-yl [3,5-bis(benzyloxy)phenyl]acetate as colourless oil (912 mg, 1.91 mmol, 98%). R_f: 0.07 (cyclohexane/EtOAc 4:1). **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ/ppm = 7.43–7.30 (m, 10H, H^{Bn}), 6.56–6.55 (m, 2H, H-2', H-6'), 6.53–6.52 (m, 1H, H-4'), 5.02 (s, 4H, PhCH_2), 4.74 (q, 1H, *J* = 6.4 Hz, H-2''), 3.53–3.48 (m, 4H, H-2, H-6''), 1.47–1.40 (m, 2H, H-5''), 1.28–1.15 (m, 2H, H-4''), 1.12 (d, 3H, *J* = 6.4 Hz, H-1''), 0.84 (s, 3H, $CH_3{}^A$), 0.82 (s, 3H, $CH_3{}^B$). **^{13}C-NMR, HSQC, HMBC** (101 MHz, $CDCl_3$): δ/ppm = 170.8 (C-1), 160.0 (C-3', C-5'), 136.8 (*ipso*-C^{Bn}), 136.5 (C-1'), 128.6 (*m*-C^{Bn}), 128.0 (*p*-C^{Bn}), 127.5 (*o*-C^{Bn}), 108.6 (C-2', C-6'), 100.7 (C-4'), 77.2 (C-2''), 70.1 (PhCH_2), 63.6 (C-6''), 42.2 (C-2), 36.4 (C-3''), 34.6 (C-4''), 27.1 (C-5''), 22.9 2 x CH_3), 14.6 (C-1''). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3432, 3065, 3034, 2943, 2873, 1725, 1595, 1498, 1453, 1378, 1292, 1158, 1058, 737, 698. **HRMS** (ESI): *m*/*z* calcd. for $[C_{30}H_{36}O_5Na]^+$: 499.2460; found: 499.2473.

3,3-Dimethyl-6-oxohexan-2-yl [3,5-bis(benzyloxy)phenyl]acetate (±)-9.

According to procedures by Nokami et al.[26] and Opatz et al.,[7] pyridinium chlorochromate (276 mg, 1.28 mmol, 1.51 eq.) was added under argon atmosphere to a solution of 6-Hydroxy-3,3-dimethylhexan-2-yl [3,5-bis(benzyloxy)phenyl]acetate (404 mg, 847 µmol, 1.00 eq.) in dichloromethane (20 mL). After stirring at room temperature overnight, the solvent was removed under reduced pressure and the residue was filtered rapidly over silica (cyclohexane/EtOAc 4:1). Aldehyde (±)-**9** was obtained as a colourless oil (349 mg, 735 µmol, 86%). Note: The product is prone to oxidation and should be stored under an inert gas atmosphere at –25 °C or used immediately after production. R_f: 0.28 (cyclohexane/EtOAc 4:1). **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ/ppm = 9.65 (t, 1H, *J* = 1.6 Hz, C*H*O), 9.44–9.26 (m, 10H, H^{Bn}), 6.55–6.53 (m, 3H, H-2', H-4', H-6'), 5.02 (s, 4H, PhCH_2), 4.73 (q, 1H, *J* = 6.4 Hz, H-2''), 3.58–3.50 (m, 2H, H-2), 2.38–2.23 (m, 2H, H-5''), 1.61–1.52 (m, 1H, H^A-4''), 1.51–1.41 (m, 1H, H^B-4''), 1.13 (d, 3H, *J* = 6.4 Hz, H-1''), 0.85 (s, 3H, $CH_3{}^A$), 0.82 (s, 3H, $CH_3{}^B$). **^{13}C-NMR, HSQC, HMBC** (101 MHz, $CDCl_3$): δ/ppm = 202.3 (*C*HO), 170.8 (C-1), 160.0 (C-3', C-5'), 136.8 (*ipso*-C^{Bn}), 136.3 (C-1'), 128.6 (*m*-C^{Bn}), 128.0 (*p*-C^{Bn}), 127.5 (*o*-C^{Bn}), 108.5 (C-2', C-6'), 100.8 (C-4'), 76.6 (C-2''), 70.0 (PhCH_2), 42.1 (C-2), 38.9 (C-5''), 36.2 (C-3''), 30.0 (C-4''), 23.1 ($CH_3{}^B$), 23.0 ($CH_3{}^A$), 14.6 (C-1''). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 2966, 2939, 2875, 2722, 1723, 1594, 1452, 1378, 1291, 1216, 1154, 1058, 834, 738, 698. **HRMS** (ESI): *m*/*z* calcd. for $[C_{30}H_{34}O_5Na]^+$: 497.2298; found: 497.2300.

Allyl (2*E*)-7-([[3,5-Bis(benzyloxy)phenyl]acetyl]oxy)-2,6,6-trimethyloct-2-enoate.

According to a previously published procedure,[7] phosphonium ylide **10** (76.2 mg, 204 µmol, 1.14 eq.) was added to a solution of aldehyde (±)-**9** (84.5 mg, 178 µmol, 1.00 eq.) in dichloromethane (10 mL). The mixture was stirred at room temperature overnight. As conversion of aldehyde (±)-**9** was incomplete, further ylide **10** (7.0 mg, 18 µmol, 0.10 eq.) was added. Stirring was continued for 24 h at room temperature, then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc 12:1) yielding the unsaturated, (*E*)-configured allyl ester as colourless oil (92.1 mg, 161 µmol, 89%). R_f: 0.18 (cyclohexane/EtOAc 12:1). **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ/ppm = 7.42–7.30 (m, 10H, H^{Bn}), 6.73–6.69 (m, 1H, H-3), 6.54–6.52 (m, 3H, H-2'', H-4'', H-6''), 5.94 (ddt, 1H, *J* = 17.2, 10.5, 5.6 Hz, OCH_2CH=CH_2), 5.34–5.29 (m, 1H, OCH_2CH=C$H_2{}^E$), 5.24–5.20 (m, 1H, OCH_2CH=C$H_2{}^Z$), 5.01 (s, 4H, PhCH_2), 4.76 (q, 1H, *J* = 6.4 Hz, H-7), 4.62–4.60 (m, 2H, OCH_2CH=CH_2), 3.57–3.50 (m, 2H, H-2'), 2.14–2.00 (m, 2H, H-4), 1.81 (s, 3H, 2-CH_3), 1.39–1.31 (m, 1H, H^A-5), 1.29–1.21 (m, 1H, H^B-5), 1.12 (d, 3H, *J* = 6.4 Hz, H-8), 0.86 (s, 6H, 2 x 6-CH_3). **^{13}C-NMR, HSQC, HMBC** (101 MHz, $CDCl_3$): δ/ppm = 170.8 (C-1'), 167.7 (C-1), 160.0 (C-3'', C-5''), 142.7 (C-3), 136.8 (*ipso*-H^{Bn}), 136.3 (C-1''), 132.6 (OCH_2CH=CH_2), 128.6 (*m*-H^{Bn}), 128.0 (*p*-H^{Bn}), 127.5 (*o*-H^{Bn}), 127.4 (C-2), 117.8 (OCH_2CH=CH_2), 108.5 (C-2'', C-6''), 100.8 (C-4''), 76.8 (C-7), 70.0 (PhCH_2), 65.1 (OCH_2CH=CH_2), 42.1 (C-2'), 37.2 (C-5), 36.7 (C-6), 23.3 (C-4), 23.0 (6-$CH_3{}^A$), 22.8 (6-$CH_3{}^B$), 14.6 (C-8), 12.3 (2-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3066, 3033, 2966, 2936, 2875, 1711, 1648, 1595, 1452, 1378, 1290, 1260, 1158, 1060, 736, 698. **HRMS** (ESI): *m*/*z* calcd. for $[C_{36}H_{42}O_6Na]^+$: 593.2879; found: 593.2892.

