Total Synthesis, Structural Reassignment, and Biological Evaluation of the Anti-Inflammatory Macrolactone 13-Hydroxy-14-deoxyoxacyclododecindione

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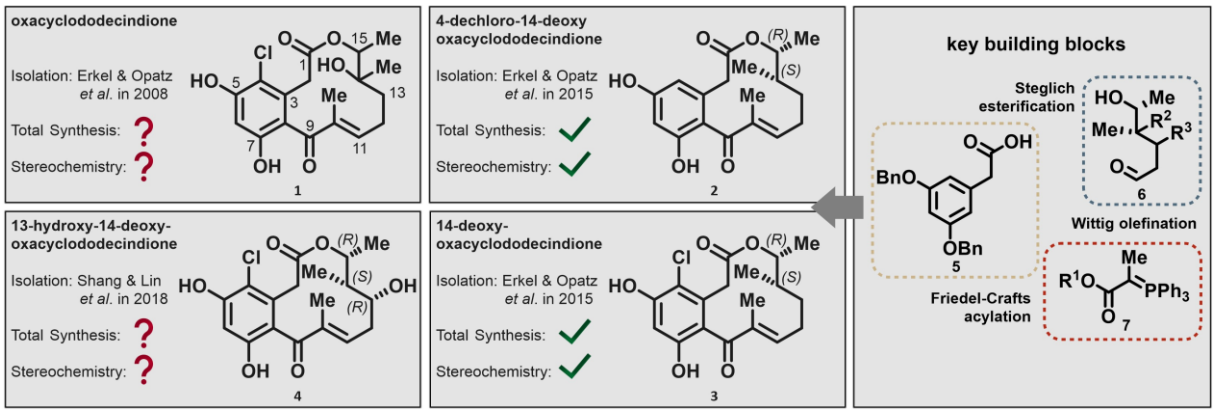
ABSTRACT: Herein, the first total synthesis of natural 13-hydroxy-14-deoxyoxacyclododecindione along with the revision of the proposed stereoconfiguration is reported. This natural product, initially discovered in 2018, belongs to the oxacyclododecindione family, renowned for their remarkable anti-inflammatory and antifibrotic activities. The synthetic route involves an esterification/Friedel-Crafts-acylation approach and uses various triol fragments. It allows the preparation of different stereoisomers, including the (revised) natural product, two *threo*-derivatives, and two *Z*-isomers of the endocyclic C=C-double bond. Furthermore, a late-stage inversion of the 13-hydroxy group could transform the originally proposed structure into the revised natural product. With this comprehensive set of compounds and the previously prepared (13*R*,14*S*,15*R*)-isomer, deeper insights into their structural properties and biological activities were obtained. A detailed analysis of the final macrolactones using spectroscopy (NMR, IR, UV-Vis) and X-ray crystallography gave new insights such as the significance of the optical rotation for the elucidation of their stereoconfiguration and the light induced *E*/*Z* double bond photoisomerization. The pharmacological potential of the compounds was underlined by remarkably low IC_{50} values in biological assays addressing the inhibition of cellular inflammatory responses.

INTRODUCTION

Macrocycles featuring a 12-membered lactone ring encompass a wide range of compounds encountered in nature.[1,2] A considerable number of these natural products exhibit promising bioactivities, such as antifungal,[3] antitumor,[4] or anti-inflammatory[5] properties, rendering the parent ring system a privileged scaffold in medicinal chemistry.[1,6] An interesting biologically active subclass defined by this structural motif is the oxacyclododecindione family. At present, this family comprises oxacyclododecindione (**1**),[7] 4-dechloro-14-deoxyoxacyclododecindione (**2**),[8] 14-deoxyoxacyclododecindione (**3**),[8] and the recently reported 13-hydroxy-14-deoxyoxacyclododecindione (**4**)[9] (Scheme 1). Isolated from the imperfect fungus *Exserohilum rostratum*, these secondary metabolites (**1**–**4**) exhibit remarkable anti-inflammatory and antifibrotic properties, positioning them as a promising starting point for the development of drugs against chronic inflammation and fibrotic diseases like asthma, rheumatoid arthritis, systemic lupus erythematosus (SLE) or neoplastic diseases.[7,9,10] Prior research on these 12-membered macrolactones, including total syntheses, derivatization studies, and the establishment of initial structure−activity relationships through bioassays has identified the enone moiety and the monochlorinated resorcinol backbone as crucial for their bioactivity, limiting the opportunities for modifications in these regions of the molecule.[11–14] To further investigate the potential of this compound family, current investigations consequently focus on the aliphatic backbone, to which molecular handles might be attached to facilitate the ongoing search for their biological target(s), which are still unknown at present. Our total synthesis of the proposed natural product **4**,[15] isolated in 2018 by Shang and Lin et al.,[9] revealed mismatching spectroscopic data and required a reassignment of the initially proposed stereoconfiguration.[15] Moreover, this synthesis led to a substantial increase in the aliphatic backbone's polarity due to the additional 13-OH moiety, a characteristic not observed in previously prepared macrolactones within this family.[12,14] This resulted in moderate to excellent IC_{50} values in the nanomolar range against TGF-β-dependent Smad2/3 and IL-4-

dependent STAT6 signalling pathways.[15] These results raised the question to what extent the configuration of this additional stereocenter impacts bioactivity. Furthermore, determination of the correct configuration of 13-hydroxy-14-deoxyoxacyclododecindione could provide insights into its biogenesis as well as into possible metabolization pathways. Due to the limited fermentation yields of the hydroxylated natural products oxacyclododecindione (**1**) and proposed 13-hydroxy-14-deoxyoxacyclododecindione (**4**), which severely impede further biological investigations, we herein present a total synthetic access to the natural product (13*S*,14*S*,15*R*,*E*)-13-hydroxy-14-deoxyoxacyclododecindione (**27**) and its derivatives **33**, **36**–**38**.

Scheme 1. Structures of all isolated members (**1**–**4**) within the oxacyclododecindione family, along with the remaining challenges to be solved. A general retrosynthetic approach to this class is illustrated, showing all three building blocks **5**–**7**.



RESULTS AND DISCUSSION

Considering all the research efforts directed towards establishing a strategy for the total synthesis of the oxacyclododecindiones, the key intramolecular Friedel-Crafts acylation (IFCA) at low substrate concentration proved to be the only successful approach for the preparation of the macrolactone core so far.[11,12,14,16] These harsh conditions may be required because of transannular hindrance imposed by the C-10 methyl group and the strain within the macrocyclic ring, which induce a perpendicular orientation of the arene and the enone moiety.

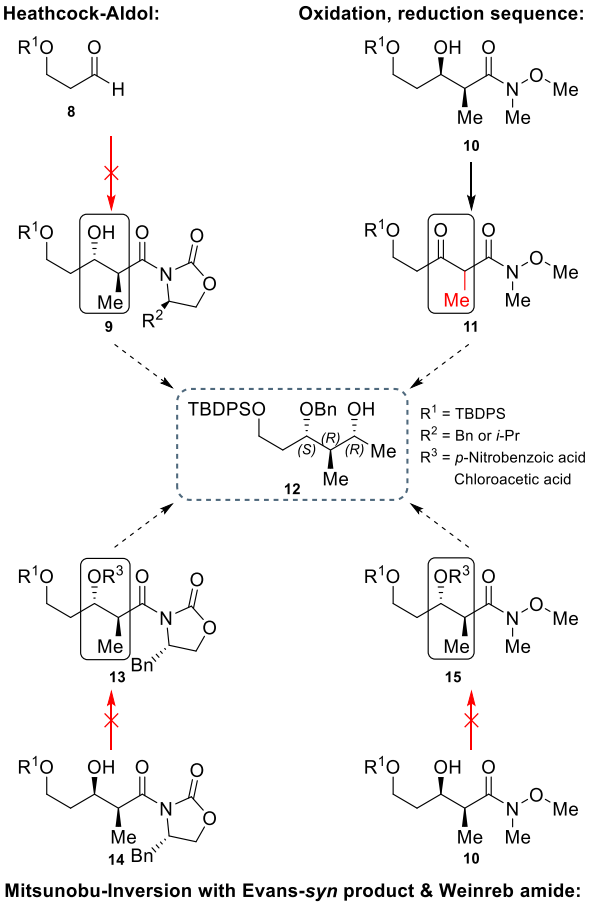
In our previous work on the total synthesis of the originally proposed (13*R*,14*S*,15*R*)-13-hydroxy-14-deoxyoxacyclododecindione (**4**), we applied this retrosynthetic approach using three building blocks **5**–**7**, producing a suitable precursor for the key IFCA by Steglich esterification and Wittig olefination.[15] As a probable alternative to the configuration proposed in 2018, the (13*R*,14*S*,15*S*)-arrangement could be consistent with the observed NOE contacts and the smaller scalar coupling constant of 4.8 Hz between H-14 and H-15.[9] However, we first decided to pursue the biosynthetically more plausible scenario, characterized by the *erythro*-arrangement of the methyl groups and an inverted hydroxy moiety, leading to a (13*S*,14*S*,15*R*)-configuration. This assumption is based on the characterized macrolactones **2** and **3** as potential biosynthetic precursors of our target molecule **27**.

The synthetic work commenced with the preparation of the building blocks **5**–**7**, with the triol system **12** being the only hitherto unknown component in this approach. In continuation of a previous study, where classical Evans conditions were employed for an Evans-*syn* orientation, various Heathcock aldol conditions using TBDPS-protected 3-hydroxypropanal **8** and two different Evans auxiliaries were initially investigated.[17–20] Instead of achieving the desired (non)-Evans-*anti* orientation **9**, we either observed no conversion or obtained the Evans-*syn* orientation **14** (Scheme 2).

Using the previously mentioned Evans-*syn* product **14** and its Weinreb amide **10**, one could also apply a known Mitsunobu reaction with different carboxylic acids to invert the alcohol.[21–

[23] However, the use of *p*-nitrobenzoic acid or chloroacetic acid produced the desired inverted esters in only minor quantities, with a maximum yield of <20% of the products **13** and **15**, and predominantly elimination product or unchanged starting material were isolated (Scheme 2). Following a known oxidation/reduction sequence[24,25] starting with a DMP oxidation of **10**, the desired β-keto amide **11** was produced, but it underwent epimerization through enolization, rendering it unsuitable for further conversion into the desired triol fragment **12** (Scheme 2).

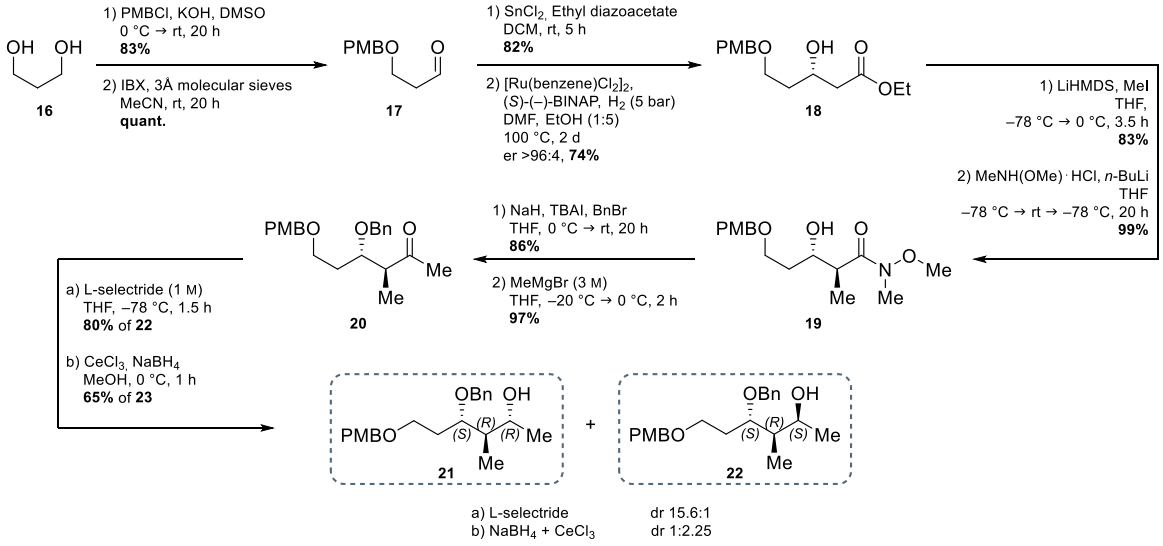
Scheme 2. Unsuccessful synthetic attempts for the key building block **12**, showing a (2*R*,3*R*,4*S*)-orientation. Starting from the known compounds **8**, **10** and **14**, the attempts included a Heathcock-aldol reaction (top left), an oxidation-reduction sequence (top right) or a Mitsunobu inversion (bottom).



Based on these results, a sequential introduction of the stereocenters into the C_6 carbon chain of the triol fragment **21** was envisioned. The sequence starting with preparation of the known enantioenriched β-hydroxy ester **18** from 1,3-propanediol (**16**) through PMB-monoprotection,[26] followed by oxidation with 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (IBX) to obtain aldehyde **17** (Scheme 3, for full stepwise details; see Supporting Information Scheme S1).[27] Subsequent Roskamp reaction with ethyl diazoacetate,[28] followed by an enantioselective Noyori hydrogenation of the corresponding β-keto ester, gave the known β-hydroxy ester **18** with an 93% *ee* in 50% yield over four steps.[28] The second stereocenter was introduced by an asymmetric Frater-Seebach alkylation using LiHMDS and iodomethane, which gave the *anti*-aldol product in 83% yield.[29] The planned acid-catalyzed *O*-benzylation using a previously established procedure proved unsuccessful with ethyl ester and its Weinreb amide **19**.[15] This was primarily attributed to the instability of the PMB group and the formation of various unidentified by-products in the presence of TfOH.[30] However, treatment of the previously prepared Weinreb amide **19**[31] with sodium hydride and benzyl iodide generated *in situ* furnished the protected secondary alcohol in an 86% yield.[32] Conversion to the desired ketone **20** was achieved by reaction with MeMgBr,[33] followed by diastereoselective reduction with L-selectride,[34] providing the appropriate alcohol **22** in 80% yield over two steps and with a diastereomeric ratio (dr) of >54:1 (determined by chiral HPLC using samples of both diastereomers) after flash chromatography. With this building block in hand, the macrolactone **27** is accessible. To gain further insights into the structural characteristics and biological activity of this compound family, the *threo* series was also of interest. The required building blocks **30** and **22** could either be obtained from previous studies[15] or should be synthesized in this study from the previously prepared β-benzyloxyketone **20**. Therefore, we initially focused on a chelation-controlled reduction using $Zn(BH_4)_2$ to achieve Cram chelate selectivity.[35,36] Unfortunately, only a low level of diastereoselectivity (1.14:1) in favor of the undesired diastereomer **21** was encountered. Luche conditions involving coordination with

$CeCl_3$[37,38] resulted in a dr of 2.25:1. Gratifyingly, the diastereomers could be separated by flash chromatography and the desired alcohol **22** could be obtained in 65% yield and an improved dr of >99:1 (determined by chiral HPLC using authentic standards). The relative configurations of **21** and **22** were determined by preparing their acetonides using a known procedure.[39] ^{13}C chemical shifts and NOE contacts of both isomers clearly identified the respective stereochemistry (Scheme S1).[39,40]

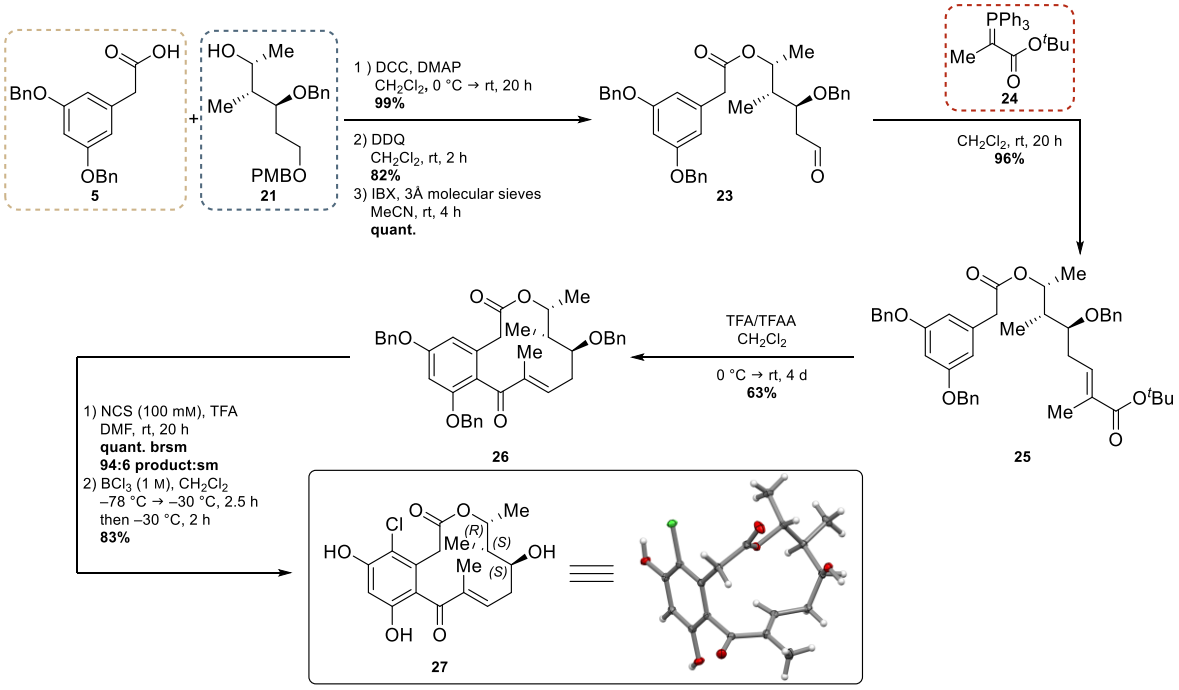
Scheme 3. Stereoselective synthesis of the triol fragments **21** and **22** as key building blocks in the total synthesis of 13-hydroxy-14-deoxyoxacyclododecindiones (**27** and **36**) – sequential introduction of the three stereogenic centers.



After obtaining building block **21**, Steglich esterification with 3,5-bis(benzyloxy)phenylacetic acid (**5**) (Scheme 4),[15] prepared using an established five-step sequence, resolved the first retrosynthetic disconnection.[41–44] To obtain a suitable precursor for the Wittig olefination (the second retrosynthetic disconnection), the ester was first converted to a primary alcohol through deprotection with DDQ[45] followed by IBX oxidation[27] to give the desired aldehyde **23** in a combined yield of 81% over three steps. Wittig olefination was carried out with ylide **24**, to give the *tert*-butyl ester **25** (96% yield) as a suitable Friedel-Crafts precursor, addressing the third retrosynthetic disconnection.[46] Treatment of the ester **25** under

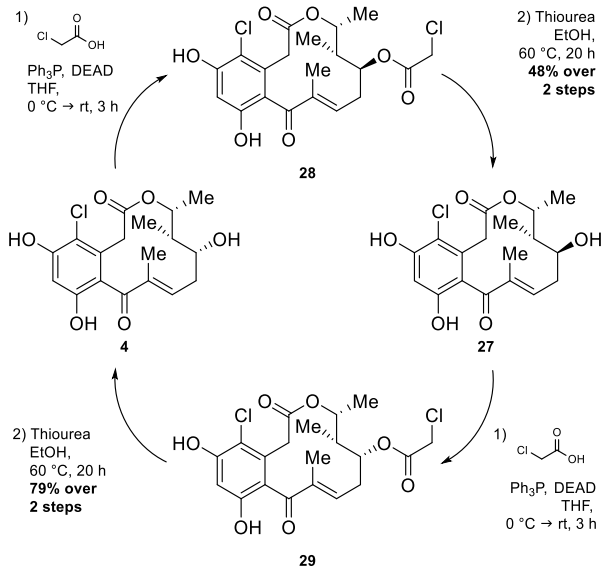
the optimized IFCA conditions provided the macrolactone **26** in a yield of 63%.[15] To complete the stereoselective synthesis of the macrolactone **27**, electrophilic chlorination with *N*-chlorosuccinimide, followed by final BCl_3-mediated debenzylation, was performed, resulting in a combined yield of 83% over two steps.[15] Following the successful synthesis in 16 linear steps with an overall yield of 11%, the target compound **27** was extensively characterized using spectroscopic methods and X-ray crystallography, unambiguously confirming the (13*S*,14*S*,15*R*)-configuration. Furthermore, a comparison of ^{1}H and ^{13}C NMR data (Table S1, Figure S141–144) revealed the consistency of the synthesized macrolactone **27** with the data of the natural product published in 2018.[9] Notably, the typical triangular NOE contacts within the oxacyclododecindione family, involving H-11, H-12b, and H-14, were observed, indicating the L-shaped molecular structure characteristic of the natural representatives of this compound class. These significant NOE contacts were however absent in the published original spectra of the natural product, presumably due to low concentration or insufficient recording time. Based on the obtained X-ray crystal structure (Flack parameter of +0.02(4)), the overall 3D-structure of the natural product **27** was found to be almost identical to the proposed structure **4**,[15] except for the orientation of the 13-hydroxy moiety. In addition to the aforementioned NMR data; IR, HRMS and optical rotation are in line with the data published in 2018, although the measured optical rotation of the synthesized macrolactone **27** showed a 2.5-fold higher value, possibly due to a contaminant in the sample of the isolated natural product.

Scheme 4. Assembly of all three synthons into ring-closure precursor **25**, followed by IFCA, chlorination and final deprotection, yielding the natural product (13*S*,14*S*,15*R*)-13-hydroxy-14-deoxyoxacyclododecindione (**27**), alongside the X-ray crystal structure of (+)-**27** represented as ORTEP ellipsoids (probability level of 50%).



Prior to the synthesis of the macrolactone **4** described above, an oxidation-reduction sequence was attempted to convert the (13*R*,14*S*,15*R*)-isomer - the proposed structure synthesized earlier - into the (13*S*,14*S*,15*R*)-isomer.[47] Remarkably, no reaction was observed under various oxidative conditions (IBX[15], DMP[48], NaOCl[49]). As an alternative, a late-stage Mitsunobu inversion might be able to convert the proposed macrolactone **4** into its revised structure **27**. Different P(III)-reagents (Ph_3P, *n*-Bu_3P, Me_3P) were tested in combination with diethyl azodicarboxylate (DEAD) and either *p*-nitrobenzoic acid or chloroacetic acid as the nucleophilic coupling partner.[50] To our delight, the combination of chloroacetic acid, DEAD and Ph_3P in THF proved successful,[51] while no conversion was observed with *p*-nitrobenzoic acid. The obtained ester **28** was cleaved with thiourea,[52] resulting in the inverted alcohol and thus the natural product **27** with 48% yield over two steps (Scheme 5). When the same sequence was applied to the natural product **27**, the inverted compound **4** was obtained in 79% yield over two steps (Scheme 5). Given these findings and the current knowledge that the 13-position is not the most important unit in the pharmacophore, the exploration of this position as a potential tool or anchor for the introduction of functional groups (e.g., necessary for target identification through “drug pulldown”) appears promising.

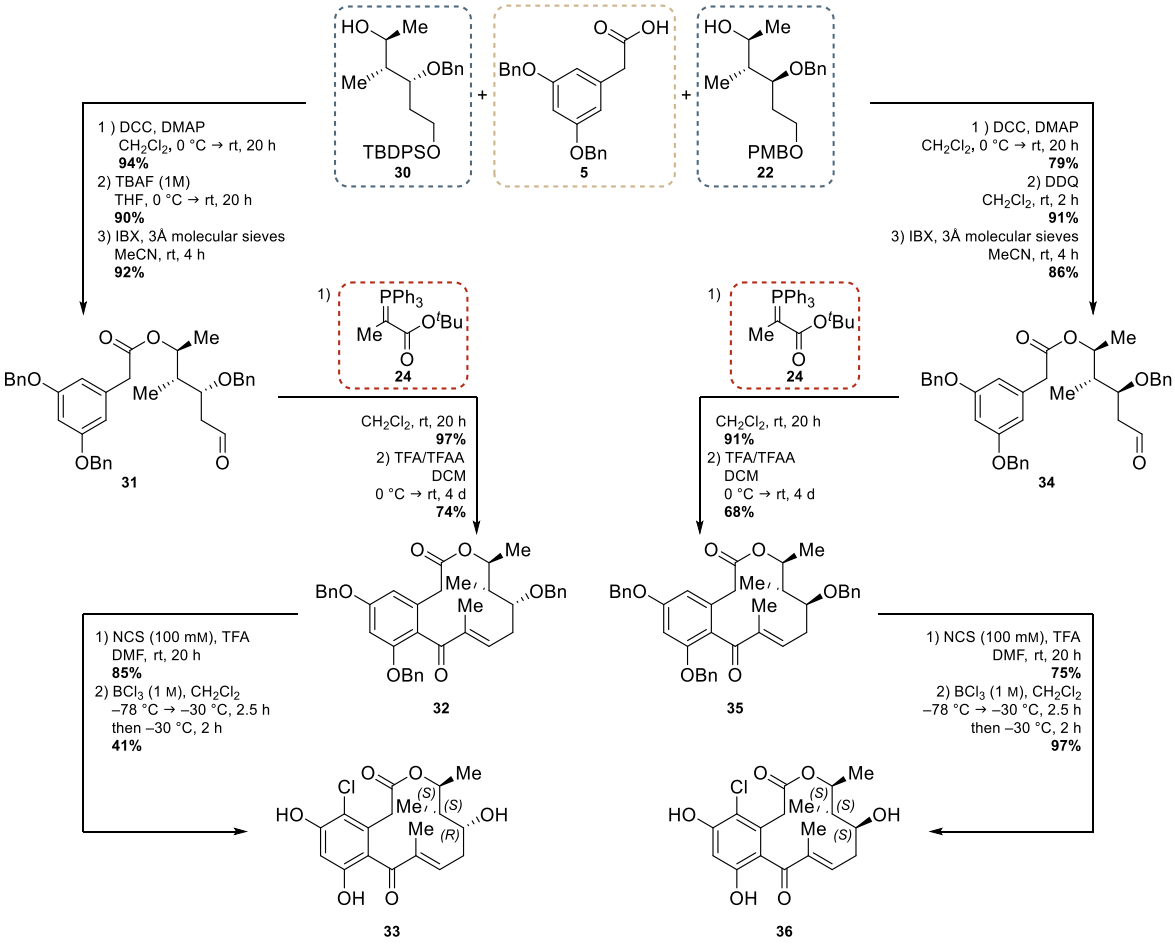
Scheme 5. Late-stage inversion of the 13-hydroxy moiety in a two-step sequence, employing Mitsunobu reaction and thiourea-mediated removal of the chloroacetyl group. Application is possible in both directions, commencing either from the proposed structure **4** or from the natural product **27**.



