CHEMMEDCHEM

DOI: 10.1002/cmdc.200800022

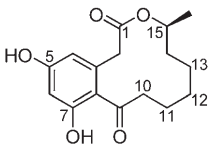
Inhibitors of Inducible NO Synthase Expression: Total Synthesis of (*S*)-Curvularin and Its Ring Homologues

Stephan Elzner,[a] Denise Schmidt,[a] Dieter Schollmeyer,[a] Gerhard Erkel,[b] Timm Anke,[b] Hartmut Kleinert,[c] Ulrich Förstermann,[c] and Horst Kunz*[a]

*(S)-Curvularin and its 13-, 14-, and 16-membered lactone homologues were synthesized through a uniform strategy in which a Kochi oxidative decarboxylation and ring-closing metathesis reactions constitute the key processes. In the evaluation of the anti-inflammatory effects of the synthesized compounds in assays using cells stably transfected with a human iNOS promoter–luciferase reporter gene construct, the 14- and 16-membered homologues showed a slightly higher inhibitory effect towards iNOS promoter activity than curvularin itself. However, the larger ring homologues also exhibited higher cytotoxicity, manifest in down-regulated eNOS promoter activity. In contrast, the di-*O*-acetyl and 4-chloro derivatives of (S)-curvularin showed higher inhibitory efficiency towards induction of the iNOS promoter and less negative effect on eNOS promoter activity than curvularin.*

Introduction

Inflammatory reactions take place after injury, infection, or trauma and induce an accumulation of inflammatory immune cells. This immune cells, together with epithelial cells and fibroblasts, synthesize and export a complex mixture of lipids, growth factors, cytokines, chemokines, and degrading enzymes, which can cause local tissue damage and fibrosis.[1] As a consequence of all these factors and interactions, immune-inflammatory reactions can occur.[2] The nitric oxide radical and prostanoids are important mediator molecules in the network of these processes. A local overexpression of NO and prostanoids is also observed in auto-immunological and chronic inflammatory diseases in which these mediators sustain the undesired inflammation and cause irreversible cell destruction at the site of inflammation.[2] Two inducible enzymes are considered responsible for the overexpression of NO and prostanoids in the inflammatory event: inducible NO synthase (iNOS)[3] and cyclooxygenase 2 (COX2).[4] The production of both enzymes is predominantly regulated at the level of gene expression. Novel strategies for the therapy of inflammatory diseases[5] are based on the development of compounds that suppress the production of inflammation-sustaining enzymes by inhibition of the corresponding signal transduction pathways or, more directly, the activity toward the transcription factors involved. We have recently shown that the fungal macrocyclic lactone (*S*)-curvularin (**1**), previously isolated from *Penicillium*, *Curvularia*, *Chochliobolus*, and *Alternaria* spp.,[6] inhibits inducible transcription and synthesis of the pro-inflammatory enzymes iNOS and COX2 in A549/8 cells without affecting the activity of the constitutive human eNOS promoter or displaying cytotoxic effects. Studies on the mode of action revealed that (*S*)-curvularin blocks the phosphorylation (and activation) of the transcription factor STAT-1α (signal transducer and activator of transcription) by the upstream tyrosine kinase JAK2 (Janus kinase), thereby interfering with a signal transduction pathway responsible for the inducible expression of many pro-inflammatory genes.[7] Therefore, (*S*)-curvularin is an anti-inflammatory compound with an interesting mode of action and thus, may offer an alternative to standard glucocorticoid therapy. (*S*)-Curvularin was also reported to arrest the cell cycle.[8] This is why natural products related to (*S*)-curvularin have received increasing attention from chemists interested in the total synthesis of biologically active natural products.[9] Considering this background, it was attractive to synthesize (*S*)-curvularin (**1**) and analogous compounds, particularly homologous macrolactones of increasing ring size, and to investigate their anti-inflammatory activity as transcription-based inhibitors of iNOS and COX2.



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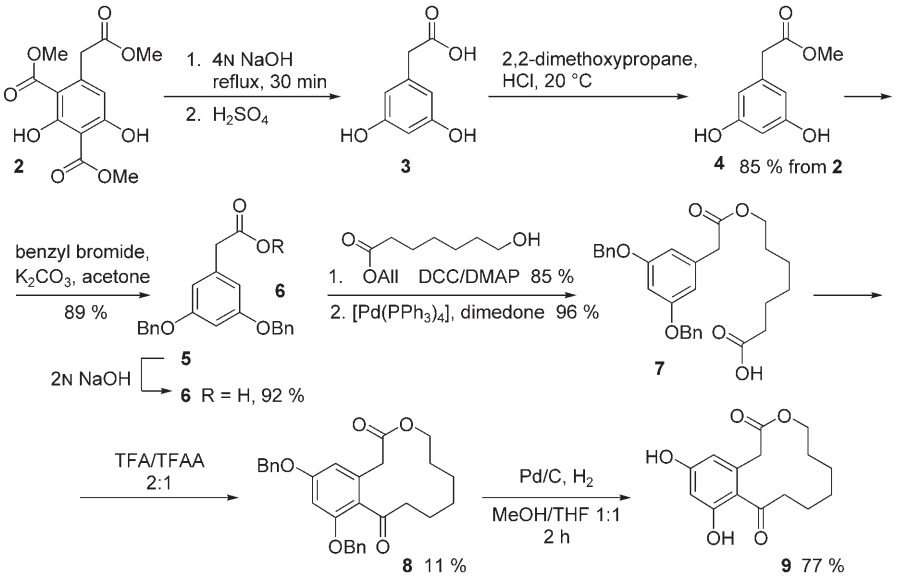
Results and Discussion

The formation of the 12-membered lactone of curvularins was first achieved by intramolecular Friedel–Crafts acylation.[10] This procedure was also used for the first total synthesis of (*S*)-curvularin[11] (**1**) and in a number of subsequent preparations proceeding via different intermediates[12,13] and protecting group techniques. The yields achieved in these acylation reactions remained unsatisfactory.

[a] *Dr. S. Elzner, D. Schmidt, Dr. D. Schollmeyer, Prof. Dr. H. Kunz*
Institut für Organische Chemie, Naturstoffsynthese-Zentrum
Universität Mainz, Duesbergweg 10–14, 55128 Mainz (Germany)

[b] *Priv.-Doz. Dr. G. Erkel, Prof. Dr. T. Anke*
Institut für Biochtechnologie und Wirkstoff-Forschung e.V.
Erwin Schrödinger-Str. 56, 67663 Kaiserslautern (Germany)

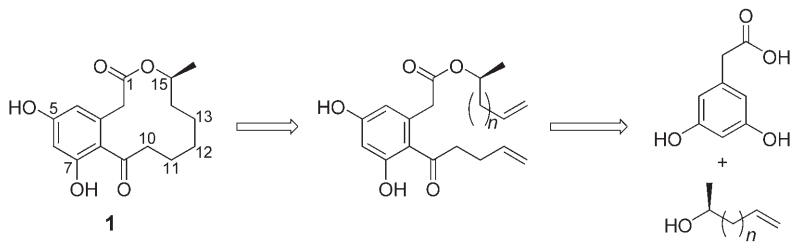
[c] *Prof. Dr. H. Kleinert, Prof. Dr. U. Förstermann*
Institut für Pharmakologie
Universität Mainz, Obere Zahlbacher Str. 67, 55101 Mainz (Germany)



Scheme 1. Synthesis of 15-desmethylcurvularin **9**.

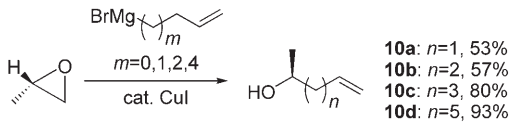
Our synthesis of 15-desmethylcurvularin (Scheme 1) paralleled these experiences. The known triester[14] **2** was converted into 3,5-dihydroxyphenylacetic acid **3**, which, on treatment with 2,2-dimethoxypropane/HCl, gave methylester[14] **4**. Reaction of **4** with benzyl bromide/K_2CO_3 afforded **5**,[11] which was saponified to give 3,5-bis(benzyloxy)phenylacetic acid[11] **6** as the crucial starting material for the syntheses of curvularins. Reaction of **6** with allyl-7-hydroxyheptanoate and subsequent Pd^0-catalyzed removal of the allyl ester using dimedone as the trapping reagent[15] gave carboxylic acid **7**. Activation of **7** with trifluoroacetic anhydride/trifluoroacetic acid[10,11,13] resulted in cyclization to give **8** in low yield, whereas reaction of **7** with oxalyl chloride/$SnCl_4$ completely failed. Hydrogenolysis of the benzyl ethers furnished 15-desmethylcurvularin **9**.

As the analogous synthesis of racemic curvularin afforded a likewise low yield (16%) in the cyclization, and because lactonization reactions of the corresponding seco acid were not successful under Yamaguchi conditions, an alternative strategy for the construction of the 12-membered lactone of **1** appeared highly desirable. Fürstner et al.[9] reported a successful alkyne metathesis reaction as the crucial cyclization step during the synthesis of citreofuran, a tricyclic compound related to curvularin.[16] Therefore, ring-closing metathesis (RCM) was expected to be useful for the efficient synthesis of curvularins according to the retrosynthetic analysis shown in Scheme 2.



Scheme 2. Retrosynthetic analysis for (*S*)-curvularin and its ring homologues.

The metathesis reaction forming the C=C double bond between C12 and C13 should neither be hindered by the methyl group at C15 nor by the neighboring keto function. Moreover, this strategy offers the advantage that ring homologues of **1** should be accessible by applying *S*-configured *sec* alcohols homologous ($n=2,3,5$) to (*S*)-4-penten-2-ol ($n=1$). These *S*-configured alcohols **10** are accessible from (*S*)-propene oxide by a copper-catalyzed ring-opening reaction with Grignard compounds[17] (Scheme 3). For introduction of the pentenoyl side chain, adipic acid was converted via its anhydride[18] into adipic acid monoallyl ester **11** (Scheme 4).

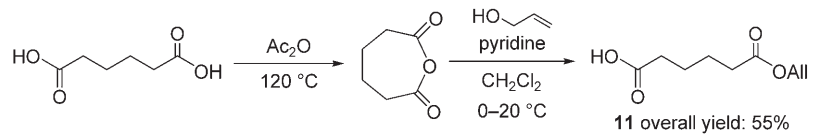


Scheme 3. Synthesis of *S*-configured alcohols **10**.

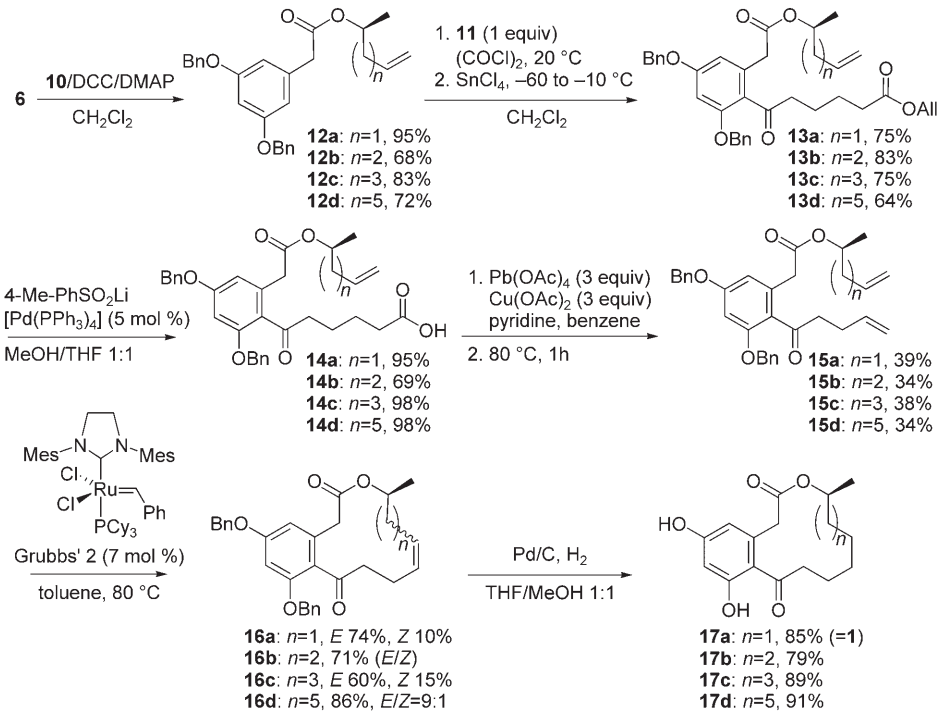
Components **6**, **10**, and **11** were applied to the syntheses of (*S*)-curvularin and its homologous macrolactones according to Scheme 5. Esterification of phenylacetic acid **6** with *S*-configured alcohols **10** afforded compounds **12**. Friedel–Crafts acylation of **12** with adipic monoester chloride obtained from **11** by treatment with oxalyl chloride gave the series of diesters **13**. Selective cleavage of the allyl ester was performed by Pd^0-catalyzed allyl transfer[15] using readily separable *p*-toluenesulfinate[19] as the trapping nucleophile to give the carboxylic acids **14**.

Kochi decarboxylation[20] of **14** using $Pb(OAc)_4$ and catalytic $Cu(OAc)_2$ in benzene/pyridine (250:1) furnished the divinyl compounds **15**. The conversion rate in this radical-type process remained incomplete. However, the unreacted starting materials **14** were recovered almost quantitatively after hydrolysis of the lead tetraacetate.

The RCM reactions were carried out with 7 mol% (compounds **15a,b**) or 10 mol% (compounds **15c,d**) of the Grubbs' second-generation catalyst[21] (Grubbs' 2) in toluene at 80 °C and gave *E*/*Z* mixtures of the unsaturated lactones **16** with the *E* diastereomer prevalent. The diastereomers were



Scheme 4. Conversion of adipic acid into adipic acid monoallyl ester **11**.



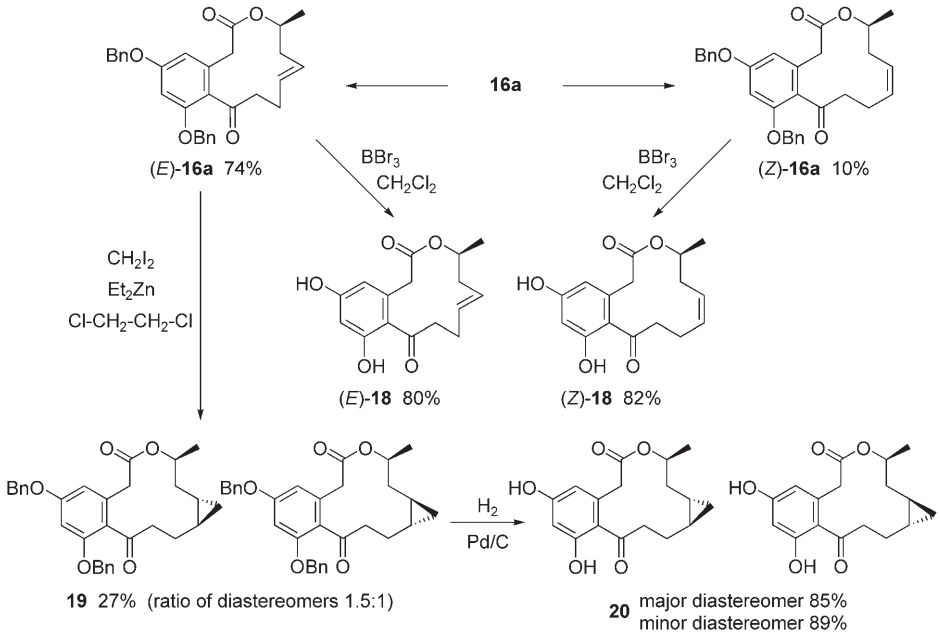
Scheme 5. Application of compounds **6**, **10**, and **11** toward the synthesis of curvularins **17**.

separable by flash chromatography on silica in mixtures of cyclohexane/EtOAc. Hydrogenation of unsaturated lactones resulted in simultaneous removal of the *O*-benzyl groups and yielded (*S*)-curvularin **17a** and its ring homologues **17b**–**d**. The physical data, in particular the optical rotation value, of **17a** (= **1**) are in agreement with those of (*S*)-curvularin published previously.[8a,22]

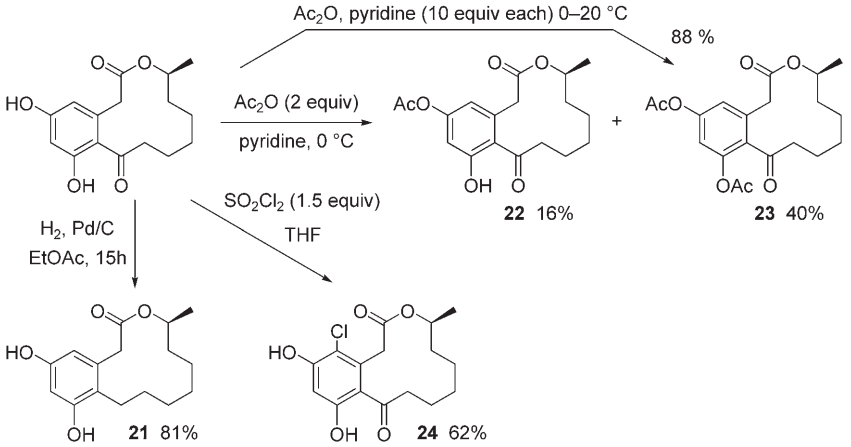
Structural variants of (*S*)-curvularin **17a** (=**1**) were synthesized from the diastereomeric precursors **16a** (Scheme 6). After chromatographic separation, the phenol ether protection was removed from *E*-**16a** and *Z*-**16a** using boron tribromide to give the diastereomers *E*-**18** and *Z*-**18** of (*S*)-12,13-dehydrocurvularin without affecting the lactone group or the double bond. Alternatively, Simmons–Smith reaction of *E*-**16a** using diiodomethane and diethyl zinc[23] afforded a mixture of diastereomers of trans-substituted cyclopropane derivatives **19**. Hydrogenolytic removal of the benzyl groups to give cyclopropylcurvularins **20** proceeded without affecting the cyclopropane structure.

Additional modified compounds were synthesized from (*S*)-curvularin (**1**). Hydrogenation over Pd/C in EtOAc for 15 h afforded 9-desoxycurvularin[23] **21** (Scheme 7). Acylation of **1** with acetic anhydride (2 equiv) at 0 °C yielded a separable mixture of 5-*O*-acetyl- **22** and 5,7-di-*O*-acetyl curvularin[8a] **23**. The latter was obtained in high yield if 10 equiv Ac_2O were applied. Finally, treatment of **1** with sulfuryl chloride afforded 4-chlorocurvularin **24** (Scheme 7).

Biological evaluations of (*S*)-curvularin and its homologues and analogues were carried out in three assays. To measure the inhibitory effect of the synthetic compounds on the interferon-γ



Scheme 6. Structural variants of (*S*)-curvularin **17a** (=**1**) were synthesized from the diastereomeric precursors **16a**.



Scheme 7. Synthesis of additional modified compounds **21**–**24** from (*S*)-curvularin (**1**).

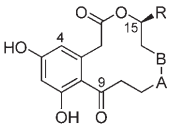
(IFN-γ)-activated JAK2–STAT pathway, transient transfection of HeLa S3 cells was carried out with a plasmid containing five copies of a γ-activated site/interferon-γ-stimulated responsive element (GAS/ISRE) upstream of the thymidine kinase promoter-driven secreted alkaline phosphatase (SEAP) gene.[7,24] Inhibition of IFN-γ-mediated activation of the transcription factor STAT-1α by curvularin and its related analogues inhibits the activation of the GAS-dependent promoter and hence of the SEAP reporter gene.