(2*E*)-7-([[3,5-Bis(benzyloxy)phenyl]acetyl]oxy)-2,6,6-trimethyloct-2-enoic acid ((±)-11).

According to a procedure by Kunz and März,[27] allyl (2*E*)-7-([[3,5-bis(benzyloxy)phenyl]acetyl]oxy)-2,6,6-trimethyloct-2-enate (356 mg, 627 µmol, 1.0 eq.), 1,3-dimethylbarbituric acid (116 mg, 743 µmol, 1.2 eq.), tetrakis(triphenylphosphine)-palladium(0) (69 mg, 60 µmol, 10 mol%) and triphenylphosphane (178 mg, 678 µmol, 1.1 eq.) were solved under argon in THF (35 mL) and stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 6:1 + 1% HOAc). Carbonic acid (±)-**11** was obtained as colourless oil (327 mg, 616 µmol, 98%). R_f: 0.22 (cyclohexane/EtOAc 3:1 + 1% HOAc). **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ/ppm = 7.42–7.29 (m, 10H, H^{Bn}), 6.80–6.76 (m, 1H, H-3), 6.56–6.52 (H-2'', H-4'', H-6''), 5.01 (s, 4H, PhCH_2), 4.75 (q,

1H, *J* = 6.5 Hz, H-7), 3.57–3.49 (m, 2H, H-2'), 2.10–2.05 (m, 2H, H-4), 1.80–1.79 (m, 3H, 2-CH_3), 1.38–1.31 (m, 1H, H^A-5), 1.28–1.20 (m, 1H, H^B-5), 1.13 (d, 3H, *J* = 6.5 Hz, H-8), 0.87 (s, 3H, 6-CH_3^A), 0.86 (s, 3H, 6-CH_3^B). **^{13}C-NMR, HSQC, HMBC** (101 MHz, $CDCl_3$): *δ*/ppm = 172.2 (C-1), 170.8 (C-1'), 160.0 (C-3'', C-5''), 145.1 (C-3), 136.8 (*ipso*-C^{Bn}), 136.3 (C-1''), 128.5 (*m*-C^{Bn}), 127.9 (*p*-C^{Bn}), 127.5 (*o*-C^{Bn}), 126.7 (C-2), 108.5 (C-2'', C-6''), 100.8 (C-4''), 77.2 (C-7), 70.0 (PhCH_2), 42.1 (C-2'), 37.1 (C-5), 36.7 (C-6), 23.4 (C-4), 23.0 (6-CH_3^A), 22.8 (6-CH_3^B), 14.6 (C-8), 11.9 (2-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3067, 3033, 2965, 2932, 2875, 1725, 1685, 1595, 1452, 1291, 1160, 1060, 737, 635. **HRMS** (ESI): *m/z* calcd. for $[C_{33}H_{38}O_6Na]^+$: 553.2566; found: 553.2542.

5,7-Bis(benzyloxy)-4-dechloro-14-methyl-14-deoxy-oxacyclododecindione ((±)-12).

According to procedures from Roberts et al.[9] and Opatz et al.,[7] a solution of trifluoroacetic acid (12 mL) and trifluoroacetic anhydride (6 mL) in dichloromethane (160 mL) was precooled to –8 °C. A solution of carboxylic acid (±)-**11** (63 mg, 0.12 mmol) in dichloromethane (3 mL) was added and the flask was left to stand at –8 °C for 48 h. The solution was neutralized by cautious washing with saturated aqueous sodium bicarbonate (3 x 80 mL). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. After flash chromatography (cyclohexane/EtOAc 15:1 + 1% HOAc), macrolactone (±)-**12** was obtained as colourless oil (55 mg, 11 mmol, 90%). **R$_f$**: 0.33 (cyclohexane/EtOAc 4:1). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3OD): *δ*/ppm = 7.40–7.38 (m, 2H, H^{Bn}), 7.36–7.33 (m, 2H, H^{Bn}), 7.31–7.24 (m, 6H, H^{Bn}), 6.65 (d, 1H, *J* = 2.1 Hz, H-6), 6.57–6.56 (m, 1H, H-4), 6.39–6.37 (m, 1H, H-11), 5.11–5.05 (m, 2H, 5-OCH_2Ph), 5.05–5.00 (m, 2H, 7-OCH_2Ph), 4.48 (q, 1H, *J* = 6.3 Hz, H-15), 3.30–3.21 (m, 2H, H-2), 2.43–2.29 (m, 2H, H-12), 1.87 (s, 3H, 10-CH_3), 1.82–1.78 (m, 1H, H^A-13), 1.46–1.42 (m, 1H, H^B-13), 0.96 (d, 3H, *J* = 6.3 Hz, 15-CH_3), 0.87 (s, 3H, 14-CH_3^A), 0.86 (s, 3H, 14-CH_3^B). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3OD): *δ*/ppm = 199.3 (C-9), 169.6 (C-1), 159.3 (C-5), 156.0 (C-7), 155.0 (C-11), 136.2 (*ipso*-C$^{5\text{-}Bn}$), 136.1 (*ipso*-C$^{7\text{-}Bn}$), 134.7 (C-10), 132.3 (C-3), 127.4 (*m*-C^{Bn}), 127.3 (*m*-C^{Bn}), 126.8 (*p*-C^{Bn}), 126.7 (*p*-C^{Bn}), 126.4 (*o*-C$^{5\text{-}Bn}$), 126.2 (*o*-C$^{7\text{-}Bn}$), 123.1 (C-8), 106.9 (C-4), 99.5 (C-6), 77.9 (C-15), 69.5 (5-OCH_2Ph), 69.2 (7-OCH_2Ph), 38.2 (C-2), 35.3 (C-14), 34.1 (very broad, C-13), 24.9 (C-12), 23.9 (very broad, 2 x 14-CH_3), 12.8 (15-CH_3), 8.1 (10-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3033, 2925, 2873, 1726, 1652, 1635, 1604, 1583, 1455, 1432, 1329, 1297, 1156, 1135, 1066, 904, 730, 650. **HRMS** (ESI): *m/z* calcd. for $[C_{33}H_{36}O_5]^+$: 513.2641; found: 513.2647.