A notable advantage of the completed synthesis of the macrolactones **4** and **27**, exhibiting an *erythro*-arrangement in the aliphatic backbone, is the concurrent preparation of the two triol fragments **22** and **30** as precursors for the synthesis of the two remaining *threo*-diastereomers within the 13-hydroxy-14-deoxyoxacyclododecindione series. Employing the same synthetic pathway utilized for **27** (Scheme 4), the two triol fragments **30** and **22** were coupled with acid **5** in a Steglich esterification, followed by the removal of the TBDPS- and PMB-protecting groups using TBAF or DDQ. The aldehydes **31** and **34** were obtained by subsequent IBX-oxidation with yields of 78% and 62%, respectively, over three steps. The following Wittig olefination and the key IFCA proceeded smoothly over two steps with a total yield of 72% (**32**) and 62% (**35**), respectively. To conclude the synthesis of both *threo*-diastereomers **33** and **36**, electrophilic aromatic chlorination with *N*-chlorosuccinimide and BCl_3-mediated debenzylation was performed. A linear 14-step sequence led to the (13*R*,14*S*,15*S*)-isomer **33**

with an overall yield of 3%, while the (13*S*,14*S*,15*S*)-isomer **36** was obtained in 16 linear steps with an overall yield of 6% (Scheme 6). As a result, macrolactones featuring a *threo*-arrangement in the aliphatic backbone were obtained for the first time, completing the analytical and structural characterization of the series of 13-hydroxy-14-deoxyoxacyclododecindione diastereomers, which were evaluated for their biological activity. The attempted late-stage Mitsunobu inversion of the 13-COH position of both *threo*-isomers **33** and **36**, using the previously established conditions, proved unsuccessful instead.

Scheme 6. Total synthesis of (13*R*,14*S*,15*S*)- (**33**) and (13*S*,14*S*,15*S*)-13-hydroxy-14-deoxyoxacyclododecindione (**36**) by Steglich esterification, Wittig olefination, and IFCA.



Gratifyingly, an X-ray crystal structure (Flack parameter of +0.02(4)) of the *threo*-isomer **36** could be obtained, enabling a structural comparison of the *threo*- and *eryhtro*-diastereomers.

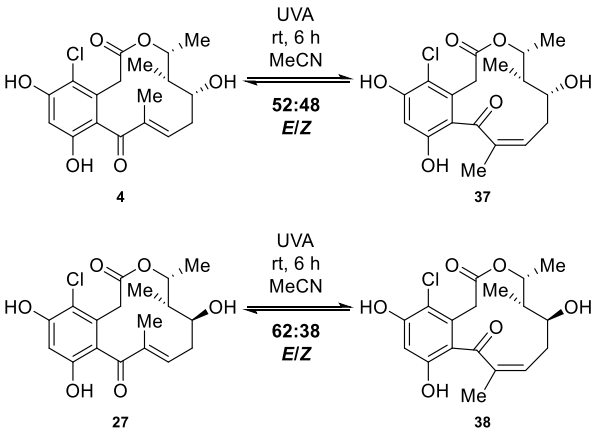
All compounds exhibit the typical L-shaped conformation, the (*Z*)-configured ester, and an almost perpendicular arrangement of the enone moiety to the aromatic system ($\Theta_{C7\text{-}C8\text{-}C9C\text{-}10}$ = 78.2°–89.7°). Furthermore, a comparison of all known X-ray crystal structures of this family revealed strikingly similar features,[13,15,53] apart from the C-12–C-14 aliphatic backbone region. These structural deviations in the aliphatic backbone also affected the UV-Vis measurements of the 13-hydroxy-14-deoxyoxacyclododecindione class. The spectra showed a hyperchromic and hypsochromic shift from ≈368 nm (*erythro*-isomers **4** and **27**) to ≈361 nm (*threo*-isomers **33** and **36**), allowing their differentiation (Scheme S156). We attributed this difference to a minor change in the properties of the arene-enone chromophore, induced by the *erythro*/*threo* substitution pattern. Moreover, this substitution pattern, particularly the configuration (*R* vs. *S*) at the 15-position, strongly influenced the aforementioned L-shaped orientation of the entire molecule. A (15*R*)-configuration caused the aliphatic backbone to point backward (compare Figure S160, resorcinol unit on the left hand side), while a (15*S*)-configuration induced a forward orientation of the aliphatic backbone (compare Figure S161, same orientation as above). This is reflected in opposite signs of the optical rotation, establishing the relationship between a (+)-(15*R*)- and a (–)-(15*S*)-configuration. A similar observation was reported by König *et al*. during the isolation of curvularin-type metabolites,[54] where the reversed sign of the optical rotation was attributed to a changed configuration at C-15. Consequently, a comparison of different curvularin-type macrolactones and members of the oxacyclododecindione family regarding the sign of their optical rotation and the C-15 configuration,[7–9,13,15,54–56] confirmed our hypothesis (compare Table S5).

Photoisomerization Study of the Oxacyclododecindione Family

Following the synthetic part and extending prior findings, a UV-light induced *E*/*Z*-photoisomerization was detected in all synthesized macrolactones of the 13-hydroxy-14-deoxyoxacyclododecindione series, prompting a more thorough investigation of the

phenomenon. Each macrolactone, namely **4**, **27**, **33**, and **36**, underwent isomerization (42 days bench storage) with a maximum *Z*-isomer content ranging from 32% to 44% in DMSO-d_6 at room temperature (compare Table S2). Attributing these observations to the photostationary state theory[57,58], we checked the thermal stability by heating the sample under light exclusion. No changes in the *E*/*Z*-isomer ratio were observed up to 90 °C, while higher temperatures led to the degradation of the macrolactones in each case. This confirms that the thermal reaction pathway does not influence the ratio and only the molar absorption coefficient of the substances would be of relevance. Based on the obtained UV-Vis spectra (see Figure S156–157), the behaviour of the *erythro*-*E*-isomers was investigated under various light sources (UV-A, UV-B, UV-C) in DMSO and MeCN. While all light sources led to the degradation of the macrolactones in MeCN, DMSO proved to be more suitable for the *E*/*Z*-isomerization. UV-A and UV-B irradiation over 1 d resulted in a slightly increased ratio up to 48% (**37**) and 38% (**38**) of the *Z*-isomers, compared to the 6-week daylight exposure of the compounds. UV-C irradiation caused the degradation of both macrolactones **4** and **27** instead. Based on these findings, the *E*/*Z*-isomerization was scaled up to obtain pure Z-isomers after 6 h of irradiation and separation by preparative HPLC from their corresponding *E*-isomers **37** and **38**, making them available for structural characterization and biological evaluation (Scheme 7).

Scheme 7. UVA-mediated *E*/*Z*-photoisomerization starting from the *erythro*-macrolactones **4** and **38** to obtain their *Z*-isomers **37** and **38** by subsequent HPLC purification. The given ratio was obtained after 6 h of irradiation (monitored by UV-DAD detection at 254 nm).



Based on NOE-contacts, we assume that the overall 3D-structure of the *Z*-isomers **37** and **38** closely resembles that of the *E*-isomers **4** and **27**, except for the NOE-triangle caused by the twisted C-10–C-11 double bond. Based on the recorded UV-Vis spectra, an *E*/*Z*-isomerization is assumed to occur via a π→π* or n→π* transition of the arene-enone chromophore. Additionally, these UV-absorption maxima exhibited a hypochromic shift from the *E*- to the *Z*-isomers in MeCN and DMSO, while a clear bathochromic shift was observed in DMSO, enabling the differentiation between the double bond isomers. However, the small difference in λ_{max} of ≈25 nm prevents separate excitation of the two isomers.

BIOLOGICAL EVALUATION

Macrolactones belonging to the oxacyclododecindione series exhibit significant inhibitory effects on TGF-β and IL-4 signaling pathways in mammalian cells. To assess their inhibitory potential, we investigated the impact on IL-4 inducible STAT6-dependent and TGF-β inducible Smad2/3-dependent transcriptional luciferase reporters in transiently transfected HepG2 cells (Table 1). Since its isolation, oxacyclododecindione (**1**) has demonstrated the best IC_{50} values with 68 nM (STAT6) and 136 nM (Smad2/3) among all isolated natural products. It was not until the synthesis of (14*S*,15*R*)-14-deoxyoxacyclododecindione (**3**) in 2015, which uncovered the most potent IL-4 inhibitor with an IC_{50} value of 20 nM. A subsequent structure-activity relationship study identified 14-deoxy-14-methyloxacyclododecindione as the most potent

inhibitor of the TGF-β-inducible Smad2/3-dependent pathway, demonstrating an IC_{50} of 30 nM. These findings position both compounds as promising candidates and as a reference for further investigation, with the synthesized natural product **3** excelling in IL-4 inhibition and the 14-deoxy-14-methyl derivative showing notable activity in the TGF-β pathway. The comparison between proposed structure **4** and its revised derivative **27** revealed excellent inhibitory activity on IL-4-induced SAT6 signaling with IC_{50} values ranging from 50 nM to 56 nM. This observation indicates the pathway's independence from the C-13 configuration, while emphasizing the advantageous influence of increased backbone polarity. In the TGF-β inducible Smad2/3 dependent pathway, the C-13 configuration emerged as crucial, with the natural product **27** demonstrating excellent inhibition (IC_{50} = 68 nM), compared to the moderate activity (IC_{50} = 236 nM) of the C-13 diastereomer. The evaluated *threo*-derivatives **33** and **36**, featuring an (–)-L-shaped core of the macrolactone, showed modest to moderate activity ranging from 1024 nM to 136 nM, indicating that the orientation and the *eryhtro*-arrangement are crucial for attaining excellent inhibitory activity. Similar to their *eryhtro*-stereoisomers, the (13*S*)-stereoisomers showed better activity. Nevertheless, the obtained results are in a comparable range to previously synthesized derivatives, which we attribute to the resorcinol moiety. Surprisingly, the *Z*-double bond isomers **37** and **38** exhibited favourable IC_{50} values (64 nM to 100 nM), with the (13*S*,14*S*,15*R*,*Z*)-configuration in a comparable range to its *E*-stereoisomer. Moreover, increased polarity played a crucial role in STAT6 reporter assays, while the C-13 configuration influenced the results of the TGF-β reporter assays. The herein synthesized natural product **27** combines the positive properties of the two most potent compound **3** and 14-deoxy-14-methyloxacyclododecindione, showing exceptional inhibitory activities in both reporter assays. As a result, it ranked second in both signaling pathways among all derivatives tested so far. These results provided new insights and indicated the importance of the (+)-L-shaped 3D-structure, the halogenated resorcinol backbone, the increased backbone

polarity and its configuration as major driving force behind the excellent activities in biological assays addressing the inhibition of cellular inflammatory responses.

Table 1. Effects of Natural and Synthetic 12-Membered Macrolactones in Two Relevant Reporter Gene Assays.[a]

	pGL3-TK-7xN$_4$ (STAT6) IC_{50} (nM)	(CAGA)$_{9x}$-MLP-Luc (Smad2/3) IC_{50} (nM)
Oxacyclododecindione[7] (isolated) (**1**)	68 ± 5	137 ± 14
(14*S*,15*R*)-14-Deoxyoxacyclododecindione[12] (synthetic) (**3**)	20 ± 1	90 ± 10
14-Deoxy-14-methyloxacyclododecindione[14] (synthetic)	79 ± 27	30 ± 11
(13*R*,14*S*,15*R*,*E*)-13-Hydroxy-14-deoxyoxacyclododecindione[15] (synthetic) (**4**)	56 ± 13	236 ± 28
(13*S*,14*S*,15*R*,*E*)-13-Hydroxy-14-deoxyoxacyclododecindione (synthetic) (**27**)	50 ± 6	68 ± 6
(13*R*,14*S*,15*S*,*E*)-13-Hydroxy-14-deoxyoxacyclododecindione (synthetic) (**33**)	1024 ± 73	239 ± 8
(13S,14*S*,15*S*,*E*)-13-Hydroxy-14-deoxyoxacyclododecindione (synthetic) (**36**)	198 ± 16	136 ± 12
(13*R*,14*S*,15*R*,*Z*)-13-Hydroxy-14-deoxyoxacyclododecindione (synthetic) (**37**)	72 ± 9	100 ± 13
(13*S*,14*S*,15*R*,*Z*)-13-Hydroxy-14-deoxyoxacyclododecindione (synthetic) (**38**)	64 ± 4	68 ± 5

[a]As internal normalization control and to exclude cytotoxic effects, the EF1α promotor in front of a renilla luciferase was co-electroporated into the HepG2 cells. All values are described as mean from three independent replicates ± SEM.

CONCLUSION

In summary, the total synthesis of the natural product 13-hydroxy-14-deoxyoxacyclododecindione, reported in 2018, is presented along with the stereochemical reassignment of its aliphatic backbone which proved to have the (13*S*,14*S*,15*R*) configuration.

A late stage-inversion of the 13-position in the *eryhtro*-macrolactones **4** and **27** via a Mitsunobu reaction proved feasible, providing a potential handle aiding target identification. Additionally, the concurrently prepared triol fragments **22** and **30** were utilized to synthesize the *threo*-macrolatones **33** and **36**, completing the series of diastereomers of 13-hydroxy-14-deoxyoxacyclododecindione. Regardless of the aliphatic backbone configuration, all isomers exhibited the characteristic features of an L-shaped conformation, the (*Z*)-configured ester, and the enone unit being almost perpendicular to the aromatic moiety according to NOE data and crystal structures. Notably, a comparison within this family underscored the significance of optical rotation in determining the C-15 configuration. In continuation of previous findings, UV light induced *E*/*Z*-photoisomerization were found in all oxacyclododecinedione-type macrolactones investigated so far, leading to a more thorough study including long-term photochemical and attempted thermal isomerization, UV-Vis analysis and the synthesis of the *eryhtro*-*Z*-isomers **37** and **38** for their structural analysis and biological evaluation. All five synthesized macrolactones **4**, **27**, **33**, and **36**–**38** were shown to be potent inhibitors of IL-4-dependent STAT6 and TGF-β-dependent Smad2/3 signaling pathways with IC_{50} values in the nanomolar range.

EXPERIMENTAL SECTION

General Experimental Procedures

Optical rotation measurements were accomplished with a Perkin-Elmer 241MC polarimeter at λ = 589 nm. The instrument was blanked with the solvent used prior to the measurement. UV-Vis absorption spectra were recorded on a Thermo Scientific Evolution 201 UV-Visible Spectrophotometer using a quartz cuvette with a layer thickness of 10 mm. Infrared (IR) spectroscopy was performed on a Bruker Tensor 27 FT-IR spectrometer including a diamond ATR unit. Measured NMR spectra were, unless otherwise mentioned, recorded at 296 K on a 300 MHz Bruker Avance-III HD 300, a 400 MHz Bruker Avance-II HD 300, a 400 MHz Bruker Avance-II HD 400 or 600 MHz Bruker Avance-III 600 spectrometer. After prior referencing to the residual solvent signal ($CDCl_3$: 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 ^1H NMR and ^{13}C NMR, respectively), all chemical shifts (δ) are reported relative to residual solvent.[59] Low resolution electron spray ionization (ESI) mass spectra were measured on a InfinityLab LC/MSD (G6125B) spectrometer. HRMS was conducted on an Agilent G6545A Q-ToF with ESI, APCI or APPI source coupled with an Agilent 1260 Infinity II HPLC system. If not describe otherwise, spectra were recorded using positive ionization mode. For reaction control by analytical thin-layer chromatography (TLC), 0.25 mm silica plates ($60F_{254}$) from Merck were used and the detection was reached by fluorescence quenching under UV-light (λ = 254 nm) or by staining with potassium permanganate reagent (solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), 5% NaOH (5 mL) and H_2O (300 mL)) followed by heating at 400 °C. Preparative column chromatography was performed on silica gel (35–70 µm, Acros Organics) using an overpressure of 0.5–0.6 bar nitrogen. The composition of the mobile phase was given as v/v. For reaction control by HPLC/MS, an Agilent Technologies 1260 Infinity II system including an Ascentis® Express C18-column (particle size: 2.7 µm, length: 30 mm, diameter: 2.1 mm, column temperature: 40 °C) with a binary pump and UV-DAD detection and an ESI

quadrupole mass spectrometer (model: G6125B, Agilent InifinityLab LC/MSD Series) was used. Mixtures of solvents A: H2O (LCMS grade and Milli-Q) + 0.1% formic acid (LCMS grade) and B: MeCN (HPLC and LCMS grade) served as eluents with a flow rate of 0.70 mL/min and a gradient of 10:90 to 90:10. For analytical HPLC separation, an Agilent Technologies 1260 Infinity II system including a Macherey-Nagel (MN) Nucleodur C_{18}-HTEC-column (particle size: 5 µm, length: 150 mm, diameter: 4.6 mm, column temperature: 40 °C, flow rate: 1 mL/min), Avantor ACE3-C_{18}-PFP-column (particle size: 3 µm, length: 150 mm, diameter: 4.6 mm, column temperature: 40 °C, flow rate: 1 mL/min) or a MN Nucleodur PFP-column (particle size: 5 µm, length: 150 mm, diameter: 4.6 mm, column temperature: 40 °C, flow rate: 1 mL/min) with UV-DAD detection was used. Preparative HPLC was performed on an Agilent Technologies 1290 Infinity II system with two high-pressure gradient K-1800 pumps and an S-260-UV-DAD detector. The separation took place on ACE 5 C_{18}-PFP (particle size: 5 µm, length: 150 mm, diameter: 30 mm, flow rate: 42.5 mL/min), Macherey-Nagel Nucleodur PFP (particle size: 5 µm, length: 150 mm, diameter: 32 mm, flow rate: 42.5 mL/min) or Macherey-Nagel Nucleodur C_{18}-HTEC (particle size: 5 µm, length: 150 mm, diameter: 32 mm, flow rate: 42.5 mL/min) columns. For both analytical and preparative HPLC, the eluent mixtures of solvents A: H_2O (LCMS grade & Milli-Q) + 0.1% formic acid (LCMS grade) and B: MeCN (HPLC & LCMS grade) were given in the v/v-ratio. X-ray crystallographic measurements were performed on a Stoe IPDS-2T with Mo-K_α radiation (graphite monochromator). Unless otherwise stated, all chemicals and solvents were obtained from commercial sources and used without prior purification. Chloroform and triethylamine were distilled over $CaCl_2$ before use. Anhydrous cyclohexane was obtained by distillation over sodium, using benzophenone as an indicator. MeCN, tetrahydrofuran (THF), CH_2Cl_2, diethyl ether and toluene were dried with an MBraun solvent purification system 5. Dimethyl sulfoxide, *N*,*N*-dimethylformamide, MeOH and EtOH were purchased from commercial suppliers as extra dry solvents stored over 3 Å molecular sieves and used without additional purification. 1-

Hydroxy-1,2-benziodoxol-3(*1H*)-one-1-oxide (IBX) was prepared according to the literature known synthesis of Henderson et al.[60] All reactions were performed under a nitrogen or argon atmosphere using Schlenk techniques and flame-dried glassware at ambient pressure. Reaction temperatures of –78 °C were achieved using a dry ice/acetone cooling bath. When a temperature gradient in the range of –78 °C to room temperature was required, a cryostat (Julabo FT902) was used. All *E*/*Z*-isomerization experiments using UV-light were performed in a Rayonet photoreactor (RPR 100, Southern New England Ultraviolet Company) with 8/16 circularly arranged lamps (UVA: Philips TL 8W BLB 1FM/10X25CC, 8.0 W, λ_{max} = 360 nm; UVB: Ushio G8T5E, 8.0 W, λ_{max} = 306 nm; UVC: Philips TUV 8W G8 T5 FAM/10X25BOX, 8.0 W, λ_{max} = 250 nm) equipped with a magnetic stirrer and internal cooling fan.

3-((4-Methoxybenzyl)oxy)propan-1-ol (**39**)

According to a previously published procedure,[26] 1,3-propanediol (**16**, 7.15 mL, 98.7 mmol, 2.50 equiv) was dissolved in anhydrous DMSO (26 mL) and ground KOH (5.54 g, 98.7 mmol, 2.50 equiv) was added portion-wise at 0 °C. After the suspension turned clear again, PMBCl (5.35 mL, 39.5 mmol, 1.00 eqiuv) was added to the ice cooled solution and the reaction mixture was allowed to warm to rt overnight. After the TLC showed full conversion of the starting material, the reaction mixture was diluted diethyl ether (200 mL) and carefully quenched with 2M HCl at 0 °C. The organic layer was separated and the aqueous layers was washed with diethyl ether (3 x 50 mL). The combined organic extracts were dried, filtered ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by column chromatography (cyclohexane/EtOAc, 3:1) furnishing PMB-ether **39** as a colorless oil (6.43 g, 32.7 mmol, 83%). R_f 0.14 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3385, 2936, 2861, 1613, 1586, 1513, 1462, 1365, 1302, 1247, 1175, 1088, 1034, 820, 572, 513. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.28–7.21 (m, 2H, 2 x *o*-CH_{PMB}), 6.90–6.84 (m, 2H, 2 x *m*-CH_{PMB}), 4.45 (s, 2H, C$H_{2\ PMB}$), 3.81 (s, 3H, OC$H_{3\ PMB}$), 3.78 (t, J = 5.7 Hz, 2H, 3-CH_2), 3.68 (t, J = 5.7 Hz, 2H, 1-CH_2), 2.01 (s_{br}, 1H, 1-CO*H*), 1.85 (p, J = 5.7 Hz, 2H, 2-CH_2). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 159.4 (1C, *p*-C_{PMB}), 130.3 (1C, *ipso*-C_{PMB}), 129.4 (2C, 2 x *o*-CH_{PMB}), 114.0 (2C, 2 x *m*-CH_{PMB}), 73.1 (1C, $CH_{2\ PMB}$), 69.3 (1C, 1-CH_2), 62.2 (1C, 3-CH_2), 55.4 (1C, $OCH_{3\ PMB}$), 32.2 (1C, 2-CH_2). HRESIMS *m/z* 235.0724 $[M+K]^+$ (calcd for $C_{11}H_{16}O_3K$, 235.0731). The analytical data are in accordance with the literature.

3-((4-Methoxybenzyl)oxy)propanal **(17)**

Using a modified procedure of Pannecoucke et al.,[27] monoprotected alcohol **39** (4.00 g, 20.4 mmol, 1.00 eq) was dissolved in dry MeCN (350 mL), IBX (10.3 g, 36.7 mmol, 1.80 eq) was added, and the reaction mixture was stirred over preactivated 3 Å molecular sieves (7.00 g). After 24 h the TLC showed full conversion and the reaction mixture was filtered through a pad

of Celite and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc, 3:1) furnishing the aldehyde **17** (3.97 g, 20.4 mmol, 100%) as a yellowish-green oil which was used immediately for the next reaction. R_f 0.45 (cyclohexane/EtOAc, 2:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2957, 2901, 2860, 2838, 2731, 1723, 1613, 1586, 1513, 1464, 1443, 1395, 1362, 1302, 1246, 1210, 1175, 1091, 1033, 819, 756, 572, 517. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 9.78 (t, J = 1.9 Hz, 1H, 1-C*H*O), 7.28–7.21 (m, 2H, 2 x *o*-CH_{PMB}), 6.91–6.84 (m, 2H, 2 x *m*-CH_{PMB}), 4.46 (s, 2H, C$H_{2\ PMB}$), 3.80 (s, 3H, OC$H_{3\ PMB}$), 3.78 (t, J = 6.1 Hz, 2H, 3-CH_2), 2.68 (td, J = 6.1, 1.9 Hz, 2H, 2-CH_2). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 201.4 (1C, 1-*C*HO), 159.5 (1C, *p*-C_{PMB}), 130.1 (1C, *ipso*-C_{PMB}), 129.5 (2C, 2 x *o*-CH_{PMB}), 114.0 (2C, 2 x *m*-CH_{PMB}), 73.1 (1C, $CH_{2\ PMB}$), 63.7 (1C, 3-CH_2), 55.4 (1C, O$CH_{3\ PMB}$), 44.0 (1C, 2-CH_2). HRESIMS *m/z* 217.0839 $[M+Na]^+$ (calcd for $C_{11}H_{14}O_3Na$, 217.0835). The analytical data are in accordance with the literature.