To analyze the effects of the synthetic compounds on the activation of more complex pro-inflammatory pathways, A549/8 cells stably transfected with a construct containing a 16-kb fragment of the human iNOS promoter upstream of a luciferase reporter gene[7,25] were used. The human iNOS promoter is regulated by various transcription factors that are activated by different pro-inflammatory signal pathways.[26] The stably transfected cells were incubated with a complex mixture of cytokines (CM; needed to induce human iNOS expression) composed of IFN-γ (100 U mL^{-1}), interleukin-1β (IL1-β; 50 U mL^{-1}), and tumor necrosis factor-α (TNF-α; 10 ng mL^{-1}) in the presence or absence of the synthetic compounds at various concentrations. The determination of luciferase activity in cell extracts directly reflects the effects of the synthetic compounds on the induction of the human iNOS promoter. Therefore, the use of this system enables analysis of the effects of the synthetic compounds on the induction of several pro-inflammatory pathways in parallel.

In a third experiment the remaining (desired) activity of the constitutive endothelial NO synthase (eNOS) promoter activity[7,25] was measured (as a percentage after treatment with substance at 10 μg mL^{-1}) using human endothelial-like ECV cells (spontaneously transformed *e*ndothelial *c*ells of human umbilical *v*ein; see Experimental Section) stably transfected with a construct containing a 3.6-kb fragment of the human eNOS promoter upstream of a luciferase reporter gene. A decrease in the activity of the constitutive active human eNOS promoter indicates either cytotoxic effects or effects of the compounds on the general transcription machinery. The effects of (*S*)-curvularin and its homologues are given in Table 1.

Analogous evaluation was performed for the derivatives of (*S*)-curvularin (Table 2). The results show that the inhibitory effects of the synthetic compounds on the simple GAS-regulated artificial promoter and on the complex iNOS promoter are different. The GAS-regulated promoter used in this assay contains only multiple copies of the binding site for the dimer of the transcription factor STAT-1α, whereas the 16-kb iNOS promoter contains binding sites for the transcription factors NF-κB, AP-1 C/EBP and the STAT family, which can be influenced by different signal transduction pathways.[26] Therefore, it is conceivable that (*S*)-curvularin and the synthetic analogues display effects on other pathways beside the JAK–STAT pathway also important for iNOS expression. The 15-methyl group of (*S*)-curvularin (**17a**, **1**) is required, as the 15-desmethyl compound **9** exhibits threefold lower inhibition toward induction of the iNOS promoter and does not inhibit INF-γ-induced activity of the GAS promoter. The 14- and 16-membered lactone homologues **17c** and **17d** exert strong effects on the activation of both the GAS

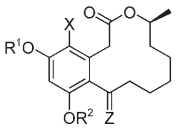
Table 1. Biological activity of synthetic (*S*)-curvularin and its ring analogues and homologues.



	R	A–B	IC_{50} [μg mL^{-1}]		Residual eNOS promoter activity[a]
			GAS	iNOS	
1/**17a**	Me	CH_2–CH_2	7.5 ± 1.5	3.7 ± 0.5	81.2 ± 3.2
9	H	CH_2–CH_2	NA[b]	9.5 ± 1.4	71.8 ± 5.9
17c	Me	$(CH_2$–$CH_2)_2$	20 ± 1.7	3.1 ± 0.4	37.9 ± 13.9
17d	Me	$(CH_2$–$CH_2)_3$	3.4 ± 1.1	2.9 ± 1.2	30.2 ± 8.9
E-**18**	Me		NA[b]	137.3 ± 60.8	107.6 ± 8.7
Z-**18**	Me		50 ± 3.2[c]	36.3 ± 9.1	108.6 ± 27.7
20 major	Me		50 ± 1.8	18.7 ± 3.5	58.0 ± 1.5
20 minor	Me		50 ± 1.3	ND[d]	ND[d]

[a] Activity after treatment with compound at 10 μg mL^{-1} as a degree of cytotoxicity. [b] No activity detected up to 50 μg mL^{-1}. [c] IC_{30} value. [d] Not determined.

Table 2. Biological activity of (*S*)-curvularin derivatives.



	R^1	R^2	X	Z	IC_{50} [μg mL^{-1}] GAS	IC_{50} [μg mL^{-1}] iNOS	Residual eNOS promoter activity[a]
21	H	H	H	H_2	22.5 ± 2.5	12.1 ± 2.1	75.9 ± 3.6
22	Ac	H	H	O	22.5 ± 2.3	3.8 ± 0.6	85.6 ± 14.6
23	Ac	Ac	H	O	10 ± 1.3	0.9 ± 0.1	82.6 ± 18.4
24	H	H	Cl	O	50 ± 1.8	0.9 ± 0.1	94.1 ± 19.9

[a] Activity after treatment of ECV cells stably transfected with the human eNOS promoter–luciferase gene construct with compound at 10 μg mL^{-1}.

and iNOS promoters (similar to **1**), but are cytotoxic (expressed in the decrease of eNOS promoter activity). These findings indicate that the macrolactone ring and its conformation are crucial for anti-inflammatory activity and its distinction from eliciting cytotoxic effects. In fact, X-ray analyses of (*S*)-curvularin and its ring homologues **17c** and **17d** reveal marked differences in the conformational behavior of the macrolactones, particularly concerning the oligomethylene region (Figure 1). The *trans*-ester conformation is strongly preferred, as well as the equatorial position of the methyl group at the stereogenic center. Astonishingly, the 9-carbonyl group is forced to adopt a position almost perpendicular to the aromatic ring in (*S*)-curvularin **1** and its 14-membered homologue **17c**.

Only in the 16-membered homologue **17d** can this 9-carbonyl group relax to a conformation coplanar with the aromatic ring, thus favoring not only mesomeric π delocalization, but also an intramolecular hydrogen bond. The importance of the aliphatic part of the compounds is also underscored by the fact that the unsaturated compounds *E*-**18** and *Z*-**18** are ineffective. The cyclopropane derivatives exhibit only minimal effects on the activation of both promoters and are cytotoxic.

The data given in Table 2 suggest that the 9-carbonyl group is essential (see compound **21**). Of the compounds with the intact macrolactone system of (*S*)-curvularin, the 5,7-di-*O*-acetyl derivative **23** and 4-chlorocurvularin **24** showed four- to fivefold higher inhibitory activity on the cytokine-mediated induction of the iNOS promoter than (*S*)-curvularin, concomitant with small to no cytotoxic effects (shown as residual activity of the eNOS promoter).

Conclusions

Ring-closing metathesis reactions were successfully applied to the total synthesis of (*S*)-curvularin, its *E*- and *Z*-configured unsaturated and cyclopropane-annulated analogues, and its 14- and 16-membered ring homologues. In assays measuring anti-inflammatory efficiency with cells transfected with iNOS promoter- and GAS-dependent-promoter–reporter gene constructs, none of these ring variants reach the inhibitory effect of (*S*)-curvularin itself. However, 4-chloro- and 5,7-di-*O*-acetylcurvularin were found to be about four- to fivefold more active than (*S*)-curvularin and exhibited less cytotoxicity than the parent compound. They might constitute useful lead compounds in the search for nonsteroidal anti-inflammatory drugs.

Experimental Section

General methods: 200 and 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR spectra were measured on a Bruker AC 300 instrument. 400 MHz ^{1}H NMR and 100.6 MHz ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument. Chemical shifts are given in δ units relative to tetramethylsilane as the internal standard. FD mass spectra were measured on a Finnigan MAT-95 spectrometer, ESI-HRMS spectra on a Waters Q-TOF-Ultima 3 equipped with a Lock-Spray interface (HCOONa or NaI/CsI as external reference). The melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected. Optical rotations were determined with a PerkinElmer polarimeter 241SW. TLC was performed on aluminum sheets coated with silica gel (60 F_{254}, Merck). Flash column chromatography was carried out on silica gel (32–63 μm, 60 Å, MP Biomedicals GmbH). Analytical RP-HPLC was performed on a Phenomenex Jupiter 300 A C_{18} 5-mm column using Knauer HPLC equipment (Maxistar K1000, DAD 2026 detector).

Methyl-[2,4-bis(methoxycarbonyl)-3,5-dihydroxyphenyl]acetate 2: The compound was synthesized according to reference. [14]. However, while heating the mixture to 110 °C, a slight vacuum of 70 mbar was applied in order to distill off MeOH and H_2O. Yield: 71% (lit.: 53%[14]), colorless needles, mp: 139 °C (lit. mp: 141 °C[14]);

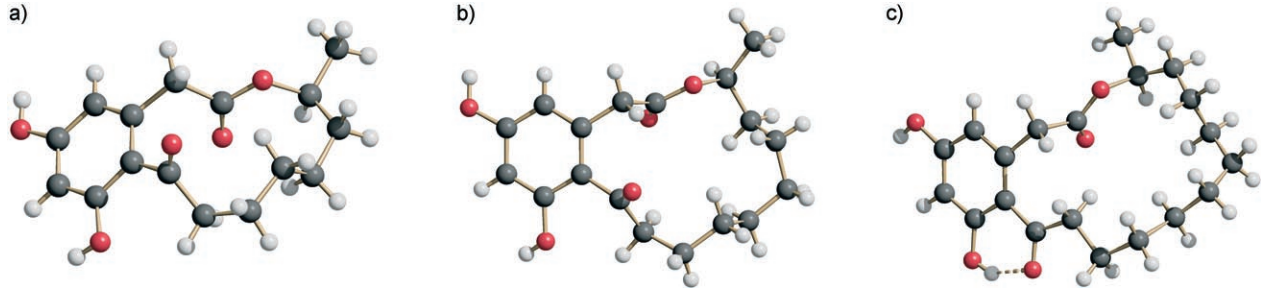


Figure 1. X-ray analysis of a) (*S*)-curvularin **1**/**17a** and b) its 14-membered-ring (compound **17c**) and c) 16-membered-ring homologues **16**.

$R_f = 0.29$ (light petroleum/EtOAc 4:1); ESI-MS (−): $m/z = 297.4$ $[M-H]^-$ (cone voltage 45 V); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 12.95$, 12.00 (s, 2H, O*H*), 6.37 (s, 1H, C*H*, Ph), 4.00, 3.86, 3.68 (3×s, 3×3H, COOCH_3), 3.80 ppm (s, 2H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta =$ 171.1, 170.9 (3C, 3×*C*OO), 166.7, 165.9 (C-3, C-5), 143.4 (C-1), 113.6 (C-6), 105.1, 101.1 (*C*-COOCH$_3$, C-2, C-4), 52.8, 52.1, 52.0 (COO*C*H$_3$), 42.8 ppm (Ph-*C*H$_2$-COO).

(3,5-Dihydroxyphenyl)acetic acid[14] **3**: Compound **2** (51 g, 174 mmol) was held at reflux in 3 N NaOH (210 mL) for 1 h. H_2SO_4 (2.5 M) was then added until pH 3 was reached. Slight evolvement of CO_2 was observed. The solution was heated at 100 °C for 5 min. After cooling, the solution was extracted with EtOAc (5×200 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The crude product **3** can be used for further conversion. Yield: 34 g (crude), slightly brownish amorphous solid, $R_f = 0.19$ (light petroleum/EtOAc/AcOH 10:10:1); ESI-MS (−): $m/z = 123.0$ $[M-H-CO_2]^-$, 167.0 $[M-H]^-$, 290.0 $[2M-H-CO_2]^-$, 334.9 $[2M-H]^-$, 503.0 $[3M-H]^-$ (cone voltage 30 V); ^{1}H NMR (200 MHz, [D$_6$]acetone): $\delta = 6.31$ (d, 2H, $^3J = 2.4$ Hz, H-2, H-6, Ph), 6.24 (d, 1H, $^3J = 2.4$ Hz, H-4, Ph), 3.44 ppm (s, 2H, CH_2); ^{13}C NMR (50.3 MHz, [D$_6$]acetone): $\delta = 172.8$ (*C*OO), 159.3 (C-3, C-5, Ph), 137.7 (C-1, Ph), 108.7 (C-2, C-6, Ph), 102.0 (C-4, Ph), 41.4 ppm (*C*H$_2$); anal. calcd for $C_8H_8O_4$ (168.04): C 57.14, H 4.80, found: C 57.45, H 4.98.

Methyl-(3,5-dihydroxyphenyl)acetate[14] **4**: HCl (concd, 20 mL) was added to the crude acid **3** (34 g) and 2,2-dimethoxypropane (250 mL). The solution was stirred for 1.5 h under argon atmosphere. $NaHCO_3$ (sat. aq, 40 mL) was added, and MeOH and acetone were removed in vacuo. After neutralization with additional sat. $NaHCO_3$, extraction with EtOAc (5×200 mL), drying over $MgSO_4$, and evaporation of the solvent, **3** was purified by flash chromatography in light petroleum/EtOAc/AcOH (60:20:1). Yield: 25.9 g (72% over two steps from **2**), colorless crystals, $R_f = 0.52$ (light petroleum/EtOAc/AcOH 50:50:1), mp: 108 °C, (lit.: mp: 110 °C;[14] ESI-MS (−): $m/z = 180.9$ $[M-H]^-$, 363.0 $[2M-H]^-$; ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 8.20$ (s, 2H, 2×O*H*), 6.28–6.24 (m, 3H, H-2, H-4, H-6, Ph), 3.62 (s, 3H, COOCH_3), 3.46 ppm (s, 2H, CH_2); ^{13}C NMR (75.5 MHz, [D$_6$]acetone): $\delta = 172.2$ (*C*OO), 159.4 (C-3, C-5, Ph), 137.7 (C-1, Ph), 108.7 (C-2, C-6, Ph), 102.0 (C-4, Ph), 51.9 (COO*C*H$_3$), 41.4 ppm (*C*H$_2$); anal. calcd for $C_9H_{10}O_4$ (182.17): C 59.34, H 5.53, found: C 59.29, H 5.72.

Methyl-[3,5-bis(benzyloxy)phenyl]acetate[11,27] **5**: Ester **5** was obtained from acid **4** (15.85 g, 87 mmol) and benzyl bromide (25 mL, 35.7 g, 209 mmol) according to reference [25]. Yield: 28.1 g (89%), colorless crystals, $R_f = 0.51$ (light petroleum/EtOAc 4:1), mp: 63 °C, (lit.: mp: 63–64 °C[27]); ESI-MS (+): $m/z = 385.3$ $[M+Na]^+$, 401.3 $[M+K]^+$, 747.3 $[2M+Na]^+$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.46$–7.30 (m, 10H, C*H*, Bn), 6.55 (br s, 3H, H-2, H-4, H-6, Ph), 5.02 (s, 4H, 2×CH_2, Bn), 3.68 (s, 3H, COOCH_3), 3.56 ppm (s, 2H, CH_2-COO); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 171.9$ (*C*OO), 160.2 (C-3, C-5, Ph), 137.0 (C$_i$, Bn), 136.2 (C-1, Ph), 128.7 (C$_o$, Bn), 128.1 (C$_p$, Bn), 127.7 (C$_m$, Bn), 108.6 (C-2, C-6, Ph), 101.0 (C-4, Ph), 70.2 (CH$_2$, Bn), 52.2 (COO*C*H$_3$), 41.6 ppm (CH$_2$-COO).

[3,5-Bis(benzyloxy)phenyl]acetic acid[11] **6**: Ester **5** (2.39 g, 6.6 mmol) was saponified in 2 N NaOH (60 mL) according to reference [11]. Yield: 2.12 g (92%), colorless solid, $R_f = 0.48$ (light petroleum/EtOAc/AcOH 60:30:1); ESI-MS (−): $m/z = 303.2$ $[M-CO_2-H]^-$, 347.1 $[M-H]^-$, 695.4 $[2M-H]^-$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46$–7.30 (m, 10H, C*H*, Bn), 6.58 (br s, 3H, H-2, H-4, H-6, Ph), 5.04 (s, 4H, 2×CH_2, Bn), 3.61 ppm (s, 2H, CH_2-COO); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.7$ (*C*OO), 160.2 (C-3, C-5, Ph), 136.9 (C$_i$, Bn), 135.4 (C-1, Ph), 128.7 (C$_o$, Bn), 128.1 (C$_p$, Bn), 127.7 (C$_m$, Bn), 108.6 (C-2, C-6, Ph), 101.0 (C-4, Ph), 70.2 (*C*H$_2$, Bn), 41.4 ppm (*C*H$_2$-COO).

Allyl-7-hydroxyheptanoate: 7-Hydroxyheptanoic acid (0.91 g, 6.23 mmol) and cesium carbonate (1.07 g, 3.60 mmol) in dry MeOH (100 mL) were stirred for 3 h. MeOH was evaporated in vacuo, and the dried cesium salt was dissolved in dry *N*,*N*-dimethylformamide (DMF, 100 mL). Allyl bromide (1.06 mL, 1.51 g, 12.5 mmol) was added at 0 °C. The solution was stirred at 0 °C for 30 min and at 20 °C for 2 h. DMF was removed in high vacuum, the residue was dissolved in CH_2Cl_2 (150 mL) and H_2O (100 mL), and the organic layer was washed with H_2O (100 mL). After drying with Mg_2SO_4, the solvent was evaporated in vacuo. The crude allyl ester can be used for further conversion. Yield: 1.364 g (crude, quant.), colorless oil, $R_f = 0.24$ (cyclohexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 5.98–5.81 (m, 1H, C*H*=CH$_2$, All), 5.32–5.19 (m, 2H, CH=C*H*$_2$, All), 4.55 (d, 2H, $^3J = 5.5$ Hz, CH-C*H*$_2$, All), 3.61 (t, 2H, $^3J = 6.6$ Hz, H-7), 2.33 (t, 1H, $^3J = 4.2$ Hz, H-2), 1.66–1.53 (m, 4H, H-3, H-6), 1.37–1.32 ppm (m, 4H, H-4, H-5); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 173.5$ (C-1), 132.4 (*C*H=CH$_2$, All), 118.2 (CH=*C*H$_2$, All), 65.1 (CH-*C*H$_2$, All), 62.9 (C-7), 34.3, 32.6 (C-2, C-6), 29.0 (C-4), 25.5, 25.0 ppm (C-3, C-5).

Allyl-7-{[3,5-bis(benzyloxy)phenyl]acetoxy}heptanoate: Crude allyl-7-hydroxyheptanoate (1.41 g, 6.9 mmol) and 4-dimethylaminopyridine (76 mg, 0.62 mmol) in dry CH_2Cl_2 (15 mL) cooled to 0 °C, and *N*,*N*′-dicyclohexylcarbodiimide (1.42 g, 6.89 mmol) were added to a solution of **6** (2.16 g, 6.23 mmol). After 10 min the ice bath was removed, and the solution was stirred for 3 h. The formed urea was filtered off, washed with CH_2Cl_2 (50 mL), the combined organic solutions were washed with 0.5 N HCl (2×50 mL) and sat. aq $NaHCO_3$, and dried over Mg_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography in cyclohexane/EtOAc 15:1. Yield: 2.67 g (85% over steps from **5**), colorless oil, $R_f = 0.42$ (cyclohexane/EtOAc 4:1); ESI-MS (+): $m/z = 539.4$ $[M+Na]^+$, 555.4 $[M+K]^+$, 1055.5 $[2M+Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$–7.33 (m, 10H, C*H*, Bn), 6.56 (br s, 3H, 3×C*H*, Ph), 5.99–5.85 (m, 1H, C*H*=CH$_2$, All), 5.35–5.22 (m, 2H, CH=C*H*$_2$, All), 5.03 (s, 4H, 2×CH_2, Bn), 4.58 (d, 2H, $^3J = 5.9$ Hz, CH-C*H*$_2$, All), 4.09 (t, 2H, $^3J = 6.6$ Hz, CH_2-O), 3.56 (s, 2H, Ph-C*H*$_2$-COO), 2.33 (t, 2H, $^3J =$ 7.5 Hz, CH$_2$-C*H*$_2$-COO), 1.68–1.58 (m, 4H, C*H*$_2$-(CH$_2$)$_2$-C*H*$_2$-CH$_2$-COO), 1.44–1.32 ppm (m, 4H, (C*H*$_2$)$_2$-CH$_2$-CH$_2$-COO); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 173.4$ (*C*OOAll), 171.5 (Ph-CH$_2$-*C*OO), 160.1 (*C*O, Ph), 137.0 (C$_i$, Bn), 136.4 (C$_i$, Ph), 132.4 (*C*H=CH$_2$), 128.7 (C$_o$, Bn), 128.1 (C$_p$, Bn), 127.6 (C$_m$, Bn), 118.2 (CH=*C*H$_2$), 108.6 (C$_o$, Ph), 100.9 (C$_p$, Ph), 70.1 (*C*H$_2$, Bn), 65.1, 65.0 (C-7, CH-*C*H$_2$, All), 41.8 (Ph-*C*H$_2$-COO), 34.3 (C-2), 28.8, 28.5 (C-4, C-6), 25.7, 24.9 ppm (C-3, C-5); anal. calcd for $C_{32}H_{36}O_6$ (516.25): C 74.39, H 7.02, found: C 74.50, H 7.08.