4-Dechloro-14-methyl-14-deoxy-oxacyclododecindione ((±)-15).

According to Opatz et al.,[7] a solution of boron trichloride in dichloromethane (1 M, 0.70 mL, 0.70 mmol, 10 eq.) was added at –78 °C to a solution of benzyl protected macrolactone (±)-**12** (34 mg, 68 µmol, 1.0 eq.) in dichloromethane (10 mL). After 1 h, saturated aqueous sodium bicarbonate (15 mL) was added upon warming to room temperature. The aqueous layer was extracted with dichloromethane (7 x 10 mL). The organic solution was dried over sodium sulfate before removal of the solvent under reduced pressure. After flash chromatography (cyclohexane/EtOAc 4:1) and preparative HPLC (C$_{18}$-PFP, MeCN/H_2O 40:60, 30 min), macrolactone (±)-**15** was obtained as colourless oil (20 mg, 60 µmol, 88%). **R$_f$**: 0.20 (cyclohexane/EtOAc 2:1). ***t$_R$*** (HPLC): 9.1 min (C$_{18}$-PFP, MeCN/H_2O 40:60). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3OD): *δ*/ppm = 6.42 (s, 1H, H-11), 6.27 (s, 1H, H-4), 6.24–6.23 (m, 1H, H-6), 4.50 (q, 1H, *J* = 6.3 Hz, H-15), 3.27–3.24 (m, 1H, H^A-2), 3.20–3.17 (m, 1H, H^B-2), 2.54–2.27 (m, 2H, H-12), 1.91–1.85 (m, 4H, 10-CH_3, H^A-13), 1.50–1.47 (m, 1H, H^B-13), 1.06 (d, 3H, *J* = 6.3 Hz, 15-CH_3), 0.91 (s, 3H, 14-CH_3^A), 0.90 (s, 3H, 14-CH_3^B). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3OD): *δ*/ppm = 200.8 (C-9), 170.0 (C-1), 158.5 (C-5), 155.6 (C-7), 154.1 (very broad, C-11), 134.8 (C-10), 132.7 (C-3), 118.4 (C-8), 106.6 (C-4), 100.4 (C-6), 77.6 (C-15), 38.3 (C-2), 35.3 (C-14), 33.5 (very broad, C-13), 24.9 (very broad, C-12), 23.8 (very broad, 2 x 14-CH_3), 12.7 (15-CH_3), 8.6 (10-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3351, 2962, 2924, 2873, 2854, 1703, 1619, 1461, 1333, 1302, 1269, 1159, 845, 757. **HRMS** (ESI): *m/z* calcd. for $[C_{19}H_{24}O_5Na]^+$: 355.1516; found: 355.1524.

14-Methyl-14-deoxyoxacyclododecindione ((±)-13).

According to previously published procedures,[7] a solution of macrolactone (±)-**15** (115 mg, 346 µmol, 1.0 eq.) and *N*-chloro-succinimide (46 mg, 0.34 mmol, 1.0 eq.) in *N*,*N*-dimethylform-amide (14 mL) was treated with trifluoroacetic acid (42 µL, 0.55 mmol, 1.6 eq.). After 48 h, the solvent was removed under reduced pressure and the residue was co-evaporated with toluene (2 x 2 mL). After flash chromatography (cyclo-hexane/EtOAc 3:1 + 1% HOAc) and preparative HPLC (C$_{18}$-PFP, MeCN/H_2O 35:65, 30 min), compound (±)-**13** was obtained as colourless oil (100 mg, 273 µmol, 79%). It should be noted that in a smaller batch (20 mg of starting material), a yield of 70% was obtained. **R$_f$**: 0.12 (cyclohexane/EtOAc 2:1). ***t$_R$*** (HPLC): 10.5 min (C$_{18}$-PFP, MeCN/H_2O 40:60). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3CN, 343 K): *δ*/ppm = 7.32 (s, 2H, 2x OH), 6.52 (s, 1H, H-6), 6.43–6.40 (m, 1H, H-11), 4.75 (q, 1H, *J* = 6.5 Hz, H-15), 3.52 (d, 1H, *J* = 16.5 Hz, H^A-2), 3.31 (d, 1H, *J* = 16.5 Hz, H^B-2), 2.52–2.45 (m, 1H, H^A-12), 2.22–2.16 (m, 1H, H^B-12), 1.91–1.87 (m, 1H, H^A-13), 1.87–1.86 (m, 3H, 10-CH_3), 1.44–1.40 (m, 1H, H^B-13), 1.04 (d, 3H, *J* = 6.5 Hz, 15-CH_3), 0.88 (s, 3H, 14-CH_3^A), 0.86 (s, 3H, 14-CH_3^B). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3CN, 293 K): *δ*/ppm = 197.4 (C-9), 167.5 (C-1), 153.7 (C-11), 152.5 (2x *C*OH), 134.1 (C-10), 131.0 (C-3), 121.2 (C-8), 111.6 (C-4), 101.6 (C-6), 76.9 (C-15), 37.4 (C-2), 35.3 (C-14), 32.4 (C-13), 25.9 (14-CH_3^A), 25.2 (C-12), 23.8 (14-CH_3^B), 13.3 (15-CH_3), 8.6 (10-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3355, 2963, 2926, 2874, 1730, 1705, 1619, 1438, 1368, 1336, 1301, 1275, 1242, 1178, 1066, 1016, 843, 655. **HRMS** (ESI): *m/z* calcd. for $[C_{19}H_{23}(^{35}Cl)O_5Na]^+$: 389.1126; found: 389.1129.

6-Chloro-14-methyl-14-deoxyoxacyclododecindione ((±)-14).

Double-chlorinated compound (±)-**14** was obtained as minor byproduct from the above stated chlorination reaction. **R$_f$**: 0.24 (cyclohexane/EtOAc 2:1). ***t$_R$*** (HPLC): 13.4 min (C$_{18}$-PFP, MeCN/H_2O 36:65). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3CN): δ/ppm = 7.51 (s, 1H, 5-OH), 7.20 (s, 1H, 7-OH), 6.45–6.43 (m, 1H, H-11), 4.71 (q, 1H, J = 6.5 Hz, H-15), 3.50–3.47 (m, 1H, H^A-2),

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3.31–3.19 (m, 1H, H^B-2), 2.56–2.44 (m, 1H, H^A-12), 2.16–2.11 (m, 1H, H^B-12), 1.92–1.87 (m, 1H, H^A-13), 1.85–1.83 (m, 3H, 10-CH_3), 1.38–1.34 (m, 1H, H^B-13), 0.99 (d, 3H, J = 6.5 Hz, 15-CH_3), 0.85 (s, 3H, 14-CH_3^A) 0.81 (s, 3H, 14-CH_3^B). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3CN): δ/ppm = 196.1 (C-9), 167.1 (C-1), 155.0 (C-11), 148.4 (C-7), 147.9 (C-5), 133.7 (C-10), 128.8 (C-3), 121.5 (C-8), 112.7 (C-4), 107.4 (C-6), 77.0 (C-15), 37.2 (C-2), 35.3 (C-14), 32.1 (C-13), 26.1 (14-CH_3^A), 25.3 (C-12), 23.6 (14-CH_3^B), 13.3 (15-CH_3), 8.5 (10-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3368, 2965, 2874, 1714, 1625, 1589, 1433, 1370, 1333, 1296, 1272, 1179, 1094, 1065, 951, 738. **HRMS** (ESI): m/z calcd. for $[C_{19}H_{23}(^{35}Cl)_2O_5]^+$: 401.0923; found: 401.0917.