Ethyl 5-((4-methoxybenzyl)oxy)-3-oxopentanoate (**40**)

The Roskamp reaction was performed according to a procedure by Anderson et al. [28] To a stirred solution of $SnCl_2$ (271 mg, 1.43 mmol, 0.23 equiv.) in CH_2Cl_2 (23 mL) was added ethyl diazoacetate (10.9 g, 14.3 mmol, 1.20 eq) at rt. The aldehyde **17** (2.31 g, 11.9 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (12 mL) and added carefully in a dropwise fashion over a period of 15 min. The solution was stirred until the nitrogen evolution had stopped (6 h). The mixture was transferred to a separating funnel, diluted with diethyl ether (200 mL) and extracted with brine (100 mL). The organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Finally, purification by flash chromatography (cyclohexane/EtOAc, 5:1) yielded the desired β-ketoester **40** (2.75 g, 9.80 mmol, 82%) as a colorless oil. R_f 0.21 (cyclohexane/EtOAc, 5:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2981, 2937, 2905, 2870, 2839, 1741, 1715, 1613, 1586, 1513, 1465, 1445, 1409, 1367, 1303, 1246, 1211, 1174, 1152,

1096, 1032, 937, 820, 758, 570, 518. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 7.27–7.17 (m, 2H, 2 x *o*-C*H*$_{PMB}$), 6.94–6.85 (m, 2H, 2 x *m*-C*H*$_{PMB}$), 4.36 (s, 2H, C*H*$_{2\ PMB}$), 4.08 (q, J = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.74 (s, 3H, OC*H*$_{3\ PMB}$), 3.63–3.55 (m, 4H, 2-C*H*$_2$, 5-C*H*$_2$), 2.76 (t, J = 6.2 Hz, 2H, 4-C*H*$_2$), 1.17 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 202.2 (1C, 3-*C*O), 167.2 (1C, 1-*C*OO), 158.7 (1C, *p*-*C*$_{PMB}$), 130.2 (1C, *ipso*-*C*$_{PMB}$), 129.2 (2C, 2 x *o*-*C*H$_{PMB}$), 113.6 (2C, 2 x *m*-*C*H$_{PMB}$), 71.7 (1C, *C*H$_{2\ PMB}$), 64.1 (1C, 5-*C*H$_2$), 60.5 (1C, O*C*H$_2$CH$_3$), 55.1 (1C, O*C*H$_{3\ PMB}$), 49.0 (1C, 2-*C*H$_2$), 42.6 (1C, 4-*C*H$_2$), 14.0 (1C, OCH$_2$*C*H$_3$). HRESIMS *m*/*z* 281.1379 $[M+H]^+$ (calcd for $C_{15}H_{20}O_5H$, 281.1384). The analytical data are in accordance with the literature.

Ethyl (2*S*,3*S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-pentanoate (**18**)

Following a modified procedure of Anderson et al.,[28] benzene ruthenium(II) chloride dimer (22.3 mg, 44.6 µL, 0.5 mol%) and (S)-(–)-BINAP (55.5 mg, 89.2 mmol, 0.1 eqiuv) were placed in a Schlenk tube and dissolved in dry, degassed DMF (1.50 mL), before the mixture was heated to 90 °C over 30 min. The reddish-brown solution was allowed to cool to rt. Simultaneously, the β-ketoester **40** (2.50 g, 8.92 mmol, 1.00 equiv) was dissolved in dry, degassed EtOH (5.00 mL) and the previously prepared active catalyst was added via syringe to the starting material. The flask was transferred to an autoclave, which was then flushed three times with hydrogen before being pressurized with 5 bar of hydrogen and the solution was stirred at 100 °C for 24 h. After the solution reached rt, the solvent was removed in vacuo. Purification of the crude product by flash chromatography (cyclohexane/EtOAc, 5:1) yielded the β-hydroxy ester **18** (1.87 g, 6.63 mmol, 74%) as a yellow oil. $[\alpha]_D^{22}$ +7.8 (*c* 1.00, $CHCl_3$). R_f 0.26 (cyclohexane/EtOAc, 2:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3484, 2979, 2939, 2916, 2867, 1731, 1613, 1586, 1513, 1464, 1444, 1420, 1371, 1301, 1247, 1209, 1174, 1094, 1033, 945, 820, 618, 593, 523. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.28–7.21 (m, 2H, 2 x *o*-C*H*$_{PMB}$), 6.91–6.83 (m, 2H, 2 x *m*-C*H*$_{PMB}$), 4.44 (s, 2H, C*H*$_{2\ PMB}$), 4.23 (dtd, J = 7.8, 6.3, 4.4 Hz, 1H, 3-C*H*), 4.16 (q, J

= 7.1 Hz, 2H, OCH_2CH$_3$), 3.80 (s, 3H, OC$H_{3\ PMB}$), 3.71–3.57 (m, 2H, 5-CH_2), 3.07 (s_{br}, 1H, 3-CO*H*), 2.48 (d, *J* = 6.3 Hz, 2H, 2-CH_2), 1.86–1.71 (m, 2H, 4-CH_2), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, CDCl$_3$) δ_C 172.6 (1C, 1-*C*OO), 159.4 (1C, *p*-C_{PMB}), 130.2 (1C, *ipso*-C_{PMB}), 129.5 (2C, 2 x *o*-CH_{PMB}), 114.0 (2C, 2 x *m*-CH_{PMB}), 73.1 (1C, $CH_{2\ PMB}$), 67.8 (1C, 5-*C*H$_2$), 67.2 (1C, 3-*C*H), 60.7 (1C, O*C*H$_2$CH$_3$), 55.4 (1C, O*C*H$_{3\ PMB}$), 41.7 (1C, 2-*C*H$_2$), 36.1 (1C, 4-*C*H$_2$), 14.3 (1C, OCH$_2$*C*H$_3$). HRESIMS *m*/*z* 305.1356 [M+Na]$^+$ (calcd for $C_{15}H_{22}O_5Na$, 305.1359).

Ethyl (2*S*,3*S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2-methylpentanoate (**41**)

Based on a literature procedure by Rychnovsky et al.,[29] to a solution of LiHMDS (1M in THF, 31.6 mL, 31.6 mmol, 2.30 equiv) in THF (93.4 mL) was added the ester **18** (3.88 g, 13.7 mmol, 1.0 equiv) in THF (21.8 mL) at –78 °C over a period of 20 min. For complete deprotonation, the solution was transferred to an ice bath and stirred for a further 90 min. MeI (1.97 mL, 31.6 mmol, 2.30 equiv) was added at the same temperature and after 2 h the mixture was quenched with 1M $NaHSO_4$-solution (50 mL). After extraction with EtOAc (3 x 100 mL) the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, concentrated and the crude product was purified by flash chromatography (cyclohexane/EtOAc, 5:1 to 3:1). The alkylated ester **41** (3.37 g, 11.4 mmol, 83%) was obtained as a colorless oil. $[\alpha]_D^{22}$ +9.3 (*c* 0.91, CHCl$_3$). R_f 0.22 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3511, 2979, 2940, 2912, 2861, 2839, 1730, 1613, 1586, 1513, 1463, 1421, 1371, 1345, 1302, 1248, 1179, 1142, 1094, 1035, 958, 845, 821, 758, 580, 517. ^{1}H NMR, COSY (400 MHz, CDCl$_3$) δ_H 7.28–7.20 (m, 2H, 2 x *o*-CH_{PMB}), 6.91–6.83 (m, 2H, 2 x *m*-CH_{PMB}), 4.45 (s, 2H, $CH_{2\ PMB}$), 4.16 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.91 (ddd, *J* = 9.5, 6.7, 2.9 Hz, 1H, 3-C*H*), 3.80 (s, 3H, OC$H_{3\ PMB}$), 3.73–3.58 (m, 2H, 5-CH_2), 2.53 (p, *J* = 7.2 Hz, 1H, 2-C*H*), 1.87–1.66 (m, 2H, 4-CH_2), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.19 (d, *J* = 7.2 Hz, 3H, 2-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, CDCl$_3$) δ_C 175.8 (1C, 1-*C*OO), 159.4 (1C, *p*-C_{PMB}), 130.2 (1C, *ipso*-C_{PMB}), 129.5 (2C, 2 x *o*-CH_{PMB}), 114.0

(2C, 2 x *m*-CH_{PMB}), 73.1 (1C, $CH_{2\ PMB}$), 72.5 (1C, 3-*C*H), 68.3 (1C, 5-CH_2), 60.6 (1C, OCH_2CH_3), 55.4 (1C, O$CH_{3\ PMB}$), 45.7 (1C, 2-*C*H), 34.0 (1C, 4-CH_2), 14.4 (1C, OCH_2CH_3), 13.9 (1C, 2-CH_3). HRESIMS *m*/*z* 319.1519 $[M+Na]^+$ (calcd for $C_{16}H_{24}O_5Na$, 319.1516).

(2*S*,3*S*)-3-Hydroxy-*N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*,2-dimethylpentanamide (**19**)

According to a procedure from Phansavath et al.,[31] *N*,*O*-dimethylhydroxylamine hydrochloride (3.95 g, 39.7 mmol, 3.50 eq) was dissolved under an argon atmosphere in THF (74 mL) and *n*-BuLi (2.5 M in hexane, 32.0 mL, 79.4 mmol, 6.00 eq) was added dropwise over 10 min at –78 °C. The solution was warmed to rt and stirred for 10 min before being cooled back to –78 °C and the ester **41** (3.92 g, 13.2 mmol, 1.00 eq) in THF (24 mL) was added over a period of 25 min. After 2 h, the reaction was quenched with saturated NH_4Cl-solution (100 mL) and extracted with EtOAc (3 x 130 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 2:1 to 1:1.5). The methyl ester **19** (4.09 g, 13.1 mmol, 99%) was obtained as a colorless oil. $[\alpha]_D^{22}$ +11.9 (*c* 0.74, $CHCl_3$). R_f 0.23 (cyclohexane/EtOAc, 1:3). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3436, 2937, 2859, 1634, 1614, 1586, 1513, 1462, 1443, 1421, 1388, 1302, 1247, 1176, 1147, 1095, 1034, 993, 951, 821. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.27–7.21 (m, 2H, 2 x *o*-CH_{PMB}), 6.89–6.83 (m, 2H, 2 x *m*-CH_{PMB}), 4.46 (d, *J* = 11.5 Hz, 1H, $CH_{2\text{-A PMB}}$), 4.42 (d, *J* = 11.5 Hz, 1H, $CH_{2\text{-B PMB}}$), 3.87 (ddd, *J* = 9.2, 5.9, 3.0 Hz, 1H, 3-C*H*), 3.80 (s, 3H, O$CH_{3\ PMB}$), 3.73–3.59 (m, 2H, 5-CH_2), 3.68 (s, 3H, NOCH_3), 3.19 (s, 3H, NCH_3), 3.02–2.88 (m, 1H, 2-C*H*), 2.87–2.56 (m, 1H, 3-O*H*), 1.88–1.66 (m, 2H, 4-CH_2), 1.19 (d, *J* = 7.1 Hz, 3H, 2-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 177.3 (1C, 1-*C*ON), 159.4 (1C, *p*-C_{PMB}), 130.4 (1C, *ipso*-C_{PMB}), 129.5 (2C, 2 x *o*-CH_{PMB}), 114.0 (2C, 2 x *m*-CH_{PMB}), 73.1 (1C, $CH_{2\ PMB}$), 72.5 (1C, 3-*C*H), 68.2 (1C, 5-CH_2), 61.7 (1C, NOCH_3), 55.4 (1C, O$CH_{3\ PMB}$), 40.4 (1C, 2-*C*H), 35.1 (1C, 4-CH_2), 32.0 (1C, NCH_3), 14.8 (1C, 2-CH_3). HRESIMS *m*/*z* 334.1623 $[M+Na]^+$ (calcd for $C_{16}H_{25}NO_5Na$, 334.1625).

(2*S*,3*S*)-3-(Benzyloxy)-*N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*,2-dimethylpentan amide (**42**)

The protected alcohol **42** was prepared using a modified procedure reported by Sarabia et al.[32] A solution of alcohol **19** (4.01 g, 12.8 mmol, 1.00 eq) in THF (60 mL) was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil, 604 mg, 15.1 mmol, 1.17 eq) was added portion wise, followed by the addition of TBAI (50.0 mg, 0.14 mmol, 0.01 eq) and BnBr (2.09 mL, 17.6 mmol, 1.37 eq). The reaction was stirred at the same temperature for 45 min, after warming to rt and stirring overnight. After 20 h water (150 mL) was added and the aqueous layer was extracted with EtOAc (4 x 120 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 4:1 to 3:1) to afford the protected β-hydroxy amide **42** (4.46 g, 11.1 mmol, 86%) as a colorless oil. $[\alpha]_D^{22}$ –19.3 (*c* 1.23, $CHCl_3$). R_f 0.25 (cyclohexane/EtOAc, 2:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2959, 2938, 2906, 2861, 1657, 1613, 1586, 1513, 1497, 1462, 1456, 1443, 1422, 1384, 1302, 1247, 1208, 1174, 1155, 1096, 1068, 1032, 994, 936, 847, 821, 740, 699. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.35–7.20 (m, 7H, 2 x *o*-C*H*$_{PMB}$, 5 x C*H*$_{Bn}$), 6.90–6.82 (m, 2H, 2 x *m*-C*H*$_{PMB}$), 4.52 (d, *J* = 11.0 Hz, 1H, C*H*$_{2\text{-A Bn}}$), 4.44 (d, *J* = 11.0 Hz, 1H, C*H*$_{2\text{-B Bn}}$), 4.44 (d, *J* = 11.5 Hz, 1H, C*H*$_{2\text{-A PMB}}$), 4.39 (d, *J* = 11.5 Hz, 1H, C*H*$_{2\text{-B PMB}}$), 3.87 (td, *J* = 8.4, 3.0 Hz, 1H, 3-C*H*), 3.79 (s, 3H, OC*H*$_{3\ PMB}$), 3.67–3.52 (m, 2H, 5-C*H*$_2$), 3.60 (s, 3H, NOC*H*$_3$), 3.26–3.15 (m, 1H, 2-C*H*), 3.19 (s, 3H, NC*H*$_3$), 2.01 (dtd, *J* = 14.4, 7.4, 3.1 Hz, 1H, 4-C*H*$_{2\text{-A}}$), 1.72 (ddt, *J* = 14.4, 8.3, 5.6 Hz, 1H, 4-C*H*$_{2\text{-B}}$), 1.10 (d, *J* = 6.9 Hz, 3H, 2-C*H*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 176.2 (1C, 1-*C*ON), 159.3 (1C, *p*-*C*$_{PMB}$), 139.0 (1C, *ipso*-*C*$_{Bn}$), 130.7 (1C, *ipso*-*C*$_{PMB}$), 129.4 (2C, 2 x *o*-*C*H$_{PMB}$), 128.3 (2C, 2 x *m*-*C*H$_{Bn}$), 128.0 (2C, 2 x *o*-*C*H$_{Bn}$), 127.5 (1C, *p*-*C*H$_{Bn}$), 113.9 (2C, 2 x *m*-*C*H$_{PMB}$), 78.5 (1C, 3-*C*H), 73.2 (1C, *C*H$_{2\ Bn}$), 72.7 (1C, *C*H$_{2\ PMB}$), 66.4 (1C, 5-*C*H$_2$), 61.5 (1C, NO*C*H$_3$), 55.4 (1C,

O*C*H$_{3\ PMB}$), 39.8 (1C, 2-*C*H), 32.2 (1C, N*C*H$_3$), 31.9 (1C, 4-*C*H$_2$), 13.6 (1C, 2-*C*H$_3$). HRESIMS *m*/*z* 402.2273 $[M+H]^+$ (calcd for $C_{23}H_{31}NO_5H$, 402.2275).

(3*S*,4*S*)-4-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-3-methylhexan-2-one (**20**)

According to Alberto Marco et al.,[33] to a precooled solution of Weinreb amide **42** (1.50 g, 3.74 mmol, 1.00 eq) in THF (47 mL) was added dropwise MeMgBr (3M in DEE, 4.86 mL, 14.6 mmol, 3.90 eq) at –20 °C within 3 min. After 1 h at –20 °C, stirring was continued 1 h at 0 °C. The reaction mixture was quenched by the addition of 100 mL saturated NH_4Cl (aq), taken up in 50 mL H_2O and diethyl ether, and the aqueous layer extracted three times with 50 mL. Drying ($MgSO_4$), filtration, and flash chromatography (cyclohexane/EtOAc, 4:1) of the crude product gave ketone **20** (1.30 g, 3.64 mmol, 97%) as a colorless oil. $[\alpha]_D^{23}$ –0.20 (*c* 1.00, $CHCl_3$). R_f 0.25 (cyclohexane/EtOAc, 4:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2935, 2897, 2862, 2839, 1711, 1615, 1586, 1512, 1455, 1433, 1423, 1402, 1359, 1302, 1247, 1209, 1174, 1095, 1063, 1033, 952, 847, 820, 740, 699, 593. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 7.36–7.18 (m, 7H, 2 x *o*-C*H*$_{PMB}$, 5 x C*H*$_{Bn}$), 6.92–6.85 (m, 2H, 2 x *m*-C*H*$_{PMB}$), 4.43 (d, *J* = 11.5 Hz, 1H, C*H*$_{2\text{-A Bn}}$), 4.39 (d, *J* = 11.5 Hz, 1H, C*H*$_{2\text{-B Bn}}$), 4.37 (d, *J* = 11.5 Hz, 1H, C*H*$_{2\text{-A PMB}}$), 4.31 (d, *J* = 11.5 Hz, 1H, C*H*$_{2\text{-B PMB}}$), 3.81 (td, *J* = 7.2, 3.7 Hz, 1H, 4-C*H*), 3.73 (s, 3H, OC*H*$_{3\ PMB}$), 3.48–3.42 (m, 2H, 6-C*H*$_2$), 2.92 (p, *J* = 6.9 Hz, 1H, 3-C*H*), 2.08 (s, 3H, 1-C*H*$_3$), 1.70–1.54 (m, 2H, 5-C*H*$_2$), 0.95 (d, *J* = 7.0 Hz, 3H, 3-C*H*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 210.3 (1C, 2-*C*O), 158.7 (1C, *p*-*C*$_{PMB}$), 138.5 (1C, *ipso*-*C*$_{Bn}$), 130.4 (1C, *ipso*-*C*$_{PMB}$), 129.2 (2C, 2 x *o*-*C*H$_{PMB}$), 128.2 (2C, 2 x *m*-*C*H$_{Bn}$), 127.6 (2C, 2 x *o*-*C*H$_{Bn}$), 127.4 (1C, *p*-*C*H$_{Bn}$), 113.6 (2C, 2 x *m*-*C*H$_{PMB}$), 76.7 (1C, 4-*C*H), 71.6 (1C, *C*H$_{2\ PMB}$), 70.8 (1C, *C*H$_{2\ Bn}$), 65.4 (1C, 6-*C*H$_2$), 55.0 (1C, O*C*H$_{3\ PMB}$), 49.4 (1C, 3-*C*H), 30.5 (1C, 5-*C*H$_2$), 29.2 (1C, 1-*C*H$_3$), 11.0 (1C, 3-*C*H$_3$). HRESIMS *m*/*z* 379.1874 $[M+Na]^+$ (calcd for $C_{22}H_{28}O_4Na$, 379.1880).

(2*R*,3*R*,4*S*)-4-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-3-methylhexan-2-ol (**21**)

Based on a known procedure by McGarvey et al.,[34] to a precooled solution of ketone **20** (1.18 g, 3.32 mmol, 1.00 eq) in THF (118 mL) was added dropwise L-selectride (1M in THF, 8.30 mL, 8.30 mmol, 2.50 eq) at –78 °C within 15 min, and the reaction mixture was stirred 2 h. After the reaction mixture was quenched by the addition of 100 mL saturated NH_4Cl (aq), the aqueous layer was extracted with EtOAc (3 x 50 mL), dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. This provided a 94:6 mixture of diastereomeric alcohols, which were separated by means of flash chromatography (cyclohexane/EtOAc, 4:1 to 3:1), to yield the *syn*-1,3-diol **21** (0.95 g, 2.65 mmol, 80%) and a mixture of both diastereomers **21** & **22** (0.19 g, 0.52 mmol, 16%) as colorless oils.

$[\alpha]_D^{22}$ –29.0 (*c* 1.01, $CHCl_3$). R_f 0.13 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3405, 2965, 2934, 2873, 1613, 1586, 1513, 1454, 1368, 1302, 1248, 1209, 1174, 1091, 1068, 1036, 937, 81, 738, 699. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 7.35–7.17 (m, 7H, 2 x *o*-CH_{PMB}, 5 x CH_{Bn}), 6.91–6.85 (m, 2H, 2 x *m*-CH_{PMB}), 4.44 (d, J = 11.7 Hz, 1H, C$H_{2\text{-A Bn}}$), 4.37 (d, J = 11.5 Hz, 1H, C$H_{2\text{-A PMB}}$), 4.37 (d, J = 5.0 Hz, 1H, 2-O*H*), 4.31 (d, J = 11.5 Hz, 1H, C$H_{2\text{-B PMB}}$), 4.30 (d, J = 11.5 Hz, 1H, C$H_{2\text{-B Bn}}$), 3.76–3.68 (m, 1H, 4-C*H*), 3.73 (s, 3H, OC$H_{3\ PMB}$), 3.57–3.40 (m, 3H, 2-C*H*, 6-CH_2), 1.86–1.71 (m, 2H, 3-C*H*, 5-C$H_{2\text{-A}}$), 1.58–1.46 (m, 1H, 5-C$H_{2\text{-B}}$), 1.03 (d, J = 6.2 Hz, 3H, 1-CH_3), 0.74 (d, J = 6.9 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 158.6 (1C, *p*-C_{PMB}), 139.1 (1C, *ipso*-C_{Bn}), 130.6 (1C, *ipso*-C_{PMB}), 129.2 (2C, 2 x *o*-CH_{PMB}), 128.1 (2C, 2 x *m*-CH_{Bn}), 127.5 (2C, 2 x *o*-CH_{Bn}), 127.2 (1C, *p*-CH_{Bn}), 113.6 (2C, 2 x *m*-CH_{PMB}), 76.3 (1C, 4-*C*H), 71.5 (1C, *C*$H_{2\ PMB}$), 70.2 (1C, *C*$H_{2\ Bn}$), 67.0 (1C, 2-*C*H), 66.5 (1C, 6-CH_2), 55.0 (1C, OC$H_{3\ PMB}$), 41.9 (1C, 3-*C*H), 29.4 (1C, 5-CH_2), 21.2 (1C, 1-CH_3), 10.1 (1C, 3-CH_3). HRESIMS *m*/*z* 381.2033 $[M+Na]^+$ (calcd for $C_{22}H_{30}O_4Na$, 381.2036).

The analytical data of the matched alcohol **21** are reported here, while the analytical data of the undesired diastereomer **22** were given in the next step of the reduction under Luche conditions.

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-3-methylhexan-2-ol (**22**)

Based on a known procedure by Crimmins et al.,[38] the ketone **20** (1.09 g, 3.05 mmol, 1.00 eq) was dissolved in methanol (56 mL) and $CeCl_3 \cdot 7H_2O$ (1.10 g, 2.96 mmol, 0.97 eq) was added at 0 °C. After the reaction mixture was stirred for 30 min, $NaBH_4$ (0.11 g, 2.96 mmol, 0.97 eq) was added portion wise and the reaction mixture was stirred for a further 2 h. It was quenched by addition of 40 mL saturated NH_4Cl (aq) the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. This provided a 69:31 mixture of diastereomeric alcohols, which were separated by means of flash chromatography (cyclohexane/EtOAc, 4:1 to 3:1), to yield the *anti*-1,3-diol **22** (0.71 g, 1.99 mmol, 65%) as a colorless oil.$[\alpha]_D^{23}$ –7.9 (*c* 1.05, $CHCl_3$). R_f 0.23 (cyclohexane/EtOAc, 2:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3474, 2968, 2935, 2866, 1613, 1513, 1455, 1366, 1302, 1248, 1173, 1090, 1065, 1037, 738, 699. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 7.35–7.17 (m, 7H, 2 x *o*-CH_{PMB}, 5 x CH_{Bn}), 6.92–6.85 (m, 2H, 2 x *m*-CH_{PMB}), 4.49 (d, *J* = 11.5 Hz, 1H, C$H_{2\text{-A Bn}}$), 4.36 (d, *J* = 11.5 Hz, 1H, C$H_{2\text{-A PMB}}$), 4.32 (d, *J* = 11.5 Hz, 1H, C$H_{2\text{-B Bn}}$), 4.29 (d, *J* = 11.5 Hz, 1H, C$H_{2\text{-B PMB}}$), 4.27 (d, *J* = 5.0 Hz, 1H, 2-O*H*), 3.74–3.65 (m, 1H, 2-C*H*), 3.73 (s, 3H, OC$H_{3\ PMB}$), 3.55–3.42 (m, 3H, 4-C*H*, 6-CH_2), 1.77 (dtd, *J* = 15.1, 7.6, 2.7 Hz, 1H, 5-C$H_{2\text{-A}}$), 1.65–1.46 (m, 2H, 3-C*H*, 5-C$H_{2\text{-B}}$), 1.03 (d, *J* = 6.4 Hz, 3H, 1-CH_3), 0.81 (d, *J* = 6.9 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 158.6 (1C, *p*-C$_{PMB}$), 139.1 (1C, *ipso*-C$_{Bn}$), 130.6 (1C, *ipso*-C$_{PMB}$), 129.2 (2C, 2 x *o*-CH$_{PMB}$), 128.1 (2C, 2 x *m*-CH$_{Bn}$), 127.6 (2C, 2 x *o*-CH$_{Bn}$), 127.2 (1C, *p*-CH$_{Bn}$), 113.6 (2C, 2 x *m*-CH$_{PMB}$), 77.2 (1C, 4-*C*H), 71.5 (1C, *C*H$_{2\ PMB}$), 70.8 (1C, *C*H$_{2\ Bn}$), 66.1 (1C, 6-*C*H$_2$), 66.0 (1C, 2-*C*H), 55.0 (1C, OCH$_{3\ PMB}$), 42.2 (1C, 3-*C*H), 30.6 (1C, 5-*C*H$_2$), 21.9 (1C, 1-*C*H$_3$), 9.2 (1C, 3-*C*H$_3$). HRESIMS *m*/*z* 381.2043 $[M+Na]^+$ (calcd for $C_{22}H_{30}O_4Na$, 381.2036).