7-{[3,5-Bis(benzyloxy)phenyl]acetoxy}heptanoic acid[11] **7**: A solution of the allyl ester described above (2.18 g, 4.21 mmol), dimedone (1.35 g, 9.67 mmol), and tetrakis(triphenylphosphine) palladium(0) (223 mg, 0.194 mmol) in THF (80 mL) was stirred under argon atmosphere for 5 h. The solvent was evaporated in vacuo, and the product **7** was purified by flash chromatography in cyclohexane/EtOAc/AcOH 100:10:1. Yield: 1.94 g (96%), colorless amorphous solid, $R_f = 0.32$ (cyclohexane/EtOAc/AcOH 60:30:1); ESI-MS (−): $m/z = 475.2$ $[M-H]^-$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$–7.33 (m, 10H, CH, Bn), 6.56 (br s, 3H, 3×CH, Ph), 5.03 (s, 4H, 2×CH$_2$, Bn), 4.09 (t, 2H, $^3J = 6.6$ Hz, *C*H$_2$-O), 3.56 (s, 2H, Ph-*C*H$_2$-COO), 2.33 (t, 2H, $^3J = 7.4$ Hz, CH$_2$-*C*H$_2$-COO), 1.66–1.58 (m, 4H, *C*H$_2$-(CH$_2$)$_2$-CH$_2$-CH$_2$-COO), 1.38–1.32 ppm (m, 4H, (*C*H$_2$)$_2$-CH$_2$-CH$_2$-COO); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 179.8$ (COOH), 171.6 (Ph-CH$_2$-COO), 160.1 (*C*O, Ph), 137.0 (C$_i$, Bn), 136.4 (C$_i$, Ph), 128.7 (C$_o$, Bn), 128.1 (C$_p$, Bn), 127.7 (C$_m$, Bn), 108.6 (C$_o$, Ph), 100.9 (C$_p$, Ph), 70.2 (CH$_2$, Bn), 65.0 (C-7), 41.8 (Ph-CH$_2$-COO), 34.0 (C-2), 28.7, 28.5 (C-4, C-6), 25.7,

24.6 ppm (C-3, C-5); anal. calcd for $C_{29}H_{32}O_6$ (476.22): C 73.09, H 6.77, found: C 72.66, H 6.57.

5,7-Di-*O*-benzyl-15-desmethylcurvularin 8: To carboxylic acid **7** (411 mg, 0.861 mmol) was added trifluoroacetic acid (14 mL) and trifluoroacetic anhydride (7 mL). The yellow solution was stirred at room temperature for 2 h. The volatile components were then removed in vacuo, the remainder dried in high vacuum for 3 h, dissolved in CH_2Cl_2 (40 mL), and the solution washed with sat. aq $NaHCO_3$ and H_2O. After drying with Mg_2SO_4 and evaporation of the solvent, the product was purified by flash chromatography in cyclohexane/EtOAc 12:1. Yield: 42 mg (11%), colorless glassy solid, $R_f = 0.44$ (cyclohexane/EtOAc 4:1); ESI-MS (+): $m/z = 481.2$ $[M+Na]^+$, 497.2 $[M+K]^+$, 939.5 $[2M+Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$, broad signals): $\delta = 7.39–7.31$ (m, 10H, CH, Bn), 6.55 (br s, 2H, H-4, H-6), 5.05 (s, 4H, $2\times CH_2$, Bn), 4.13 (t, 2H, $^3J = 5.2$ Hz, H-15), 3.63–2.45 (br, 4H, H-2, H-10), 1.86–1.23 ppm (br, 8H, H-11, H-12, H-13, H-14); ^{13}C NMR (75.5 MHz, $CDCl_3$, broad signals): $\delta = 207.4$ (C-9), 171.1 (C-1), 160.5 (C-5), 158.1 (C-7), 136.4, 136.2 (C_i, Bn), 135.2 (C-3), 128.8 (C_o, Bn), 128.34, 128.27 (C_p, Bn), 127.8, 127.5 (C_m, Bn), 124.4 (C-8), 111.9 (C-4), 102.6 (C-6), 70.9, 70.3 (CH_2, Bn), 66.8 (C-15), 43.9 (C-10), 38.9 (C-2), 27.2, 26.3, 25.3 (C-11, C-13, C-14), 22.9 ppm (C-12).

15-Desmethylcurvularin 9: Pd (10%) on charcoal (11 mg) was added to a solution of **8** (41 mg, 0.0895 mmol) in MeOH/THF. The mixture was stirred under hydrogen atmosphere for 2 h, the catalyst filtered off, washed with EtOAc, and the filtrate evaporated in vacuo. The remaining residue was purified by flash chromatography in cyclohexane/EtOAc 3:1. Yield: 18.5 mg (74%), colorless amorphous solid, $R_f = 0.24$ (cyclohexane/EtOAc/AcOH 50:50:1); analytical HPLC (LUNA C_{18}, 250×4.6 mm, 20→40% CH_3CN, 0.1% TFA, 30 min): $t_R = 19.7$ min; ESI-HRMS (+): $m/z = 301.1052$ $[M+Na]^+$ (calcd: 301.1052); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 9.10$ (br s, 7-OH), 8.75 (br s, 1H, 5-OH), 6.40 (d, 1H, $^4J = 2.2$ Hz, H-6), 6.34 (d, 1H, $^4J = 2.2$ Hz, H-4), 4.06 (t, 2H, $^3J = 5.2$ Hz, H-15), 3.77 (m, 2H, H-2), 3.05–2.96 (m, 2H, H-10), 1.67–1.56 (m, 4H, H-11, H-14), 1.44–1.40 ppm (m, 4H, H-12, H-13); ^{13}C NMR (75.5 MHz, [D$_6$]acetone): $\delta = 206.5$ (C-9), 171.1 (C-1), 160.2 (C-5), 158.5 (C-7), 137.1 (C-3), 121.2 (C-8), 112.1 (C-4), 102.7 (C-6), 66.4 (C-15), 44.2 (C-10), 39.5 (C-2), 27.7, 26.5, 25.9 (C-11, C-13, C-14), 23.4 ppm (C-12).

(*S*)-Alk-ω-en-2-ols 10: General procedure: At −78 °C, the corresponding Grignard solution (1.5 equiv, 1 M vinylmagnesium bromide and allylmagnesium bromide in Et_2O, butenylmagnesium bromide and hexenylmagnesium bromide in THF) was added to Cu^{I}I (0.15 equiv) in THF (20 mL, if 1 mL, 15 mmol propene oxide is applied) and the mixture was stirred at this temperature for 30 min. (*S*)-Propene oxide (1.0 equiv) was added dropwise within 5 min. The mixture was stirred and allowed to warm to −20 °C within 4 h, while the color of the mixture changed to dark brown. After stirring for 16 h at −20 °C, the mixture was poured into a mixture of sat. aq NH_4Cl/ice (1:1) and stirred at room temperature for an additional hour. The yellowish organic layer was separated and the aqueous solution extracted three times with Et_2O. The combined organic solutions were dried with $MgSO_4$ and the solvent cautiously removed by distillation.

(*S*)-Pent-4-en-2-ol[28] **10a**: Distillation at 200 mbar in a ball-tube apparatus gave a solution containing 40 wt% **10a**. A portion was purified by repeated distillation, bp: 70 °C (200 mbar), lit.: 115 °C (1013 mbar).[17a] Yield: 46%, colorless liquid; $[\alpha]_D^{22} = 8.8$ ($c = 1.0$, Et_2O), Ref. [28]: $[\alpha]_D^{22} = 9.06$ ($c = 9.18$, Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.87–5.75$ (m, 1H, H-4), 5.16–5.11 (m, 2H, H-5), 3.88–3.82 (m, 1H, H-2), 2.69–2.14 (m, 2H, H-3), 1.19 ppm (d, 3H, $^3J = 5.9$ Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 134.7$ (C-4), 118.0 (C-5), 66.9 (C-2), 43.7 (C-3), 22.7 ppm (C-1).

(*S*)-Hex-5-en-2-ol[17a] **10b**: This compound was prepared as described for **10a**. Yield: 57%; bp: 75 °C (200 mbar); $[\alpha]_D^{22} = 10.2$ ($c = 1$, $CHCl_3$), Ref. [29]: $[\alpha]_D^{22} = 17.3$ ($c = 1.1$, Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.90–5.77$ (m, 1H, H-5), 5.08–4.94 (m, 2H, H-6), 3.87–3.77 (m, 1H, H-2), 2.22–2.08 (m, 2H, H-3), 1.58–1.50 (m, 2H, H-4), 1.19 ppm (d, 3H, $^3J = 5.9$ Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 138.5$ (C-5), 114.7 (C-6), 67.6 (C-2), 22.7 ppm (C-1).

(*S*)-Hept-6-en-2-ol[17b] **10c**: Purification was performed by flash chromatography in pentane/Et_2O 4:1. Yield: 80%, colorless liquid, $R_f = 0.38$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22} = 9.9$ ($c = 1.45$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.81$ (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, H-6), 5.05–4.93 (m, 2H, H-7), 3.86–3.73 (m, 1H, H-2), 2.11–2.04 (m, 1H, H-5), 1.59–1.30 (m, 4H, H-3, H-4), 1.19 ppm (d, 3H, $^3J = 6.2$ Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 138.8$ (C-6), 114.7 (C-7), 68.1 (C-2), 38.8 (C-3), 33.8 (C-5), 25.1 (C-1), 23.6 ppm (C-4).

(*S*)-Non-8-en-2-ol 10d: Purification was performed by flash chromatography in pentane/Et_2O 4:1. Yield: 93%, colorless liquid, $R_f = 0.45$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22} = 8.9$ ($c = 1.34$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.81$ (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, H-8), 5.03–4.91 (m, 2H, H-9), 3.86–3.73 (m, 1H, H-2), 2.08–2.01 (m, 2H, H-7), 1.49–1.28 (m, 8H, H-3, H-4, H-5, H-6), 1.19 ppm (d, 3H, $^3J = 6.2$ Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 139.2$ (C-8), 114.3 (C-9), 68.2 (C-2), 39.4 (C-3), 33.8 (C-7), 29.2, 29.0 (C-5, C-6), 25.7 (C-1), 23.6 ppm (C-4).

Adipic acid monoallyl ester 11: Adipic acid (35 g, 239 mmol) and acetic anhydride (75 mL) were held at reflux for 4 h. Acetic acid and acetic anhydride were evaporated in vacuo, and the remainder dissolved in dry CH_2Cl_2 (250 mL). Allyl alcohol (30 mL, 25 g, 430 mmol), DMAP (1 g), and pyridine (53 mL, 51 g, 645 mmol) were cautiously added to the stirred solution at 0 °C and under cooling with an ice bath. After 30 min the cooling was removed, and the solution was stirred at room temperature for 2 h. Solvent and pyridine were evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (250 mL), and extracted with 2 N HCl (2×250 mL) and H_2O (250 mL). The organic solution was dried with $MgSO_4$, the solvent evaporated in vacuo, and the oily remainder purified by chromatography on silica in cyclohexane/EtOAc/AcOH 180:40:1. Yield: 25.28 g (57%), colorless oil, $R_f = 0.14$ (cyclohexane/EtOAc 4:1); ESI-MS (−): $m/z = 185.0$ $[M-H]^-$ (cone voltage: 30 V); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.26$ (br s, COO*H*), 5.96–5.83 (m, 1H, C*H*=CH$_2$, All), 5.32–5.19 (m, 2H, CH=C*H*$_2$, All), 4.57–4.54 (m, 2H, CH-C*H*$_2$, All), 2.38–2.33 (m, 4H, C*H*$_2$-CH$_2$-CH$_2$-C*H*$_2$), 1.74–1.59 ppm (m, 4H, CH$_2$-C*H*$_2$-C*H*$_2$-CH$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 179.6$ (*C*OOH), 173.1 (*C*OOAll), 132.2 (*C*H=CH$_2$, All), 118.4 (CH=*C*H$_2$, All), 65.2 (*C*H$_2$-CH, All), 33.9, 33.7 (*C*H$_2$-CH$_2$-CH$_2$-*C*H$_2$), 24.4, 24.2 ppm (CH$_2$-*C*H$_2$-*C*H$_2$-CH$_2$).

Esterification of [3,5-bis(benzyloxy)phenyl]acetic acid 6 using DCC/DMAP): The (*S*)-configured alcohol **10** (20 mmol), [3,5-bis(benzyloxy)phenyl]acetic acid **6** (1.0–1.2 equiv), and DMAP (0.1 equiv) in dry CH_2Cl_2 (50 mL) were stirred at 0 °C. Under cooling with an ice bath, DCC (1.2–1.4 equiv) was added. After 30 min, the cooling was removed and the stirring was continued for 90 min. The formed urea was filtered off, washed with a few mL CH_2Cl_2, and the combined organic solutions were washed with 1 N HCl and sat. aq $NaHCO_3$ (50 mL each) and dried with $MgSO_4$. The solvent was evaporated in vacuo and the remaining product **12** purified by flash chromatography in cyclohexane/EtOAc mixtures.

(*S*)-1-Methylbut-3-en-1-yl-[3,5-bis(benzyloxy)phenyl]acetate 12a: The compound was obtained from (*S*)-pent-4-en-2-ol **10a** (1.72 g, 19.9 mmol) and purified by flash chromatography in cyclohexane/EtOAc 40:1. Yield: 8.2 g (98%), colorless oil, $R_f = 0.34$ (cyclohexane/EtOAc 20:1); $[\alpha]_D^{23} = -3.4$ ($c = 1.0$, $CHCl_3$); ESI-MS (+): $m/z = 439.2$ $[M+Na]^+$; ESI-HRMS (+): $m/z = 439.1873$ $[M+Na]^+$ (calcd: 439.1885); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.44–7.30$ (m, 10H, C*H*, Bn), 6.54 (br s, 3H, C*H*, Ph), 5.71 (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, CH_2-C*H*=CH_2), 5.08–4.92 (m, 3H, C*H*-CH_2, CH=C*H*$_2$), 5.02 (s, 4H, 2×C*H*$_2$, Bn), 3.52 (s, 2H, C*H*$_2$-COO), 2.37–2.21 (m, 2H, C*H*$_2$-CH=CH_2), 1.21 ppm (d, 3H, $^3J = 6.6$ Hz, CHC*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.0$ (*C*OO), 160.1 (*C*O, Ph), 137.0 (C_i, Bn), 136.5 (C_i, Ph), 133.7 (*C*H=CH_2), 128.7 (C_o, Bn), 128.1 (C_p, Bn), 127.7 (C_m, Bn), 117.9 (CH=*C*H$_2$), 108.6 (C_o, Ph), 101.0 (C_p, Ph), 70.8 (*C*H-CH_3), 70.2 (*C*H$_2$, Bn), 42.0 (*C*H$_2$-COO), 40.3 (CH-*C*H$_2$), 19.5 ppm (CH*C*H$_3$).

(*S*)-1-Methylpent-4-en-1-yl-[3,5-bis(benzyloxy)phenyl]acetate 12b: The compound was obtained from (*S*)-hex-5-en-2-ol **10b** (1.82 g, 18.2 mmol) and purified by chromatography in cyclohexane/EtOAc 10:1. Yield: 5.27 g (67%), colorless oil, $R_f = 0.61$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22} = 5.3$ ($c = 1.0$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.44–7.29$ (m, 10H, C*H*, Bn), 6.56–6.53 (br s, 3H, C*H*, Ph), 5.77 (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, CH_2-C*H*=CH_2), 5.02 (s, 4H, 2×C*H*$_2$, Bn), 5.00–4.89 (m, 3H, C*H*-CH_2, CH=C*H*$_2$), 3.53 (s, 2H, C*H*$_2$-COO), 2.08–1.94 (m, 2H, C*H*$_2$-CH=CH_2), 1.72–1.50 (m,3H, CH-C*H*$_2$-CH_2), 1.21 ppm (d, 3H, $^3J = 6.3$ Hz, CHC*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.1$ (*C*OO), 160.2 (*C*O, Ph), 136.8 (C_i, Bn), 136.5 (C_i, Ph), 135.7 (*C*H=CH_2), 128.8 (C_o, Bn), 128.1 (C_p, Bn), 127.7 (C_m, Bn), 117.9 (CH=CH_2), 108.6 (C_o, Ph), 101.0 (C_p, Ph), 70.6 (*C*H-CH_3), 70.2 (*C*H$_2$, Bn), 42.0 (*C*H$_2$-COO), 35.0, 24.2 (CH-*C*H$_2$-*C*H$_2$-CH), 19.5 ppm (CH*C*H$_3$).

(*S*)-1-Methylhex-5-en-1-yl-[3,5-bis(benzyloxy)phenyl]acetate 12c: The compound was obtained from (*S*)-hept-6-en-2-ol **10c** (100 mg, 0.88 mmol) and purified by flash chromatography in cyclohexane/EtOAc 40:1. Yield: 5.27 g (67%), colorless oil, $R_f = 0.64$ (cyclohexane/EtOAc 4:1), Yield: 323 mg (83%), colorless oil, $R_f = 0.64$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22} = 5.7$ ($c = 1.0$, $CHCl_3$); ESI-MS (+): $m/z = 467.3$ $[M+Na]^+$; ESI-HRMS (+): $m/z = 467.2186$ $[M+Na]^+$ (calcd: 467.2198); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.46–7.32$ (m, 10H, C*H*, Bn), 6.58 (d, 2H, $^4J = 2.2$ Hz, C*H*$_o$, Ph), 6.56 (d, 1H, $^4J = 2.2$ Hz, C*H*$_p$, Ph), 5.78 (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, CH_2-C*H*=CH_2), 5.04 (s, 4H, 2×C*H*$_2$, Bn), 5.00–4.91 (m, 3H, CH_3-C*H*, CH=C*H*$_2$), 3.55 (s, 2H, C*H*$_2$-COO), 2.08–2.01 (m, 2H, C*H*$_2$-CH=CH_2), 1.63–1.35 (m, 4H, CH-C*H*$_2$-C*H*$_2$), 1.23 ppm (d, 3H, $^3J = 6.3$ Hz, CHC*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.1$ (*C*OO), 160.1 (*C*O, Ph), 138.5 (C_i, Bn), 137.0 (C_i, Ph), 136.6 (*C*H=CH_2), 128.7 (C_o, Bn), 128.1 (C_p, Bn), 127.6 (C_m, Bn), 114.9 (CH=CH_2), 108.6 (C_o, Ph), 100.9 (C_p, Ph), 71.5 (*C*H-CH_3), 70.2 (*C*H$_2$, Bn), 42.1 (*C*H$_2$-COO), 35.4, 33.5 (*C*H$_2$-CH_2-CH_2), 24.7 (CH_2-*C*H$_2$-CH_2), 20.0 ppm (CH*C*H$_3$).