4-Fluoro-14-methyl-14-deoxyoxacyclododecindione ((±)-16).

A solution of macrolactone **(±)-15** (13.1 mg, 40.6 µmol, 1.00 eq.), Selectfluor® (20.8 mg, 58.7 µmol, 1.44 eq.) and trifluoroacetic acid in *N*,*N*-dimethylformamide (2.2 mL) was stirred at room temperature for 7 d. Water (3 mL) was added and the aqueous layer was extracted with diethyl ether (6 x 3 mL). The organic layers were washed with water (2 x 2 mL) and brine (2 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. After flash chromatography (cyclohexane/EtOAc 2:1) and subsequent preparative HPLC (C_{18}-PFP, MeCN/H_2O 35:65),), a 3:2 mixture of fluorinated compound (±)-**16** and the starting material (±)-**15** due to incomplete conversion was obtained as a brown oil (in total 6.45 mg containing 3.93 mg of (±)-**16**, 11.2 µmol, 28% (calculated based on ^{1}H NMR)). The purest fractions were used for biological evaluation (0.57 mg, please refer to the supporting information). R_f: 0.19 (cyclohexane/EtOAc 2:1). t_R (HPLC): 12.2 min (C_{18}-PFP, MeCN/H_2O 35:65). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3OD): δ/ppm = 6.53–6.49 (m, 1H, H-11), 6.39 (d, 1H, *J* = 7.2 Hz, H-6), 4.67 (q, 1H, *J* = 6.4 Hz, H-15), 3.48–3.43 (m, 1H, H^A-2), 3.16–3.11 (m, 1H, H^B-2), 2.56–2.48 (m, 1H, H^A-12), 2.29–2.26 (m, 1H, H^B-12), 1.94–1.84 (m, 4H, 10-CH_3, H^A-13), 1.49–1.46 (m, 1H, H^B-13), 1.07 (m, 3H, *J* = 6.4 Hz, 15-CH_3), 0.90 (s, 3H, 14-CH_3^A), 0.87 (s, 3H, 14-CH_3^B). **^{13}C-NMR, HSQC, HMBC*** (151 MHz, CD_3OD): δ/ppm = 201.1 (C-9), 170.7 (C-1), 157.5 (very broad, C-11), 152.3 (C-5), 145.5 (d, *J* = 237.8 Hz, C-4), 137.0 (C-10), 121.4 (d, *J* = 15.7 Hz, C-8), 104.8 (C-6), 79.6 (C-15), 37.4 (C-14), 34.7 (C-2), 30.8 (br, C-13), 27.0 (C-12), 25.8 (14-CH_3^A), 15.1 (15-CH_3), 14.7 (br, 14-CH_3^B), 10.4 (10-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3340, 2966, 1725, 1621, 1455, 1266, 1156, 1118, 1067, 736. **HRMS** (ESI, neg.): *m/z* calcd. for $[C_{19}H_{22}FO_5]^-$: 349.1444; found: 349.1451.

*The resonances of C-3 and C-7 could not be assigned due to missing HMBC crosspeaks.

4-Bromo-4-dechloro-14-methyl-14-deoxyoxacyclododecindione ((±)-17).

A 0.06 M solution of *N*-bromosuccinimide in *N*,*N*-dimethylformamide (0.50 mL, 30 µmol, 0.50 eq.) was added to a solution of macrolactone (±)-**15** (20.0 mg, 60.2 µmol, 1.0 eq.) and trifluoroacetic acid (10 µL, 0.13 mmol, 2.2 eq.) in *N*,*N*-dimethylformamide (3 mL). Portions of NBS solution (each time 0.25 mL, 15 µmol, 0.25 eq.) were added to the mixture three times in intervals of 24 h, until the starting material (±)-**15** was completely consumed after 4 d. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 4:1 + 1% HOAc) and subsequent preparative HPLC (C_{18}-PFP, MeCN/H_2O 40:60), yielding mono-brominated macrolactone (±)-**17** (12.3 mg, 29.9 µmol, 50%, brown oil) as major product. R_f: 0.17 (cyclohexane/EtOAc 2:1). t_R (HPLC): 8.3 min (C_{18}-PFP, MeCN/H_2O 40:60). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3CN): δ/ppm = 7.45 (s, 2H, 2 x OH), 6.48 (s, 1H, H-6), 6.43 (d, 1H, *J* = 11.3 Hz, H-11), 4.74 (q, 1H, *J* = 6.5 Hz, H-15), 3.48 (d, 1H, *J* = 6.7 Hz, H^A-2), 3.29–3.25 (m, 1H, H^B-2), 2.53–2.46 (m, 1H, H^A-12), 2.18–2.12 (m, 1H, H^B-12), 1.91–1.86 (m, 1H, H^A-13), 1.82 (s, 3H, 10-CH_3), 1.38–1.33 (m, 1H, H^B-13), 1.01 (d, 3H, *J* = 6.5 Hz, 15-CH_3), 0.85 (s, 3H, 14-CH_3^A), 0.81 (s, 3H, 14-CH_3^B). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3CN): δ/ppm = 197.4 (C-9), 167.4 (C-1), 153.9 (C-11), 153.4 (*C*OH), 153.0 (*C*OH), 134.0 (C-10), 132.5 (C-3), 121.7 (C-8), 102.4 (C-4), 101.2 (C-6), 76.9 (C-15), 39.7 (C-2), 35.3 (C-14), 32.4 (C-13), 25.9 (14-CH_3^A), 25.2 (C-12), 23.9 (14-CH_3^B), 13.3 (15-CH_3), 8.5 (10-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3341, 2965, 2928, 2872, 1728, 1703, 1620, 1432, 1336, 1300, 1241, 1176, 1065, 1015, 948, 841. **HRMS** (ESI): *m/z* calcd. für $[C_{19}H_{24}(^{79}Br)O_5]^+$: 411.0802; found: 411.0789.