The analytical data of the mismatched alcohol **22** are reported here, while the analytical data of the diastereomer **21** were given in the previous step of the L-selectride reduction.

(4*S*,5*R*,6*R*)-4-(2-((4-Methoxybenzyl)oxy)ethyl)-2,2,5,6-tetramethyl-1,3-dioxane (**43**)

Following a modified procedure of Olsson et al.,[39] secondary alcohol **21** (50.0 mg, 139 µmol, 1.00 eq) was dissolved in degassed MeOH (2.0 mL) and 10% Pd/C (22.3 mg, 20.9 µmol, 0.15 eq) was added. The suspension was stirred under a hydrogen atmosphere (5 bar) at rt until complete consumption of the starting material by TLC was detected. The reaction mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The resulting diol was taken up in 2,2-dimethoxypropane (0.86 mL) and camphorsulfonic acid (3.24 mg, 14.0 µmol, 0.10 eq) was added. After 2 h the reaction was stopped by the addition of saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the crude product was purified by preparative HPLC (C_{18}-HTEC, isocratic 70% MeCN in H_2O, 20 min). The *syn*-1,3-diol-acetonide **43** (22.0 mg, 71.0 mmol, 51%) was obtained as a colorless oil. $[\alpha]_D^{23}$ –37.7 (*c* 2.09, CH_2Cl_2). R_f 0.60 (cyclohexane/EtOAc, 2:1). t_R (HPLC) 8.68 min (C_{18}-HTEC, isocratic 70% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2990, 2935, 2857, 1613, 1513, 1462, 1379, 1301, 1246, 1201, 1177, 1156, 1121, 1089, 1060, 1036, 995, 978, 919, 821, 519. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 7.25–7.20 (m, 2H, 2 x *o*-C*H*$_{PMB}$), 6.92–6.87 (m, 2H, 2 x *m*-C*H*$_{PMB}$), 4.39 (d, J = 11.7 Hz, 1H, C$H_{2\text{-A PMB}}$), 4.32 (d, J = 11.7 Hz, 1H, C$H_{2\text{-B PMB}}$), 3.73 (s, 3H, OC$H_{3\ PMB}$), 3.60–3.53 (m, 2H, 4-C*H*, 6-C*H*), 3.46–3.41 (m, 2H, 8-CH_2), 1.88 (dtd, J = 13.9, 7.7, 2.3 Hz, 1H, 7-C$H_{2\text{-A}}$), 1.47–1.39 (m, 1H, 7-C$H_{2\text{-B}}$), 1.35 (s, 3H, 2-C$H_{3\ ax}$), 1.22 (s, 3H, 2-C$H_{3\ eq}$), 1.10–1.01 (m, 1H, 5-C*H*), 1.06 (d, J = 6.1 Hz, 3H, 6-CH_3), 0.74 (d, J = 6.6 Hz, 3H, 5-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 158.6 (1C, *p*-C$_{PMB}$), 130.6 (1C, *ipso*-C$_{PMB}$), 129.1 (2C, 2 x *o*-CH$_{PMB}$), 113.6 (2C, 2 x *m*-CH$_{PMB}$), 97.3 (1C, 2-C$_q$), 71.6 (1C, C$H_{2\ PMB}$), 70.7 (1C, 4-*C*H), 69.9 (1C, 6-*C*H), 65.6 (1C, 8-*C*H_2), 55.1 (1C, OC$H_{3\ PMB}$), 40.6 (1C, 5-*C*H), 33.0 (1C, 7-*C*H_2), 30.0 (1C, 2-*C*$H_{3\ eq}$), 19.8 (1C, 6-*C*H_3), 19.7 (1C, 2-*C*$H_{3\ ax}$), 12.1 (1C, 5-*C*H_3). HRESIMS *m*/*z* 331.1881 $[M+Na]^+$ (calcd for $C_{18}H_{28}O_4Na$, 331.1880).

(4*S*,5*R*,6*S*)-4-(2-((4-Methoxybenzyl)oxy)ethyl)-2,2,5,6-tetramethyl-1,3-dioxane (**44**)

Following a modified procedure of Olsson et al.,[39] secondary alcohol **22** (50.0 mg, 139 µmol, 1.00 eq) was dissolved in degassed MeOH (2 mL) and 10% Pd/C (22.3 mg, 20.9 µmol, 0.15 eq) was added. The suspension was stirred under a hydrogen atmosphere (5 bar) at rt until complete consumption of the starting material by TLC was detected. The reaction mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The resulting diol was taken up in 2,2-dimethoxypropane (0.86 mL) and camphorsulfonic acid (3.24 mg, 14.0 µmol, 0.10 eq) was added. After 2 h the reaction was stopped by the addition of saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the crude product was purified by preparative HPLC (C_{18}-HTEC, isocratic 65% MeCN in H_2O, 20 min). In addition to starting material **22** (23.0 mg, 65.0 µmol, 47%), the *anti*-1,3-diol-acetonide **44** (13.3 mg, 43.1 mmol, 31%) was obtained as a colorless oil. $[\alpha]_D^{23}$ –6.7 (*c* 1.11, CH_2Cl_2). R_f 0.68 (cyclohexane/EtOAc, 2:1). t_R (HPLC) 12.33 min (C_{18}-HTEC, isocratic 65% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2982, 2936, 2873, 1613, 1514, 1461, 1379, 1302, 1247, 1230, 1184, 1151, 1097, 1036, 1010, 821. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 7.25–7.20 (m, 2H, 2 x *o*-C*H*$_{PMB}$), 6.91–6.87 (m, 2H, 2 x *m*-C*H*$_{PMB}$), 4.38 (d, *J* = 11.6 Hz, 1H, C*H*$_{2\text{-A PMB}}$), 4.33 (d, *J* = 11.6 Hz, 1H, C*H*$_{2\text{-B PMB}}$), 3.97 (qd, *J* = 6.6, 5.3 Hz, 1H, 6-C*H*), 3.73 (s, 3H, OC*H*$_{3\ PMB}$), 3.43 (dd, *J* = 7.5, 5.2 Hz, 2H, 8-CH_2), 3.31 (ddd, *J* = 9.5, 8.2, 3.1 Hz, 1H, 4-C*H*), 1.78 (dtd, *J* = 14.0, 7.5, 3.0 Hz, 1H, 7-C*H*$_{2\text{-A}}$), 1.63–1.51 (m, 2H, 7-C*H*$_{2\text{-B}}$, 5-C*H*), 1.22 (s, 3H, 2-C*H*$_{3\ A}$), 1.18 (s, 3H, 2-C*H*$_{3\ A}$), 0.97 (d, *J* = 6.6 Hz, 3H, 6-C*H*$_3$), 0.73 (d, *J* = 6.9 Hz, 3H, 5-C*H*$_3$). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 158.7 (1C, *p*-C$_{PMB}$), 130.6 (1C, *ipso*-C$_{PMB}$), 129.2 (2C, 2 x *o*-CH$_{PMB}$), 113.6 (2C, 2 x *m*-CH$_{PMB}$), 99.7 (1C, 2-C_q), 71.6 (1C, *C*H$_{2\ PMB}$), 70.9 (1C, 4-*C*H), 66.0 (1C, 8-*C*H_2), 64.3 (1C, 6-*C*H), 55.0 (1C, OC*H*$_{3\ PMB}$), 39.8 (1C, 5-*C*H), 34.2 (1C, 7-*C*H_2), 25.0 (1C, 2-*C*H$_{3\ A}$), 23.9 (1C, 2-*C*H$_{3\ B}$), 16.5 (1C, 6-*C*H_3), 11.4 (1C, 5-*C*H_3). HRESIMS *m*/*z* 331.1873 $[M+Na]^+$ (calcd for $C_{18}H_{28}O_4Na$, 331.1880).

(2*R*,3*R*,4*S*)-4-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-3-methylhexan-2-yl 2-[3,5-bis (benzyloxy)phenyl]acetate (**45**)

According to procedures by Opatz et al.,[53] a solution of *N*,*N*'-dicyclohexylcarbodiimide (0.25M in CH_2Cl_2, 10.5 mL, 2.62 mmol, 1.20 eq) was added dropwise to an ice-cooled solution of hexan-2-ol **21** (783 mg, 2.19 mmol, 1.00 eq), (3,5-bis(benzyloxy)-phenyl)acetic acid (**5**, 837 mg, 2.40 mmol, 1.10 eq), and 4-(dimethylamino)pyridine (53.4 mg, 437 µmol, 0.20 eq) in CH_2Cl_2 (72 mL). The reaction mixture was stirred at 0 °C for 3 h until another portion of *N*,*N*'-dicyclohexylcarbodiimide (0.25M in CH_2Cl_2, 1.75 mL, 0.44 mmol, 0.20 eq) and 4-(dimethylamino)pyridine (26.7 mg, 218 µmol, 0.10 eq) were added and the solution was then warmed to rt overnight. After the addition of 100 mL saturated NH_4Cl (aq) the aqueous layer was washed with CH_2Cl_2 (3 x 100 mL), dried ($MgSO_4$) and filtered. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 5:1) yielding ester **45** (1.50 g, 2.18 mmol, 99%) as a colorless solid. $[\alpha]_D^{23}$ –26.8 (*c* 0.95, $CHCl_3$). R_f 0.45 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3033, 2935, 2866, 1727, 1594, 1512, 1498, 1453, 1377, 1344, 1292, 1247, 1211, 1156, 1086, 1060, 1030, 950, 828, 737, 698. ^{1}H NMR, COSY (400 MHz, CD_3CN) δ_H 7.42–7.21 (m, 15H, CH_{arom}), 7.21–7.15 (m, 2H, 2 x *o*-CH_{PMB}), 6.86–6.80 (m, 2H, 2 x *m*-CH_{PMB}), 6.54–6.47 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.00 (s, 4H, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.84 (dq, *J* = 8.0, 6.3 Hz, 1H, 2-C*H*), 4.40 (d, *J* = 11.3 Hz, 1H, 4-C$H_{2\text{-A Bn}}$), 4.32 (d, *J* = 11.5 Hz, 1H, 6-C$H_{2\text{-A PMB}}$), 4.27 (d, *J* = 11.5 Hz, 1H, 6-C$H_{2\text{-B PMB}}$), 4.24 (d, *J* = 11.3 Hz, 1H, 4-C$H_{2\text{-B Bn}}$), 3.71 (s, 3H, OC$H_{3\ PMB}$), 3.53–3.33 (m, 5H, 4-C*H*, 6-CH_2, 2'-CH_2), 2.13–2.01 (m, 1H, 3-C*H*), 1.66 (dddd, *J* = 14.1, 8.1, 7.1, 2.7 Hz, 1H, 5-C$H_{2\text{-A}}$), 1.53 (dddd, *J* = 14.1, 9.3, 6.2, 4.7 Hz, 1H, 5-C$H_{2\text{-B}}$), 1.15 (d, *J* = 6.3 Hz, 3H, 1-CH_3), 0.83 (d, *J* = 7.0 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, CD_3CN) δ_C 171.4 (1C, 1'-*C*OO), 160.9 (2C, 3''-, 5''-*C*), 160.1 (1C, *p*-C_{PMB}), 140.1 (1C, *ipso*-4-C_{Bn}), 138.2 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 138.1 (1C, *ipso*-1''-*C*), 131.9 (1C, *ipso*-C_{PMB}), 130.3 (2C, 2 x *o*-CH_{PMB}), 129.5 (4C, 2 x *m*-3'', 2 x *m*-5''-CH_{Bn}), 129.2 (2C,

2 x CH_{arom}), 128.9 (2C, 2 x CH_{arom}), 128.8 (2C, 2 x *o*-4-CH_{Bn}), 128.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH_{Bn}), 128.4 (1C, *p*-4-CH_{Bn}), 114.5 (2C, 2 x *m*-CH_{PMB}), 109.6 (2C, 2''-, 6''-*C*H), 101.4 (1C, 4''-*C*), 77.2 (1C, 4-*C*H), 72.9 (1C, 2-*C*H), 72.9 (1C, 6-$CH_{2\ PMB}$), 71.9 (1C, 4-$CH_{2\ Bn}$), 70.7 (2C, 3''-, 5''-$CH_{2\ Bn}$), 67.5 (1C, 6-CH_2), 55.8 (1C, $OCH_{3\ PMB}$), 42.3 (1C, 2'-CH_2), 40.7 (1C, 3-*C*H), 30.8 (1C, 5-CH_2), 17.9 (1C, 1-CH_3), 10.4 (1C, 3-CH_3). HRESIMS *m*/*z* 711.3294 $[M+Na]^+$ (calcd for $C_{44}H_{48}O_7Na$, 711.3292).

(2*R*,3*R*,4*S*)-4-(Benzyloxy)-6-hydroxy-3-methylhexan-2-yl 2-[3,5-bis(benzyloxy)phenyl] acetate (**46**)

Following a previously published procedure,[45] PMB-ether **45** (1.34 g, 1.95 mmol, 1.00 eq) was dissolved in CH_2Cl_2 (60 mL) and phosphate buffer (pH = 7.63 mM, 3 mL) was added. After the addition of DDQ (0.49 g, 2.15 mmol, 1.10 eq) the reaction was stirred for 1.5 h at ambient temperature before another portion of DDQ (44.3 mg, 0.20 mmol, 0.10 eq) was added and stirred further 30 min. The reaction was quenched by the addition of water (300 mL) and the aqueous layer was washed with CH_2Cl_2 (4 x 100 mL), dried ($MgSO_4$) and filtered. After flash chromatography (cyclohexane/EtOAc, 3:1 to 2:1) the primary alcohol **46** (907 mg, 1.60 mmol, 82%) could be obtained as a colorless oil. $[\alpha]_D^{23}$ –28.5 (*c* 0.85, $CHCl_3$). R_f 0.13 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3447, 3064, 3032, 2940, 2878, 1727, 1594, 1497, 1453, 1378, 1291, 1250, 1213, 1159, 1117, 1058, 1029, 965, 834, 737, 698. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 7.44–7.22 (m, 15H, CH_{arom}), 6.59–6.51 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.04 (s, 4H, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.84 (pseudo-p, *J* = 6.3 Hz, 1H, 2-C*H*), 4.40 (d, *J* = 11.6 Hz, 1H, 4-C$H_{2\text{-A Bn}}$), 4.40 (t, *J* = 5.3 Hz, 1H, 6-O*H*), 4.32 (d, *J* = 11.6 Hz, 1H, 4-C$H_{2\text{-B Bn}}$), 3.55 (s, 2H, 2'-CH_2), 3.53–3.37 (m, 3H, 4-C*H*, 6-CH_2), 2.07–1.97 (m, 1H, 3-C*H*), 1.62–1.42 (m, 2H, 5-CH_2), 1.10 (d, *J* = 6.3 Hz, 3H, 1-CH_3), 0.80 (d, *J* = 7.0 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 170.1 (1C, 1'-*C*OO), 159.4 (2C, 3''-, 5''-*C*), 138.9 (1C, *ipso*-4-C_{Bn}), 136.9 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 136.6 (1C, *ipso*-1''-*C*), 128.4

(4C, 2 x *m*-3'', 2 x *m*-5''-*C*H$_{Bn}$), 128.2 (2C, 2 x *C*H$_{arom}$), 127.8 (2C, 2 x *C*H$_{arom}$), 127.7 (4C, 2 x *o*-3'', 2 x *o*-5''-*C*H$_{Bn}$), 127.5 (2C, 2 x *o*-4-*C*H$_{Bn}$), 127.3 (1C, *p*-4-*C*H$_{Bn}$), 108.5 (2C, 2''-, 6''-*C*H), 100.2 (1C, 4''-*C*), 76.2 (1C, 4-*C*H), 71.4 (1C, 2-*C*H), 70.4 (1C, 4-*C*H$_{2\ Bn}$), 69.3 (2C, 3''-, 5''-*C*H$_{2\ Bn}$), 57.8 (1C, 6-*C*H$_2$), 41.0 (1C, 2'-*C*H$_2$), 39.3 (1C, 3-*C*H), 33.0 (1C, 5-*C*H$_2$), 16.8 (1C, 1-*C*H$_3$), 10.0 (1C, 3-*C*H$_3$). HRESIMS *m*/*z* 591.2704 $[M+Na]^+$ (calcd for $C_{36}H_{40}O_6Na$, 591.2717).

(2*R*,3*R*,4*S*)-4-(Benzyloxy)-3-methyl-6-oxohexan-2-yl 2-[3,5-bis(benzyloxy)phenyl] acetate (**23**)

Using a modified procedure of Pannecoucke et al.,[27] primary alcohol **46** (907 mg, 1.60 mmol, 1.00 eq) was dissolved in dry MeCN (44 mL), IBX (1.12 g, 3.99 mmol, 2.50 eq) was added, and the reaction mixture was stirred over preactivated 3 Å molecular sieves (0.50 g). After 2 h, another portion IBX (223 mg, 798 µmol, 0.50 eq) was added and the reaction mixture was stirred for another 2 h until the solvent was removed under reduced pressure at rt and the residue was taken up in EtOAc (50 mL). The mixture was filtered through a pad of Celite and silica gel, after removing the solvent under reduced pressure the aldehyde **23** (910 mg, 1.60 mmol, 100%) was obtained as a yellowish-green oil. $[\alpha]_D^{22}$ –13.1 (*c* 0.78, $CHCl_3$). R_f 0.43 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3065, 3032, 2980, 2932, 2885, 1727, 1594, 1495, 1453, 1379, 1344, 1291, 1248, 1214, 1160, 1119, 1059, 1029, 952, 832, 739, 698. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 9.57–9.52 (m, 1H, 6-C*H*O), 7.45–7.19 (m, 15H, C*H*$_{arom}$), 6.60–6.50 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.04 (s, 4H, 3''-C*H*$_{2\ Bn}$, 5''-C*H*$_{2\ Bn}$), 4.81 (pseudo-p, *J* = 6.3 Hz, 1H, 2-C*H*), 4.41 (d, *J* = 11.5 Hz, 1H, 4-C*H*$_{2\text{-A Bn}}$), 4.33 (d, *J* = 11.5 Hz, 1H, 4-C*H*$_{2\text{-B Bn}}$), 3.90 (ddd, *J* = 8.0, 5.1, 4.1 Hz, 1H, 4-C*H*), 3.61–3.51 (m, 2H, 2'-C*H*$_2$), 2.47–2.35 (m, 2H, 5-C*H*$_2$), 2.11 (pseudo-td, *J* = 7.1, 5.0 Hz, 1H, 3-C*H*), 1.13 (d, *J* = 6.3 Hz, 3H, 1-C*H*$_3$), 0.80 (d, *J* = 7.0 Hz, 3H, 3-C*H*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 202.2 (1C, 6-*C*HO), 170.2 (1C, 1'-*C*OO), 159.5 (2C, 3''-, 5''-*C*), 138.3 (1C, *ipso*-4-*C*$_{Bn}$), 136.9

(2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 136.6 (1C, *ipso*-1''-*C*), 128.4 (4C, 2 x *m*-3'', 2 x *m*-5''-CH_{Bn}), 128.2 (2C, 2 x CH_{arom}), 127.8 (2C, 2 x CH_{arom}), 127.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH_{Bn}), 127.6 (2C, 2 x *o*-4-CH_{Bn}), 127.5 (1C, *p*-4-CH_{Bn}), 108.5 (2C, 2''-, 6''-*C*H), 100.2 (1C, 4''-*C*), 74.0 (1C, 4-*C*H), 71.4 (1C, 2-*C*H), 70.2 (1C, 4-$CH_{2\ Bn}$), 69.3 (2C, 3''-, 5''-$CH_{2\ Bn}$), 44.1 (1C, 5-CH_2), 41.0 (1C, 2'-CH_2), 39.1 (1C, 3-*C*H), 17.0 (1C, 1-CH_3), 10.0 (1C, 3-CH_3). HRESIMS *m*/*z* 589.2557 $[M+Na]^+$ (calcd for $C_{36}H_{38}O_6Na$, 589.2561).

tert-Butyl (5*S*,6*R*,7*R*,*E*)-5-(benzyloxy)-7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (**25**)

According to procedures from Jiang and Chen et al.,[46] phosphonium ylide **24** (704 mg, 1.80 mmol, 1.20 eq) was added to a solution of aldehyde **23** (851 mg, 1.50 mmol, 1.00 eq) in CH_2Cl_2 (60 mL) at ambient temperature. After 3 h, another portion of phosphonium ylide **24** (117 mg, 0.30 mmol, 0.20 eq) was added and the solution was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc, 15:1 to 10:1) yielding the unsaturated *tert*-butyl ester **25** (978 mg, 1.44 mmol, 96%) as a colorless oil in an *E*/*Z* ratio of >95:5. $[\alpha]_D^{23}$ –6.5 (*c* 0.95, $CHCl_3$). R_f 0.40 (cyclohexane/EtOAc, 10:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3064, 3033, 2977, 2931, 2881, 1730, 1703, 1650, 1595, 1498, 1453. 1368, 1344, 1291, 1250, 1216, 1158, 1113, 1085, 1061, 1029, 1001, 957, 852, 737, 698. ^{1}H NMR, COSY (400 MHz, CD_3CN) δ_H 7.43–7.23 (m, 15H, CH_{arom}), 6.69 (tq, *J* = 7.3, 1.5 Hz, 1H, 3-C*H*), 6.53–6.48 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.02 (s, 4H, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.96 (pseudo-p, *J* = 6.4 Hz, 1H, 7-C*H*), 4.42 (d, *J* = 11.3 Hz, 1H, 5-C$H_{2\text{-A}\ Bn}$), 4.37 (d, *J* = 11.3 Hz, 1H, 5-C$H_{2\text{-B}\ Bn}$), 3.50 (s, 2H, 2'-CH_2), 3.45 (ddd, *J* = 7.5, 5.8, 4.1 Hz, 1H, 5-C*H*), 2.39–2.22 (m, 2H, 4-CH_2), 2.05 (pseudo-td, *J* = 7.0, 5.8 Hz, 1H, 6-C*H*), 1.72–1.70 (m, 3H, 2-CH_3), 1.43 (s, 9H, OC(CH_3)$_3$), 1.13 (d, *J* = 6.4 Hz, 3H, 8-CH_3), 0.86 (d, *J* = 7.0 Hz, 3H, 6-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, CD_3CN) δ_C 171.4 (1C, 1'-*C*OO), 167.9 (1C, 1-*C*OO^{t}Bu), 160.9 (2C, 3''-, 5''-*C*), 139.8 (1C, *ipso*-5-C_{Bn}), 138.7 (1C, 3-*C*H), 138.2 (2C, *ipso*-

3'', *ipso*-5''-C_{Bn}), 138.0 (1C, *ipso*-1''-*C*), 131.2 (1C, 2-*C*), 129.5 (4C, 2 x *m*-3'', 2 x *m*-5''-CH_{Bn}), 129.3 (2C, 2 x CH_{arom}), 128.9 (2C, 2 x CH_{arom}), 128.8 (2C, 2 x *o*-5-CH_{Bn}), 128.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH_{Bn}), 128.5 (1C, *p*-5-CH_{Bn}), 109.5 (2C, 2''-, 6''-*C*H), 101.5 (1C, 4''-*C*), 80.5 (1C, O*C*$(CH_3)_3$), 79.6 (1C, 5-*C*H), 72.7 (1C, 7-*C*H), 71.9 (1C, 5-$CH_{2\ Bn}$), 70.7 (2C, 3''-, 5''-$CH_{2\ Bn}$), 42.4 (1C, 2'-CH_2), 41.0 (1C, 6-*C*H), 30.0 (1C, 4-CH_2), 28.3 (3C, OC(CH_3)$_3$), 17.1 (1C, 8-CH_3), 12.9 (1C, 2-CH_3), 10.6 (1C, 6-CH_3). HRESIMS *m*/*z* 696.3888 $[M+NH_4]^+$ (calcd for $C_{43}H_{50}O_7NH_4$, 696.3895).