(*S*)-1-Methyloct-7-en-1-yl-[3,5-bis(benzyloxy)phenyl]acetate 12d: The compound was obtained from (*S*)-non-8-en-2-ol **10d** (100 mg, 0.70 mmol) and purified by flash chromatography in cyclohexane/EtOAc 40:1. Yield: 241 mg (72%), colorless oil, $R_f = 0.68$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22} = 6.0$ ($c = 1.0$, $CHCl_3$); ESI-MS (+): $m/z = 495.3$ $[M+Na]^+$, 511.3 $[M+K]^+$; ESI-HRMS (+): $m/z = 495.2495$ $[M+Na]^+$ (calcd: 495.2511); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.42–7.30$ (m, 10H, CH, Bn), 6.58 (d, 2H, $^4J = 1.8$ Hz, CH_o, Ph), 6.55 (d, 1H, $^4J = 1.8$ Hz, CH_p, Ph), 5.79 (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, CH_2-CH=CH_2), 5.03 (s, 4H, 2×CH_2, Bn), 4.96–4.89 (m, 3H, CH-CH_2, CH=CH_2), 3.54 (s, 2H, CH_2-COO), 2.06–1.99 (m, 2H, CH_2-CH=CH_2), 1.63–1.25 (m, 8H, CH-$(CH_2)_4$), 1.21 ppm (d, 3H, $^3J = 6.2$ Hz, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.0$ (COO), 160.0 (*C*O, Ph), 139.0 (C_i, Bn), 136.9 (C_i, Ph), 136.5 (CH=CH_2), 128.6 (C_o, Bn), 128.0 (C_p, Bn), 127.5 (C_m, Bn), 114.3 (CH=CH_2), 108.4 (C_o, Ph), 100.8 (C_p, Ph), 71.6 (CH-CH_3), 70.0 (CH_2, Bn), 42.0 (CH_2-COO), 35.8, 33.6, 28.9, 28.8, 25.2 ($CH(CH_2)_5$), 19.9 ppm ($CHCH_3$).

Allyl-(*S*)-6-{2,4-bis(benzyloxy)-6-[(1-methylbut-3-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoate 13a: DMF (1 drop) and oxalyl dichloride (2.01 mL, 23.66 mmol) were added to a stirred solution of adipic monoallyl ester **11** (3.72 g, 20.02 mmol) in dry CH_2Cl_2 (100 mL). After the release of gas had ceased (1 h), volatile components were removed from the reaction mixture in vacuo, the remainder was dried in high vacuum, dissolved in CH_2Cl_2 (100 mL), and cooled to −78 °C. $SnCl_4$ (2.77 mL, 6.16 g, 23.66 mmol) was added, the yellowish solution stirred for 15 min and a solution of the ester **12a** (7.6 g, 18.22 mmol) in dry CH_2Cl_2 (100 mL) was added. While stirring, the mixture was allowed to warm to −20 °C within 4 h. When the starting material **12a** could no longer be detected by TLC, the solution was poured on ice (100 g). H_2O (100 mL) and CH_2Cl_2 were added and the layers separated. The organic solution was washed with sat. aq $NaHCO_3$ and H_2O, dried with $MgSO_4$, and the solvent was evaporated in vacuo. The product **13a** was purified by flash chromatography in cyclohexane/EtOAc 12:1. Yield: 8.81 g (83%), colorless oil, $R_f = 0.50$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{23} = -6.2$ ($c = 1.0$, $CHCl_3$); ESI-MS (+): $m/z = 607.3$ $[M+Na]^+$, 623.3 $[M+K]^+$; ESI-HRMS (+): $m/z = 585.2848$ $[M+H]^+$ (calcd: 585.2852); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.46–7.31$ (m, 10H, C*H*, Bn), 6.54 (d, 1H, $^4J = 2.2$ Hz H-4, Ph), 6.48 (d, 1H, $^4J = 2.2$ Hz, H-6, Ph), 5.98–5.85 (m, 1H, C*H*=CH_2, All), 5.72 (tdd, 1H, $^3J_{trans} = 17.3$ Hz, $^3J_{cis} = 10.7$ Hz, $^3J = 7.0$ Hz, CH_2-C*H*=CH_2), 5.33–5.20 (m, 2H, CH=C*H*$_2$, All), 5.09–4.89 (m, 3H, CH_3-C*H*, CH_2-CH=C*H*$_2$), 5.04, 5.02 (2 s, 2×2H, 2×C*H*$_2$, Bn), 4.55 (d, 2H, $^3J = 5.5$ Hz, CH-C*H*$_2$, All), 3.60 (s, 2H, Ph-C*H*$_2$-COO), 2.84 (t, 2H, $^3J = 7.2$ Hz, Ph-CO-C*H*$_2$), 2.36–2.17 (m, 4H, C*H*$_2$-COOAll, CH-C*H*$_2$), 1.65–1.43 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.21 ppm (d, 3H, $^3J = 6.3$ Hz, CHC*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 206.3$ (*C*O, carbonyl), 173.3 (*C*OOAll), 170.9 (Ph-CH_2-*C*OO), 160.6 (C-4, Ph), 158.1 (C-2, Ph), 136.5, 136.2 (C_i, Bn), 134.8 (C-6, Ph), 133.7 (*C*H=CH_2), 132.5 (CH=CH_2, All), 128.8 (C_o, Bn), 128.4, 128.3 (C_p, Bn), 127.8, 127.7 (C_m, Bn), 124.8 (C-1, Ph), 118.2 (CH=*C*H$_2$, All), 117.9 (CH=CH_2), 109.3 (C-5, Ph), 99.6 (C-3, Ph), 70.9, 70.3 (*C*H$_2$, Bn), 70.8 (*C*H-CH_3), 65.0 (CH_2, All), 44.2 (Ph-CO-*C*H$_2$), 40.3, 39.2 (CH-*C*H$_2$-CH, Ph-*C*H$_2$-COO), 34.2 (*C*H$_2$-COOAll), 24.7, 23.7 (CH_2-*C*H$_2$-*C*H$_2$-CH_2), 19.5 ppm (CH-*C*H$_3$).

Allyl-(*S*)-6-{2,4-bis(benzyloxy)-6-[(1-methylpent-4-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoate 13b: Compound **13b** was synthesized in analogous manner as described for **13a** starting from **12b** (3 g, 5.17 mmol) and using the same ratios of reagents and solvents. The product **13b** was purified by flash chromatography in cyclohexane/EtOAc 10:1. Yield: 2.6 g (83%), colorless oil, $R_f = 0.48$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22} = 1.27$ ($c = 1.0$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.40–7.31$ (m, 10H, C*H*, Bn), 6.54 (d, 1H, $^4J = 2.2$ Hz, H-3, Ph), 6.48 (d, 1H, $^4J = 2.2$ Hz, H-5, Ph), 5.84–5.71 (m, 1H, CH_2-C*H*=CH_2), 5.04, 5.02 (2 s, 2×2H, 2×C*H*$_2$, Bn), 4.99–4.86 (m, 3H, CH_3-C*H*, CH_2-CH=C*H*$_2$), 3.62, (s, 2H, Ph-C*H*$_2$-COO), 2.84 (t, 2H, $^3J = 7.5$ Hz, Ph-CO-C*H*$_2$), 2.21 (t, 2H, $^3J = 7.2$ Hz, C*H*$_2$-COOH), 2.07–1.08 (m, 2H, C*H*$_2$-CH=CH_2), 1.75–1.43 (m, 6H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.21 ppm (d, $^3J = 6.3$ Hz, C*H*-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 206.1$ (*C*O, carbonyl), 179.2 (*C*OOH), 170.9 (Ph-CH_2-*C*OO), 160.4 (C-4, Ph), 158.0 (C-2, Ph), 137.8 (*C*H=CH_2), 136.3, 135.9 (C_i, Bn), 134.7 (C-6, Ph), 128.6 (C_o, Bn), 128.3, 128.2 (C_p, Bn), 127.7, 127.5 (C_m, Bn), 124.5 (C-1, Ph), 114.9 (CH=*C*H$_2$), 109.1 (C-5, Ph), 99.4 (C-3, Ph), 71.1 (*C*H-CH_3), 70.8, 70.2 (*C*H$_2$, Bn), 43.9 (Ph-CO-*C*H$_2$), 39.1 (Ph-CH_2-COO), 35.0, 33.7 (*C*H$_2$-COOH, CH_3-CH-*C*H$_2$-CH_2-CH), 24.2, 23.4, 20.7

(CH_2-CH_2-CH_2-CH_2, CH_2-CH_2-CH=CH_2), 19.9 ppm (CH-CH_3); anal. calcd for $C_{37}H_{42}O_7$ (598.7): C 77.32, H 7.08, found: 77.14, H 6.98.

Allyl-(*S*)-6-{2,4-bis(benzyloxy)-6-[(1-methylhex-5-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoate 13c: Compound **13c** was synthesized in analogous manner as described for **13a** starting from **12c** (223 mg, 0.502 mmol) and using the same ratios of reagents and solvents. The product **13c** was purified by flash chromatography in cyclohexane/EtOAc 15:1. Yield: 187 mg (61%), colorless waxy solid, $R_f = 0.47$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{21} = 0.3$ ($c = 1.0$, $CHCl_3$); ESI-MS (+): $m/z = 635.4$ $[M+Na]^+$, 651.3 $[M+K]^+$; ESI-HRMS (+): $m/z = 635.3000$ $[M+Na]^+$ (calcd: 635.2985); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–7.34 (m, 10H, C*H*, Bn), 6.54 (d, 1H, $^4J = 2.2$ Hz H-3, Ph), 6.49 (d, 1H, $^4J = 1.8$ Hz, H-5, Ph), 5.98–5.84 (m, 1H, C*H*=CH_2, All), 5.75 (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, C*H*=CH_2), 5.34–5.21 (m, 2H, CH=C*H*$_2$, All), 5.04, 5.02 (2 s, 2×2H, 2×C*H*$_2$, Bn), 4.96–4.84 (m, 3H, CH_3-C*H*, CH=C*H*$_2$), 4.56 (d, 2H, $^3J = 5.9$ Hz, CH-C*H*$_2$, All), 3.61 (s, 2H, Ph-C*H*$_2$-COO), 2.85 (t, 2H, $^3J = 7.2$ Hz, Ph-CO-C*H*$_2$), 2.22 (t, 2H, $^3J = 7.2$ Hz, C*H*$_2$-COOAll), 2.07–2.00 (m, 2H, C*H*$_2$-CH_2=CH), 1.63–1.32 (m, 8H, CH_3-CH-C*H*$_2$-C*H*$_2$, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.21 ppm (d, 3H, $^3J = 6.3$ Hz, C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 206.2$ (*C*O, carbonyl), 173.2 (*C*OOAll), 171.0 (Ph-CH_2-*C*OO), 160.5 (C-4, Ph), 171.0 (C-2, Ph), 138.6 (*C*H=CH_2), 136.4, 136.1 (C_i, Bn), 134.9 (C-6, Ph), 132.4 (*C*H=CH_2, All), 128.8 (C_o, Bn), 128.4, 128.3 (C_p, Bn), 127.8, 127.7 (C_m, Bn), 124.7 (C-1, Ph), 118.1 (CH=*C*H$_2$, All), 114.8 (CH=*C*H$_2$), 109.2 (C-5, Ph), 99.5 (C-3, Ph), 71.6 (*C*H-CH_3), 70.9, 70.3 (*C*H$_2$, Bn), 65.0 (*C*H$_2$, All), 44.1 (Ph-CO-*C*H$_2$), 39.3 (Ph-*C*H$_2$-COO), 35.4, 34.2, 33.6 (CH-*C*H$_2$-CH$_2$, *C*H$_2$-COOAll, *C*H$_2$-CH=CH_2), 24.7, 24.6, 23.7 (CH_2-*C*H$_2$-*C*H$_2$-CH_2, *C*H$_2$-CH_2-CH=CH_2), 20.1 ppm (CH-*C*H$_3$).

Allyl-(*S*)-6-{2,4-bis(benzyloxy)-6-[(1-methyloct-7-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoate 13d: The compound was synthesized in analogous manner as described for **13a** starting from **12d** (137 mg, 0.29 mmol) and using the same ratios of reagents and solvents. The product **13d** was purified by flash chromatography in cyclohexane/EtOAc 15:1. Yield: 119 mg (64%), colorless waxy solid, $R_f = 0.51$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{21} = 0.5$ ($c = 1.0$, $CHCl_3$); ESI-MS (+): $m/z = 663.4$ $[M+Na]^+$, 679.3 $[M+K]^+$; ESI-HRMS (+): $m/z = 663.3330$ $[M+Na]^+$ (calcd: 663.3298); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–7.33 (m, 10H, C*H*, Bn), 6.54 (d, 1H, $^4J = 2.2$ Hz, H-3, Ph), 6.49 (br s, 1H, H-5, Ph), 5.98–5.84 (m, H, C*H*=CH_2, All), 5.75 (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, CH_2-C*H*=CH_2), 5.34–5.21 (m, 2H, CH=C*H*$_2$, All), 5.04, 5.02 (2 s, 2×2H, 2×C*H*$_2$, Bn), 4.96–4.84 (m, 3H, CH_3-C*H*, CH_2-CH=C*H*$_2$), 4.56 (d, 2H, $^3J = 5.5$ Hz, CH-C*H*$_2$, All), 3.61 (s, 2H, Ph-C*H*$_2$-COO), 2.85 (t, 2H, $^3J = 7.0$ Hz, Ph-CO-C*H*$_2$), 2.21 (t, 2H, $^3J = 7.2$ Hz, C*H*$_2$-COOAll), 2.24–1.99 (m, 2H, C*H*$_2$-CH_2=CH), 1.70–1.26 (m, 12H, CH-(C*H*$_2$)$_4$-CH_2, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.20 ppm (d, 3H, $^3J = 6.3$ Hz, CH-C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 206.3$ (*C*O, carbonyl), 173.2 (*C*OOAll), 171.0 (Ph-CH_2-*C*OO), 160.5 (C-4, Ph), 158.0 (C-2, Ph), 139.1 (*C*H=CH_2), 136.5, 136.1 (C_i, Bn), 134.9 (C-6, Ph), 132.5 (*C*H=CH_2, All), 128.8 (C_o, Bn), 128.4, 128.3 (C_p, Bn), 127.8, 127.7 (C_m, Bn), 124.7 (C-1, Ph), 118.2 (CH=*C*H$_2$, All), 114.4 (CH=*C*H$_2$), 109.2 (C-5, Ph), 99.5 (C-3, Ph), 71.8 (*C*H-CH_3), 70.9, 70.3 (*C*H$_2$, Bn), 65.0 (*C*H$_2$, All), 44.2 (Ph-CO-*C*H$_2$), 39.3 (Ph-*C*H$_2$-COO), 35.9, 34.2, 33.8 (CH-CH_2-CH_2, *C*H$_2$-COOAll, *C*H$_2$-CH=CH_2), 29.0, 25.29, 25.27, 24.6, 23.7 (CO-CH_2-CH_2-CH_2-CH_2, *C*H$_2$-*C*H$_2$-*C*H$_2$-CH_2-CH=CH_2), 20.1 ppm (CH-*C*H$_3$).

Cleavage of allyl esters 13 using $[Pd(PPh_3)_4]$ and *p*-toluenesulfinate. General procedure: Under argon atmosphere, the allyl ester **13** was dissolved in MeOH/THF 1:1. Lithium *p*-toluenesulfinate (1.5–2 equiv) and tetrakis(triphenylphosphine) palladium(0) (3–5 mol%) were added, and the mixture was stirred at room temperature for 2 h (monitoring by TLC). After complete conversion of **13**, the solvent was evaporated in vacuo, the remainder dissolved in CH_2Cl_2, the solution washed with 1 N HCl, and the organic solution dried with $MgSO_4$. The solvent was evaporated in vacuo, and the brownish oily product **14** was purified by flash chromatography in cyclohexane/EtOAc/AcOH 175:50:1.

(*S*)-6-{2,4-Bis(benzyloxy)-6-[(1-methylbut-3-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoic acid 14a: The compound was obtained from **13a** (7.50 g, 12.83 mmol) in THF/MeOH 1:1 (350 mL). Yield: 6.64 g (95%), yellow amorphous solid, $R_f = 0.29$ (cyclohexane/EtOAc/AcOH 60:30:1); $[\alpha]_D^{23} = -6.7$ ($c = 1.0$, $CHCl_3$); ESI-MS (−): $m/z = 457.0$ $[M-C_5H_9OH-H]^-$, 543.1 $[M-H]^-$; ESI-HRMS (+): $m/z = 567.2381$ $[M+Na]^+$ (calcd: 567.2359); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–7.31 (m, 10H, C*H*, Bn), 6.54 (d, 1H, $^4J = 1.8$ Hz, H-3, Ph), 6.48 (d, 1H, $^4J = 2.2$ Hz, H-5, Ph), 5.72 (tdd, 1H, $^3J_{trans} = 17.7$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, CH_2-C*H*=CH_2), 5.79–5.65 (m, 1H, CH_2-C*H*=CH_2), 5.08–4.91 (m, 3H, CH_3-C*H*, CH_2-CH=C*H*$_2$), 5.04, 5.02 (2 s, 2×2H, 2×C*H*$_2$, Bn), 3.61 (s, 2H, Ph-C*H*$_2$-COO), 2.85 (t, 2H, $^3J = 7.2$ Hz, Ph-CO-C*H*$_2$), 2.46–2.19 (m, 4H, C*H*$_2$-COOH, C*H*$_2$-CH_2=CH), 1.66–1.47 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.21 ppm (d, 3H, $^3J = 6.3$ Hz, CH-C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 206.3$ (*C*O, carbonyl), 179.6 (*C*OOH), 170.9 (Ph-CH_2-*C*OO), 160.5 (C-4, Ph), 158.1 (C-2, Ph), 136.5, 136.1 (C_i, Bn), 134.8 (C-6, Ph), 133.7 (*C*H=CH_2), 128.8 (C_o, Bn), 128.4, 128.3 (C_p, Bn), 127.9, 127.7 (C_m, Bn), 124.7 (C-1, Ph), 117.8 (CH=*C*H$_2$), 109.3 (C-5, Ph), 99.5 (C-3, Ph), 70.9, 70.3 (*C*H$_2$, Bn), 70.9 (*C*H-CH_3), 44.1 (Ph-CO-*C*H$_2$), 40.3, 39.2 (CH-*C*H$_2$-CH, Ph-*C*H$_2$-COO), 33.9 (*C*H$_2$-COOH), 24.3, 23.6 (CH_2-*C*H$_2$-*C*H$_2$-CH_2), 19.5 ppm (CH-*C*H$_3$).