4,6-Dibromo-4-dechloro-14-methyl-14-deoxy-oxacyclododecindione ((±)-18).

Dibrominated compound (±)-**18** (10.7 mg, 21.8 µmol, 36%) was obtained as minor product from the bromination reaction described above as brown oil. R_f: 0.36 (cyclohexane/EtOAc 2:1). t_R (HPLC): 12.5 min (C_{18}-PFP, MeCN/H_2O 40:60). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3CN): δ/ppm = 7.37 (s, 1H, OH), 7.15 (s, 1H, OH), 6.47 (d, 1H, *J* = 11.2 Hz, H-11), 4.77 (q, 1H, *J* = 6.5 Hz, H-15), 3.50 (d, 1H, *J* = 16.8 Hz, H^A-2), 3.35–3.32 (m, 1H, H^B-2), 2.58–2.50 (m, 1H, H^A-12), 2.17–2.13 (m, 1H, H^B-12), 1.96–1.89 (m, 1H, H^A-13), 1.87–1.86 (m, 3H, 10-CH_3), 1.43–1.37 (m, 1H, H^B-13), 1.04 (d, 3H, *J* = 6.5 Hz, 15-CH_3), 0.87 (s, 3H, 14-CH_3^A), 0.84 (s, 3H, 14-CH_3^B). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3CN): δ/ppm = 196.3 (C-9), 167.0 (C-1), 155.0 (C-11), 150.2 (*C*OH), 149.6 (*C*OH), 133.7 (C-10), 131.2 (C-3), 122.1 (C-8), 103.3 (C-4), 97.7 (C-6), 77.1 (C-15), 39.1 (C-2), 35.3 (C-14), 32.2 (C-13), 26.1 (14-CH_3^A), 25.4 (C-12), 23.8 (14-CH_3^B), 13.3 (15-CH_3), 8.5 (10-CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3401, 2966, 2925, 2872, 1719, 1626, 1581, 1423, 1367, 1293, 1271, 1174, 1065, 1017. **HRMS** (ESI): *m/z* calcd. for $[C_{19}H_{23}(^{79}Br)_2O_5]^+$: 488.9912; found: 488.9907.

Allyl 2-bromobutanoate.

On the basis of a previously published procedure,[7] a solution of 4-(dimethylamino)pyridine (1.22 g, 9.98 mmol, 5.0 mol%), 2-bromobutyric acid ((±)-**19**, 21.0 mL, 195 mmol, 1.00 eq.) and allyl alcohol (16.4 mL, 240 mmol, 1.23 eq.) in dichloromethane (150 mL) was treated at 0 °C with a solution of *N*,*N*'-dicyclohexylcarbodiimide (40.2 g, 194 mmol, 1.00 eq.) in dichloromethane (30 mL). After stirring for 4 h at 0 °C, the mixture was filtered over celite®. The solvent was removed carefully under reduced pressure. Distillation yielded allyl 2-bromobutanoate as colourless liquid (37.5 g, 181 mmol, 94%). **Bp**: 79–82 °C (18 mbar), lit.: 189–193 °C (atm.)[28]. R_f: 0.30 (cyclohexane). **^{1}H-NMR, COSY** (300 MHz, $CDCl_3$): δ/ppm = 5.92 (ddt, 1H, *J* =

17.3, 10.4, 5.7 Hz, $OCH_2CH{=}CH_2$), 5.40–5.33 (m, 1H, $OCH_2CH{=}CH_2^E$), 5.29–5.24 (m, 1H, $OCH_2CH{=}CH_2^Z$), 4.72–4.60 (m, 2H, $OCH_2CH{=}CH_2$), 4.20–4.16 (m, 1H, H-2), 2.19–1.93 (m, 2H, H-3), 1.02 (t, 3H, J = 7.3 Hz, H-4). **^{13}C-NMR, HSQC, HMBC** (75.5 MHz, $CDCl_3$): δ/ppm = 169.4 (C-1), 131.3 ($OCH_2CH{=}CH_2$), 118.9 ($OCH_2CH{=}CH_2$), 66.3 ($OCH_2CH{=}CH_2$), 47.5 (C-2), 28.4 (C-3), 11.9 (C-4). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3088, 2974, 2939, 2879, 1737, 1650, 1457, 1382, 1372, 1300, 1256, 1234, 1205, 1149, 1076, 984, 931, 809, 750. **HRMS** (APPI): m/z calcd. for $[C_7H_{11}(^{81}Br)O_2]^+$: 205.9937; found: 205.9935.

(1-Allyloxy-1-oxobutan-2-yl)triphenylphosphonium bromide ((±)-20).

Allyl 2-bromobutyrate (2.00 g, 7.40 mmol, 1.00 eq.) was added under an argon atmosphere dropwise within 2 h to a boiling suspension of triphenylphosphane (1.94 g, 7.40 mmol, 1.00 eq.) in degassed water (32 mL). The resulting mixture was refluxed for 18 h and washed with diethyl ether (2 x 2 mL). The aqueous layer containing the phosphonium salt was evaporated to dryness under reduced pressure, yielding (±)-**20** as colourless foam (3.27 g, 6.97 mmol, 94%). **^{1}H-NMR, COSY** (300 MHz, CD_3OD): δ/ppm = 7.95–7.73 (m, 15H, H^{Ph}), 5.69 (ddt, 1H, J = 17.2, 10.3, 6.2 Hz, $OCH_2CH{=}CH_2$), 5.30–5.19 (m, 2H, $OCH_2CH{=}CH_2$), 5.05 (ddd, 1H, J = 13.3, 11.4, 3.0 Hz, H-2, signal vanishes after a few hours in CD_3OD due to C-H acidity related deuterium exchange), 4.58–4.44 (m, 2H, $OCH_2CH{=}CH_2$), 2.21–2.04 (m, 1H, H^A-3), 2.02–1.87 (m, 1H, H^B-3), 1.21–1.16 (m, 3H, H-4). **^{13}C-NMR, HSQC, HMBC** (75.5 MHz, CD_3OD): δ/ppm = 166.6 (C-1), 134.5 (d, ^4J = 3.2 Hz, p-C^{Ph}), 133.3 (d, ^3J = 10.0 Hz, m-C^{Ph}), 129.8 ($OCH_2CH{=}CH_2$), 129.4 (d, ^2J = 13.0 Hz, o-C^{Ph}), 118.7 ($OCH_2CH{=}CH_2$), 116.4 (d, ^1J = 86.3 Hz, $ipso$-C^{Ph}), 66.4 ($OCH_2CH{=}CH_2$), 41.9 (very broad, C-2), 21.9 (d, ^2J = 2.8 Hz, C-3), 10.9 (d, ^3J = 15.2 Hz, C-4). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3407, 3053, 2985, 2937, 2877, 2823, 1730, 1646, 1622, 1587, 1485, 1438, 1326, 1270, 1221, 1178, 1109, 996, 754, 725, 692, 530, 515. **HRMS** (APCI): m/z calcd. for $[C_{25}H_{26}O_2P]^+$: 389.1665; found: 389.1659.