(13*S*,14*R*,15*R*)-5,7,13-Tris(benzyloxy)-4-dechloro-14-deoxyoxacyclododecindione (**26**)

Following modified procedures of Roberts et al. and Opatz et al.,[15,16] a solution of CH_2Cl_2 (2207 mL), trifluoroacetic acid (71.7 mL), and trifluoroacetic anhydride (35.8 mL) was precooled to –8 °C in a 6 L round-bottom flask and *tert*-butyl (5*S*,6*R*,7*R*,*E*)-5-(benzyloxy)-7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (**25**) (1.02 g, 1.50 mmol, 1.00 eq) in CH_2Cl_2 (55 mL) was added dropwise. The reaction mixture was left to stand at –8 °C for 24 h and then gradually warmed to 0 °C and rt to stir for another 3 d. The reaction mixture was neutralized by careful addition of saturated $NaHCO_3$ (aq) and washing of the organic layer (3 x 100 mL). The organic residue was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. After purification by flash chromatography (cyclohexane/EtOAc, 10:1 to 6:1) the 12-membered macrolactone **26** (575 mg, 0.95 mmol, 63%) was obtained as colorless oil. $[\alpha]_D^{22}$ +54.0 (*c* 0.82, CH_2Cl_2). R_f 0.40 (cyclohexane/EtOAc, 4:1, 1% AcOH). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3064, 3031, 2978, 2935, 2879, 1726, 1639, 1603, 1583, 1497, 1454, 1431, 1376, 1340, 1296, 1263, 1231, 1170, 1147, 1089, 1067, 1028, 1005, 965, 834, 738, 697. ^{1}H NMR, COSY (600 MHz, CD_3CN) δ_H 7.48–7.16 (m, 15H, CH_{arom}), 6.61 (d, *J* = 2.1 Hz, 1H, 6-C*H*), 6.56–6.46 (m, 1H, 4-C*H*), 6.41–6.29 (m, 1H, 11-C*H*), 5.06 (s, 2H, 5-$CH_{2\ Bn}$), 5.04 (s, 2H, 7-$CH_{2\ Bn}$), 4.65 (pseudo-p, *J* = 6.3 Hz, 1H, 15-C*H*), 4.50–4.42 (m, 2H, 13-$CH_{2\ Bn}$), 3.73 (ddd, *J* = 9.7, 3.1, 0.8 Hz, 1H, 13-C*H*), 3.35–3.11 (m, 2H, 2-CH_2), 2.69 (dt, *J* = 15.6,

9.6 Hz, 1H, 12-C$H_{2\text{-A}}$), 2.57–2.42 (m, 1H, 12-C$H_{2\text{-B}}$), 1.99–1.94 (m, 1H, 14-C*H*), 1.86 (s, 3H, 10-CH_3), 1.08–0.96 (m, 3H, 15-CH_3), 0.89 (d, J = 7.3 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN) δ_C 199.4 (1C, 9-*C*O), 170.4 (1C, 1-*C*OO), 160.6 (1C, 5-*C*), 157.4 (1C, 7-*C*), 149.6 (1C, 11-*C*H), 139.8 (1C, *ipso*-13-C_{Bn}), 137.9 (1C, *ipso*-7-C_{Bn}), 137.9 (1C, *ipso*-5-C_{Bn}), 137.6 (1C, 10-*C*), 134.3 (1C, 3-*C*), 129.5 (2C, 2 x *m*-CH_{Bn}), 129.4 (2C, 2 x *m*-CH_{Bn}), 129.2 (2C, 2 x *m*-CH_{Bn}), 129.0 (1C, *p*-CH_{Bn}), 128.9 (1C, *p*-CH_{Bn}), 128.7 (2C, 2 x *o*-CH_{Bn}), 128.6 (2C, 2 x *o*-CH_{Bn}), 128.4 (1C, *p*-CH_{Bn}), 128.3 (2C, 2 x *o*-CH_{Bn}), 125.0 (1C, 8-*C*), 108.1 (1C, 4-*C*H), 100.8 (1C, 6-*C*H), 78.2 (1C, 13-*C*H), 73.7 (1C, 15-*C*H), 71.4 (1C, 13-$CH_{2\ Bn}$), 70.9 (1C, 7-$CH_{2\ Bn}$), 70.8 (1C, 5-$CH_{2\ Bn}$), 43.5 (1C, 14-*C*H), 39.9 (1C, 2-CH_2), 33.0 (1C, 12-CH_2), 18.6 (1C, 15-CH_3), 14.2 (1C, 14-CH_3), 10.5 (1C, 10-CH_3). HRESIMS *m*/*z* 605.2892 $[M+H]^+$ (calcd for $C_{39}H_{40}O_6H$, 605.2898).

(13*S*,14*R*,15*R*)-5,7,13-Tris(benzyloxy)-14-deoxyoxacyclododecindione (**47**)

Following modified procedures of Opatz et al.,[15] a solution of macrolactone **26** (574 mg, 949 µmol, 1.00 eq) in *N*,*N*-dimethylformamide (45 mL) was treated with trifluoroacetic acid (110 µL, 1.42 mmol, 1.50 eq) and a freshly prepared solution of *N*-chlorosuccinimide (100mM in DMF, 5.70 mL, 570 µmol, 0.60 eq) was added slowly within 15 min at rt. After further addition of *N*-chlorosuccinimide (day 2: 100mM in DMF, 2.85 mL, 285 µmol, 0.30 eq; day 3:100mM in DMF, 1.14 mL, 114 µmol, 0.12 eq) and trifluoroacetic acid (day 3: 11 µL, 0.14 mmol, 0.15 eq), the reaction mixture was quenched by the addition of H_2O (50 mL) on day 5. The aqueous phase was extracted with diethyl ether (4 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc, 8:1 to 6:1) to yield the 14-deoxyoxacyclododecindione (**47**) as an inseparable mixture with the starting material **26** (609 mg, 100%brsm, ratio of 94:6) as a colorless oil. $[\alpha]_D^{23}$ +81.3 (*c* 0.89, CH_2Cl_2). R_f 0.43 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3064, 3032, 2975, 2934, 1731, 1655,

1638, 1593, 1576, 1498, 1454, 1412, 1383, 1298, 1254, 1222, 1177, 1157, 1089, 1068, 1026, 967, 943, 738, 698. ^{1}H NMR, COSY (600 MHz, CD_3CN) δ_H 7.46–7.23 (m, 15H, CH_{arom}), 6.86 (s, 1H, 6-C*H*), 6.36–6.30 (m, 1H, 11-C*H*), 5.21 (d, J = 12.0 Hz, 1H, 5-C$H_{2\text{-A Bn}}$), 5.18 (d, J = 12.0 Hz, 1H, 5-C$H_{2\text{-B Bn}}$), 5.08 (d, J = 12.5 Hz, 1H, 7-C$H_{2\text{-A Bn}}$), 5.06 (d, J = 12.5 Hz, 1H, 7-C$H_{2\text{-B Bn}}$), 5.00–4.92 (m, 1H, 15-C*H*), 4.51 (d, J = 12.1 Hz, 1H, 13-C$H_{2\text{-A Bn}}$), 4.47 (d, J = 12.1 Hz, 1H, 13-C$H_{2\text{-B Bn}}$), 3.70 (dd, J = 9.1, 3.2 Hz, 1H, 13-C*H*), 3.53 (d, J = 16.6 Hz, 1H, 2-C$H_{2\text{-A}}$), 3.18 (d, J = 16.6 Hz, 1H, 2-C$H_{2\text{-B}}$), 2.81–2.67 (m, 1H, 12-C$H_{2\text{-A}}$), 2.36 (d, J = 15.3 Hz, 1H, 12-C$H_{2\text{-B}}$), 1.97–1.95 (m, 1H, 14-C*H*), 1.85–1.82 (m, 3H, 10-CH_3), 1.01 (d, J = 6.6 Hz, 3H, 15-CH_3), 0.85 (d, J = 7.3 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN) δ_C 198.1 (1C, 9-*C*O), 168.8 (1C, 1-*C*OO), 155.5 (1C, 5-*C*), 155.3 (1C, 7-*C*), 150.1 (1C, 11-*C*H), 139.9 (1C, *ipso*-13-C_{Bn}), 137.7 (1C, 10-*C*), 137.6 (1C, *ipso*-7-C_{Bn}), 137.4 (1C, *ipso*-5-C_{Bn}), 132.5 (1C, 3-*C*), 129.6 (2C, 2 x *m*-CH_{Bn}), 129.5 (2C, 2 x *m*-CH_{Bn}), 129.2 (2C, 2 x *m*-CH_{Bn}), 129.2 (1C, *p*-CH_{Bn}), 129.1 (1C, *p*-CH_{Bn}), 128.7 (2C, 2 x *o*-CH_{Bn}), 128.6 (2C, 2 x *o*-CH_{Bn}), 128.5 (2C, 2 x *o*-CH_{Bn}), 128.4 (1C, *p*-CH_{Bn}), 125.9 (1C, 8-*C*), 116.4 (1C, 4-*C*Cl), 100.7 (1C, 6-*C*H), 78.5 (1C, 13-*C*H), 73.2 (1C, 15-*C*H), 71.9 (1C, 5-$CH_{2\ Bn}$), 71.6 (1C, 13-$CH_{2\ Bn}$), 71.5 (1C, 7-$CH_{2\ Bn}$), 43.3 (1C, 14-*C*H), 38.7 (1C, 2-CH_2), 33.4 (1C, 12-CH_2), 18.6 (1C, 15-CH_3), 15.1 (1C, 14-CH_3), 10.5 (1C, 10-CH_3). HRESIMS *m*/*z* 639.2499 $[M+H]^+$ (calcd for $C_{39}H_{39}ClO_6H$, 639.2508).

(13*S*,14*S*,15*R*)-13-Hydroxy-14-deoxyoxacyclododecindione (**27**)

Following a modified procedure of Opatz et al.,[15] boron trichloride (1M in heptane, 8.57 mL, 8.57 mmol, 9.00 eq) was added to a solution of benzyl protected macrolactone **47** (609 mg, 0.95 mmol, 1.00 eq) in CH_2Cl_2 (174 mL) at –78 °C. Within 2.5 h, the deep orange solution was gradually warmed to –30 °C and stirred for another 2 h at the same temperature. After complete conversion of the starting material, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) while warming to rt. The aqueous layer was extracted

with CH_2Cl_2 (7 x 80 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 3:1, 1% AcOH to 1:1, 1% AcOH) and the natural product (13*S*,14*S*,15*R*)-13-hydroxy-14-deoxyoxacyclododecindione (**27**) (290 mg, 787 µmol, 83%) was obtained as a colorless solid. For its biological evaluation the natural product **27** was further purified by preparative HPLC (C_{18}-HTEC, isocratic 25% MeCN in H_2O, 20 min). $[\alpha]_D^{22}$ +77.9 (*c* 0.20, MeOH). R_f 0.10 (cyclohexane/EtOAc, 1:1, 1% AcOH). t_R (HPLC): 6.07 min (PFP, isocratic 25% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3360, 2924, 2855, 1709, 1624, 1438, 1350, 1298, 1243, 1154, 1091, 1069, 1006, 979, 946, 849, 736, 703, 655, 587. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 10.21 (s, 1H, 7-CO*H*), 9.66 (s, 1H, 5-CO*H*), 6.49 (s, 1H, 6-C*H*), 6.39–6.34 (m, 1H, 11-C*H*), 4.84 (pseudo-p, *J* = 6.4 Hz, 1H, 15-C*H*), 4.72 (d, *J* = 4.2 Hz, 1H, 13-O*H*), 3.93 (dt, *J* = 8.6, 4.0 Hz, 1H, 13-C*H*), 3.40 (d, *J* = 16.4 Hz, 1H, 2-C$H_{2\text{-A}}$), 3.00 (d, *J* = 16.4 Hz, 1H, 2-C$H_{2\text{-B}}$), 2.56–2.51 (m, 1H, 12-C$H_{2\text{-A}}$), 2.25 (d, *J* = 14.9 Hz, 1H, 12-C$H_{2\text{-B}}$), 1.79–1.72 (m, 4H, 10-CH_3, 14-C*H*), 1.04 (d, *J* = 6.5 Hz, 3H, 15-CH_3), 0.76 (d, *J* = 7.3 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 197.7 (1C, 9-*C*O), 167.9 (1C, 1-*C*OO), 153.4 (1C, 7-*C*), 153.2 (1C, 5-*C*), 148.6 (1C, 11-*C*H), 135.9 (1C, 10-*C*), 130.8 (1C, 3-*C*), 121.3 (1C, 8-C), 111.0 (1C, 4-*C*Cl), 102.4 (1C, 6-*C*H), 71.7 (1C, 15-*C*H), 69.0 (1C, 13-*C*H), 43.9 (1C, 14-*C*H), 37.8 (1C, 2-*C*H_2), 35.5 (1C, 12-*C*H_2), 18.4 (1C, 15-*C*H_3), 14.1 (1C, 14-*C*H_3), 10.3 (1C, 10-*C*H_3). HRESIMS *m*/*z* 369.1096 $[M+H]^+$ (calcd for $C_{18}H_{21}ClO_6H$, 369.1099).

(13*S*,14*R*,15*R*)-13-Chloroacetoxy-14-deoxyoxacyclododecindione (**28**)

Using a modified procedure of Gille and Hiersemann et al.,[51] the alcohol **4** (8.00 mg, 21.7 µmol, 1.00 eq), chloroacetic acid (6.80 mg, 71.6 µmol, 3.30 eq) and PPh_3 (18.8 mg, 71.6 µmol, 3.30 eq) were dissolved in dry THF (0.4 mL) and cooled to 0 °C. DEAD (2.2M in toluene, 32.5 µL, 71.6 µmol, 3.30 eq) was added dropwise to the solution and the reaction was stirred 1 h at 0 °C and for additional 1.5 h at rt. The mixture was diluted by the addition of 5 mL

saturated NH_4Cl (aq) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. For its analytical evaluation, the crude product was purified by preparative HPLC (C_{18}-HTEC, isocratic 40% MeCN in H_2O, 20 min) to yield the ester **28** (1.50 mg, 3.37 µmol, 16%) as a colorless oil. $[\alpha]_D^{22}$ +59.9 (*c* 0.15, MeOH). R_f 0.08 (cyclohexane/EtOAc, 3:1, 1% AcOH). t_R (HPLC): 9.32 min (C18-HTEC, isocratic 40% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3362, 2980, 2934, 1729, 1684, 1654, 1646, 1636, 1616, 1608, 1465, 1456, 1437, 1419, 1375, 1350, 1293, 1251, 1176, 1157, 1100, 1070, 1021, 974, 945, 848, 733, 656. ^{1}H NMR, COSY (600 MHz, CD_3CN) δ_H 6.55–6.49 (m, 2H, 6-C*H*, 11-C*H*), 5.14 (ddd, *J* = 8.0, 2.8, 1.5 Hz, 1H, 13-C*H*), 4.84 (pseudo-p, *J* = 6.5 Hz, 1H, 15-C*H*), 4.09 (s, 2H, 13-CO_2CH_2Cl), 3.51 (d, *J* = 16.9 Hz, 1H, 2-$CH_{2\text{-A}}$), 3.22 (d, *J* = 16.9 Hz, 1H, 2-$CH_{2\text{-B}}$), 2.84 (ddd, *J* = 14.8, 11.5, 8.0 Hz, 1H, 12-$CH_{2\text{-A}}$), 2.33 (d, *J* = 14.8 Hz, 1H, 12-$CH_{2\text{-B}}$), 2.00–1.95 (m, 1H, 14-C*H*), 1.83 (t, *J* = 1.40 Hz, 3H, 10-CH_3), 1.12 (d, *J* = 6.4 Hz, 3H, 15-CH_3), 0.95 (d, *J* = 7.3 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN) δ_C 199.1 (1C, 9-*C*O), 168.9 (1C, 1-*C*OO), 167.8 (1C, 13-*C*O_2CH_2Cl), 154.5 (1C, 7-*C*), 154.4 (1C, 5-*C*), 146.3 (1C, 11-*C*H), 139.5 (1C, 10-*C*), 132.7 (1C, 3-*C*), 122.6 (1C, 8-*C*), 113.5 (1C, 4-*C*Cl), 103.5 (1C, 6-*C*H), 76.9 (1C, 13-*C*H), 72.3 (1C, 15-*C*H), 42.7 (1C, 14-*C*H), 42.2 (1C, 13-$CO_2C$$H_2$Cl), 39.1 (1C, 2-$C$$H_2$), 33.4 (1C, 12-$C$$H_2$), 18.8 (1C, 15-$C$$H_3$), 16.0 (1C, 14-$C$$H_3$), 10.7 (1C, 10-$C$$H_3$). HRESIMS *m/z* 445.0812 $[M+H]^+$ (calcd for $C_{20}H_{22}Cl_2O_7H$, 445.0815).

(13*S*,14*S*,15*R*)-13-Hydroxy-14-deoxyoxacyclododecindione (**27**)

Following a published procedure,[52] the chloroacetyl ester **28** (1.45 mg, 3.26 µmol, 1.00 eq) and thiourea (0.27 mg, 3.59 µmol, 1.10 eq) were dissolved in EtOH (0.15 mL) and heated overnight at 60 °C. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (cyclohexane/EtOAc, 1:1, 1% AcOH) to yield the natural

product 13-hydroxy-14-deoxyoxacyclododecindione **27** (0.69 mg, 1.56 µmol, 48%) as a colorless oil. The analytical data are identical to those previously reported in this manuscript.

(13*R*,14*R*,15*R*)-13-Chloroacetoxy-14-deoxyoxacyclododecindione (**29**)

Using a modified procedure of Gille and Hiersemann et al.,[51] the alcohol **27** (13.0 mg, 35.2 µmol, 1.00 eq), chloroacetic acid (11.0 mg, 116 µmol, 3.30 eq) and PPh_3 (30.5 mg, 116 µmol, 3.30 eq) were dissolved in dry THF (0.65 mL) and cooled to 0 °C. DEAD (2.2M in toluene, 52.9 µL, 116 µmol, 3.30 eq) was added dropwise to the solution and the reaction was stirred 1 h at 0 °C and for an additional 2 h at rt. The mixture was diluted by the addition of 5 mL saturated NH_4Cl (aq) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. For its analytical evaluation the crude product was purified by preparative HPLC (C_{18}-HTEC, isocratic 40% MeCN in H_2O, 20 min) to yield the ester **29** (1.34 mg, 3.64 µmol, 10%) as a colorless oil. $[\alpha]_D^{22}$ +58.2 (*c* 0.11, MeOH). R_f 0.38 (cyclohexane/EtOAc, 1:1, 1% AcOH). t_R (HPLC): 6.80 min (C18-HTEC, isocratic 40% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2986, 2928, 2856, 2740, 1729, 1673, 1612, 1462, 1433, 1397, 1245, 1200, 1136, 1070, 1028, 1011, 986, 949, 834, 799, 721, 683, 650, 587, 570, 512. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 10.29 (s, 1H, 7-CO*H*), 9.76 (s, 1H, 5-CO*H*), 6.51 (s, 1H, 6-C*H*), 6.44–6.36 (m, 1H, 11-C*H*), 4.76–4.68 (m, 1H, 15-C*H*), 4.43 (d, *J* = 15.2 Hz, 1H, 13-$CO_2CH_{2\text{-A}}Cl$), 4.39 (d, *J* = 15.2 Hz, 1H, 13-$CO_2CH_{2\text{-A}}Cl$), 4.36–4.29 (m, 1H, 13-C*H*), 3.50 (d, *J* = 17.2 Hz, 1H, 2-$CH_{2\text{-A}}$), 3.04 (d, *J* = 17.2 Hz, 1H, 2-$CH_{2\text{-B}}$), 2.60–2.52 (m, 1H, 12-$CH_{2\text{-A}}$), 2.47–2.39 (m, 1H, 12-$CH_{2\text{-B}}$), 1.93–1.84 (m, 1H, 14-C*H*), 1.81 (s, 3H, 10-CH_3), 1.02 (d, *J* = 6.2 Hz, 3H, 15-CH_3), 0.77 (d, *J* = 7.4 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 197.8 (1C, 9-*C*O), 167.8 (1C, 1-*C*OO), 167.1 (1C, 13-CO_2CH_2Cl), 153.7 (1C, 7-*C*), 153.4 (1C, 5-*C*), 144.2 (1C, 11-*C*H), 139.0 (1C, 10-*C*), 130.8 (1C, 3-*C*), 120.8 (1C, 8-*C*), 111.4 (1C, 4-*C*Cl), 102.4 (1C, 6-*C*H), 76.1 (1C, 13-*C*H), 74.7 (1C, 15-*C*H), 42.2 (1C, 14-*C*H), 41.2 (1C, 13-CO_2CH_2Cl), 37.5 (1C, 2-CH_2),

34.6 (1C, 12-*C*H_2), 18.0 (1C, 15-*C*H_3), 10.9 (1C, 14-*C*H_3), 10.3 (1C, 10-*C*H_3). HRESIMS *m/z* 445.0811 $[M+H]^+$ (calcd for $C_{20}H_{22}Cl_2O_7H$, 445.0815).

(13*R*,14*S*,15*R*)-13-Hydroxy-14-deoxyoxacyclododecindione (**4**)

Following a previously published procedure,[52] the chloroacetate ester **29** (1.45 mg, 3.26 µmol, 1.00 eq) and thiourea (0.30 mg, 3.91 µmol, 1.20 eq) were dissolved in EtOH (0.15 mL) and heated overnight at 60 °C. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (cyclohexane/EtOAc, 1:1, 1% AcOH) to yield the proposed natural product 13-hydroxy-14-deoxyoxacyclododecindione **4** (0.95 mg, 2.58 µmol, 79%) as a colorless oil. The analytical data are identical to the data that were previously reported.[15]

(2*S*,3*R*,4*R*)-4-(Benzyloxy)-6-((*tert*-butyldiphenylsilyl)oxy)-3-methylhexan-2-yl 2-[3,5-bis (benzyloxy)phenyl]acetate (**48**)

According to procedures from Opatz et al.,[53] a solution of *N*,*N*'-dicyclohexylcarbodiimide (0.25M in CH_2Cl_2, 3.18 mL, 0.79 mmol, 1.20 eq) was added dropwise to an ice-cooled solution of hexan-2-ol **30** (315 mg, 0.66 mmol, 1.00 eq), (3,5-bis(benzyloxy)-phenyl)acetic acid (**5**, 254 mg, 0.73 mmol, 1.10 eq), and 4-(dimethylamino)pyridine (16.2 mg, 132 µmol, 0.20 eq) in CH_2Cl_2 (22 mL). The reaction mixture was stirred at 0 °C for 3 h until another portion of *N*,*N*'-dicyclohexylcarbodiimide (0.25M in CH_2Cl_2, 0.53 mL, 0.13 mmol, 0.20 eq) and 4-(dimethylamino)pyridine (8.08 mg, 66.1 µmol, 0.10 eq) were added and the solution was then warmed to rt overnight. After the addition of 100 mL saturated NH_4Cl (aq) the aqueous layer was washed with CH_2Cl_2 (3 x 40 mL), dried ($MgSO_4$) and filtered. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 15:1) yielding ester **48** (500 g, 0.62 mmol, 94%) as a colorless oil. $[\alpha]_D^{22}$ +8.3 (*c* 1.03, $CHCl_3$). R_f 0.67 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3070, 3032, 2930, 2858, 1728, 1595, 1497, 1453, 1428, 1377, 1345,

1291, 1251, 1213, 1158, 1110, 1061, 1029, 998, 939, 824, 790, 736, 700, 614, 581, 505, 489, 461, 420. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.70–7.61 (m, 4H, CH_{arom}), 7.44–7.19 (m, 21H, CH_{arom}), 6.58–6.49 (m, 3H, 2''-CH, 4''-CH, 6''-CH), 5.09–4.92 (m, 5H, 2-CH, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.44 (d, J = 11.5 Hz, 1H, 4-C$H_{2\text{-A Bn}}$), 4.40 (d, J = 11.5 Hz, 1H, 4-C$H_{2\text{-B Bn}}$), 3.81–3.66 (m, 2H, 6-CH_2), 3.66–3.58 (m, 1H, 4-CH), 3.52 (d, J = 14.7 Hz, 1H, 2'-C$H_{2\text{-A}}$), 3.47 (d, J = 14.7 Hz, 1H, 2'-C$H_{2\text{-B}}$), 1.85–1.77 (m, 1H, 3-CH), 1.77–1.66 (m, 2H, 5-CH_2), 1.17 (d, J = 6.4 Hz, 3H, 1-CH_3), 1.05 (s, 9H, C(CH_3)$_3$), 0.92 (d, J = 7.0 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 170.8 (1C, 1'-COO), 160.1 (2C, 3''-, 5''-C), 138.9 (1C, *ipso*-4-C_{Bn}), 137.0 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 136.5 (1C, *ipso*-1''-C), 135.7 (4C, 4 x *o*-CH$_{TBDPS}$), 133.9 (2C, 2 x *ipso*-C_{TBDPS}), 129.8 (2C, 2 x *p*-CH$_{TBDPS}$), 128.7 (4C, 2 x *m*-3'', 2 x *m*-5''-CH$_{Bn}$), 128.4 (2C, 3''-, 5''-*p*-CH$_{Bn}$), 128.1 (2C, 2 x *m*-4-CH$_{Bn}$), 127.8 (4C, 4 x *m*-CH$_{TBDPS}$), 127.7 (2C, 2 x *o*-4-CH$_{Bn}$), 127.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH$_{Bn}$), 127.5 (1C, *p*-4-CH$_{Bn}$), 108.6 (2C, 2''-, 6''-CH), 100.9 (1C, 4''-C), 77.4 (1C, 4-CH), 72.7 (1C, 2-CH), 71.8 (1C, 4-CH$_{2\ Bn}$), 70.2 (2C, 3''-, 5''-CH$_{2\ Bn}$), 60.7 (1C, 6-CH$_2$), 42.2 (1C, 2'-CH$_2$), 41.2 (1C, 3-CH), 34.1 (1C, 5-CH$_2$), 27.0 (3C, SiC(CH$_3$)$_3$), 19.3 (1C, SiC(CH$_3$)$_3$), 18.7 (1C, 1-CH$_3$), 10.6 (1C, 3-CH$_3$). HRESIMS *m/z* 829.3895 $[M+Na]^+$ (calcd for $C_{52}H_{58}O_6SiNa$, 829.3895).