(*S*)-6-{2,4-Bis(benzyloxy)-6-[(1-methylpent-4-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoic acid 14b: The compound was obtained from **13b** (2.35 g, 3.92 mmol) in THF/MeOH 1:1 (105 mL). Yield: 1.52 g 69%), yellow oil, $R_f = 0.32$ (cyclohexane/EtOAc/AcOH 60:30:1); $[\alpha]_D^{22} = -4.3$ ($c = 1.0$, $CHCl_3$); ESI-MS (−): $m/z = 557.24$ $[M-H]^-$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.31 (m, 10H, C*H*, Bn), 6.54 (d, 1H, $^4J = 2.2$ Hz, H-3, Ph), 6.48 (d, 1H, $^4J = 2.2$ Hz, H-5, Ph), 5.84–5.71 (m, 1H, CH_2-C*H*=CH_2), 5.04, 5.02 (2 s, 2×2H, 2×C*H*$_2$, Bn), 4.99–4.86 (m, 3H, CH_3-C*H*, CH2-CH=C*H*$_2$), 3.62, (s, 2H, Ph-C*H*$_2$-COO), 2.84 (t, 2H, $^3J = 7.5$ Hz, Ph-CO-C*H*$_2$), 2.21 (t, 2H, $^3J = 7.2$ Hz, C*H*$_2$-COOH), 2.07–1.08 (m, 2H, C*H*$_2$-CH=CH_2), 1.75–1.43 (m, 6H, CH_2-C*H*$_2$- C*H*$_2$- CH_2), 1.21 ppm (d, $^3J = 6.3$ Hz, C*H*-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 206.1$ (*C*O, carbonyl), 179.2 (*C*OOH), 170.9 (Ph-CH_2-*C*OO), 160.4 (C-4, Ph), 158.0 (C-2, Ph), 137.8 (*C*H=CH_2), 136.3, 135.9 (C_i, Bn), 134.7 (C-6, Ph), 128.6 (C_o, Bn), 128.3, 128.2 (C_p, Bn), 127.7, 127.5 (C_m, Bn), 124.5 (C-1, Ph), 114.9 (CH=*C*H$_2$), 109.1 (C-5, Ph), 99.4 (C-3, Ph), 71.1 (*C*H-CH_3), 70.8, 70.2 (*C*H$_2$, Bn), 43.9 (Ph-CO-*C*H$_2$), 39.1 (Ph-CH_2-COO), 35.0, 33.7 (*C*H$_2$-COOH, CH_3-CH-*C*H$_2$-CH_2-CH), 24.2, 23.4, 20.7 (CH_2-*C*H$_2$-*C*H$_2$-CH_2, *C*H$_2$-CH_2-CH=CH_2), 19.9 ppm (CH-*C*H$_3$); anal. calcd for $C_{34}H_{38}O_7$ (558.7): C 73.10, H 6.86, found: 72.80, H 6.64.

(*S*)-6-{2,4-Bis(benzyloxy)-6-[(1-methylhex-5-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoic acid 14c: The compound was obtained from **13c** (880 mg, 1.44 mmol) in THF/MeOH 1:1 (40 mL). Yield: 786 mg (98%), yellow oil, $R_f = 0.34$ (cyclohexane/EtOAc/AcOH 60:30:1); $[\alpha]_D^{23} = 0.3$ ($c = 1.0$, $CHCl_3$); ESI-MS (−): $m/z = 457.0$ $[M-C_7H_{13}OH-H]^-$, 571.2 $[M-H]^-$; ESI-HRMS (+): $m/z = 595.2650$ $[M+Na]^+$ (calcd: 595.2672 g mol^{-1}); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–7.34 (m, 10H, C*H*, Bn), 6.55 (d, 1H, $^4J = 1.8$ Hz H-3, Ph), 6.49 (d, 1H, $^4J = 2.2$ Hz, H-5, Ph), 5.77 (tdd, 1H, $^3J_{trans} = 16.9$ Hz, $^3J_{cis} = 10.3$ Hz, $^3J = 6.6$ Hz, CH_2-C*H*=CH_2), 5.04, 5.02 (2 s, 2×2H, 2×C*H*$_2$, Bn), 4.98–4.84 (m, 3H, CH_3-C*H*, CH_2-CH=C*H*$_2$), 3.62 (s, 2H, Ph-C*H*$_2$-COO), 2.85 (t, 2H, $^3J = 7.7$ Hz, Ph-CO-C*H*$_2$), 2.22 (t, 2H, $^3J = 7.4$ Hz, C*H*$_2$-COOH), 2.07–2.00 (m, 2H, C*H*$_2$-CH_2=CH), 1.67–1.32 (m, 8H, CH-C*H*$_2$-C*H*$_2$-CH_2, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.21 ppm (d, 3H, $^3J = 6.3$ Hz, CH-C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 206.3$ (*C*O, carbonyl), 179.6 (*C*OOH), 171.1 (Ph-CH_2-*C*OO), 160.6 (C-4, Ph), 158.1 (C-2, Ph), 138.1

(*C*H=CH_2), 136.5, 136.1 (C_i, Bn), 134.9 (C-6, Ph), 128.8 (C_o, Bn), 128.5, 128.3 (C_p, Bn), 127.9, 127.7 (C_m, Bn), 124.7 (C-1, Ph), 114.8 (CH=*C*H_2), 109.2 (C-5, Ph), 99.5 (C-3, Ph), 71.7 (*C*H-CH_3), 70.9, 70.3 (*C*H_2, Bn), 44.1 (Ph-CO-*C*H_2), 39.3 (Ph-*C*H_2-COO), 35.4, 33.9, 33.6 (*C*H_2-COOH, *C*H_2-CH_2-*C*H_2-CH), 24.7, 24.3, 23.6 (CH_2-*C*H_2-*C*H_2-CH_2, *C*H_2-CH_2-CH=CH_2), 20.1 ppm (CH-*C*H_3).

(*S*)-6-{2,4-Bis(benzyloxy)-6-[(1-methyloct-7-en-1-yl)oxycarbonylmethyl]phenyl}-6-oxohexanoic acid 14d: The compound was obtained from **13d** (638 mg, 1.0 mmol) in THF/MeOH 1:1 (30 mL). Yield: 548 mg (92%), yellowish oil, R_f=0.36 (cyclohexane/EtOAc/AcOH 60:30:1); $[\alpha]_D^{23}$=0.3 (c=1.0, $CHCl_3$); ESI-MS (−): m/z=599.2 $[M-H]^-$, 457.0 $[M-C_9H_{17}OH-H]^-$; ESI-HRMS (+): m/z=623.2960 $[M+Na]^+$ (calcd: 623.2985 g mol^{-1}); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.41–7.34 (m, 10H, C*H*, Bn), 6.55 (d, 1H, ^4J=2.2 Hz, H-3, Ph), 6.49 (d, 1H, ^4J=1.7 Hz, H-5, Ph), 5.79 (tdd, 1H, $^3J_{trans}$=16.9 Hz, $^3J_{cis}$= 10.3 Hz, ^3J=6.6 Hz, CH_2-C*H*=CH_2), 5.04, 5.02 (2 s, 2×2H, 2×CH_2, Bn), 4.96–4.86 (m, 3H, CH_3-C*H*, CH_2-CH=C*H*$_2$), 3.62 (s, 2H, Ph-C*H*$_2$-COO), 2.85 (t, 2H, ^3J=7.2 Hz, Ph-CO-C*H*$_2$), 2.22 (t, 2H, ^3J=7.3 Hz, C*H*$_2$-COOH), 2.06–1.99 (m, 2H, C*H*$_2$-CH_2=CH), 1.70–1.27 (m, 12H, CH-(C*H*$_2$)$_4$-CH_2, CO-CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.21 ppm (d, 3H, ^3J=6.3 Hz, CH-C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=206.3 (*C*O, carbonyl), 179.5 (*C*OOH), 171.1 (Ph-CH_2-*C*OO), 160.6 (C-4, Ph), 158.0 (C-2, Ph), 139.1 (CH=CH_2), 136.5, 136.1 (C_i, Bn), 135.0 (C-6, Ph), 128.8 (C_o, Bn), 128.5, 128.3 (C_p, Bn), 127.9, 127.7 (C_m, Bn), 124.7 (C-1, Ph), 114.4 (CH=*C*H_2), 109.2 (C-5, Ph), 99.5 (C-3, Ph), 71.8 (*C*H-CH_3), 70.9, 70.3 (*C*H_2, Bn), 44.1 (Ph-CO-*C*H_2), 39.3 (Ph-*C*H_2-COO), 35.9, 33.9, 33.7 (CH_3-CH-*C*H_2, *C*H_2-CH=CH_2, *C*H_2-COOH), 29.0, 28.9, 25.3, 24.3, 23.6 (CO-CH_2-CH_2-*C*H_2-CH_2, *C*H_2-CH_2-CH_2-CH_2-CH=CH_2), 20.0 ppm (CH-*C*H_3).

Oxidative decarboxylation of carboxylic acids 14. General procedure: Cu^{II} acetate and pyridine (0.3 mL) were added to a solution of the carboxylic acid **14** (1 mmol) in benzene (10 mL). The mixture was stirred for 5 min. Pb^{IV} acetate was added to the deeply green solution, and the mixture was stirred at room temperature for 1 h and under reflux for 3 h. At room temperature, 1 N HCl/brine/H_2O (1:1:2, 10 mL) was added, and the mixture was stirred for 15 min. The greenish-brown precipitate was filtered through zeolite, washed with CH_2Cl_2, and the aqueous phase separated. The organic solution was washed with 0.1 N HCl, dried with $MgSO_4$, and the solvent was evaporated in vacuo. The crude product **15** was purified by flash chromatography in cyclohexane/EtOAc (15–18:1). The staring material **14** can be recovered by elution with cyclohexane/EtOAc/AcOH (175:50:1).

(*S*)-1-Methylbut-3-en-1-yl-[3,5-bis(benzyloxy)-2-(pent-4-enoyl)-phenyl}acetate 15a: The compound was synthesized according to the general procedure from **14a** (2 g, 3.67 mmol), $Cu(OAc)_2$ (200 mg, 1.1 mmol), $Pb(OAc)_4$ (4.89 g, 11.03 mmol), pyridine (1.1 mL) in benzene (35 mL) and purified by flash chromatography in cyclohexane/EtOAc 15:1. Yield: 719 mg (39%), recovered **14a**: 1.12 g (56%), colorless crystals, mp: 59 °C, R_f=0.48 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{23}$=−7.5 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=521.2 $[M+Na]^+$, 1019.2 $[2M+Na]^+$; ESI-HRMS (+): m/z=521.2293 $[M+Na]^+$ (calcd: 521.2304); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.29 (m, 10H, C*H*, Bn), 6.54 (d, 1H, ^4J=2.2 Hz H-3, Ph), 6.49 (d, 1H, ^4J= 1.9 Hz, H-5, Ph), 5.82–5.66 (m, 2H, 2×CH_2-C*H*=CH_2), 5.09–4.86 (m, 5H, 2×CH_2-CH=C*H*$_2$, CH_3-C*H*), 5.04, 5.03 (2 s, 2×2H, 2×CH_2, Bn), 3.61 (s, 2H, Ph-C*H*$_2$-COO), 2.95 (t, 1H, ^3J=7.5 Hz, Ph-CO-C*H*$_2$), 2.38–2.21 (m, 4H, Ph-CO-CH_2-C*H*$_2$, CH-C*H*$_2$-CH_2=CH), 1.22 ppm (d, 3H, ^3J=6.3 Hz, CH-C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=205.9 (*C*O, carbonyl), 170.9 (*C*OO), 160.6 (C-5, Ph), 158.0 (C-3, Ph), 137.8 ((C*H*$_2$)$_2$-C*H*=CH_2), 136.5, 136.2 (C_i, Bn), 134.9 (C-6, Ph), 133.7 (CH-CH_2-CH=CH_2), 128.78, 128.76 (C_o, Bn), 128.3 (C_p, Bn), 127.71, 127.66 (C_m, Bn), 124.7 (C-1, Ph), 117.8 (CH-CH_2-CH=*C*H_2), 114.8 ((C*H*$_2$)$_2$-CH=*C*H_2), 109.2 (C-5, Ph), 99.5 (C-3, Ph), 70.9, 70.3 (*C*H_2, Bn), 70.8 (*C*H-CH_3), 43.7 (Ph-CO-*C*H_2), 40.3 (CH-CH_2-CH_2=CH), 39.2 (Ph-*C*H_2-COO), 28.3 (CO-CH_2-*C*H_2), 19.5 ppm (CH-*C*H_3).

(*S*)-1-Methylpent-4-en-1-yl-[3,5-bis(benzyloxy)-2-(pent-4-enoyl)-phenyl]acetate 15b: The compound was synthesized according to the general procedure from **14b** (0.79 g, 1.41 mmol), $Cu(OAc)_2$ (71.1 mg, 0.39 mmol), $Pb(OAc)_4$ (1.88 g, 4.23 mmol), pyridine (0.46 mL) in benzene (13 mL) and purified by flash chromatography in cyclohexane/EtOAc 15:1. Yield: 197 mg (34%), recovered **14b**: 390 mg (54%), colorless amorphous solid, R_f=0.56 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22}$=−1.32 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=513.11 $[M+H]^+$, 535.23 $[M+Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.42–7.33 (m, 10H, C*H*, Bn), 6.54 (d, 1H, ^4J=2.0 Hz, H-3, Ph), 6.49 (d, 1H, ^4J= 2.2 Hz, H-5, Ph), 5.83–5.67 (m, 2H, 2×CH_2-C*H*=CH_2), 4.97–4.86 (m, 5H, 2×CH_2-CH=C*H*$_2$, CH_3-C*H*), 5.04, 5.03 (2 s, 2×2H, 2×C*H*$_2$, Bn), 3.62 (s, 2H, Ph-C*H*$_2$-COO), 2.95 (t, 1H, ^3J=7.6 Hz, Ph-CO-C*H*$_2$), 2.38–2.30 (m, 2H, Ph-CO-CH_2-C*H*$_2$), 1.71–1.48 ppm (m, 4H, CH-C*H*$_2$-C*H*$_2$-CH=CH), 1.21 (d, 3H, ^3J=6.3 Hz, CH-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=205.7 (*C*O, carbonyl), 170.8 (Ph-CH_2-*C*OO), 160.4 (C-5, Ph), 158.0 (C-3, Ph), 137.8, 137.7 (2×*C*H=CH_2), 136.3, 136.0 (C_i, Bn), 134.8 (C-1, Ph), 128.7, 128.6 (C_o, Bn), 128.2 (C_p, Bn), 127.6, 127.5 (C_m, Bn), 124.5 (C-2, Ph), 114.9, 114.6 (2×CH=*C*H_2), 109.0 (C-6, Ph), 99.4 (C-4, Ph), 71.1 (*C*H-CH_3), 70.7, 70.2 (2×*C*H_2, Bn), 43.5 (Ph-CO-*C*H_2), 39.1 (Ph- *C*H_2-COO), 35.0 (CH_3-CH-*C*H_2-CH_2), 28.2 (CO-CH_2-CH_2-CH), 26.9 (CH_3-CH-CH_2-CH_2), 19.9 ppm (CH-CH_3); anal. calcd for $C_{34}H_{37}O_5$ (512.6): C 77.32, H 7.08, found: C 77.14, H 6.98.

(*S*)-1-Methylhex-5-en-1-yl-[3,5-bis(benzyloxy)-2-(pent-4-enoyl)-phenyl]acetate 15c: The compound was synthesized according to the general procedure from **14c** (730 mg, 1.27 mmol), $Cu(OAc)_2$ (64 mg, 0.352 mmol), $Pb(OAc)_4$ (1.69 g, 3.81 mmol), pyridine (0.41 mL), and dry benzene (12 mL) and purified by flash chromatography in cyclohexane/EtOAc 18:1. Yield: 245 mg (38%), colorless amorphous solid, R_f=0.55 (cyclohexane/EtOAc 6:1); $[\alpha]_D^{22}$=1.4 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=549.2 $[M+Na]^+$, 565.2 $[M+K]^+$, 1075.5 $[2M+Na]^+$; ESI-HRMS (+): m/z=549.2631 $[M+Na]^+$ (calcd: 549.2617); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.41–7.33 (m, 10H, C*H*, Bn), 6.55 (d, 1H, ^4J=2.2 Hz H-3, Ph), 6.51 (d, 1H, ^4J=2.2 Hz, H-5, Ph), 5.85–5.69 (m, 2H, 2×CH_2-C*H*=CH_2), 5.05, 5.04 (2 s, 2×2H, 2×C*H*$_2$, Bn), 4.97–4.88 (m, 5H, 2×CH_2-CH=C*H*$_2$, CH_3-C*H*), 3.63 (s, 2H, Ph-C*H*$_2$-COO), 2.96 (t, 2H, ^3J=7.1 Hz, Ph-CO-C*H*$_2$), 2.39–2.32 (m, 2H, Ph-CO-CH_2-C*H*$_2$), 2.07–2.00 (m, 2H, (C*H*$_2$)$_2$-C*H*$_2$-CH_2=CH), 1.73–1.28 (m, 4H, (C*H*$_2$)$_2$-CH_2-CH_2=CH), 1.21 ppm (d, 3H, ^3J=6.3 Hz, CH-C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=205.9 (*C*O, carbonyl), 171.0 (Ph-CH_2-*C*OO), 160.6 (C-5, Ph), 158.0 (C-3, Ph), 138.6, 137.8 (2×*C*H=CH_2), 136.5, 136.1 (C_i, Bn), 135.0 (C-1, Ph), 128.8, 128.7 (C_o, Bn), 128.3 (C_p, Bn), 127.71, 127.68 (C_m, Bn), 124.6 (C-2, Ph), 114.8, 114.7 (2×CH=*C*H_2), 109.2 (C-6, Ph), 99.5 (C-4, Ph), 71.6 (*C*H-CH_3), 70.8, 70.3 (2×*C*H_2, Bn), 43.7 (Ph-CO-*C*H_2), 39.3 (Ph-*C*H_2-COO), 35.4, 33.6 (CH_3-CH-*C*H_2-CH_2-CH_2), 28.3, 24.7 (CH_2-*C*H_2-CH_2, CO-CH_2-*C*H_2), 20.1 ppm (CH-*C*H_3).

(*S*)-1-Methyloct-7-en-1-yl-[3,5-bis(benzyloxy)-2-(pent-4-enoyl)-phenyl]acetate 15d: The compound was synthesized according to the general procedure from **14d** (566 mg, 0.96 mmol), $Cu(OAc)_2$ (49 mg, 0.27 mmol), $Pb(OAc)_4$ (1.28 g, 2.88 mmol), pyridine (0.31 mL), in dry benzene (10 mL) and purified by flash chromatography in cyclohexane/EtOAc 18:1. Yield: 179 mg (0.322 mmol, 34%), colorless waxy solid, R_f=0.59 (cyclohexane/EtOAc 6:1); $[\alpha]_D^{21}$=0.8 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=577.3 $[M+Na]^+$, 593.3 $[M+K]^+$, 1131.6 $[2M+Na]^+$; ESI-HRMS (+): m/z=577.2954 $[M+]^+$ (calcd: 577.2930); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.42–7.32 (m, 10H, C*H*, Bn), 6.55 (d, 1H, ^4J=1.8 Hz H-3, Ph), 6.51 (d, 1H, ^4J=1.8 Hz, H-5, Ph), 5.87–5.69 (m, 2H, 2×CH_2-C*H*=CH_2), 5.05, 5.04 (2 s, 2×2H, 2×

CH_2, Bn), 4.96–4.88 (m, 5H, 2×CH_2-CH=CH_2, CH_3-CH), 3.63 (s, 2H, Ph-CH_2-COO), 2.96 (t, 2H, ^3J=7.5 Hz, Ph-CO-CH_2), 2.39–2.32 (m, 2H, Ph-CO-CH_2-CH_2), 2.08–2.01 (m, 2H, $(CH_2)_2$-CH_2-CH_2=CH), 1.65–1.31 (m, 8H, $(CH_2)_4$-CH_2-CH_2=CH), 1.22 ppm (d, 3H, ^3J=6.3 Hz, CH-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=205.9 (CO, carbonyl), 171.0 (Ph-CH_2-COO), 160.5 (C-5, Ph), 158.0 (C-3, Ph), 139.1, 137.8 (2×CH=CH_2), 136.5, 136.1 (C_i, Bn), 135.0 (C-1, Ph), 128.8, 128.7 (C_o, Bn), 128.3 (C_p, Bn), 127.71, 127.68 (C_m, Bn), 124.7 (C-2, Ph), 114.7, 114.4 (2×CH=CH_2), 109.2 (C-6, Ph), 99.5 (C-4, Ph), 71.8 (CH-CH_3), 70.8, 70.3 (CH_2, Bn), 43.7 (Ph-CO-CH_2), 39.3 (Ph-CH_2-COO), 35.9, 35.2 (CH_3-CH-CH_2, $(CH_2)_2$-CH_2-CH=CH_2), 28.9, 28.3, 25.3, 25.3 ($(CH_2)_3$-CH_2-CH=CH_2, CO-CH_2-CH_2), 20.1 ppm (CH-CH_3).