Allyl 2-(triphenylphosphoranylidene)butanoate (21).

On the basis of a previously published procedure,[7] a solution of phosphonium bromide (±)-**20** (3.08 g, 6.56 mmol) in dichloromethane (150 mL) and aqueous sodium hydroxide (0.1 M, 150 mL) was mixed at 0 °C. The biphasic system was vigorously stirred for 2 h at room temperature. The aqueous layer was extracted with dichloromethane (2 x 30 mL) and the the organic solution was dried over magnesium sulfate. After solvent removal under reduced pressure, phosphonium ylide (±)-**20** was obtained as yellow solid (2.50 g, 6.44 mmol, 98%). **Mp:** 93–100 °C (dichloromethane). NMR-spectra of compound (±)-**20** in DMSO-d_6 exhibit at room temperature a twofold set of signals resulting from two rotamers A and B at the ratio of 1.1:1.0. However, an assignment of the ^{13}C signals to the corresponding rotamer was not possible in the range 132.0-131.4 ppm. Rotamer A: **^{1}H-NMR, COSY** (400 MHz, DMSO-d_6): δ/ppm = 7.65–7.54 (m, 15 H, H^{Ph}), 5.97–5.88 (m, 1H, $OCH_2CH{=}CH_2$), 5.31–5.26 (m, 1H, $OCH_2CH{=}CH_2^E$), 5.15–5.10 (m, 1H, $OCH_2CH{=}CH_2^Z$), 4.40–4.37 (m, 2H, $OCH_2CH{=}CH_2$), 1.88–1.77 (m, 2H, H-3), 0.80–0.72 (m, 3H, H-4). **^{13}C-NMR, HSQC, HMBC** (101 MHz, DMSO-d_6): δ/ppm = 169.3 (d, ^2J = 19.0 Hz, C-1), 135.6 ($OCH_2CH{=}CH_2$), 133.1 (d, ^2J = 9.3 Hz, o-C^{Ph}), 132.2–131.4 (m, p-C^{Ph}), 128.7 (d, ^3J = 11.8 Hz, m-C^{Ph}), 127.0 (d, ^1J = 89.8 Hz, $ipso$-C^{Ph}), 114.9 ($OCH_2CH{=}CH_2$), 61.6 ($OCH_2CH{=}CH_2$), 40.3 (d, ^1J = 178.1 Hz, C-2), 20.5 (d, ^2J = 12.2 Hz, C-3), 18.5 (C-4). Rotamer B: **^{1}H-NMR, COSY** (400 MHz, DMSO-d_6): δ/ppm = 7.65–7.54 (m, 15 H, H^{Ph}), 5.20–5.11 (m, 1H, $OCH_2CH{=}CH_2$), 4.61–4.57 (m, 1H, $OCH_2CH{=}CH_2^Z$), 4.49–4.43 (m, 1H, $OCH_2CH{=}CH_2^E$), 4.03–4.00 (m, 2H, $OCH_2CH{=}CH_2$), 1.88–1.77 (m, 2H, H-3), 0.80–0.72 (m, 3H, H-4). **^{13}C-NMR, HSQC, HMBC** (101 MHz, DMSO-d_6): δ/ppm = 167.8 (d, ^2J = 13.8 Hz, C-1), 134.2 ($OCH_2CH{=}CH_2$), 133.1 (d, J = 9.6 Hz, o-C^{Ph}), 132.2–131.4 (m, p-C^{Ph}), 128.7 (d, ^3J = 11.8 Hz, m-C^{Ph}), 127.7 (d, ^1J = 89.6 Hz, $ipso$-C^{Ph}), 114.7 ($OCH_2CH{=}CH_2$), 61.6 ($OCH_2CH{=}CH_2$), 39.0 (d, ^1J = 169.0 Hz, C-2), 19.3 (d, ^2J = 11.7 Hz, C-3), 17.7 (C-4). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3057, 2948, 2920, 2861, 1625, 1599, 1483, 1437, 1362, 1312, 1267, 1178, 1100, 1089, 1060, 1028, 736, 714, 694, 576, 519. **HRMS** (ESI): m/z calcd. for $[C_{25}H_{26}O_2P]^+$: 389.1665; found: 389.1673.

Allyl (2*E*)-7-([[3,5-Bis(benzyloxy)phenyl]acetyl]oxy)-2-ethyl-6,6-dimethyloct-2-enoate ((±)-22).

According to a previously published procedure,[7] phosphonium ylide **21** (102 mg, 263 µmol, 1.00 eq.) was added to a solution of aldehyde (±)-**9** (83.5 mg, 175 µmol, 1.00 eq.) in dichloromethane (10 mL). The mixture was stirred at room temperature overnight. As conversion of aldehyde (±)-**9** was incomplete, further ylide **21** (14.6 mg, 37.5 µmol, 0.21 eq.) was added. Stirring was continued for 4 d at room temperature, then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc 20:1) yielding the unsaturated, (*E*)-configurated allyl ester as colourless oil (70.1 mg, 120 µmol, 67%). **R_f**: 0.59 (cyclohexane/EtOAc 3:1). **^{1}H-NMR, COSY** (600 MHz, $CDCl_3$): δ/ppm = 7.42–7.40 (m, 4H, o-H^{Bn}), 7.39–7.37 (m, 4H, m-H^{Bn}), 7.34–7.31 (m, 2H, p-H^{Bn}), 6.67 (t, 1H, J = 7.5 Hz, H-3), 6.55–6.54 (m, 2H, H-2'', H-6''), 6.53–6.52 (m, 1H, H-4''), 5.95 (ddt, 1H, J = 17.2, 10.5, 5.6 Hz, $OCH_2CH{=}CH_2$), 5.34–5.30 (m, 1H, $OCH_2CH{=}CH_2^E$), 5.23–5.21 (m, 1H, $OCH_2CH{=}CH_2^Z$), 5.02 (s, 4H, $PhCH_2$), 4.76 (q, 1H, J = 6.4 Hz, H-7), 4.62–4.61 (m, 2H, $OCH_2CH{=}CH_2$), 3.56–3.51 (m, 2H, H-2'), 2.29 (q, 2H, J = 7.5 Hz, 2-CH_2CH_3), 2.14–2.04 (m, 2H, H-4), 1.38–1.33 (m, 1H, H^A-5), 1.29–1.24 (m, 1H, H^B-5), 1.13 (d, 3H, J = 6.4 Hz, H-8), 1.00 (t, 3H, J =7.5 Hz, 2-CH_2CH_3), 0.87 (s, 6H, 2 x 6-CH_3). **^{13}C-NMR, HSQC, HMBC** (151 MHz, $CDCl_3$): δ/ppm = 170.8 (C-1'), 167.4 (C-1), 159.9 (C-3'', C-5''), 142.4 (C-3), 136.8 ($ipso$-C^{Bn}), 136.3 (C-1''), 133.7 (C-2), 132.5 ($OCH_2CH{=}CH_2$), 128.6 (m-C^{Bn}), 128.0 (p-C^{Bn}), 127.5 (o-C^{Bn}), 117.8 ($OCH_2CH{=}CH_2$), 108.4 (C-2'', C-6''), 100.8 (C-4''), 76.8 (C-7), 70.0 ($PhCH_2$), 65.0 ($OCH_2CH{=}CH_2$), 42.1 (C-2'), 37.7 (C-5), 36.7 (C-6), 23.0 (6-CH_3^A), 22.9 (C-4), 22.8 (6-CH_3^B), 20.0 (2-CH_2CH_3), 14.6 (C-8), 14.0 (2-CH_2CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3033, 2967, 2936, 2874, 1710, 1594, 1453, 1291, 1247, 1228, 1157, 1059, 989, 934, 833, 736, 698. **HRMS** (ESI): m/z calcd. for $[C_{37}H_{44}O_6Na]^+$: 607.3030; found: 607.3015.