(2*S*,3*R*,4*R*)-4-(Benzyloxy)-6-hydroxy-3-methylhexan-2-yl 2-[3,5-bis(benzyloxy)phenyl] acetate (**49**)

Following a published procedure,[61] silyl ether **48** (614 mg, 760 µmol, 1.00 eq) was dissolved in THF (5.5 mL) and TBAF (1M in THF, 988 µL, 988 µmol, 1.30 eq) was added dropwise at 0 °C. The reaction mixture was stirred overnight at ambient temperature before it was quenched with 35 mL saturated NH_4Cl (aq). The aqueous layer was washed with EtOAc (3 x 50 mL), dried ($MgSO_4$) and filtered. After flash chromatography (cyclohexane/EtOAc, 3:1) the primary alcohol **49** (387 mg, 681 µmol, 90%) could be obtained as a colorless oil. $[\alpha]_D^{21}$ +22.7 (*c* 0.93, $CHCl_3$). R_f 0.34 (cyclohexane/EtOAc, 2:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3434, 3062, 3032, 2978. 2938,

2875, 1725, 1594, 1497, 1453, 1377, 1345, 1291, 1252, 1207, 1157, 1100, 1057, 1029, 948, 908, 834, 737, 698. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 7.45–7.19 (m, 15H, CH_{arom}), 6.60–6.49 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.05 (s, 4H, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.91 (pseudo-p, J = 6.3 Hz, 1H, 2-C*H*), 4.46 (d, J = 11.6 Hz, 1H, 4-C$H_{2\text{-A Bn}}$), 4.44 (t, J = 5.1 Hz, 1H, 6-O*H*), 4.37 (d, J = 11.6 Hz, 1H, 4-C$H_{2\text{-B Bn}}$), 3.54 (s, 2H, 2'-CH_2), 3.50–3.39 (m, 3H, 4-C*H*, 6-CH_2), 1.84–1.72 (m, 1H, 3-C*H*), 1.64–1.53 (m, 2H, 5-CH_2), 1.11 (d, J = 6.3 Hz, 3H, 1-CH_3), 0.85 (d, J = 6.9 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 170.3 (1C, 1'-*C*OO), 159.4 (2C, 3''-, 5''-*C*), 139.0 (1C, *ipso*-4-*C*$_{Bn}$), 137.0 (2C, *ipso*-3'', *ipso*-5''-*C*$_{Bn}$), 136.6 (1C, *ipso*-1''-*C*), 128.4 (4C, 2 x *m*-3'', 2 x *m*-5''-*C*H$_{Bn}$), 128.2 (2C, 2 x *C*H$_{arom}$), 127.8 (2C, 2 x *C*H$_{arom}$), 127.7 (4C, 2 x *o*-3'', 2 x *o*-5''-*C*H$_{Bn}$), 127.4 (2C, 2 x *o*-4-*C*H$_{Bn}$), 127.3 (1C, *p*-4-*C*H$_{Bn}$), 108.5 (2C, 2''-, 6''-*C*H), 100.2 (1C, 4''-*C*), 77.0 (1C, 4-*C*H), 71.5 (1C, 2-*C*H), 70.7 (1C, 4-*C*H$_{2\ Bn}$), 69.3 (2C, 3''-, 5''-*C*H$_{2\ Bn}$), 57.6 (1C, 6-*C*H$_2$), 41.0 (1C, 2'-*C*H$_2$), 40.3 (1C, 3-*C*H), 33.8 (1C, 5-*C*H$_2$), 18.3 (1C, 1-*C*H$_3$), 10.0 (1C, 3-*C*H$_3$). HRESIMS *m*/*z* 591.2709 [M+Na]$^+$ (calcd for $C_{36}H_{40}O_6Na$, 591.2717).

(2*S*,3*R*,4*R*)-4-(Benzyloxy)-3-methyl-6-oxohexan-2-yl 2-[3,5-bis(benzyloxy)phenyl] acetate (**31**)

Using a modified procedure of Pannecoucke et al.,[27] primary alcohol **49** (361 mg, 635 µmol, 1.00 eq) was dissolved in dry MeCN (17.5 mL), IBX (444 mg, 1.59 mmol, 2.50 eq) was added, and the reaction mixture was stirred over preactivated 3 Å molecular sieves (0.50 g). After 2 h, another portion IBX (88.9 mg, 317 µmol, 0.50 eq) was added and the reaction mixture was stirred for another 3 h until the solvent was removed under reduced pressure at rt and the residue was taken up in EtOAc (50 mL). The mixture was filtered through a pad of celite and silica gel and the crude product was purified by flash chromatography (cyclohexane/EtOAc, 6:1), yielding the aldehyde **31** (329 mg, 581 µmol, 92%) was obtained as a yellowish oil. $[\alpha]_D^{22}$ +26.5 (*c* 0.97, $CHCl_3$). R_f 0.20 (cyclohexane/EtOAc, 6:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3065, 3032, 2980, 2934,

2879, 1723, 1594, 1497, 1453, 1377, 1344, 1291, 1249, 1212, 1153, 1081, 1058, 1028, 952, 911, 834, 737, 698, 634. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 9.62–9.59 (m, 1H, 6-C*H*O), 7.44–7.22 (m, 15H, CH_{arom}), 6.59–6.51 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.05 (s, 4H, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.95–4.86 (m, 1H, 2-C*H*), 4.45 (d, J = 11.6 Hz, 1H, 4-C$H_{2\text{-A Bn}}$), 4.39 (d, J = 11.6 Hz, 1H, 4-C$H_{2\text{-B Bn}}$), 3.91 (dt, J = 7.2, 4.8 Hz, 1H, 4-C*H*), 3.55 (s, 2H, 2'-CH_2), 2.59–2.50 (m, 2H, 5-CH_2), 1.91–1.81 (m, 1H, 3-C*H*), 1.13 (d, J = 6.4 Hz, 3H, 1-CH_3), 0.86 (d, J = 7.0 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 202.3 (1C, 6-*C*HO), 170.2 (1C, 1'-*C*OO), 159.4 (2C, 3''-, 5''-*C*), 138.4 (1C, *ipso*-4-C_{Bn}), 137.0 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 136.6 (1C, *ipso*-1''-*C*), 128.4 (4C, 2 x *m*-3'', 2 x *m*-5''-CH_{Bn}), 128.2 (2C, 2 x CH_{arom}), 127.8 (2C, 2 x CH_{arom}), 127.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH_{Bn}), 127.5 (2C, 2 x *o*-4-CH_{Bn}), 127.5 (1C, *p*-4-CH_{Bn}), 108.5 (2C, 2''-, 6''-*C*H), 100.3 (1C, 4''-*C*), 74.8 (1C, 4-*C*H), 70.7 (1C, 2-*C*H), 70.6 (1C, 4-$CH_{2\ Bn}$), 69.2 (2C, 3''-, 5''-$CH_{2\ Bn}$), 45.2 (1C, 5-CH_2), 41.1 (1C, 2'-CH_2), 40.4 (1C, 3-*C*H), 18.1 (1C, 1-CH_3), 9.9 (1C, 3-CH_3). HRESIMS *m*/*z* 589.2565 $[M+Na]^+$ (calcd for $C_{36}H_{38}O_6Na$, 589.2561).

tert-Butyl (5*R*,6*R*,7*S*,*E*)-5-(benzyloxy)-7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (**50**)

According to procedures from Jiang and Chen et al.,[46] phosphonium ylide **24** (295 mg, 755 µmol, 1.30 eq) was added to a solution of aldehyde **31** (329 mg, 581 µmol, 1.00 eq) in CH_2Cl_2 (35 mL) at ambient temperature and the solution was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc, 12:1) yielding the unsaturated *tert*-butyl ester **50** (381 mg, 562 µmol, 97%) as a colorless oil in an *E*/*Z* ratio of >95:5. $[\alpha]_D^{22}$ +8.4 (*c* 0.96, $CHCl_3$). R_f 0.31 (cyclohexane/EtOAc, 10:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3065, 3033, 2978, 2932, 1728, 1703, 1650, 1595, 1497, 1454, 1368, 1345, 1291, 1251, 1216, 1159, 1083, 1061, 1028, 961, 851, 737, 698. ^{1}H NMR, COSY (400 MHz, CD_3CN) δ_H 7.44–7.21 (m, 15H, CH_{arom}), 6.69 (tt, J = 7.5, 1.4 Hz,

1H, 3-C*H*), 6.54–6.50 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.03 (s, 4H, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.96 (qd, J = 6.5, 4.7 Hz, 1H, 7-C*H*), 4.46 (d, J = 11.3 Hz, 1H, 5-C$H_{2\text{-A Bn}}$), 4.38 (d, J = 11.3 Hz, 1H, 5-C$H_{2\text{-B Bn}}$), 3.50 (s, 2H, 2'-CH_2), 3.41 (dt, J = 6.2, 5.2 Hz, 1H, 5-C*H*), 2.34–2.27 (m, 2H, 4-CH_2), 1.78–1.70 (m, 4H, 2-CH_3, 6-C*H*), 1.44 (s, 9H, OC(CH_3)$_3$), 1.16 (d, J = 6.4 Hz, 3H, 8-CH_3), 0.93 (d, J = 7.0 Hz, 3H, 6-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, CD_3CN) δ_C 171.5 (1C, 1'-*C*OO), 167.9 (1C, 1-*C*OO^{t}Bu), 160.9 (2C, 3''-, 5''-*C*), 139.9 (1C, *ipso*-5-C_{Bn}), 138.3 (1C, 3-*C*H), 138.2 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 138.1 (1C, *ipso*-1''-*C*), 131.4 (1C, 2-*C*), 129.5 (4C, 2 x *m*-3'', 2 x *m*-5''-CH_{Bn}), 129.3 (2C, 2 x CH_{arom}), 128.9 (2C, 2 x CH_{arom}), 128.8 (2C, 2 x *o*-5-CH_{Bn}), 128.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH_{Bn}), 128.5 (1C, *p*-5-CH_{Bn}), 109.6 (2C, 2''-, 6''-C*H*), 101.4 (1C, 4''-*C*), 80.6 (1C, O*C*(CH_3)$_3$), 80.4 (1C, 5-C*H*), 72.4 (1C, 5-C$H_{2\ Bn}$), 72.3 (1C, 7-C*H*), 70.7 (2C, 3''-, 5''-C$H_{2\ Bn}$), 42.5 (1C, 2'-CH_2), 42.1 (1C, 6-C*H*), 31.3 (1C, 4-CH_2), 28.3 (3C, OC(CH_3)$_3$), 18.5 (1C, 8-CH_3), 12.9 (1C, 2-CH_3), 10.3 (1C, 6-CH_3). HRESIMS *m*/*z* 701.3450 $[M+Na]^+$ (calcd for $C_{43}H_{50}O_7Na$, 701.3449).

(13*R*,14*R*,15*S*)-5,7,13-Tris(benzyloxy)-4-dechloro-14-deoxyoxacyclododecindione (**32**)

Following modified procedures of Roberts et al. and Opatz et al.,[15,16] a solution of CH_2Cl_2 (994 mL), trifluoroacetic acid (32.5 mL), and trifluoroacetic anhydride (16.3 mL) was precooled to –8 °C in a 4 L round-bottom flask and *tert*-butyl (5*R*,6*R*,7*S*,*E*)-5-(benzyloxy)-7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (**50**) (452 mg, 666 µmol, 1.00 eq) in CH_2Cl_2 (27 mL) was added dropwise. The reaction mixture was left to stand at –8 °C for 24 h and then gradually warmed to 0 °C and rt to stir for another 2 d. The reaction mixture was neutralized by careful addition of saturated $NaHCO_3$ (aq) and washing of the organic layer (3 x 100 mL). The organic residue was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. After purification by flash chromatography (cyclohexane/EtOAc, 15:1, 1%AcOH to 13:1, 1% AcOH) the 12-membered macrolactone **32** (296 mg, 489 µmol, 74%) was obtained as colorless oil. $[\alpha]_D^{22}$ –21.3 (*c* 0.60, CH_2Cl_2). R_f 0.49

(cyclohexane/EtOAc, 3:1, 1% AcOH). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3063, 3032, 2981, 2927, 2874, 1725, 1651, 1603, 1583, 1541, 1497, 1454, 1433, 1374, 1338, 1309, 1279, 1213, 1167, 1145, 1122, 1067, 1028, 1002, 958, 906, 885, 833, 736, 698, 665, 632. ^{1}H NMR, COSY (600 MHz, CD_3CN) δ_H 7.48–7.24 (m, 15H, CH_{arom}), 6.69–6.64 (m, 1H, 4-C*H*), 6.64–6.61 (m, 1H, 6-C*H*), 6.22 (t, *J* = 7.7 Hz, 1H, 11-C*H*), 5.09 (s, 2H, 5-C$H_{2\ Bn}$), 5.04 (s, 2H, 7-C$H_{2\ Bn}$), 4.89–4.79 (m, 1H, 15-C*H*), 4.62 (d, *J* = 11.5 Hz, 1H, 13-C$H_{2\text{-A Bn}}$), 4.44 (d, *J* = 11.5 Hz, 1H, 13-C$H_{2\text{-B Bn}}$), 3.56–3.43 (m, 1H, 13-C*H*), 3.34 (d, *J* = 14.2 Hz, 1H, 2-C$H_{2\text{-A}}$), 3.22–3.05 (m, 1H, 2-C$H_{2\text{-B}}$), 2.80–2.64 (m, 1H, 12-C$H_{2\text{-A}}$), 2.41–2.33 (m, 1H, 12-C$H_{2\text{-B}}$), 1.92–1.84 (m, 4H, 10-CH_3, 14-C*H*), 1.11 (d, *J* = 6.6 Hz, 3H, 15-CH_3), 0.91 (d, *J* = 7.3 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN) δ_C 199.2 (1C, 9-*C*O), 170.8 (1C, 1-*C*OO), 160.5 (1C, 5-*C*), 157.2 (1C, 7-*C*), 146.9 (1C, 11-*C*H), 140.4 (1C, 10-*C*), 139.8 (1C, *ipso*-13-C_{Bn}), 137.9 (1C, *ipso*-7-C_{Bn}), 137.9 (1C, *ipso*-5-C_{Bn}), 134.1 (1C, 3-*C*), 129.5 (2C, 2 x *m*-CH_{Bn}), 129.4 (2C, 2 x *m*-CH_{Bn}), 129.2 (2C, 2 x *m*-CH_{Bn}), 129.0 (1C, *p*-CH_{Bn}), 128.9 (1C, *p*-CH_{Bn}), 128.8 (2C, 2 x *o*-CH_{Bn}), 128.6 (2C, 2 x *o*-CH_{Bn}), 128.4 (1C, *p*-CH_{Bn}), 128.3 (2C, 2 x *o*-CH_{Bn}), 124.4 (1C, 8-*C*), 110.1 (1C, 4-*C*H), 100.7 (1C, 6-*C*H), 78.1 (1C, 13-*C*H), 73.9 (1C, 15-*C*H), 71.6 (1C, 13-$CH_{2\ Bn}$), 70.9 (1C, 7-$CH_{2\ Bn}$), 70.9 (1C, 5-$CH_{2\ Bn}$), 41.7 (1C, 14-*C*H), 39.8 (1C, 2-CH_2), 32.5 (1C, 12-CH_2), 15.2 (1C, 15-CH_3), 11.4 (1C, 14-CH_3), 10.8 (1C, 10-CH_3). HRESIMS *m*/*z* 643.2437 [M+K]$^+$ (calcd for $C_{39}H_{40}O_6K$, 643.2456).

(13*R*,14*R*,15*S*)-5,7,13-Tris(benzyloxy)-14-deoxyoxacyclododecindione (**51**)

Following modified procedures of Opatz et al.,[15] a solution of macrolactone **32** (276 mg, 457 µmol, 1.00 eq) in *N*,*N*-dimethylformamide (19 mL) was treated with trifluoroacetic acid (52.8 µL, 686 µmol, 1.50 eq) and a freshly prepared solution of *N*-chlorosuccinimide (100mM in DMF, 2.74 mL, 274 µmol, 0.60 eq) was added slowly within 15 min at rt. After further addition of *N*-chlorosuccinimide (day 2: 100mM in DMF, 1.37 mL, 137 µmol, 0.30 eq; day 3:100mM in DMF, 0.685 mL, 68.5 µmol, 0.15 eq) and trifluoroacetic acid (day 3: 18 µL,

229 µmmol, 0.50 eq), the reaction mixture was quenched by the addition of H_2O (50 mL) on day 4. The aqueous phase was extracted with diethyl ether (4 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc, 13:1, 1%AcOH to 10:1, 1% AcOH) to yield the protected oxacyclododecindione **51** (249 mg, 390 µmol, 85%) as a colorless oil. $[\alpha]_D^{22}$ –67.2 (*c* 0.86, CH_2Cl_2). R_f 0.14 (cyclohexane/EtOAc, 10:1, 1% AcOH). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3064, 3032, 2980, 2931, 2877, 1725, 1655, 1592, 1575, 1531, 1497, 1454, 1412, 1385, 1334, 1315, 1254, 1223, 1184, 1158, 1089, 1068, 1027, 1003, 964, 909, 845, 812, 737, 697, 669, 629. ^{1}H NMR, COSY (600 MHz, CD_3CN) δ_H 7.51–7.23 (m, 15H, CH_{arom}), 6.87 (s, 1H, 6-C*H*), 6.20 (t, *J* = 7.8 Hz, 1H, 11-C*H*), 5.21 (s, 2H, 5-C$H_{2\ Bn}$), 5.08 (s, 2H, 7-C$H_{2\ Bn}$), 4.92–4.81 (m, 1H, 15-C*H*), 4.62 (d, *J* = 11.7 Hz, 1H, 13-C$H_{2\text{-A Bn}}$), 4.44 (d, *J* = 11.7 Hz, 1H, 13-C$H_{2\text{-B Bn}}$), 4.01–3.00 (m, 2H, 2-CH_2), 3.48 (dt, *J* = 8.2, 4.0 Hz, 1H, 13-C*H*), 2.69–2.30 (m, 2H, 12-CH_2), 1.99–1.95 (m, 1H, 14-C*H*), 1.90–1.78 (m, 3H, 10-CH_3), 1.06 (d, *J* = 6.6 Hz, 3H, 15-CH_3), 0.86 (d, *J* = 7.4 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN) δ_C 198.2 (1C, 9-*C*O), 169.1 (1C, 1-*C*OO), 155.8 (1C, 5-*C*), 155.2 (1C, 7-*C*), 147.1 (1C, 11-*C*H), 139.9 (1C, *ipso*-13-C_{Bn}), 137.5 (1C, *ipso*-7-C_{Bn}), 137.4 (1C, *ipso*-5-C_{Bn}), 137.2 (1C, 10-*C*), 132.0 (1C, 3-*C*), 129.6 (2C, 2 x *m*-CH_{Bn}), 129.5 (2C, 2 x *m*-CH_{Bn}), 129.2 (2C, 2 x *m*-CH_{Bn}), 129.2 (1C, *p*-CH_{Bn}), 129.1 (1C, *p*-CH_{Bn}), 128.7 (2C, 2 x *o*-CH_{Bn}), 128.6 (2C, 2 x *o*-CH_{Bn}), 128.5 (2C, 2 x *o*-CH_{Bn}), 128.4 (1C, *p*-CH_{Bn}), 125.5 (1C, 8-*C*), 117.0 (1C, 4-*C*Cl), 100.7 (1C, 6-*C*H), 77.9 (1C, 13-*C*H), 74.4 (1C, 15-*C*H), 71.9 (1C, 5-$CH_{2\ Bn}$), 71.8 (1C, 13-$CH_{2\ Bn}$), 71.5 (1C, 7-$CH_{2\ Bn}$), 41.8 (1C, 14-*C*H), 37.7 (1C, 2-CH_2), 33.6 (1C, 12-CH_2), 15.0 (1C, 15-CH_3), 11.4 (1C, 14-CH_3), 10.7 (1C, 10-CH_3). HRESIMS *m*/*z* 639.2486 $[M+H]^+$ (calcd for $C_{39}H_{39}ClO_6H$, 639.2508).

(13*R*,14*S*,15*S*)-13-Hydroxy-14-deoxyoxacyclododecindione (**33**)

Following a modified procedure of Opatz et al.,[15] boron trichloride (1M in heptane, 3.16 mL, 3.16 mmol, 9.00 eq) was added to a solution of benzyl protected macrolactone **51** (225 mg, 351 µmmol, 1.00 eq) in CH_2Cl_2 (65 mL) at –78 °C. Within 2.5 h, the deep orange solution was gradually warmed to –30 °C and stirred for another 2 h at the same temperature. After complete conversion of the starting material, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (60 mL) while warming to rt. The aqueous layer was extracted with CH_2Cl_2 (7 x 80 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 3:1, 1% AcOH to 1:1, 1% AcOH) and the macrolactone (13*R*,14*S*,15*S*)-13-hydroxy-14-deoxyoxacyclododecindione (**33**) (52.7 mg, 143 µmol, 41%) was obtained as a colorless solid. For its biological evaluation the macrolactone **33** was further purified by preparative HPLC (C_{18}-HTEC, isocratic 25% MeCN in H_2O, 20 min). $[\alpha]_D^{22}$ –75.6 (*c* 0.22, MeOH). R_f 0.19 (cyclohexane/EtOAc, 1:1, 1% AcOH). t_R (HPLC): 7.55 min (PFP, isocratic 25% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3375, 2983, 2939, 1706, 1627, 1606, 1439, 1356, 1292, 1239, 1156, 1115, 1069, 1051, 1008, 986, 949, 848, 653, 592. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 10.24 (s, 1H, 7-CO*H*), 9.72 (s, 1H, 5-CO*H*), 6.48 (s, 1H, 6-C*H*), 6.18 (t, *J* = 7.7 Hz, 1H, 11-C*H*), 4.82 (d, *J* = 4.8 Hz, 1H, 13-O*H*), 4.80–4.73 (m, 1H, 15-C*H*), 3.62 (pseudo-p, *J* = 5.1 Hz, 1H, 13-C*H*), 3.35–3.21 (m, 2H, 2-CH_2), 2.37–2.29 (m, 2H, 12-CH_2), 1.80–1.70 (m, 4H, 10-CH_3, 14-C*H*), 1.06 (d, *J* = 6.6 Hz, 3H, 15-CH_3), 0.79 (d, *J* = 7.4 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 197.8 (1C, 9-*C*O), 168.1 (1C, 1-*C*OO), 153.8 (1C, 7-*C*), 153.1 (1C, 5-*C*), 146.5 (1C, 11-*C*H), 138.3 (1C, 10-*C*), 130.1 (1C, 3-*C*), 120.9 (1C, 8-*C*), 111.8 (1C, 4-*C*Cl), 102.4 (1C, 6-*C*H), 73.3 (1C, 15-*C*H), 67.9 (1C, 13-*C*H), 40.8 (1C, 14-*C*H), 37.5 (1C, 12-*C*H_2), 36.8 (1C, 2-*C*H_2), 14.5 (1C, 15-*C*H_3), 11.0 (1C, 14-*C*H_3), 10.5 (1C, 10-*C*H_3). HRESIMS *m*/*z* 369.1086 $[M+H]^+$ (calcd for $C_{18}H_{21}ClO_6H$, 369.1099).