RCM reaction on precursors 15. General procedure: Benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (Grubbs' 2 catalyst,[21] 5–10 mol%) and the di-olefin **15** were dissolved under argon atmosphere in degassed toluene (c=0.005 M) and stirred at 80 °C for 2 h. The reaction was terminated by stirring the solution on air for 1 h. The solvent was evaporated in vacuo, and the dehydrolactones **16** were purified by flash chromatography.

(15*S*)-5,7-Di-*O*-benzyl-12,13-dehydrocurvularin 16a: The synthesis was performed using **15a** (1.35 g, 2.71 mmol) and benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (161 mg, 0.189 mmol, 7 mol%) in dry toluene (540 mL). The product was purified by flash chromatography in cyclohexane/EtOAc 18:1.

***E* Isomer: (15*S*,12*E*)-5,7-Di-*O*-benzyl-12,13-dehydrocurvularin (*E*)-16a**: Yield: 946 mg (74%), colorless crystals, R_f=0.58 (cyclohexane/EtOAc 4:1), mp: 130 °C; $[\alpha]_D^{23}$=14.9 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=471.3 [M+H]$^+$, 493.3 [M+Na]$^+$, 509.2 [M+K]$^+$, 963.5 [2M+Na]$^+$, 979.5 [2M+K]$^+$; ESI-HRMS (+): m/z=493.1988 [M+Na]$^+$ (calcd: 493.1991); ^{1}H NMR, ^{1}H-COSY, HMQC (400 MHz, $CDCl_3$): δ=7.45–7.32 (m, 10H, C*H*, Bn), 6.52 (d, 1H, ^4J=1.2 Hz, H-6), 6.44 (d, 1H, ^4J=2.0 Hz, H-4), 5.76–5.69 (m, 1H, H-12), 5.41–5.32 (m, 1H, H-13), 5.09–4.98 (m, 1H, H-15), 5.03, 5.02 (2 s, 2×2H, 2×CH_2, Bn), 4.04 (d, 1H, ^2J=17.6 Hz, H-2a), 3.25 (d, 1H, ^2J=17.6 Hz, H-2b), 3.06–2.95 (m, 2H, H-10), 2.52–2.40 (m, 1H, H-11a), 2.29–2.40 (m, 1H, H-14a), 2.08–1.95 (m, 2H, H-11b, H-14b), 1.25 ppm (d, 3H, ^3J=6.3 Hz, 15-CH_3); ^{13}C NMR, HMQC (100.6 MHz, $CDCl_3$): δ=207.1 (C-9), 171.4 (C-1), 160.2 (C-5), 156.8 (C-7), 136.6, 136.4 (C_i, Bn), 133.8 (C-3), 133.3 (C-12), 128.8 (C_m, Bn), 128.31, 128.27 (C_p, Bn), 127.7, 127.49 (C_o, Bn), 127.45 (C-13), 125.8 (C-8), 110.3 (C-4), 99.5 (C-6), 70.7, 77.3 (CH_2, Bn), 70.0 (C-15), 45.7 (C-10), 40.4 (C-14), 38.6 (C-2), 24.8 (C-11), 20.5 ppm (15-CH_3).

***Z* Isomer: (15*S*,12*Z*)-5,7-Di-*O*-benzyl-12,13-dehydrocurvularin (*Z*)-16a**: Yield: 122 mg (0.259 mmol, 10%), colorless waxy solid, R_f=0.48 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{23}$=12.8 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=471.3 [M+H]$^+$, 493.3 [M+Na]$^+$, 509.3 [M+K]$^+$, 963.5 [2M+Na]$^+$, 979.5 [2M+K]$^+$; ESI-HRMS (+): m/z=493.2006 [M+Na]$^+$ (calcd: 493.1991); ^{1}H NMR (300 MHz, $CDCl_3$, broad signals): δ=7.50–7.28 (m, 10H, C*H*, Bn), 6.51 (d, 1H, ^4J=2.2 Hz, H-6), 6.51 (d, 1H, ^4J=1.8 Hz, H-4), 5.54–5.25 (m, 2H, H-12, H-13), 5.06, 5.05 (2 s, 2×H, 2×CH_2, Bn), 4.99–4.87 (m, 1H, H-15), 4.02–3.81 (br, 1H, H-2a), 3.79–3.56 (br, 1H, H-2b), 3.16–2.90 (br, 2H, H-10), 2.61–2.39 (m, 1H, H-11a), 2.36–2.04 (m, 3H, H11b, H-14), 1.22 ppm (d, 3H, ^3J=6.6 Hz, 15-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=206.5 (C-9), 170.8 (C-1), 160.7 (C-5), 158.5 (C-7), 136.4, 136.2, 136.1 (C-3, 2×Ci, Bn), 132.3 (C-12), 128.7 (C_m, Bn), 128.2 (C_p, Bn), 127.6, 127.4 (C_o, Bn), 125.0 (C-13), 123.5 (C-8), 110.1 (C-4), 99.6 (C-6), 70.9, 70.3 (CH_2, Bn), 70.4 (C-15), 44.8 (C-10), 39.0 (C-14), 34.3 (C-2), 23.5 (C-11), 20.1 ppm (15-CH_3).

(8*S*,11*E*/*Z*)-1,3-Dibenzyloxy-8-methyl-9,10,13,14-tetrahydro-5*H*,8*H*-7-oxabenzocyclotridecene-6,15-dione 16b: The synthesis was performed with **15b** (173 mg, 0.34 mmol), benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (20.2 mg, 0.024 mmol, 7 mol%) in dry toluene (70 mL), and the product was purified by flash chromatography in cyclohexane/EtOAc 20:1. The *E*/*Z* ratio (5:1) was determined by NMR spectroscopy. Yield: 116 mg (0.24 mmol, 71%), colorless waxy solid, R_f=0.49 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{21}$=36.3 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=485.1 [M+H]$^+$, 507.0 [M+Na]$^+$, 522.9 [M+K]$^+$, 990.8 [2M+Na]$^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.31 (m, 10H, C*H*, Bn), 6.53 (d, 1H, ^4J=2.2 Hz, H-2), 6.50 (d, 1H, ^4J=2.1 Hz, H-4), 5.36–5.25 (m, 2H, H-11, H-12), 5.05, 5.02 (2 s, 2×2H, 2×CH_2, Bn), 4.97–4.93 (m, 1H, H-8), 3.96 (d, 1H, ^2J=16.4 Hz, H-5a), 3.34 (d, 1H, ^2J=16.5 Hz, H-5b), 3.03–2.83 (m, 1H, H-14a), 2.30–2.22 (m, 1H, H-14b), 2.14–1.93 (m, 2H, H-13), 1.75–1.64 (m, 4H, H-9, H-10), 1.17 ppm (d, 3H, ^{3}J=6.3 Hz, 8-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=206.9 (C-15), 171.2 (C-6), 160.1 (C-3), 157.8 (C-1), 136.5, 136.3 (C_i, Bn), 134.4 (C-4a), 130.1, 129.5 (C-11, C-12), 128.5, 128.3 (C_o, Bn), 128.21 (C_p, Bn), 127.6, 127.4 (C_m, Bn), 124.7 (C-15a), 109.0 (C-4), 99.5 (C-2), 70.4 (C-8), 70.7, 70.2 (2×CH_2, Bn), 43.2 (C-14), 38.9 (C-5), 34.5 (C-9), 26.3, 25.4 (C-10, C-13), 20.3 ppm (8-CH_3).

(8*S*,12*E*/*Z*)-1,3-Dibenzyloxy-8-methyl-8,9,10,11,14,15-hexahydro-5*H*-7-oxabenzocyclotetradecene-6,16-dione 16c: The synthesis was performed with **15c** (98 mg, 0.174 mmol), benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (14.7 mg, 0.0174 mmol, 10 mol%) in dry toluene (92 mL), and the product was purified by flash chromatography in cyclohexane/EtOAc 25:1. Separation of the *E*/*Z* isomers was achieved by preparative HPLC: analytical HPLC (LUNA C_{18}, 250×4.6 mm, 80→100% CH_3CN, 30 min): t_R=16.5 min ((*Z*)-**16c**), 17.9 ((*E*)-**16c**); preparative HPLC (LUNA C_{18}, 250×50 mm, 80→100% CH_3CN, 90 min): t_R=63.8 min ((*Z*)-**16c**), 68.2 ((*E*)-**16c**).

***Z* Isomer: (8*S*,12*Z*)-1,3-Dibenzyloxy-8-methyl-8,9,10,11,14,15-hexahydro-5*H*-7-oxabenzocyclotetradecene-6,16-dione (*Z*)-16c**: Yield: 14 mg (0.028 mmol, 15%), colorless waxy solid, R_f=0.44 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{21}$=60.3 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=521.3 [M+Na]$^+$, 537.2 [M+K]$^+$, 1019.3 [2M+Na]$^+$; ESI-HRMS (+): m/z=521.2291 [M+Na]$^+$ (calcd: 521.2304); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.43–7.33 (m, 10H, C*H*, Bn), 6.53 (s, 2H, H-2, H-4), 5.52–5.41 (m, 2H, $^3J_{cis}$=10.7 Hz, H-12, H-13), 5.14–4.97 (m, 1H, H-8), 5.04 (s, 4H, 2×CH_2, Bn), 3.93 (d, 1H, ^2J=16.5 Hz, H-5a), 3.48 (d, 1H, ^2J=16.5 Hz, H-5b), 2.99–2.77 (m, 2H, H-15), 2.34–2.27 (2H), 2.19–2.06 (1H), 1.92–1.81 (1H) (3 m, 4H, H-11, H-14), 1.63–1.31 (m, 4H, H-9, H-10), 1.20 ppm (d, 3H, ^3J=6.3 Hz, 8-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=206.8 (C-16), 171.3 (C-6), 160.4 (C-3), 157.6 (C-1), 136.5, 136.4 (C_i, Bn), 134.2 (C-4a), 130.1, 129.5 (C-12, C-13), 128.8 (C_o, Bn), 128.31, 128.26 (C_p, Bn), 127.7, 127.4 (C_m, Bn), 124.9 (C-16a), 109.7 (C-4), 99.8 (C-2), 70.9 (C-8), 70.8, 70.3 (CH_2, Bn), 44.8 (C-15), 39.0 (C-5), 34.0 (C-9), 26.4, 25.6 (C-11, C-14), 22.4 (C-10), 20.8 ppm (8-CH_3).

***E* Isomer: (8*S*,12*E*)-1,3-Dibenzyloxy-8-methyl-8,9,10,11,14,15-hexahydro-5*H*-7-oxabenzocyclotetradecene-6,16-dione (*E*)-16c**: Yield: 52 mg (0.104 mmol, 60%), colorless waxy solid, R_f=0.49 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{22}$=51.1 (c=1.0, $CHCl_3$); ESI-MS (+): m/z=521.2 [M+Na]$^+$, 537.2 [M+K]$^+$, 1019.2 [2M+Na]$^+$; ESI-HRMS (+): m/z=521.2286 [M+Na]$^+$ (calcd: 521.2304); ^{1}H NMR, ^{1}H-COSY, HMQC, HMBC (400 MHz, $CDCl_3$): δ=7.41–7.32 (m, 10H, C*H*, Bn), 6.54 (d, 1H, ^4J=2.4 Hz, H-2), 6.44 (d, 1H, ^4J=2.0 Hz, H-4), 5.52–5.39 (m, 2H, $^3J_{trans}$=15.7 Hz, H-12, H-13), 5.07–4.97 (m, 1H, H-8), 5.06, 5.04 (2 s, 2×2H, 2×CH_2, Bn), 4.08 (d, 1H, ^2J=17.6 Hz, H-5a), 3.45 (d, 1H, ^2J=17.6 Hz, H-5b), 3.23 (ddd, 1H, ^2J=18.8 Hz, ^3J=7.0 Hz,

^3J = 2.0 Hz, H-15a), 2.94 (ddd, 1H, ^2J = 18.4 Hz, ^3J = 10.9 Hz, ^3J = 2.4 Hz, H-15b), 2.60–2.53 (m, 1H, H-14a), 2.21–2.08 (m, 2H, H-14b, H-11a), 1.91–1.80 (m, 1H, H-11b), 1.77–1.65 (m, 1H, H-9a), 1.61–1.44 (m, 3H, H-10a, H-10b, H-9b), 1.20 ppm (d, 3H, ^3J = 6.7 Hz, 8-CH_3); ^{13}C NMR, HMQC, HMBC (100.6 MHz, $CDCl_3$): δ = 206.1 (C-16), 171.2 (C-6), 160.2 (C-3), 157.5 (C-1), 136.5, 136.3 (C_i, Bn), 134.7 (C-4a), 130.0, 129.9 (C-12, C-13), 128.7 (C_o, Bn), 128.24, 128.21 (C_p, Bn), 127.6, 127.4 (C_m, Bn), 125.2 (C-16a), 109.8 (C-16), 99.6 (C-2), 70.8, 70.2 (*C*H_2, Bn), 70.6 (C-8), 43.8 (C-15), 38.5 (C-5), 33.3 (C-9), 29.5 (C-11), 26.0 (C-14), 21.4 (C-10), 19.2 ppm (8-*C*H_3).

(8*S*,9*E*/*Z*)-1,3-Dibenzyloxy-8-methyl-8,9,10,11,12,13,16,17-octahydro-5*H*-7-oxabenzocyclohexadecene-6,18-dione 16 d: The synthesis was performed with **15 d** (77.2 mg, 0.139 mmol), benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (11.8 mg, 0.014 mmol, 10 mol%) in dry toluene (80 mL), and the product was purified by flash chromatography in cyclohexane/EtOAc 28:1. The *E*/*Z* isomers were separable by flash chromatography, but were not obtained in pure form. Therefore, the pure *E*/*Z* mixture was isolated by preparative HPLC. Analytical HPLC (LUNA C_{18}, 250×4.6 mm, 80→100% CH_3CN, 30 min): t_R = 23.8 min; preparative HPLC (LUNA C_{18}, 250×50 mm, 85→100% CH_3CN, 90 min): t_R = 66.5 min (*E*/*Z*)-**16 d**. Yield: 43 mg (59%), colorless waxy solid, ratio *E*/*Z* = 3:2 (^{1}H NMR, H-10a$_{(E)}$), R_f = 0.32, ((*E*)-**16 d**); R_f = 0.31, (*Z*)-**16 d** (cyclohexane/EtOAc 10:1); $[\alpha]_D^{22}$ = 10.5 (*c* = 1.0, $CHCl_3$); ESI-MS (+): *m*/*z* = 549.2 [*M*+Na]$^+$, 565.2 [*M*+K]$^+$, 1075.4 [2*M*+Na]$^+$; ESI-HRMS (+): *m*/*z* = 549.2621 [*M*+Na]$^+$ (calcd: 549.2617); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 10H, C$H_{(E/Z)}$, Bn), 6.54 (s, 2H, H-10$_{(Z)}$, H-4$_{(Z)}$), 6.52 (d, 1H, ^4J = 1.8 Hz, H-2$_{(E)}$), 6.48 (d, 1H, ^4J = 1.8 Hz, H-4$_{(E)}$), 5.60–5.53, 5.51–5.37 (2 m, 2×1H, H-14$_{(E)}$, H-15$_{(E)}$), 5.41–5.27 (m, 2H, H-14$_{(Z)}$, H-15$_{(Z)}$), 5.06–4.85 (m, 5H, H-8$_{(E/Z)}$, 2×C$H_{2(E/Z)}$, Bn), 3.73 (d, 1H, ^2J = 16.9 Hz, H-5a$_{(E)}$), 3.70 (d, 1H, ^2J = 16.0 Hz, H-5a$_{(Z)}$), 3.51 (d, 1H, ^2J = 16.0 Hz, H-5b$_{(Z)}$), 3.44 (d, 1H, ^2J = 16.9 Hz, H-5b$_{(E)}$), 3.13 (ddd, 1H; ^2J = 18.8 Hz, ^3J = 7.4 Hz, ^3J = 3.3 Hz, H-17a$_{(E)}$), 2.97–2.86 (m, 3H, H-17b$_{(E)}$, H-13a$_{(Z)}$, H-17b$_{(Z)}$), 2.48–1.99 (m, 4H, H-13$_{(E/Z)}$, H-16$_{(E/Z)}$), 1.66–1.22 (m, 8H, H-9$_{(E/Z)}$, H-10$_{(E/Z)}$, H-11$_{(E/Z)}$, H-12$_{(E/Z)}$), 1.19 (d, 3H, ^3J = 6.3 Hz, 8-C$H_{3(E)}$), 1.16 ppm (d, 3H, ^3J = 6.3 Hz, 8-C$H_{3(Z)}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 206.7 (C-18$_{(Z)}$), 206.9 (C-18$_{(E)}$), 171.1 (C-6$_{(Z)}$), 171.1 (C-6$_{(E)}$), 160.3 (C-3$_{(Z)}$), 160.2 (C-3$_{(E)}$), 157.3 (C-1$_{(Z)}$), 156.8 (C-1$_{(E)}$), 136.6, 136.5 ($C_{i(E)}$, Bn), 136.4, 136.3 ($C_{i(Z)}$, Bn), 134.2 (C-4a$_{(Z)}$), 133.6 (C-4a$_{(E)}$), 130.7, 130.1 (C-14, C-15), 128.8, 128.7 (C_o, Bn), 128.3, 128.1 (C_p, Bn), 127.7, 127.6 (C_m, Bn), 125.9 (C-18a$_{(E)}$), 125.1 (C-18a$_{(Z)}$), 108.8 (C-4$_{(E)}$), 108.6 (C-4$_{(Z)}$), 99.8 (C-2$_{(E)}$), 99.8 (C-2$_{(Z)}$), 72.0 (C-8$_{Z)}$), 71.1 (C-8$_{(E)}$), 70.6, 70.5, 70.2 (C$H_{2(E/Z)}$, Bn), 45.1 (C-17$_{(E)}$), 44.5 (C-17$_{(Z)}$), 38.8 (C-5$_{(Z)}$), 38.5 (C-5$_{(E)}$), 35.8 (C-9$_{(E)}$), 35.7 (C-9$_{(Z)}$), 31.0 (C-13$_{(E)}$), 27.8, 26.9, 26.6 (C-11$_{(E)}$, C-12$_{(E)}$, C-16$_{(E)}$), 27.5, 26.7, 24.8, 23.2 (C-11$_{(Z)}$, C-12$_{(Z)}$, C-13$_{(Z)}$, C-16$_{(Z)}$), 24.5 (C-10$_{(E)}$), 22.1 (C-10$_{(Z)}$), 20.6 (8-C$H_{3(E)}$), 19.8 ppm (8-C$H_{3(Z)}$).

Hydrogenolysis of benzyl ethers and C=C double bonds. General procedure: Palladium on charcoal was added to the solution of the *O*-benzyl-protected compounds (**16** and **19**) in MeOH/THF (1:1), and the suspension was stirred under hydrogen atmosphere. If monitoring by TLC after 2 h did not indicate complete conversion, an additional amount of Pd/C was added, and the hydrogenation continued for additional 2 h. The mixture was filtered through a 4-cm layer of silica, which was washed with EtOH (250–300 mL). The combined filtrates were evaporated in vacuo, and the remaining residue was purified by flash chromatography.