(2*E*)-7-([[3,5-Bis(benzyloxy)phenyl]acetyl]oxy)-2-ethyl-6,6-trimethyloct-2-enoic acid.

According to a procedure by Kunz and März,[27] allyl ester (±)-**22** (363 mg, 629 µmol, 1.0 eq.), 1,3-dimethylbarbituric acid

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(116 mg, 743 µmol, 1.2 eq.), tetrakis(triphenylphosphine)-palladium(0) (37 mg, 32 µmol, 5.0 mol%) and triphenylphosphane (182 mg, 694 µmol, 1.1 eq.) were solved under argon in THF (35 mL) and stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 7:1 + 1% HOAc), yielding (2*E*)-7-([[3,5-Bis-(benzyloxy)phenyl]acetyl]oxy)-2-ethyl-6,6-trimethyloct-2-enic acid as colourless oil (327 mg, 616 µmol, 98%). **R$_f$**: 0.43 (cyclohexane/EtOAc 3:1 + 1% AcOH). **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): δ/ppm = 7.42–7.29 (m, 10H, H^{Bn}), 6.75 (t, 1H, *J* = 6.8 Hz, H-3), 6.55–6.53 (m, 3H, H-2'', H-4'', H-6''), 5.01 (s, 4H, PhCH_2), 4.76 (q, 1H, *J* = 6.4 Hz, H-7), 3.53 (s, 2H, H-2'), 2.27 (q, 2H, *J* = 7.5 Hz, 2-CH_2CH$_3$), 2.13–2.06 (m, 2H, H-4), 1.39–1.21 (m, 2H, H-5), 1.15 (d, 3H, *J* = 6.4 Hz, H-8), 1.00 (t, 3H, *J* = 7.5 Hz, 2-CH$_2$CH_3), 0.87 (s, 6H, 2 x 6-CH_3). **^{13}C-NMR, HSQC, HMBC** (101 MHz, $CDCl_3$): δ/ppm = 172.2 (C-1), 170.8 (C-1'), 160.0 (C-3'', C-5''), 144.8 (C-3), 136.8 (*ipso*-C^{Bn}), 136.3 (C-1''), 133.0 (C-2), 128.6 (*m*-C^{Bn}), 128.0 (*p*-C^{Bn}), 127.5 (*o*-C^{Bn}), 108.5 (C-2'', C-6''), 100.8 (C-4''), 76.7 (C-7), 70.0 (Ph*C*H$_2$), 42.1 (C-2'), 37.5 (C-5), 36.7 (C-6), 23.1 (C-4), 23.0 (6-*C*H$_3^A$), 22.8 (6-CH_3^B), 19.7 (2-*C*H$_2$CH$_3$), 14.6 (C-8), 13.9 (2-CH$_2$*C*H$_3$). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3064, 3033, 2967, 2935, 2874, 1723, 1681, 1594, 1452, 1377, 1292, 1256, 1151, 1058, 947, 833, 735, 697. **HRMS** (ESI): *m*/*z* calcd. for $[C_{34}H_{40}O_6Na]^+$: 567.2717; found: 567.2710.

5,7-Bis(benzyloxy)-4-dechloro-10-ethyl-14-methyl-14-deoxy-oxacyclododecindione ((±)-23).

According to procedures from Roberts et al.[9] and Opatz et al.,[7] five round bottom flasks were each equipped with dichloromethane (60 mL), trifluoroacetic acid (12 mL) and trifluoroacetic anhydride (6 mL) and precooled to –8 °C. To every flask, solutions of 53.4 mg (2*E*)-7-([[3,5-Bis(benzyloxy)-phenyl]acetyl]oxy)-2-ethyl-6,6-trimethyloct-2-enic acid (267 mg, 489 µmol in total) in dichloromethane (1 mL) were added and the flasks were left to stand at –8 °C for 4 d. The reaction mixtures were combined, cautiously neutralized by washing with saturated aqueous sodium bicarbonate (3 x 250 mL), washed with brine (250 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 10:1) yielding macrolactone (±)-**23** as colourless solid (203 mg, 385 µmol, 79%). **Mp**: 112–113 °C (cyclohexane/EtOAc). **R$_f$**: 0.58 (cyclohexane/EtOAc 3:1). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3OD): δ/ppm = 7.42–7.41 (m, 2H, H^{Bn}), 7.38–7.34 (m, 2H, H^{Bn}), 7.32–7.25 (m, 6H, H^{Bn}), 6.69–6.68 (m, 1H, H-6), 6.50–6.46 (m, 1H, H-4), 6.44–6.42 (m, 1H, H-11), 5.13–5.01 (m, 4H, PhCH_2), 4.51–4.46 (m, 1H, H-15), 3.37–3.33 (m, 1H, H^A-2), 3.21–3.19 (m, 1H, H^B-2), 2.69–2.58 (m, 1H, H^A-12), 2.52–2.47 (m, 1H, 10-CH_2^ACH$_3$), 2.38–2.35 (m, 1H, 10-CH_2^BCH$_3$), 2.27–2.18 (m, 1H, H^B-12), 1.85–1.81 (m, 1H, H^A-13), 1.42–1.40 (m, 1H, H^B-13), 1.02 (t, 3H, *J* = 7.5 Hz, 10-CH$_2$CH_3), 0.88–0.83 (m, 9H, 2 x 14-CH_3, 15-CH_3). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3OD): δ/ppm = 199.2 (C-9), 169.3 (C-1), 159.3 (C-5), 156.0 (C-11), 155.9 (C-7), 140.0 (C-10), 136.2 (*ipso*-C$^{5\text{-}Bn}$), 136.1 (*ipso*-C$^{7\text{-}Bn}$), 132.2 (C-3), 127.4 (*m*-C^{Bn}), 127.2 (*m*-C^{Bn}), 126.9 (*p*-C^{Bn}), 126.7 (*p*-C^{Bn}), 126.4 (*o*-C^{Bn}), 126.2 (*o*-C^{Bn}), 122.8 (C-8), 105.6 (C-4), 99.0 (C-6), 77.6 (C-15), 69.1 (5-O*C*H$_2$Ph), 68.9 (7-OCH$_2$Ph), 37.9 (C-2), 35.3 (C-14), 32.8 (C-13), 26.5 (14-*C*H$_3^A$), 24.8 (C-12), 22.9 (14-CH_3^B), 16.8 (10-*C*H$_2$CH$_3$), 12.4 (15-*C*H$_3$), 11.6 (10-CH$_2$*C*H$_3$). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3032, 2965, 2933, 2873, 1724, 1649, 1630, 1602, 1581, 1454, 1431, 1377, 1300, 1277, 1264, 1226, 1154, 1135, 1054, 838, 749, 696. **HRMS** (ESI): *m*/*z* calcd. for $[C_{34}H_{39}O_5]^+$: 527.2792; found: 527.2774.