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-3-methylhexan-2-yl 2-[3,5-bis (benzyloxy)phenyl]acetate (**52**)

According to procedures from Opatz et al.,[53] a solution of *N*,*N*'-dicyclohexylcarbodiimide (0.25M in CH_2Cl_2, 7.96 mL, 1.99 mmol, 1.20 eq) was added dropwise to an ice-cooled solution of hexan-2-ol **22** (594 mg, 1.66 mmol, 1.00 eq), (3,5-bis(benzyloxy)-phenyl)acetic acid (**5**, 636 mg, 1.82 mmol, 1.10 eq), and 4-(dimethylamino)pyridine (40.5 mg, 332 µmol, 0.20 eq) in CH_2Cl_2 (42 mL). The reaction mixture was stirred at 0 °C for 3 h until another portion of *N*,*N*'-dicyclohexylcarbodiimide (0.25M in CH_2Cl_2, 1.33 mL, 0.33 mmol, 0.20 eq) and 4-(dimethylamino)pyridine (20.3 mg, 166 µmol, 0.10 eq) were added and the solution was then warmed to rt overnight. After the addition of 100 mL saturated NH_4Cl (aq) the aqueous layer was washed with CH_2Cl_2 (3 x 60 mL), dried ($MgSO_4$) and filtered. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 5:1) yielding ester **52** (904 mg, 1.31 mmol, 79%) as a colorless oil. $[\alpha]_D^{22}$ +3.4 (*c* 0.87, $CHCl_3$). R_f 0.52 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3063, 3032, 2934, 2864, 1728, 1607, 1594, 1512, 1498, 1453, 1376, 1345, 1292, 1248, 1212, 1159, 1098, 1061, 1038, 1030, 953, 910, 825, 737, 698. ^{1}H NMR, COSY (400 MHz, CD_3CN) δ_H 7.43–7.18 (m, 15H, CH_{arom}), 7.23–7.15 (m, 2H, 2 x *o*-CH_{PMB}), 6.88–6.81 (m, 2H, 2 x *m*-CH_{PMB}), 6.56–6.47 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.09 (dq, *J* = 6.5, 3.8 Hz, 1H, 2-C*H*), 5.00 (s, 4H, 3''-C$H_{2\ Bn}$, 5''-C$H_{2\ Bn}$), 4.36 (d, *J* = 11.6 Hz, 1H, 6-C$H_{2\text{-A}\ PMB}$), 4.30 (d, *J* = 11.6 Hz, 1H, 6-C$H_{2\text{-B}\ PMB}$), 4.24 (d, *J* = 11.0 Hz, 1H, 4-C$H_{2\text{-A}\ Bn}$), 4.16 (d, *J* = 11.0 Hz, 1H, 4-C$H_{2\text{-B}\ Bn}$), 3.74 (s, 3H, OC$H_{3\ PMB}$), 3.53–3.42 (m, 4H, 6-CH_2, 2'-CH_2), 3.30 (td, *J* = 7.6, 3.2 Hz, 1H, 4-C*H*), 1.87–1.70 (m, 2H, 3-C*H*, 5-C$H_{2\text{-A}}$), 1.59 (ddt, *J* = 14.5, 7.6, 5.6 Hz, 1H, 5-C$H_{2\text{-B}}$), 1.16 (d, *J* = 6.5 Hz, 3H, 1-CH_3), 0.88 (d, *J* = 7.0 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, CD_3CN) δ_C 171.6 (1C, 1'-*C*OO), 160.9 (2C, 3''-, 5''-*C*), 160.1 (1C, *p*-C_{PMB}), 140.0 (1C, *ipso*-4-C_{Bn}), 138.2 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 138.2 (1C, *ipso*-1''-*C*), 131.9 (1C, *ipso*-C_{PMB}), 130.3 (2C, 2 x *o*-CH_{PMB}), 129.5 (4C, 2 x *m*-3'', 2 x *m*-5''-CH_{Bn}), 129.2 (2C, 2 x CH_{arom}), 128.9 (2C, 2 x *o*-4-CH_{Bn}), 128.9 (2C, 2 x CH_{arom}), 128.7 (4C, 2 x *o*-3'', 2 x

o-5''-*C*H$_{Bn}$), 128.4 (1C, *p*-4-*C*H$_{Bn}$), 114.6 (2C, 2 x *m*-*C*H$_{PMB}$), 109.6 (2C, 2''-, 6''-*C*H), 101.5 (1C, 4''-*C*), 78.2 (1C, 4-*C*H), 73.0 (1C, 6-*C*H$_{2\ PMB}$), 72.5 (1C, 4-*C*H$_{2\ Bn}$), 71.8 (1C, 2-*C*H), 70.7 (2C, 3''-, 5''-*C*H$_{2\ Bn}$), 66.9 (1C, 6-*C*H$_2$), 55.8 (1C, O*C*H$_{3\ PMB}$), 42.5 (1C, 2'-*C*H$_2$), 42.2 (1C, 3-*C*H), 31.9 (1C, 5-*C*H$_2$), 18.5 (1C, 1-*C*H$_3$), 10.0 (1C, 3-*C*H$_3$). HRESIMS *m*/*z* 711.3283 $[M+Na]^+$ (calcd for $C_{44}H_{48}O_7Na$, 711.3292).

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-6-hydroxy-3-methylhexan-2-yl 2-[3,5-bis(benzyloxy)phenyl] acetate (**53**)

Following a previously published procedure,[45] PMB-ether **52** (880 g, 1.28 mmol, 1.00 eq) was dissolved in CH_2Cl_2 (39 mL) and phosphate buffer (pH = 7.63 mM, 2 mL) was added. After the addition of DDQ (348 mg, 1.53 mmol, 1.20 eq) the reaction was stirred for 1.5 h at ambient temperature before another portion of DDQ (29.0 mg, 0.13 mmol, 0.10 eq) was added and stirred a further 30 min. The reaction was quenched by the addition of water (100 mL) and the aqueous layer was washed with CH_2Cl_2 (4 x 60 mL), dried ($MgSO_4$) and filtered. After flash chromatography (cyclohexane/EtOAc, 3:1 to 2:1), the primary alcohol **53** (658 mg, 1.16 mmol, 91%) could be obtained as a colorless oil. $[\alpha]_D^{22}$ +15.1 (*c* 0.96, $CHCl_3$). R_f 0.24 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3455, 3064, 3032, 2977, 2939, 2878, 1727, 1594, 1497, 1453, 1377, 1344, 1292, 1250, 1213, 1159, 1059, 1029, 990, 952, 831, 738, 698. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 7.45–7.21 (m, 15H, C*H*$_{arom}$), 6.59–6.50 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.06–4.97 (m, 5H, 2-C*H*, 3''-C*H*$_{2\ Bn}$, 5''-C*H*$_{2\ Bn}$), 4.40 (t, *J* = 5.2 Hz, 1H, 6-O*H*), 4.34 (d, *J* = 11.2 Hz, 1H, 4-C*H*$_{2\text{-A Bn}}$), 4.21 (d, *J* = 11.2 Hz, 1H, 4-C*H*$_{2\text{-B Bn}}$), 3.60–3.41 (m, 4H, 2'-C*H*$_2$, 6-C*H*$_2$), 3.33–3.26 (m, 1H, 4-C*H*), 1.79 (td, *J* = 7.0, 4.4 Hz, 1H, 3-C*H*), 1.65 (dtd, *J* = 14.3, 7.4, 3.1 Hz, 1H, 5-C*H*$_{2\text{-A}}$), 1.51 (dtd, *J* = 14.3, 7.0, 5.1 Hz, 1H, 5-C*H*$_{2\text{-B}}$), 1.14 (d, *J* = 6.4 Hz, 3H, 1-C*H*$_3$), 0.83 (d, *J* = 7.0 Hz, 3H, 3-C*H*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 170.4 (1C, 1'-*C*OO), 159.4 (2C, 3''-, 5''-*C*), 138.8 (1C, *ipso*-4-*C*$_{Bn}$), 136.9 (2C, *ipso*-3'', *ipso*-5''-*C*$_{Bn}$), 136.7 (1C, *ipso*-1''-*C*), 128.4 (4C, 2 x *m*-3'', 2 x *m*-5''-*C*H$_{Bn}$), 128.1

(2C, 2 x CH_{arom}), 127.8 (2C, 2 x CH_{arom}), 127.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH_{Bn}), 127.6 (2C, 2 x *o*-4-CH_{Bn}), 127.3 (1C, *p*-4-CH_{Bn}), 108.5 (2C, 2''-, 6''-*C*H), 100.2 (1C, 4''-*C*), 76.7 (1C, 4-*C*H), 70.9 (1C, 4-$CH_{2\ Bn}$), 70.6 (1C, 2-*C*H), 69.3 (2C, 3''-, 5''-$CH_{2\ Bn}$), 57.2 (1C, 6-CH_2), 41.1 (1C, 2'-CH_2), 40.5 (1C, 3-*C*H), 33.5 (1C, 5-CH_2), 18.0 (1C, 1-CH_3), 9.6 (1C, 3-CH_3). HRESIMS *m*/*z* 591.2723 $[M+Na]^+$ (calcd for $C_{36}H_{40}O_6Na$, 591.2717).

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-3-methyl-6-oxohexan-2-yl 2-[3,5-bis(benzyloxy)phenyl] acetate (**34**)

Using a modified procedure of Pannecoucke et al.,[27] primary alcohol **53** (626 mg, 1.10 mmol, 1.00 eq) was dissolved in dry MeCN (31 mL), IBX (771 mg, 2.75 mmol, 2.50 eq) was added, and the reaction mixture was stirred over preactivated 3 Å molecular sieves (0.50 g). After 2 h, another portion IBX (154 mg, 551 µmol, 0.50 eq) was added and the reaction mixture was stirred for another 2 h until the solvent was removed under reduced pressure at rt and the residue was taken up in EtOAc (50 mL). The mixture was filtered through a pad of celite and silica gel, after removing the solvent under reduced pressure the aldehyde **34** (535 mg, 944 µmol, 86%) was obtained as a yellowish-green oil. $[\alpha]_D^{22}$ +23.4 (*c* 0.98, $CHCl_3$). R_f 0.44 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3064, 3033, 2979, 2874, 2728, 1725, 1594, 1497, 1453, 1378, 1344, 1291, 1250, 1214, 1159, 1083, 1058, 1029, 990, 832, 738, 698. ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ_H 9.63 (dd, *J* = 3.0, 1.5 Hz, 1H, 6-C*H*O), 7.45–7.17 (m, 15H, CH_{arom}), 6.60–6.51 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.07–4.99 (m, 5H, 2-C*H*, 3''-$CH_{2\ Bn}$, 5''-$CH_{2\ Bn}$), 4.37 (d, *J* = 11.2 Hz, 1H, 4-$CH_{2\text{-A Bn}}$), 4.22 (d, *J* = 11.2 Hz, 1H, 4-$CH_{2\text{-B Bn}}$), 3.72 (td, *J* = 7.2, 4.0 Hz, 1H, 4-C*H*), 3.58 (d, *J* = 14.9 Hz, 1H, 2'-$CH_{2\text{-A}}$), 3.53 (d, *J* = 14.9 Hz, 1H, 2'-$CH_{2\text{-B}}$), 2.60 (ddd, *J* = 16.5, 4.0, 1.6 Hz, 1H, 5-$CH_{2\text{-A}}$), 2.50–2.43 (m, 1H, 5-$CH_{2\text{-B}}$), 1.89 (qd, *J* = 7.1, 3.7 Hz, 1H, 3-C*H*), 1.16 (d, *J* = 6.4 Hz, 3H, 1-CH_3), 0.84 (d, *J* = 7.1 Hz, 3H, 3-CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ_C 202.3 (1C, 6-*C*HO), 170.3 (1C, 1'-*C*OO), 159.5 (2C, 3''-, 5''-*C*), 138.2 (1C, *ipso*-4-C_{Bn}), 136.9 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 136.6

(1C, *ipso*-1''-*C*), 128.4 (4C, 2 x *m*-3'', 2 x *m*-5''-*C*H$_{Bn}$), 128.2 (2C, 2 x *C*H$_{arom}$), 127.8 (2C, 2 x *C*H$_{arom}$), 127.7 (2C, 2 x *o*-4-*C*H$_{Bn}$), 127.7 (4C, 2 x *o*-3'', 2 x *o*-5''-*C*H$_{Bn}$), 127.5 (1C, *p*-4-*C*H$_{Bn}$), 108.5 (2C, 2''-, 6''-*C*H), 100.2 (1C, 4''-*C*), 75.2 (1C, 4-*C*H), 70.6 (1C, 4-*C*H$_{2\ Bn}$), 70.2 (1C, 2-*C*H), 69.3 (2C, 3''-, 5''-*C*H$_{2\ Bn}$), 44.9 (1C, 5-*C*H$_2$), 41.1 (1C, 2'-*C*H$_2$), 40.6 (1C, 3-*C*H), 17.9 (1C, 1-*C*H$_3$), 9.2 (1C, 3-*C*H$_3$). HRESIMS *m*/*z* 589.2560 $[M+Na]^+$ (calcd for $C_{36}H_{38}O_6Na$, 589.2561).

tert-Butyl (5*S*,6*R*,7*S*,*E*)-5-(benzyloxy)-7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (**54**)

According to procedures from Jiang and Chen et al.,[46] phosphonium ylide **24** (443 mg, 1.13 mmol, 1.20 eq) was added to a solution of aldehyde **34** (535 mg, 944 µmol, 1.00 eq) in CH_2Cl_2 (38 mL) at ambient temperature. After 3 h, another portion of phosphonium ylide **24** (73.8 mg, 189 µmol, 0.20 eq) was added and the solution was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc, 15:1 to 10:1) yielding the unsaturated *tert*-butyl ester **54** (584 mg, 860 µmol, 91%) as a colorless oil in an *E*/*Z* ratio of >95:5. $[\alpha]_D^{21}$ +27.5 (*c* 0.87, $CHCl_3$). R_f 0.14 (cyclohexane/EtOAc, 15:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3065, 3032, 2977, 2930, 1729, 1703, 1650, 1595, 1497, 1454, 1368, 1344, 1291, 1250, 1215, 1160, 1090, 1061, 1029, 987, 950, 911, 851, 738, 698, 671, 665. ^{1}H NMR, COSY (400 MHz, CD_3CN) δ_H 7.43–7.21 (m, 15H, C*H*$_{arom}$), 6.70 (tq, *J* = 8.0, 1.5 Hz, 1H, 3-C*H*), 6.57–6.49 (m, 3H, 2''-C*H*, 4''-C*H*, 6''-C*H*), 5.21 (qd, *J* = 6.5, 2.9 Hz, 1H, 7-C*H*), 5.01 (s, 4H, 3''-C*H*$_{2\ Bn}$, 5''-C*H*$_{2\ Bn}$), 4.30 (d, *J* = 10.8 Hz, 1H, 5-C*H*$_{2\text{-A Bn}}$), 4.08 (d, *J* = 10.8 Hz, 1H, 5-C*H*$_{2\text{-B Bn}}$), 3.53 (d, *J* = 14.5 Hz, 1H, 2'-C*H*$_{2\text{-A Bn}}$), 3.48 (d, *J* = 10.8 Hz, 1H, 2'-C*H*$_{2\text{-B Bn}}$), 3.24 (ddd, *J* = 8.5, 6.0, 3.9 Hz, 1H, 5-C*H*), 2.51–2.41 (m, 1H, 4-C*H*$_{2\text{-A}}$), 2.35–2.24 (m, 1H, 4-C*H*$_{2\text{-B}}$), 1.77–1.63 (m, 4H, 6-C*H*, 2-C*H*$_3$), 1.43 (s, 9H, OC(C*H*$_3$)$_3$), 1.18 (d, *J* = 6.5 Hz, 3H, 8-C*H*$_3$), 0.88 (d, *J* = 7.0 Hz, 3H, 6-C*H*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, CD_3CN) δ_C 171.6 (1C, 1'-*C*OO), 167.9 (1C, 1-*C*OO^tBu), 161.0 (2C, 3''-, 5''-*C*),

139.7 (1C, *ipso*-5-C_{Bn}), 138.2 (2C, *ipso*-3'', *ipso*-5''-C_{Bn}), 138.2 (1C, *ipso*-1''-*C*), 137.8 (1C, 3-*C*H), 131.6 (1C, 2-*C*), 129.5 (4C, 2 x *m*-3'', 2 x *m*-5''-CH_{Bn}), 129.2 (2C, 2 x CH_{arom}), 129.0 (2C, 2 x *o*-5-CH_{Bn}), 128.9 (2C, 2 x CH_{arom}), 128.7 (4C, 2 x *o*-3'', 2 x *o*-5''-CH_{Bn}), 128.5 (1C, *p*-5-CH_{Bn}), 109.7 (2C, 2''-, 6''-*C*H), 101.4 (1C, 4''-*C*), 80.6 (1C, O*C*$(CH_3)_3$), 80.1 (1C, 5-*C*H), 72.5 (1C, 5-$CH_{2\ Bn}$), 71.1 (1C, 7-*C*H), 70.7 (2C, 3''-, 5''-$CH_{2\ Bn}$), 42.6 (1C, 2'-CH_2), 42.4 (1C, 6-*C*H), 30.7 (1C, 4-CH_2), 28.3 (3C, OC$(CH_3)_3$), 18.3 (1C, 8-CH_3), 13.0 (1C, 2-CH_3), 9.8 (1C, 6-CH_3). HRESIMS *m*/*z* 696.3889 $[M+NH_4]^+$ (calcd for $C_{43}H_{50}O_7NH_4$, 696.3895).

(13*S*,14*R*,15*S*)-5,7,13-Tris(benzyloxy)-4-dechloro-14-deoxyoxacyclododecindione (**35**)

Following modified procedures of Roberts et al. and Opatz et al.,[15,16] a solution of CH_2Cl_2 (1210 mL), trifluoroacetic acid (39.0 mL), and trifluoroacetic anhydride (19.5 mL) was precooled to –8 °C in a 3 L round-bottom flask and *tert*-butyl (5*S*,6*R*,7*S*,*E*)-5-(benzyloxy)-7-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)-2,6-dimethyloct-2-enoate (**54**) (560 mg, 824 µmol, 1.00 eq) in CH_2Cl_2 (30 mL) was added dropwise. The reaction mixture was left to stand at –8 °C for 24 h and then gradually warmed to 0 °C and rt to stir for another 4 d. The reaction mixture was neutralized by careful addition of saturated $NaHCO_3$ (aq) and washing of the organic layer (3 x 100 mL). The organic residue was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. After purification by flash chromatography (cyclohexane/EtOAc, 10:1 to 6:1) the 12-membered macrolactone **35** (339 mg, 561 µmol, 68%) was obtained as colorless oil. $[\alpha]_D^{22}$ –26.1 (*c* 0.67, CH_2Cl_2). R_f 0.16 (cyclohexane/EtOAc, 10:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3063, 3033, 2980, 2930, 2875, 1725, 1679, 1657, 1650, 1641, 1604, 1582, 1497, 1454, 1433, 1378, 1310, 1282, 1226, 1177, 1152, 1131, 1085, 1066, 1029, 1000, 963, 942, 909, 836, 738, 698, 642. ^{1}H NMR, COSY (600 MHz, CD_3CN) δ_H 7.50–7.28 (m, 15H, CH_{arom}), 6.69–6.63 (m, 2H, 4-C*H*, 6-C*H*), 6.22–6.08 (m, 1H, 11-C*H*), 5.11 (s, 2H, 5-C$H_{2\ Bn}$), 5.06 (s, 2H, 7-C$H_{2\ Bn}$), 4.92 (qd, *J* = 6.4, 1.90 Hz, 1H, 15-C*H*), 4.52 (s, 2H, 13-C$H_{2\ Bn}$), 3.49–3.43 (m, 1H, 13-C*H*), 3.31 (d, *J* = 14.3 Hz, 1H, 2-C$H_{2\text{-A}}$), 3.26–3.14 (m, 1H, 2-C$H_{2\text{-B}}$), 2.70–

2.50 (m, 2H, 12-CH_2), 2.12–2.05 (m, 1H, 14-C*H*), 1.90 (s, 3H, 10-CH_3), 1.19 (d, J = 6.4 Hz, 3H, 15-CH_3), 0.95 (d, J = 7.3 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN) δ_C 199.3 (1C, 9-*C*O), 170.9 (1C, 1-*C*OO), 160.6 (1C, 5-*C*), 157.2 (1C, 7-*C*), 147.4 (1C, 11-*C*H), 139.9 (1C, *ipso*-13-C_{Bn}), 139.0 (1C, 10-*C*), 137.9 (1C, *ipso*-7-C_{Bn}), 137.9 (1C, *ipso*-5-C_{Bn}), 133.7 (1C, 3-*C*), 129.5 (2C, 2 x *m*-CH_{Bn}), 129.4 (2C, 2 x *m*-CH_{Bn}), 129.3 (2C, 2 x *m*-CH_{Bn}), 129.0 (1C, *p*-CH_{Bn}), 128.9 (1C, *p*-CH_{Bn}), 128.8 (2C, 2 x *o*-CH_{Bn}), 128.7 (2C, 2 x *o*-CH_{Bn}), 128.4 (1C, *p*-CH_{Bn}), 128.3 (2C, 2 x *o*-CH_{Bn}), 124.6 (1C, 8-*C*), 109.5 (1C, 4-*C*H), 100.9 (1C, 6-*C*H), 83.2 (1C, 13-*C*H), 75.3 (1C, 15-*C*H), 71.4 (1C, 13-$CH_{2\ Bn}$), 70.9 (1C, 7-$CH_{2\ Bn}$), 70.9 (1C, 5-$CH_{2\ Bn}$), 43.7 (1C, 14-*C*H), 39.8 (1C, 2-CH_2), 32.8 (1C, 12-CH_2), 18.8 (1C, 15-CH_3), 10.6 (1C, 10-CH_3), 7.9 (1C, 14-CH_3). HRESIMS *m/z* 605.2894 $[M+H]^+$ (calcd for $C_{39}H_{40}O_6H$, 605.2898).

(13*S*,14*R*,15*S*)-5,7,13-Tris(benzyloxy)-14-deoxyoxacyclododecindione (**55**)

Following modified procedures of Opatz et al.,[15] a solution of macrolactone **35** (323 mg, 533 µmol, 1.00 eq) in *N*,*N*-dimethylformamide (25 mL) was treated with trifluoroacetic acid (61.6 µL, 800 µmol, 1.50 eq) and a freshly prepared solution of *N*-chlorosuccinimide (100mM in DMF, 3.20 mL, 320 µmol, 0.60 eq) was added slowly within 15 min at rt. After further addition of *N*-chlorosuccinimide (day 2: 100 mM in DMF, 1.60 mL, 160 µmol, 0.30 eq; day 3:100 mM in DMF, 0.80 mL, 80.0 µmol, 0.15 eq) and trifluoroacetic acid (day 3: 28.8 µL, 0.373 mmol, 0.70 eq), the reaction mixture was quenched by the addition of H_2O (50 mL) on day 4. The aqueous phase was extracted with diethyl ether (4 x 80 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc, 8:1 to 6:1) to yield the protected oxacyclododecindione **55** (256 mg, 401 µmol, 75%) as a colorless oil. $[\alpha]_D^{22}$ –88.5 (*c* 0.52, CH_2Cl_2). R_f 0.12 (cyclohexane/EtOAc, 10:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3064, 3032, 2978, 2931, 2873, 1726, 1658, 1639, 1593, 1574, 1537, 1497, 1454, 1413, 1383, 1369, 1333, 1300, 1249, 1206, 1167, 1135, 1083, 1065, 1028, 990, 964, 941, 909, 872, 843, 812, 735,

696, 659, 620, 563, 465. ^{1}H NMR, COSY (600 MHz, CD_3CN) δ_H 7.48–7.22 (m, 15H, CH_{arom}), 6.85 (s, 1H, 6-C*H*), 6.34–6.21 (m, 1H, 11-C*H*), 5.22 (d, *J* = 12.2 Hz, 1H, 5-C$H_{2\text{-A Bn}}$), 5.19 (d, *J* = 12.2 Hz, 1H, 5-C$H_{2\text{-B Bn}}$), 5.07 (s, 2H, 7-C$H_{2\text{ Bn}}$), 4.98–4.90 (m, 1H, 15-C*H*), 4.51 (s, 2H, 13-C$H_{2\text{ Bn}}$), 3.76–3.45 (m, 1H, 2-C$H_{2\text{-A}}$), 3.39–3.24 (m, 1H, 13-C*H*), 3.24–2.98 (m, 1H, 2-C$H_{2\text{-B}}$), 2.81–2.63 (m, 1H, 12-C$H_{2\text{-A}}$), 2.38–2.19 (m, 1H, 12-C$H_{2\text{-B}}$), 2.07 (qd, *J* = 7.5, 2.4 Hz, 1H, 14-C*H*), 1.81 (s, 3H, 10-CH_3), 1.12 (d, *J* = 6.4 Hz, 3H, 15-CH_3), 0.80 (d, *J* = 7.5 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN) δ_C 198.3 (1C, 9-*C*O), 169.2 (1C, 1-*C*OO), 155.6 (1C, 5-*C*), 155.1 (1C, 7-*C*), 147.9 (1C, 11-*C*H), 139.8 (1C, *ipso*-13-C_{Bn}), 139.0 (1C, 10-*C*), 137.5 (1C, *ipso*-7-C_{Bn}), 137.4 (1C, *ipso*-5-C_{Bn}), 132.0 (1C, 3-*C*), 129.6 (2C, 2 x *m*-CH_{Bn}), 129.5 (2C, 2 x *m*-CH_{Bn}), 129.3 (2C, 2 x *m*-CH_{Bn}), 129.2 (1C, *p*-CH_{Bn}), 129.1 (1C, *p*-CH_{Bn}), 128.7 (2C, 2 x *o*-CH_{Bn}), 128.6 (2C, 2 x *o*-CH_{Bn}), 128.6 (2C, 2 x *o*-CH_{Bn}), 128.5 (1C, *p*-CH_{Bn}), 125.6 (1C, 8-*C*), 116.6 (1C, 4-*C*Cl), 100.9 (1C, 6-*C*H), 82.6 (1C, 13-*C*H), 75.5 (1C, 15-*C*H), 71.9 (1C, 5-*C*$H_{2\text{ Bn}}$), 71.4 (1C, 13-*C*$H_{2\text{ Bn}}$), 71.4 (1C, 7-*C*$H_{2\text{ Bn}}$), 43.5 (1C, 14-*C*H), 38.1 (1C, 2-*C*H_2), 32.7 (1C, 12-*C*H_2), 18.1 (1C, 15-*C*H_3), 10.1 (1C, 10-*C*H_3), 8.1 (1C, 14-*C*H_3). HRESIMS *m*/*z* 661.2324 $[M+Na]^+$ (calcd for $C_{39}H_{39}ClO_6Na$, 661.2327).