(*S*)-Curvularin 1 (= 17 a): The target compound was obtained by hydrogenolysis of (*E*)-**16 a** (50 mg, 0.106 mmol) using 10% Pd/C (15 mg) in THF/MeOH 1:1 (5 mL), and was purified by flash chromatography in cyclohexane/EtOAc/AcOH 3.5:1. Yield: 26.4 mg (85%), colorless crystals (from MeOH/toluene), R_f = 0.37 (cyclohexane/EtOAc/AcOH 60:30:1); mp: 203 °C; mp: (isolated from *Basidiomycetes*) 202 °C; mp: (Ref. [21]) 203 °C; mp: (Ref. [8a]) 206–207 °C; $[\alpha]_D^{22}$ = −33.0 (*c* = 2.0, EtOH); Ref. [8a]: $[\alpha]_D^{22}$ = −33.9 (*c* = 2.0, EtOH); Ref. [21]: $[\alpha]_D^{22}$ = −28.3 (*c* = 1.06, EtOH); ESI-MS (−): *m*/*z* = 247.1 [*M*−CO_2−H]$^-$, 291.1 [*M*−H]$^-$; ESI-HRMS (+): *m*/*z* = 315.1220 [*M*+Na]$^+$ (calcd: 315.1208); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 9.17 (br s, 1H, 7-O*H*), 8.75 (br s, 1H, 5-O*H*), 6.38 (d, 1H, ^4J = 2.2 Hz, H-6), 6.33 (d, 1H, ^4J = 2.2 Hz, H-4), 4.94–4.87 (m, 1H, H-15), 3.77 (d, 1H, ^2J = 15.5 Hz, H-2a), 3.68 (d, 1H, ^2J = 15.5 Hz, H-2b), 3.10 (ddd, 1H, ^2J = 15.5 Hz, ^3J = 8.5 Hz, ^3J = 2.9 Hz, H-10a), 2.75 (ddd, 1H, ^2J = 15.5 Hz, ^3J = 9.6 Hz, ^3J = 2.9 Hz, H-10b), 1.78–1.70 (m, 1H, ^3J = 9.6 Hz, H-11a), 1.63–1.22 (m, 7H, H-11b, H-12, H-13, H-14), 1.10 ppm (d, 3H, ^3J = 6.3 Hz, 15-CH_3); ^{13}C NMR (75.5 MHz, [D_6]acetone): δ = 206.7 (C-9), 171.0 (C-1), 160.1 (C-5), 158.2 (C-7), 136.9 (C-3), 121.3 (C-8), 112.2 (C-4), 102.4 (C-6), 72.6 (C-15), 44.0 (C-10), 39.7 (C-2), 32.9 (C-14), 27.5 (C-12), 24.6 (C-13), 23.5 (C-11), 20.6 ppm (15-CH_3). Crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre quoting number CCDC 678696 via http://www.ccdc.cam.ac.uk/data_request/cif.

(8*S*)-1,3-Dihydroxy-8-methyl-9,10,11,12,13,14-hexahydro-5*H*,8*H*-7-oxabenzocyclotridecene-6,15-dione 17 b: The compound was obtained by hydrogenolysis of (*E*/*Z*)-**16 b** (66 mg, 0.14 mmol) using 10% Pd/C (20 mg) in THF/MeOH 1:1 (7 mL) and purified by flash chromatography in cyclohexane/EtOAc/AcOH 3.5:1. Yield: 34 mg (79%), colorless crystals, R_f = 0.34 (cyclohexane/EtOAc/AcOH 60:30:1); mp: 195 °C; $[\alpha]_D^{21}$ = 43.6 (*c* = 1.0, $CHCl_3$); ESI-HRMS (+): *m*/*z* = 307.16 [*M*+H]$^+$, 329.19 [*M*+Na]$^+$; ^{1}H NMR (300 MHz, [D_6]acetone): δ = 6.25 (d, 1H, ^4J = 2.2 Hz, H-2), 6.23 (d, 1H, ^4J = 2.2 Hz, H-4), 5.22–5.12 (m, 1H, H-8), 3.98 (d, 1H, ^2J = 17.6 Hz, H-5a), 3.64 (d, 1H, ^2J = 17.6 Hz, H-5b), 2.86–2.70 (m, 2H, H-14), 1.90–1.75 (m, 2H, H-13), 1.67–1.22 (m, 8H, H-12, H-11, H-10, H-9), 1.28 ppm (d, 3H, ^3J = 6.3 Hz, 8-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 206.7 (C-15), 171.4 (C-6), 161.3 (C-3), 160.4 (C-1), 137.1 (C-4a), 122.3 (C-15a), 112.4 (C-4), 102.6 (C-2), 70.9 (C-8), 43.8 (C-14), 39.7 (C-5), 33.6 (C-9), 27.4, 25.7, 24.2, 21.9 (C-13, C-12, C-8, C-10), 20.5 ppm (8-CH_3).

(8*S*)-1,3-Dihydroxy-8-methyl-8,9,10,11,12,13,14,15-octahydro-5*H*-7-oxabenzocyclotetradecene-6,16-dione 17 c: The compound was obtained by hydrogenolysis of (*E*)-**16 c** (51 mg, 0.102 mmol) using 10% Pd/C (12 mg) in THF/MeOH 1:1 (6 mL) and purified by flash chromatography in cyclohexane/EtOAc/AcOH 3.5:1. Yield: 29 mg (89%), colorless crystals, R_f = 0.31 (cyclohexane/EtOAc/AcOH 60:30:1); mp: 191–192 °C; $[\alpha]_D^{21}$ = 33.8 (*c* = 1.0, $CHCl_3$); ESI-MS (−): *m*/*z* = 275.0 [*M*−CO_2−H]$^-$, 319.0 [*M*−H]$^-$, 639.2 [2*M*−H]$^-$; ESI-HRMS (+): *m*/*z* = 343.1519 [*M*+Na]$^+$ (calcd: 343.1521); ^{1}H NMR (300 MHz, [D_6]acetone): δ = 10.40–9.18 (br s, 2H, 1-O*H*, 3-O*H*), 6.36–6.33 (m, 2H, H-2, H-4), 5.02–4.92 (m, 1H, H-8), 4.06 (d, 1H, ^2J = 17.3 Hz, H-5a), 3.57 (d, 1H, ^2J = 17.3 Hz, H-5b), 2.98 (ddd, 1H, ^2J = 16.5 Hz, ^3J = 7.7 Hz, ^3J = 5.9 Hz, H-15a), 2.80 (ddd, 1H, ^2J = 16.5 Hz, ^3J = 5.9 Hz, ^3J = 5.5 Hz, H-15b), 1.78–1.23 (m, 12H, H-9 H-10, H-11, H-12, H-13, H-14), 1.17 ppm (d, 3H, ^3J = 6.3 Hz, 8-CH_3); ^{13}C NMR (75.5 MHz, [D_6]acetone): δ = 206.9 (C-16), 171.8 (C-6), 161.0, 160.8 (C-1, C-3), 137.2 (C-4a), 120.4 (C-16a), 112.8 (C-4), 102.7 (C-2), 70.8 (C-8), 43.6 (C-15), 39.9 (C-5), 34.6 (C-9), 27.5, 26.9, 26.6, 24.1, 22.5 (C-10, C-11, C-12 C-13, C-14), 20.5 ppm (8-CH_3). Crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre quoting number CCDC 678697 via http://www.ccdc.cam.ac.uk/data_request/cif.

(16*S*)-1,3-Dihydroxy-8-methyl-8,9,10,11,12,13,14,15,16,17-decahydro-5*H*-7-oxabenzocyclohexadecene-6,18-dione 17 d: The compound was obtained by hydrogenolysis of (*E*)-**16 d** (35 mg, 0.0665 mmol) using 10% Pd/C (10 mg) in THF/MeOH 1:1 (6 mL)

and purified by flash chromatography in cyclohexane/EtOAc/AcOH 3.5:1. Yield: 21 mg (91%), colorless crystals, $R_f = 0.35$ (cyclohexane/EtOAc/AcOH 60:30:1); mp: 132 °C; $[\alpha]_D^{22} = 51.0$ ($c = 1.0$, $CHCl_3$); ESI-MS (+): $m/z = 303.0$ $[M-CO_2-H]^-$, 347.0 $[M-H]^-$, 695.2 $[2M-H]^-$; ESI-HRMS (+): $m/z = 371.1827$ $[M+Na]^+$ (calcd: 371.1834); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 10.38$ (br s, 1-O*H*), 8.83 (br s, 3-O*H*), 6.34 (d, 1H, $^4J = 2.2$ Hz, H-2), 6.31 (d, 1H, $^4J = 2.2$ Hz, H-4), 5.04–4.94 (m, 1H, H-8), 4.02 (d, 1H, $^2J = 17.7$ Hz, H-5a), 3.53 (d, 1H, $^2J = 17.7$ Hz, H-5b), 3.00–2.86 (m, 2H, H-17), 1.83–1.21 (m, 16H, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16), 1.18 ppm (d, 3H, $^3J = 6.3$ Hz, 8-CH_3); ^{13}C NMR (75.5 MHz, [D$_6$]acetone): $\delta = 206.5$ (C-18), 171.7 (C-6), 160.9, 160.8 (C-1, C-3), 137.2 (C-4a), 120.5 (C-18a), 112.3 (C-4), 102.7 (C-2), 70.8 (C-8), 43.0 (C-17), 40.3 (C-5), 36.2 (C-9), 28.1, 27.4, 26.8, 26.45, 26.43 (C-11, C-12, C-13, C-14, C-15), 24.2, 23.1 (C-10, C-16), 20.8 ppm (8-CH_3). Crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre quoting number CCDC 678698 via http://www.ccdc.cam.ac.uk/data_request/cif.

Selective cleavage of benzyl ethers 16 using BBr_3: A freshly prepared solution of BBr_3 in CH_2Cl_2 was added to the solution of benzyl ether **16** in CH_2Cl_2 (3–5 mL) at −20 °C. After 20–30 min, complete conversion was detected by TLC. The cooling was removed, $NaHCO_3$ (sat. aq, 5 mL) was added, and stirring was continued for 5 min. After neutralization with 1 N HCl (30 mL), stirring was continued for 15 min. The mixture was extracted three times with EtOAc (30 mL), the combined organic layers were washed with 1 N HCl and brine (15 mL each), dried with $MgSO_4$, and the solvent was evaporated in vacuo. The products **18** were purified by flash chromatography.

(15*S*,12*E*)-12,13-Dehydrocurvularin (*E*)-18: The compound was obtained from (*E*)-**16a** (37.3 mg, 0.0794 mmol) and BBr_3 in CH_2Cl_2 (0.079 M, 2 mL, 0.160 mmol) and purified by flash chromatography in cyclohexane/EtOAc/AcOH 120:40:1. Yield: 18.4 mg (80%), colorless amorphous solid, $R_f = 0.18$ (cyclohexane/EtOAc/AcOH 60:30:1); $[\alpha]_D^{22} = 1.5$ ($c = 1.0$, $CHCl_3$); ESI-MS (−): $m/z = 244.9$ $[M-CO_2-H]^-$, 289.0 $[M-H]^-$, 579.1 $[2M-H]^-$, 869.0 $[3M-H]^-$; ESI-HRMS (+): $m/z = 313.1051$ $[M+Na]^+$ (calcd: 313.1052); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 8.23$–9.10 (br s, 5-O*H*, 7-O*H*), 6.35 (br s, 1H, H-6), 6.27 (br s, 1H, H-4), 5.60–5.53 (m, 1H, H-12), 5.33–5.52 (m, 1H, H-13), 5.04–4.92 (m, 1H, H-15), 3.84 (d, 1H, $^2J = 16.9$ Hz, H-2a), 3.38 (d, 1H, $^2J = 16.9$ Hz, H-2b), 3.10 (ddd, 1H, $^2J = 17.7$ Hz, $^3J = 5.5$ Hz, $^3J = 3.7$ Hz, H-10a), 2.97–2.86 (m, 1H, H-10b), 2.34–2.20 (m, 2H, H-11a, H-14a), 2.04–1.88 (m, 2H, H-11b, H-14b), 1.20 ppm (d, 3H, $^3J = 6.6$ Hz, 15-CH_3); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 205.8$ (C-9), 170.5 (C-1), 158.6 (C-5), 156.0 (C-7), 134.1 (C-3), 132.7 (C-12), 126.7 (C-13), 121.1 (C-8), 111.0 (C-4), 101.2 (C-6), 69.3 (C-15), 44.7 (C-10), 39.4, 37.7 (C-2, C-14), 25.1 (C-11), 20.2 ppm (15-CH_3).

(15*S*,12*Z*)-12,13-Dehydrocurvularin (*Z*)-18: The compound was obtained from (*Z*)-**16a** (40 mg, 0.085 mmol) and BBr_3 in CH_2Cl_2 (0.085 M, 2 mL, 0.160 mmol), and purified by flash chromatography in cyclohexane/EtOAc/AcOH 120:40:1. Yield: 20.2 mg (82%), waxy solid, $R_f = 0.32$ (cyclohexane/EtOAc/AcOH 50:50:1); $[\alpha]_D^{22} = -18.0$ ($c = 0.75$, MeOH); ESI-MS (−): $m/z = 244.9$ $[M-CO_2-H]^-$, 289.0 $[M-H]^-$, 579.1 $[2M-H]^-$; ESI-HRMS (+): $m/z = 313.1043$ $[M+Na]^+$ (calcd: 313.1052); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 10.83$–9.55 (br s, 7-O*H*), 9.47–8.54 (br s, 1H, 5-O*H*), 6.38 (d, 1H, $^4J = 2.2$ Hz, H-6), 6.33 (d, 1H, $^4J = 2.2$ Hz, H-4), 5.62–5.27 (m, 2H, H-12, H-13), 4.93–4.87 (m, 1H, H-15), 3.81 (s, 2H, H-2), 3.23 (ddd, 1H, $^2J = 13.6$ Hz, $^3J = 8.1$ Hz, $^3J = 5.2$ Hz, H-10a), 2.89 (ddd, 1H, $^2J = 13.6$ Hz, $^3J = 8.8$ Hz, $^3J = 5.1$ Hz, H-10b), 2.51–2.41 (m, 1H, H-11a), 2.39–2.17 (m, 3H, H-11b, H-14), 1.18 ppm (d, 3H, $^3J = 6.6$ Hz, 15-CH_3); ^{13}C NMR (75.5 MHz, [D$_6$]acetone): $\delta = 206.0$ (C-9), 170.7 (C-1), 161.3, 161.2 (C-5, C-7), 138.4 (C-3), 133.2 (C-12), 125.7 (C-13), 118.9 (C-8), 113.1 (C-4), 102.8 (C-6), 70.9 (C-15), 44.6 (C-10), 40.1 (C-2), 33.9 (C-14), 24.6 (C-11), 19.9 ppm (15-CH_3).

(15*S*)-5,7-Di-*O*-benzylcyclopropa[12,13]curvularin 19: Diethylzinc in *n*-hexane (1 M, 1.12 mL) and diiodomethane (0.156 mL, 513 mg, 1.92 mmol) were added to a solution of (*E*)-**16a** (90 mg, 0.188 mmol) in dry dichloroethane (6 mL) at room temperature. The mixture was stirred at 40 °C for 30 min. NH_4Cl (sat. aq, 30 mL) was added, and the mixture was stirred for 5 min and extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were washed with H_2O, dried with $MgSO_4$, and the solvent was evaporated in vacuo. Preparative HPLC yielded 45 mg (50%) starting material (*E*)-**16a**, 10.1 mg minor diastereomer **19b**, and 14.6 mg major diastereomer **19a**. Analytical HPLC (LUNA C_{18}, 250×4.6 mm, 75→95% CH_3CN, 30 min): $t_R = 18.1$ min (**19b**), 18.6 (**19a**); preparative HPLC (LUNA C_{18}, 250×50 mm, 75→95% CH_3CN, 90 min): $t_R = 63.0$ min (starting material (*E*)-**16a**), 68.8 (**19b**), 70.5 (**19a**).

*Major diastereomer **19a***: Yield: 14.6 mg (16%), colorless glassy solid, $R_f = 0.58$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{21} = -20.0$ ($c = 0.75$, $CHCl_3$); ESI-MS (+): $m/z = 507.3$ $[M+Na]^+$, 523.3 $[M+K]^+$; ESI-HRMS (+): $m/z = 485.2327$ $[M+H]^+$ (calcd: 485.2328); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.25 (m, 10H, C*H*, Bn), 6.52 (d, 1H, $^4J = 2.2$ Hz, H-6), 6.50 (d, 1H, $^4J = 2.2$ Hz, H-4), 5.13–4.96 (br, 1H, H-15), 5.04, 5.02 (2 s, 2×2H, 2×CH_2-Bn), 4.04–4.23 (br, H-2a), 3.48–2.94 (br, H-2b, H-10), 2.11–1.90 (br, H-11a, H-14a), 1.16 (d, 3H, $^3J = 6.6$ Hz, 15-CH_3), 1.08–0.70 (br, H-14b, H-11b, H-12), 0.64–0.35 (br, H-13), 0.32–0.15 ppm (m, 2H, CH_2-cyclopropyl); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 136.5, 136.3 (C_i, Bn), 128.8 (C_o, Bn), 128.3 (C_p, Bn), 127.8 (C_m, Bn), 99.8 (C-6), 71.3 (C-15), 70.9, 70.3 (*C*H_2, Bn), 44.0 (C-10), 39.5 ppm (C-14).

*Minor diastereomer **19b***: Yield: 10.1 mg (11%), colorless glassy solid, $R_f = 0.58$ (cyclohexane/EtOAc 4:1); $[\alpha]_D^{21} = -19.7$ ($c = 0.7$, $CHCl_3$); ESI-MS (+): $m/z = 507.3$ $[M+Na]^+$, 523.3 $[M+K]^+$, 538.2 $[M+Na+CH_3CN]^+$; ESI-HRMS (+): $m/z = 485.2317$ $[M+H]^+$ (calcd: 485.2328); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.49$–7.21 (m, 10H, C*H*, Bn), 6.53 (d, 1H, $^4J = 1.8$ Hz, H-6), 6.51 (d, 1H, $^4J = 1.8$ Hz, H-4), 5.02–4.92 (m, 5H, H-15, 2×CH_2, Bn), 3.88 (d, 1H, $^2J = 15.4$ Hz, H-2a), 3.26 (d, 1H, $^2J = 15.4$ Hz, H-2b), 3.12–3.03 (m, 1H, H-10a), 2.68 (ddd, 1H, $^2J = 19.4$ Hz, $^3J = 12.1$ Hz, $^3J = 1.8$ Hz, H-10b), 2.49–2.40 (m, 1H, H-11a), 2.08–2.03 (m, 1H, H-14a), 1.18 (d, 3H, $^3J = 5.9$ Hz, 15-CH_3), 1.18–1.01 (m, 1H, H-12), 0.88–0.76 (m, 1H, H-14b), 0.52–0.37 (m, 1H, H-11b), 0.36–0.24 (m, 1H, H-13), 0.23–0.11 ppm (m, 2H, CH_2, cyclopropyl); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 207.5$ (C-9), 171.5 (C-1), 160.1 (C-5), 156.1 (C-7), 136.6, 136.5 (C_i, Bn), 133.0 (C-3), 128.79, 128.75 (C_o, Bn), 128.3, 128.1 (C_p, Bn), 127.7, 127.1 (C_m, Bn), 125.9 (C-8), 110.0 (C-4), 99.9 (C-6), 73.1 (C-15), 70.6, 70.4 (*C*H_2, Bn), 43.9 (C-10), 40.8, 39.2 (C-2, C-14), 28.0 (C-11), 21.3 (15-CH_3), 17.9, 15.8 (C-12, C-13), 11.5 ppm (*C*H_2-cyclopropane).