4-Dechloro-10-ethyl-14-methyl-14-deoxy-oxacyclododecindione.

According to previously published procedures,[7] a solution of boron trichloride in dichloromethane (1 M, 3.70 mL, 3.70 mmol, 9.95 eq.) was added dropwise at –78 °C to a solution of macrolactone (±)-**23** (196 mg, 372 µmol, 1.00 eq.) in dichloromethane (80 mL). After 1 h, saturated aqueous sodium bicarbonate (50 mL) was added upon warming to room temperature. The aqueous layer was extracted with dichloromethane (4 x 20 mL) and the combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 4:1), yielding 4-Dechloro-10-ethyl-14-methyl-14-deoxyoxacyclododecindione as colourless oil (112 mg, 323 µmol, 87%). **R$_f$**: 0.18 (cyclohexane/EtOAc 2:1). **^{1}H-NMR, COSY** (300 MHz, CD_3OD): δ/ppm = 6.42–6.41 (m, 1H, H-11), 6.28–6.26 (m, 1H, H-4), 6.25–6.24 (m, 1H, H-6), 4.52 (q, 1H, *J* = 6.4 Hz, H-15), 3.32–3.19 (m, 2H, H-2), 2.51–2.36 (m, 4H, H-12, 10-CH_2CH$_3$), 1.94–1.84 (m, 1H, H^A-13), 1.51–1.43 (m, 1H, H^B-13), 1.10–1.04 (m, 6H, 10-CH$_2$CH_3, 15-CH_3), 0.91 (s, 6H, 2 x 14-CH_3). **^{13}C-NMR, HSQC, HMBC** (75.5 MHz, CD_3OD): δ/ppm = 200.4 (C-9), 170.0 (C-1), 158.3 (*C*OH), 154.8 (*C*OH), 153.2 (C-11), 140.7 (C-10), 132.8 (C-3), 118.5 (very broad, C-8), 106.6 (C-4), 100.4 (C-6), 77.7 (C-15), 38.1 (C-2), 35.4 (C-14), 34.6 (very broad, C-13), 24.6 (C-12), 24.1 (very broad, 2 x 14-*C*H$_3$) 17.5 (10-*C*H$_2$CH$_3$), 12.7 (15-*C*H$_3$), 11.6 (10-CH$_2$*C*H$_3$). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3356, 2967, 2933, 2875, 1729, 1701, 1614, 1593, 1451, 1251, 1156, 1067, 1025, 842, 735, 701, 643, 591. **HRMS** (ESI): *m*/*z* calcd. for $[C_{20}H_{27}O_5]^+$: 347.1853; found: 347.1854.

10-Ethyl-14-methyl-14-deoxyoxacyclododecindione ((±)-24).

According to a previously published procedure,[7] a solution of 4-Dechloro-10-ethyl-14-methyl-14-deoxyoxacyclododecindione (77.8 mg, 224 µmol, 1.0 eq.), *N*-chlorosuccinimide (29.4 mg, 225 µmol, 1.0 eq.) and trifluoroacetic acid (17 µL, 0.34 mmol, 1.5 eq.) in *N*,*N*-dimethylformamide (9 mL) was stirred for 8 d at room temperature under an argon atmosphere. More *N*-chlorosuccinimide (6.0 mg, 45 µmol, 0.2 eq.) was added and stirring was continued for 3 d. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc 3:1 + 1% HOAc) and subsequent preparative HPLC (C_{18}-PFP, MeCN/H_2O 40:60) yielding compound (±)-**24** as colourless oil (64.3 mg, 169 µmol, 75%). **R$_f$**: 0.08 (cyclohexane/EtOAc 4:1 + 1% HOAc). ***t$_R$*** (HPLC): 10.8 min (C_{18}-PFP, MeCN/H_2O 40:60). **^{1}H-NMR, COSY, NOESY** (600 MHz, CD_3CN): δ/ppm = 6.50 (s, 1H, H-6), 6.44 (s, 1H, H-11), 4.72 (q, 1H, *J* = 6.5 Hz, H-15), 3.50 (d, 1H, *J* = 16.7 Hz, H^A-2), 3.28–3.20 (m, 1H, H^B-2), 2.55–2.49 (m, 1H,

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H^A-12), 2.41–2.33 (m, 1H, 10-CH_2CH$_3$), 2.21–2.13 (m, 1H, H^B-12), 1.89–1.85 (m, 1H, H^A-13), 1.39–1.31 (m, 1H, H^B-13), 1.21–0.99 (m, 6H, 10-CH$_2$CH_3, 15-CH_3), 0.84 (s, 6H, a x 14-CH_3). **^{13}C-NMR, HSQC, HMBC** (151 MHz, CD_3CN): δ/ppm = 197.3 (C-9), 167.5 (C-1), 153.5 (C-11), 153.0 (C-5), 152.8 (C-7), 140.1 (C-10), 130.9 (C-3), 120.7 (C-8), 111.6 (C-4), 101.8 (C-6), 76.9 (C-15), 37.4 (C-2), 35.4 (C-14), 33.1 (C-13), 25.1 (14-CH_3^A), 24.9 (C-12), 24.3 (14-CH_3^B), 17.1 (10-CH$_2$CH$_3$), 13.4 (15-CH_3), 12.2 (10-CH$_2$CH_3). **IR** (ATR): $\tilde{\nu}$/cm^{-1} = 3338, 2968, 2935, 2875, 1727, 1612, 1436, 1340, 1303, 1236, 1177, 1141, 1065, 1016, 946, 843, 667, 590. **HRMS** (ESI, neg.): *m/z* calcd. for $[C_{20}H_{24}(^{35}Cl)O_5]^-$: 379.1318; found: 379.1321.

Conflicts of interest

There are no conflicts to declare.

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