(13*S*,14*S*,15*S*)-13-Hydroxy-14-deoxyoxacyclododecindione (**36**)

Following a modified procedure of Opatz et al.,[15] boron trichloride (1M in heptane, 3.46 mL, 3.46 mmol, 9.00 eq) was added to a solution of benzyl protected macrolactone **55** (246 mg, 385 µmol, 1.00 eq) in CH_2Cl_2 (70 mL) at –78 °C. Within 2.5 h, the deep orange solution was gradually warmed to –30 °C and stirred for another 2 h at the same temperature. After complete conversion of the starting material, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL) while warming to rt. The aqueous layer was extracted with CH_2Cl_2 (7 x 80 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 3:1, 1% AcOH to 1:1, 1% AcOH) and the (13*S*,14*S*,15*S*)-13-hydroxy-14-

deoxyoxacyclododecindione (**36**) (138 mg, 374 µmol, 97%) was obtained as a colorless solid. For its biological evaluation the macrolactone **36** was further purified by preparative HPLC (C_{18}-HTEC, isocratic 25% MeCN in H_2O, 20 min). $[\alpha]_D^{22}$ –67.4 (*c* 0.23, MeOH). R_f 0.20 (cyclohexane/EtOAc, 1:1, 1% AcOH). t_R (HPLC): 6.38 min (PFP, isocratic 25% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3357, 2978, 2923, 2852, 1708, 1630, 1606, 1440, 1360, 1294, 1245, 1206, 1166, 1136, 1113, 1084, 1030, 977, 948, 875, 844, 729, 649, 628, 587, 566. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 10.23 (s, 1H, 7-CO*H*), 9.68 (s, 1H, 5-CO*H*), 6.50 (s, 1H, 6-C*H*), 6.35–6.25 (m, 1H, 11-C*H*), 4.98–4.89 (m, 2H, 13-O*H*, 15-C*H*), 3.52–3.41 (m, 2H, 2-C$H_{2\text{-A}}$, 13-C*H*), 3.16–3.04 (m, 1H, 2-C$H_{2\text{-B}}$), 2.56–2.51 (m, 1H, 12-C$H_{2\text{-A}}$), 2.26–2.15 (m, 1H, 12-C$H_{2\text{-B}}$), 1.82 (qd, *J* = 7.5, 2.2 Hz, 1H, 14-C*H*), 1.77 (s, 3H, 10-CH_3), 1.07 (d, *J* = 6.4 Hz, 3H, 15-CH_3), 0.79 (d, *J* = 7.5 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 197.9 (1C, 9-*C*O), 168.3 (1C, 1-*C*OO), 153.6 (1C, 7-*C*), 153.1 (1C, 5-*C*), 146.2 (1C, 11-*C*H), 137.4 (1C, 10-*C*), 130.1 (1C, 3-*C*), 120.9 (1C, 8-*C*), 111.3 (1C, 4-*C*Cl), 102.4 (1C, 6-*C*H), 73.7 (1C, 15-*C*H), 73.6 (1C, 13-*C*H), 45.1 (1C, 14-*C*H), 37.2 (1C, 2-*C*H_2), 34.8 (1C, 12-*C*H_2), 17.9 (1C, 15-*C*H_3), 10.0 (1C, 10-*C*H_3), 7.0 (1C, 14-*C*H_3). HRESIMS *m*/*z* 369.1099 $[M+H]^+$ (calcd for $C_{18}H_{21}Cl_1O_6H$, 369.1099).

(13*R*,14*S*,15*R*)-13-Hydroxy-14-deoxyoxacyclododecindione (*Z*-Isomer) (**37**)

The *E*-isomer **4** (20.1 mg, 54.5 µmol, 1.00 eq) was placed in a quartz tube under nitrogen atmosphere and was dissolved in DMSO (10 mL). The reaction tube was degassed, transferred in a Rayonet photoreactor, and the vessel was irradiated with UV-A (λ= 400–340 nm, 16×8 W) at room temperature. After 6 h the HPLC/ESI-MS indicated a sufficient *E*/*Z*-ratio of 52:48 and the solvent was removed under reduced pressure. The separation of both stereoisomers by preparative HPLC (C_{18}-HTEC, isocratic 25% MeCN in H_2O, 20 min) furnished the *Z*-isomer **37** (7.50 mg, 20.3 µmol, 37%, 70% brsm) as a colorless solid. $[\alpha]_D^{22}$ +87.4 (*c* 0.11, MeOH). R_f 0.29 (cyclohexane/EtOAc, 1:1, 1% AcOH). t_R (HPLC): 11.43 min (PFP, isocratic 25% MeCN in

H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3319, 2980, 2923, 2854, 1709, 1593, 1489, 1446, 1372, 1337, 1319, 1254, 1163, 1148, 1104, 1085, 1044, 1023, 1001, 973, 953, 925, 845, 756, 738, 699, 659, 628, 585. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 10.54 (s, 1H, 7-CO*H*), 9.94 (s, 1H, 5-CO*H*), 6.47 (s, 1H, 6-C*H*), 6.10–6.04 (m, 1H, 11-C*H*), 4.66 (d, J = 5.8 Hz, 1H, 13-O*H*), 4.84 (dq, J = 9.2, 6.1 Hz, 1H, 15-C*H*), 3.90 (d, J = 16.5 Hz, 1H, 2-C$H_{2\text{-A}}$), 3.72 (d, J = 16.5 Hz, 1H, 2-C$H_{2\text{-B}}$), 2.96–2.86 (m, 1H, 13-C*H*), 2.48–2.35 (m, 1H, 12-C$H_{2\text{-A}}$), 1.87 (s, 3H, 10-CH_3), 1.75–1.57 (m, 1H, 12-C$H_{2\text{-B}}$), 1.37 (q, J = 7.6 Hz, 1H, 14-C*H*), 1.09 (d, J = 6.1 Hz, 3H, 15-CH_3), 0.78 (d, J = 6.9 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 198.8 (1C, 9-*C*O), 167.9 (1C, 1-*C*OO), 155.3 (1C, 7-*C*), 155.2 (1C, 5-*C*), 137.2 (1C, 10-*C*), 135.2 (1C, 11-*C*H), 131.2 (1C, 3-*C*), 122.7 (1C, 8-*C*), 112.8 (1C, 4-*C*Cl), 102.5 (1C, 6-*C*H), 75.2 (1C, 15-*C*H), 73.6 (1C, 13-*C*H), 43.7 (1C, 14-*C*H), 37.0 (1C, 12-*C*H_2), 35.3 (1C, 2-*C*H_2), 20.8 (1C, 10-*C*H_3), 19.3 (1C, 15-*C*H_3), 13.9 (1C, 14-*C*H_3). HRESIMS m/z 369.1092 $[M+H]^+$ (calcd for $C_{18}H_{21}ClO_6H$, 369.1099).

(13*S*,14*S*,15*R*)-13-Hydroxy-14-deoxyoxacyclododecindione (*Z*-Isomer) (**38**)

The *E*-isomer **27** (23.8 mg, 64.4 µmol, 1.00 eq) was placed in a quartz tube under nitrogen atmosphere and dissolved in DMSO (10 mL). The reaction tube was degassed, transferred to a Rayonet photoreactor, and the vessel was irradiated with UV-A (λ= 400–340 nm, 16×8 W) at room temperature. After 6 h the HPLC/ESI-MS indicated a sufficient *E*/*Z*-ratio of 62:38 and the solvent was removed under reduced pressure. The separation of both stereoisomers by preparative HPLC (C_{18}-HTEC, isocratic 25% MeCN in H_2O, 20 min) furnished the *Z*-isomer **38** (9.90 mg, 26.8 µmol, 42%, 89% brsm) as a colorless solid. $[\alpha]_D^{22}$ –51.1 (*c* 0.10, MeOH). R_f 0.24 (cyclohexane/EtOAc, 1:1, 1% AcOH). t_R (HPLC): 11.19 min (PFP, isocratic 25% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3288, 2924, 2853, 1712, 1585, 1440, 1376, 1244, 1151, 1104, 1070, 1041, 1019, 952, 929, 845, 782, 737, 705, 627, 618, 595, 576. ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ_H 10.52 (s, 1H, 7-CO*H*), 9.88 (s, 1H, 5-CO*H*), 6.45 (s, 1H, 6-C*H*), 5.95–5.82 (m,

1H, 11-C*H*), 4.67–4.59 (m, 2H, 13-O*H*, 15-C*H*), 3.86 (d, *J* = 14.2 Hz, 1H, 2-C$H_{2\text{-A}}$), 3.67 (d, *J* = 14.2 Hz, 1H, 2-C$H_{2\text{-B}}$), 3.56–3.50 (m, 1H, 13-C*H*), 2.20–1.89 (m, 2H, 12-CH_2), 1.87 (s, 3H, 10-CH_3), 1.60–1.53 (m, 1H, 14-C*H*), 1.04 (d, *J* = 6.3 Hz, 3H, 15-CH_3), 0.76 (d, *J* = 7.1 Hz, 3H, 14-CH_3). ^{13}C NMR, HSQC, HMBC (151 MHz, DMSO-d_6) δ_C 198.6 (1C, 9-*C*O), 167.7 (1C, 1-*C*OO), 155.3 (1C, 7-*C*), 155.2 (1C, 5-*C*), 137.3 (1C, 10-*C*), 134.9 (1C, 11-*C*H), 130.5 (1C, 3-*C*), 123.3 (1C, 8-*C*), 112.7 (1C, 4-*C*Cl), 102.5 (1C, 6-*C*H), 72.2 (1C, 15-*C*H), 72.1 (1C, 13-*C*H), 40.4 (1C, 14-*C*H), 35.5 (1C, 12-*C*H_2), 35.3 (1C, 2-*C*H_2), 20.8 (1C, 10-*C*H_3), 18.7 (1C, 15-*C*H_3), 15.2 (1C, 14-*C*H_3). HRESIMS *m*/*z* 369.1095 $[M+H]^+$ (calcd for $C_{18}H_{21}ClO_6H$, 369.1099).

(2*S*,3*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide (**10**)

Following a procedure of Evans et al.,[62] Me_3Al (2M in toluene, 1.42 mL, 2.84 mmol, 3.10 eq) was added dropwise at 0 °C to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (268 mg, 2.75 mmol, 3.00 eq) in 3.2 mL THF. After cooling the suspension to –78 °C, amide **14** (0.50 mg, 0.92 mmol, 1.00 eq) was added in 1.9 mL dry THF. The solution was stirred for 15 min and then allowed to warm to 0 °C and stirred for a further hour. It was quenched by the addition of 25 mL saturated NH_4Cl (aq) and 3 drops HCl (conc.) and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were extracted with 1N HCl (14 mL), saturated $NaHCO_3$ (7 mL), brine (14 mL), and dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 5:1 to 4:1). The amide **10** (341 mg, 0.79 mmol, 87%) was obtained as a colorless oil. $[\alpha]_D^{23}$ +2.2 (*c* 0.67, $CHCl_3$). R_f 0.19 (cyclohexane/EtOAc, 3:1). t_R (HPLC): 5.80 min (C_{18}-HTEC, isocratic 80% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3475, 3070, 3048, 2956, 2932, 2858, 1638, 1471, 1461, 1427, 1388, 1362, 1310, 1178, 1110, 1084, 996, 940, 823, 738, 703, 688, 614, 5050, 490, 449, 438. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.71–7.61 (m, 4H,

CH_{arom}), 7.47–7.34 (m, 6H, CH_{arom}), 4.12 (dt, J = 8.6, 4.1 Hz, 1H, 3-CH), 4.00 (s, 1H, 3-COH), 3.90–3.79 (m, 2H, 5-CH_2), 3.67 (s, 3H, NOCH_3), 3.19 (s, 3H, NCH_3), 3.07–2.91 (m, 1H, 2-CH), 1.79 (dddd, J = 14.0, 8.8, 6.7, 5.2 Hz, 1H, 4-C$H_{2\text{-A}}$), 1.71–1.60 (m, 1H, 4-C$H_{2\text{-B}}$), 1.22 (d, J = 7.0 Hz, 3H, 2-CH_3), 1.05 (s, 9H, C(CH_3)$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 177.8 (1C, 1-CON), 135.7 (2C, 2 x o-CH$_{TBDPS}$), 135.7 (2C, 2 x o-CH$_{TBDPS}$), 133.5 (1C, $ipso$-C_{TBDPS}), 133.4 (1C, $ipso$-C_{TBDPS}), 129.9 (2C, 2 x p-CH$_{TBDPS}$), 127.8 (4C, 4 x m-CH$_{TBDPS}$), 71.1 (1C, 3-CH), 62.5 (1C, 5-CH$_2$), 61.7 (1C, NOCH$_3$), 39.8 (1C, 2-CH), 36.4 (1C, 4-CH$_2$), 32.1 (1C, NCH$_3$), 27.0 (3C, SiC(CH$_3$)$_3$), 19.2 (1C, SiC(CH$_3$)$_3$), 11.7 (1C, 2-CH$_3$). HRESIMS m/z 430.2400 $[M+H]^+$ (calcd for $C_{24}H_{35}NO_4SiH$, 430.2408).

(5*S*,6*S*)-3,5,11,11-Tetramethyl-4-oxo-10,10-diphenyl-2,9-dioxa-3-aza-10-siladodecan-6-yl 4-nitrobenzoate (**15**); (*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-*N*-methoxy-*N*,2-dimethylpent-2-enamid (**56**)

Using a modified procedure of Chen, Quan, and Yang et al.,[22] the alcohol **10** (39.9 mg, 92.9 µmol, 1.00 eq), 4-nitrobenzoic acid (31.0 mg, 186 µmol, 2.00 eq) and PPh_3 (48.7 mg, 186 µmol, 2.00 eq) were dissolved in dry toluene (3.10 mL) and cooled to 0 °C. DEAD (2.2M in toluene, 84.4 µL, 186 µmol, 2.00 eq) was added dropwise to the solution and the reaction was stirred at 0 °C for 1 h and warmed to rt overnight. The solvent was removed under reduced pressure. Since it was not possible to separate the compounds by flash column chromatography, the mixture was purified by preparative HPLC (C_{18}-HTEC, isocratic 70% MeCN in H_2O, 30 min) to give the desired product **15** (8.60 mg, 14.9 µmol, 16%), the eliminated olefin **56** (15.0 mg, 36.4 µmol, 39%), and the starting material **10** (30.4 mg, 70.8 µmol, 76%) as colorless oils. Nitrobenzoate (**15**): $[\alpha]_D^{22}$ –0.4 (c 0.52, $CHCl_3$). R_f 0.20 (cyclohexane/EtOAc, 3:1). t_R (HPLC): 12.26 min (C_{18}-HTEC, isocratic 80% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3071, 2960, 2933, 2888, 2858, 1725, 1662, 1607, 1569, 1559, 1528, 1507, 1497, 1472, 1464, 1428, 1387, 1348, 1320, 1272, 1160, 1105, 1077, 1029, 1014, 996, 941, 873, 841, 824, 784, 739, 719, 703,

614, 591, 578, 548, 505, 491, 468, 430. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 8.28–8.22 (m, 2H, 2 x *m*-C$H_{p\text{-NO2-Bz}}$), 8.14–8.07 (m, 2H, 2 x *o*-C$H_{p\text{-NO2-Bz}}$), 7.66–7.56 (m, 4H, CH_{arom}), 7.43–7.22 (m, 6H, CH_{arom}), 5.59 (td, J = 7.7, 3.2 Hz, 1H, 3-C*H*), 3.82–3.66 (m, 2H, 5-CH_2), 3.73 (s, 3H, NOCH_3), 3.62–3.46 (m, 1H, 2-C*H*), 3.15 (s, 3H, NCH_3), 2.11 (dtd, J = 14.1, 6.7, 3.1 Hz, 1H, 4-C$H_{2\text{-A}}$), 1.99 (ddt, J = 14.1, 8.2, 5.5 Hz, 1H, 4-C$H_{2\text{-B}}$), 1.20 (d, J = 7.0 Hz, 3H, 2-CH_3), 1.01 (s, 9H, C(CH_3)$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 174.6 (1C, 1-*C*ON), 163.8 (1C, 3-*C*OO$_{p\text{-NO2-Bz}}$), 150.6 (1C, *ipso*-$C_{p\text{-NO2-Bz}}$), 136.0 (1C, *p*-C$H_{p\text{-NO2-Bz}}$), 135.7 (4C, 4 x *o*-CH$_{TBDPS}$), 133.7 (1C, *ipso*-C_{TBDPS}), 133.4 (1C, *ipso*-C_{TBDPS}), 130.8 (2C, 2 x *o*-C$H_{p\text{-NO2-Bz}}$), 129.8 (1C, *p*-CH$_{TBDPS}$), 129.8 (1C, *p*-CH$_{TBDPS}$), 127.8 (2C, 2 x *m*-CH$_{TBDPS}$), 127.7 (2C, 2 x *m*-CH$_{TBDPS}$), 123.6 (2C, 2 x *m*-C$H_{p\text{-NO2-Bz}}$), 74.2 (1C, 3-*C*H), 61.9 (1C, NO*C*H$_3$), 60.0 (1C, 5-*C*H$_2$), 38.9 (1C, 2-*C*H), 33.1 (1C, 4-*C*H$_2$), 32.5 (1C, N*C*H$_3$), 26.9 (3C, SiC(*C*H$_3$)$_3$), 19.2 (1C, SiC(*C*H$_3$)$_3$), 12.9 (1C, 2-*C*H$_3$). HRESIMS m/z 579.2502 $[M+H]^+$ (calcd for $C_{31}H_{38}N_2O_7Si_1$, 579.2521). Alkene (**56**): R_f 0.20 (cyclohexane/EtOAc, 3:1). t_R (HPLC): 8.57 min (C_{18}-HTEC, isocratic 80% MeCN in H_2O). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3071, 3050, 2998, 2957, 2931, 2893, 2858, 1650, 1589, 1472, 1462, 1428, 1374, 1261, 1231, 1191, 1110, 1091, 1030, 1006, 999, 939, 855, 823, 740, 703, 688, 613, 569, 505, 489, 441, 433, 421. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.70–7.63 (m, 4H, CH_{arom}), 7.46–7.34 (m, 6H, CH_{arom}), 5.86 (tq, J = 7.3, 1.5 Hz, 1H, 3-C*H*), 3.73 (t, J = 6.7 Hz, 2H, 5-CH_2), 3.60 (s, 3H, NOCH_3), 3.21 (s, 3H, NCH_3), 2.38 (qd, J = 6.7, 1.0 Hz, 2H, 4-CH_2), 1.84–1.81 (m, 3H, 2-CH_3), 1.04 (s, 9H, C(CH_3)$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 172.8 (1C, 1-*C*ON), 135.7 (4C, 4 x *o*-CH$_{TBDPS}$), 133.9 (2C, 2 x *ipso*-C_{TBDPS}), 132.8 (1C, 2-C_q), 130.3 (1C, 3-*C*H), 129.8 (2C, 2 x *p*-CH$_{TBDPS}$), 127.8 (4C, 4 x *m*-CH$_{TBDPS}$), 62.9 (1C, 5-*C*H$_2$), 61.1 (1C, NO*C*H$_3$), 33.9 (1C, N*C*H$_3$), 31.5 (1C, 4-*C*H$_2$), 27.0 (3C, SiC(*C*H$_3$)$_3$), 19.3 (1C, SiC(*C*H$_3$)$_3$), 14.2 (1C, 2-*C*H$_3$). HRESIMS m/z 434.2113 $[M+Na]^+$ (calcd for $C_{24}H_{33}NO_3SiNa$, 434.2122).

(*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-*N*-methoxy-*N*,2-dimethyl-3-oxopentanamide (**11**)

Using a modified procedure of Takamura et al.,[24] secondary alcohol **10** (62.0 mg, 144 µmol, 1.00 eq) was dissolved in dry CH_2Cl_2 (1.72 mL), DMP (245 mg, 577 µmol, 4.00 eq) was added, and the reaction mixture was stirred for 66 h under reflux conditions. The mixture was filtered through a pad of celite and silica gel pad to give the ketone **11** (47.0 mg, 110 µmol, 76%) as a yellowish oil. $[\alpha]_D^{23}$ +1.0 (*c* 0.60, $CHCl_3$). R_f 0.19 (cyclohexane/EtOAc, 3:1). IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3070, 3049, 3025, 3010, 2996, 2933, 2886, 2858, 1722, 1664, 1590, 1463, 1428, 1384, 1331, 1271, 1177, 1111, 1036, 994, 921, 861, 849, 823, 779, 772, 761, 740, 704, 615, 595, 558, 548, 539, 506, 494, 474, 433, 416. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ_H 7.69–7.62 (m, 4H, CH_{arom}), 7.46–7.35 (m, 6H, CH_{arom}), 3.93 (qt, *J* = 10.3, 6.2 Hz, 2H, 5-CH_2), 3.79 (q, *J* = 7.2 Hz, 1H, 2-C*H*), 3.61 (s, 3H, NOCH_3), 3.19 (s, 3H, NCH_3), 2.72 (td, *J* = 6.3, 3.1 Hz, 2H, 4-CH_2), 1.34 (d, *J* = 7.2 Hz, 3H, 2-CH_3), 1.02 (s, 9H, C(CH_3)$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ_C 205.1 (1C, 3-*C*O), 171.8 (1C, 1-*C*ON), 135.7 (4C, 4 x *o*-CH_{TBDPS}), 133.6 (1C, *ipso*-C_{TBDPS}), 133.5 (1C, *ipso*-C_{TBDPS}), 129.8 (2C, 2 x *p*-CH_{TBDPS}), 127.8 (4C, 4 x *m*-CH_{TBDPS}), 61.3 (1C, NOCH_3), 59.3 (1C, 5-*C*H_2), 51.0 (1C, 2-*C*H), 43.4 (1C, 4-*C*H_2), 32.7 (1C, N*C*H_3), 26.9 (3C, SiC(*C*H_3)$_3$), 19.3 (1C, SiC(*C*H_3)$_3$), 12.9 (1C, 2-*C*H_3). HRESIMS *m*/*z* 428.2247 $[M+H]^+$ (calcd for $C_{24}H_{33}NO_4SiH$, 428.2252).

Biological Assays

HepG2 cells (DSMZ ACC 180) were maintained in DMEM supplemented with 10% fetal calf serum (FCS) and antibiotics (65 µg/mL penicillin G, 100 µg/mL streptomycin sulfate) at 37 °C and 5% CO_2. The cells were transfected with the indicated plasmids by electroporation. The cells were suspended in DMEM at 1 x 10^7 cells/mL and electroporated with 50 µg plasmid DNA at 220 V in a 4 mm gap cuvette (Nepagene, Nepa21) and then seeded at 2 x 10^5 cells/mL in 24-well plates. After 24 h incubation at 37 °C, 5% CO_2, the culture medium was replaced by DMEM (containing 0.5% FCS and antibiotics) with 5 ng/mLof either IL-4 or TGF-β and the test compounds. Untreated cells and cells treated with the respective cytokine were used as

control. After 24 h the medium was removed, and the luciferase levels detected using the luciferase assay system (Promega) according to manufacturer's instruction. The plasmids used were pGL3-TK-7xN4 and TOPO-Stat6[7] to test for inhibition of IL-4 signaling and $(CAGA)_{9x}$-MLP-Luc to test for inhibition of TGF-β induced signalling as described in Opatz et al.[14] As an internal normalization control and to exclude cytotoxic effects, the constitutively active pRL-EF1α construct (Promega) was co-electroporated into the HepG2 cells. The $(CAGA)_{9x}$-MLP-Luc plasmid was kindly provided by Prof. S. Dooley (University of Mannheim, Germany).

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its supporting information.

Supporting Information

The Supporting Information is available free of charge at.

Overview of the detailed synthetic route to macrolactones **27**, **33**, and **36**–**38**, additional ^{1}H-, ^{13}C{^{1}H} and 2D (COSY, HSQC, HMBC, NOESY) spectra of compounds, *E*/*Z*-isomerization studies, UV-Vis spectra, X-ray crystallographic analysis, optical rotation comparison of natural products and derivatives of the curvularin and oxacyclododecindione families (pdf). Crystallographic Information File of compounds **27** and **36** (cif file).

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Notes

The authors declare no competing financial interest.

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