(15*S*)-Cyclopropa[12,13]curvularin 20, major diastereomer: The compound was obtained according to the general procedure for hydrogenolysis from **19a** (10 mg, 0.0206 mmol), 10% Pd/C (5 mg) in THF/MeOH 1:1 (4 mL) and purified by flash chromatography in cyclohexane/EtOAc/AcOH 140:40:1. Yield: 5.2 mg (83%), colorless amorphous solid, $R_f = 0.53$ (cyclohexane/EtOAc/AcOH 50:50:1); $[\alpha]_D^{21} = -12.9$ ($c = 0.5$, MeOH); analytical HPLC (LUNA C_{18}, 250×4.6 mm, 30→50% CH_3CN, 30 min, 0.1% TFA): $t_R = 27.7$ min; ESI-MS (−): $m/z = 303.1$ $[M-H]^-$; ESI-HRMS (+): $m/z = 327.1206$ $[M+Na]^+$ (calcd: 327.1208); ^{1}H NMR, ^{1}H-COSY, HMQC, HMBC (400 MHz, [D$_6$]acetone): $\delta = 8.91$ (br s, 1H, 7-O*H*), 8.63 (br s, 1H, 5-O*H*), 6.37 (d, 1H, $^4J = 2.2$ Hz, H-6), 6.31 (d, 1H, $^4J = 2.2$ Hz, H-4), 4.94–4.88 (m, 1H, H-15), 4.05 (d, 1H, $^2J = 14.4$ Hz, H-2a), 3.31 (d, 1H, $^2J = 14.7$ Hz, H-

2b), 3.17–3.11 (m, 2H, H-10), 2.45 (m, 1H, H-11a), 2.02–1.95 (m, 1H, H-14a), 1.13 (d, 3H, ^3J=6.2 Hz, 15-CH_3), 0.98–0.76 (m, 3H, H-14b, H11b, H12), 0.68–0.58 (m, 1H, H-13), 0.26–0.13 ppm (m, 2H, CH_2, cyclopropane); ^{13}C NMR, HMQC, HMBC (100.6 MHz, [D$_6$]acetone): δ=206.0 (C-9), 170.7 (C-1), 159.6 (C-5), 157.1 (C-7), 135.8 (C-3), 123.0 (C-8), 111.0 (C-4), 102.5 (C-6), 71.3 (C-15), 44.1 (C-10), 39.7 (C-2), 39.2 (C-14), 27.9 (C-11), 18.9 (C-12), 18.7 (15-CH_3), 12.2 (CH_2, cyclopropyl), 12.0 ppm (C-13).

(15*S*)-Cyclopropa[12,13]curvularin 20, minor diastereomer: The compound was obtained according to the general procedure for hydrogenolysis from **19b** (7.1 mg, 0.0147 mmol), 10% Pd/C (3 mg) in THF/MeOH 1:1 (4 mL) and purified by flash chromatography in cyclohexane/EtOAc/AcOH 140:40:1. Yield: 4.0 mg (89%), colorless amorphous solid, R_f=0.53 (cyclohexane/EtOAc/AcOH 50:50:1); $[\alpha]_D^{21}=-42.2$ (c=0.4, EtOH); ESI-MS (−): m/z=302.9 [M−H]$^-$, 607.3 [2M−H]$^-$; ESI-HRMS (+): m/z=327.1217 [M+Na]$^+$ (calcd: 327.1208); ^{1}H NMR, ^{1}H-COSY, HMQC, HMBC (400 MHz, [D$_6$]acetone): δ=9.04 (br s, 1H, 7-O*H*), 8.60 (br s, 1H, 5-O*H*), 6.35–6.34 (m, 2H, H-6, H-4), 5.03–4.96 (m, 1H, H-15), 3.76 (d, 1H, ^2J=15.3 Hz, H-2a), 3.32 (d, 1H, ^2J=15.3 Hz, H-2b), 3.11 (ddd, 1H, ^2J=19.2 Hz, ^3J=5.5 Hz, ^3J=2.4 Hz, H-10a), 2.66 (ddd, 1H, ^2J=15.7 Hz, ^3J=11.7 Hz, ^3J=2.4 Hz, H-10b), 2.40–2.32 (m, 1H, H-11a), 2.03 (m, 1H, H-14a), 1.13 (d, 3H, ^3J=6.3 Hz, 15-CH_3), 1.11–0.99 (m, 1H, H-12), 0.82–0.73 (m, 1H, H-14b), 0.57–0.49 (m, 1H, H-11b), 0.39–0.30 (m, 1H, H-13), 0.17–0.13 ppm (m, 2H, CH_2, cyclopropane); ^{13}C NMR, HMQC, HMBC (75.5 MHz, [D$_6$]acetone): δ=207.3 (C-9), 171.6 (C-1), 159.7 (C-5), 156.4 (C-7), 134.8 (C-3), 123.1 (C-8), 111.8 (C-4), 102.3 (C-6), 73.1 (C-15), 43.8 (C-10), 41.4 (C-14), 39.6 (C-2), 28.9 (C-11), 21.3 (15-CH_3), 18.8 (C-12), 16.3 (C-13), 11.6 ppm (CH_2, cyclopropyl).

(*S*)-9-Deoxycurvularin 21[23]: Pd/C 10% (9 mg) was added to a solution of (*S*)-curvularin **17a** (=**1**) (21.3 mg, 0.073 mmol) in EtOAc (5 mL). The suspension was stirred under hydrogen atmosphere for 16 h. The catalyst was filtered off, washed with EtOAc (100 mL), and the solvent was evaporated from the combined filtrates. The residue was purified by flash chromatography in cyclohexane/EtOAc 5:1. Yield: 17.0 mg (84%), colorless amorphous solid, R_f= 0.33 (light petroleum/EtOAc 2:1); $[\alpha]_D^{21}=-2.9$ (c=1.0, MeOH); analytical HPLC (LUNA C$_{18}$, 250×4.6 mm, 40→60% CH$_3$CN, 0.1% TFA, 30 min): t_R=19.9 min, $C_{16}H_{22}O_4$ (278.15 g mol^{-1}); ESI-MS (−): m/z= 233.1 [M−CO$_2$−H]$^-$, 277.2 [M−H]$^-$; ESI-HRMS (+): m/z=301.1414 [M+Na]$^+$ (calcd: 301.1416); ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.12–7.83 (br s, 2H, 5-O*H*, 7-O*H*), 6.32 (d, 1H, ^4J=2.4 Hz, H-6), 6.29 (d, 1H, ^4J= 2.0 Hz, H-4), 5.16–4.98 (m, 1H, H-15), 3.71 (d, 1H, ^2J=15.1 Hz, H-2a), 3.36 (d, 1H, ^2J=15.1 Hz, H-2b), 2.62–2.45 (m, 2H, H-9), 1.81–1.20 (m, 8H, H-11, H-12, H-13, H-14), 1.19 ppm (d, 3H, ^3J=6.4 Hz, 15-CH_3); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ=172.0 (C-1), 157.2 (C-5), 156.4 (C-7), 135.8 (C-3), 120.1 (C-8), 111.3 (C-4), 102.5 (C-6), 73.4 (C-15), 40.3 (C-2), 34.0 (C-14), 27.43, 27.38, 27.0, 25.4, 25.2 (C-9, C-10, C-11, C-12, C-13), 20.9 ppm (15-CH_3).

(*S*)-5-*O*-Acetylcurvularin 22: Acetic anhydride (3 mL) was added dropwise under ice cooling over the course of 40 min to a solution of (*S*)-curvularin **17a** (=**1**) (50 mg, 0.171 mmol) in pyridine (6 mL) at 0 °C. The solution was stirred for 1 h and then poured in iced water (30 mL). After the addition of CH_2Cl_2 (50 mL) and separation of the layers, the organic solution was washed with 1 N HCl, sat. aq NaHCO$_3$, and H$_2$O (30 mL each), and dried with MgSO$_4$. After removal of the solvent in vacuo, the residue was purified twice by flash chromatography in CH_2Cl_2/MeOH (150:1) to give both the diacetyl compound (40%, see below) and the monoacylated compound **22**. Yield: 9 mg (16%), colorless amorphous solid, R_f=0.33 (cyclohexane/EtOAc 1:1); ESI-MS (+): m/z=357.1 [M+Na]$^+$, 373.2 [M+K]$^+$; ESI-HRMS (+): m/z=357.1317 [M+Na]$^+$ (calcd: 357.1314); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=10.41 (br s, 1H, 7-O*H*), 6.61 (d, 1H, ^4J=2.0 Hz, H-6), 6.56 (d, 1H, ^4J=2.2 Hz, H-4), 4.96–4.87 (m, 1H, H-15), 3.70 (d, 1H, ^2J=16.0 Hz, H-2a), 3.61 (d, 1H, ^2J=16.0 Hz, H-2b), 3.01–2.95 (m, 1H, H-10a), 2.80–2.74 (m, 1H, H-10b), 2.26 (COOCH_3, Ac), 1.73–1.63 (m, 1H, H-11a), 1.62–1.21 (m, 7H, H-11b, H-12, H-13, H-14), 1.10 ppm (d, 3H, ^3J=6.3 Hz, 15-CH_3); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ=206.5 (C-9), 170.0 (C-1), 168.7 (*C*OO, Ac), 155.3, 151.1 (C-5, C-7), 134.0 (C-3), 126.4 (C-8), 115.9, 108.4 (C-4, C-6), 72.0 (C-15), 42.3 (C-10), 37.6 (C-2), 32.0 (C-14), 26.5 (C-12), 23.5, 21.7 (C-11, C-13), 20.8, 20.2 ppm (15-CH_3, CH_3COO).

(15*S*)-5,7-Di-*O*-acetylcurvularin 23: Acetic anhydride (0.483 mL, 524 mg, 5.14 mmol) was added dropwise to (*S*)-curvularin **17a** (250 mg, 0.856 mmol) in pyridine (0.692 mL, 677 mg, 8.56 mmol) at 0 °C. The solution was stirred for 1 h and then poured in iced water. After the addition of CH_2Cl_2 (50 mL) and separation of the phases, the organic solution was washed with 1 N HCl, sat. aq NaHCO$_3$, and H$_2$O (30 mL each), and dried with MgSO$_4$. After removal of the solvent in vacuo, the residue was purified by flash chromatography (cyclohexane/EtOAc 4:1). For complete removal of the solvent, the waxy product was dissolved in EtOH (5 mL) and precipitated by the addition of H$_2$O (15 mL), and finally lyophilized. Yield: 276 mg (86%), colorless, highly viscous oil, R_f=0.37 (cyclohexane/EtOAc 1:1); $[\alpha]_D^{21}=3.1$ (c=1.0, EtOH), Ref. [8a]: $[\alpha]_D^{21}=3.5$ (c=2.4, EtOH); ESI-HRMS (+): m/z=399.1436 [M+Na]$^+$ (calcd: 399.1420); ^{1}H NMR (300 MHz, CDCl$_3$): δ=7.00, 6.98 (2d, 2×1H, ^4J= 2.2 Hz, H-4, H-6), 5.05–4.95 (m, 1H, H-15), 3.80 (d, 1H, ^2J=15.8 Hz, H-2a), 3.67 (br d, 1H, ^2J=15.8 Hz, H-2b), 2.83–2.76 (m, 2H, H-10), 2.29, 2.26 (2×s, 2×3H, 2×CH_3, Ac), 1.94–1.70 (m, 1H, H-11a), 1.65–1.22 (m, 7H, H-11b, H-12, H-13, H-14), 1.17 ppm (d, 3H, ^3J=6.3 Hz, 15-CH_3); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ=205.2 (C-9), 170.3 (C-1), 168.6, 168.3 (2×*C*OO, Ac), 151.1 (C-5), 147.8 (C-7), 134.3, 131.9 (C-3, C-8), 122.6, 115.5 (C-4, C-6), 73.4 (C-15), 43.2 (C-10), 38.6 (C-2), 32.8 (C-14), 27.1 (C-12), 24.2 (C-13), 22.4 (C-11), 21.3 (COOCH_3, Ac), 20.6 ppm (15-CH_3).

(*S*)-4-Chlorcurvularin 24: A solution of SO_2Cl_2 (0.185 M, 1.5 mL, 0.273 mmol) in dry THF was added to (*S*)-curvularin **17a** (50 mg, 0.171 mmol) in dry THF (3 mL) at 0 °C. After stirring for 2 h, the cooling was removed and the solution was stirred for additional 5 h. After further addition of the SO_2Cl_2 solution (0.185 M, 0.5 mL, 0.0925 mmol) in dry THF, the stirring was continued for 16 h. NaHCO$_3$ (sat. aq, 20 mL) and subsequently EtOAc (30 mL) were added. After extraction, the organic solution was washed with H$_2$O (20 mL) and dried with MgSO$_4$. The solvent was removed in vacuo, and the residue was purified by flash chromatography in cyclohexane/EtOAc 3:1 and by recrystallization from CH_2Cl_2/light petroleum (1:20 *v*/*v* (mL)). Yield: 35 mg (62%), colorless amorphous solid, R_f= 0.56 (CH_2Cl_2/EtOAc 1:1); $[\alpha]_D^{21}=-73.7$ (c=1.15, MeOH); analytical HPLC (LUNA C$_{18}$, 250×4.6 mm, 30→50% CH$_3$CN, 0.1% TFA, 30 min): t_R=16.5 min; ESI-MS (+): m/z=359.0 [$C_{16}H_{19}{}^{35}ClO_5$+Na]$^+$, 361.0 [$C_{16}H_{19}{}^{37}ClO_5$+Na]$^+$; ESI-HRMS (+): m/z=359.0821 [M+Na]$^+$ (calcd: 359.0819); ^{1}H NMR, HMQC, HMBC (400 MHz, [D$_6$]acetone): δ=9.17 (br s, 7-O*H*), 8.91 (br s, 5-O*H*), 6.64 (s, 1H, H-6), 4.95–4.88 (m, 1H, H-15), 4.18 (d, 1H, ^2J=17.2 Hz, H-2a), 3.69 (d, 1H, ^2J= 16.8 Hz, H-2b), 3.35 (ddd, 1H, ^2J=14.9 Hz, ^3J=7.8 Hz, ^3J=2.5 Hz, H-10a), 2.53 (ddd, 1H, ^2J=16.8 Hz, ^3J=10.9 Hz, ^3J=2.4 Hz, H-10b), 1.87–1.76 (m, 1H, H-11a), 1.59–1.18 (m, 7H, H-11b, H-12, H-13, H-14), 1.11 ppm (d, 3H, ^3J=6.3 Hz, 15-CH_3); ^{13}C NMR, HMQC, HMBC (100.6 MHz, [D$_6$]acetone): δ=207.5 (C-9), 169.8 (C-1), 155.7 (C-5), 155.4 (C-7), 133.7 (C-3), 122.8 (C-8), 114, 9 (C-4), 103.6 (C-6), 73.6 (C-15), 44.8 (C-10), 36.2 (C-2), 32.4 (C-14), 27.9 (C-12), 26.0 (C-13), 23.7 (C-11), 20.9 ppm (15-CH_3).

Biological evaluation of the synthesized compounds: *Reagents*: Trypsin, glutamine, and pyruvate solutions as well as bovine serum albumin (BSA) were purchased from Sigma, Deisenhofen (Germany). Human IFN-γ, IL-1β, and TNF-α were obtained from Strathmann, Hannover (Germany). Fetal calf serum (FCS) and Dulbecco's modified Eagle's medium (DMEM) were purchased from PAN-Systems, Nürnberg (Germany). The Dual-Luciferase Reporter Assay System and the Passive Lysis Buffer were purchased from Promega, Heidelberg (Germany).

Cell culture: HeLa S3 (ATCC) cells were maintained in DMEM supplemented with FCS (10%), penicillin G (65 $\mu g\,mL^{-1}$), and streptomycin sulfate (100 $\mu g\,mL^{-1}$). Human alveolar epithelial A549/8-pNOS2(16)Luc cells[25] stably transfected with a construct containing a 16-kb fragment of the human iNOS promoter upstream of the luciferase reporter gene and human ECV-pNOS-III-Hu-3500-Luc-neo cells[7,25] stably transfected with a construct containing a 3.6-kb fragment of the constitutively active human eNOS promoter were grown in DMEM with fetal bovine serum (FBS, 5–10%), L-glutamine (2 mM), penicillin, and streptomycin. For experiments involving luciferase activity determinations, cells were plated onto 6-well plates (9.6 $cm^2\,well^{-1}$) or 24-well plates (1.75 $cm^2\,well^{-1}$). Eighteen hours prior to cytokine induction, cells were washed with phosphate-buffered saline (PBS) and incubated with DMEM containing L-glutamine (2 mM) in the absence of serum and phenol red. During this incubation time as well as the following induction period, the cells were treated with or without various concentrations of (*S*)-curvularin or its derivatives.

Transient transfection of reporter gene constructs and determination of secreted alkaline phosphatase (SEAP) activity: The reporter plasmid pGE3-GAS/ISRE was constructed essentially as described earlier by cloning five copies of a GAS/ISRE consensus oligonucleotide (5′-AAG TAC TTT CAG TTT CAT ATT ACT CTA-3′) immediately upstream of the thymidine kinase promoter-driven SEAP reporter gene.[24] The plasmid pRL-CMV for normalizing transfection efficiency was obtained from Promega (Dual-Luciferase Reporter Assay). Transfections of HeLa S3 cells were performed by electroporation of 3×10^6 cells suspended in 1 mL PBS containing 30 μg of the reporter constructs at 500 $V\,cm^{-1}$ and $\tau = 20$–23 ms using a gene pulser apparatus (BioRad). After electroporation, the cells were seeded at 1×10^5 $cells\,mL^{-1}$ in Opti-MEM (Invitrogen) containing 10% FCS in a 24-well tissue culture plate and allowed to recover for 16 h. For induction of SEAP expression, cells were treated with the indicated inducers with or without test compounds in Opti-MEM containing 0.5% FCS. The activity of the SEAP in the culture medium was determined 48 h after transfection using the Phospha-Light chemiluminescent reporter gene assay (TROPIX, MA, USA) according to the manufacturer's instructions.

Analysis of human iNOS promoter activity and human eNOS promoter activity: To determine the effect of the various compounds on cytokine-induced human iNOS promoter activity, A549/8-pNOS2(16)Luc cells were incubated for 18 h with DMEM without FCS and without phenol red in the presence or absence of different concentrations of (*S*)-curvularin or its derivatives. Cells were then incubated with a cytokine mixture (CM) composed of IFN-γ (100 $U\,mL^{-1}$), IL1-β (50 $U\,mL^{-1}$), and TNF-α (10 $ng\,mL^{-1}$) for 4.5 h in the presence or absence of the compounds. The cells were then lysed in 1× Passive Lysis Buffer.

To determine the effect of the various compounds on the constitutive human eNOS promoter activity, ECV-pNOS-III-Hu-3500-Luc-neo cells were incubated for 24 h with DMEM without FCS and without phenol red in the presence or absence of various concentrations of (*S*)-curvularin or its derivatives. The cells were then lysed in 1× Passive Lysis Buffer.[7,25]

Firefly luciferase activity was determined using the Dual-Luciferase Assay Kit (Promega, Madison, USA) as described by the manufacturer. Protein concentrations of the extracts were determined by Bradford reagent using BSA as the standard. Protein content of the extracts was used for normalization of the luciferase activity.

Calculations: All data regarding the biological effects of the compounds are presented as mean ± SEM. Differences between means were tested for statistical significance using factorial ANOVA followed by Fisher's PLSD test as the post-hoc test (StatView software, SAS Institute). Concentrations of compounds producing half-maximal inhibition were determined using GraphPad Prism 4 software (GraphPad Software Inc.).[7]

Acknowledgements

This work was supported by the Stiftung Rheinland-Pfalz für Innovation and by the Naturstoffsynthese-Zentrum Mainz, a collaborative research initiative of BASF AG, Boehringer Ingelheim Pharma GmbH, and the Regional Government of Rheinland-Pfalz.

Keywords: anti-inflammatory drugs · curvularin · macrolactones · metathesis · nonsteroidal inhibitors

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Received: January 30, 2008
Revised: February 20, 2008
Published online on March 25, 2008

