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Total Synthesis and Evaluation of the Actin-Binding Properties of Microcarpalide and a Focused Library of Analogues

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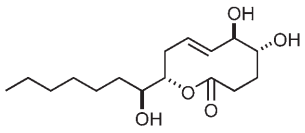
Abstract: A comparative investigation shows that hydroxylated 10-membered lactones modeled around the fungal metabolites microcarpalide (**1**) and pinolidoxin (**2**) are endowed with selective actin-binding properties. Although less potent than the marine natural product latrunculin A, which represents the standard in the field, nonenolides of this type are significantly less toxic and accommodate substantial structural editing. Most notable is the fact that even an intramolecular transesterification with formation of a hydroxylated butanolide skeleton does not annihilate their microfilament disrupting capacity. This finding calls for a reinvestigation of the biological profile of other fungal metabolites that embody a similar motif. Microcarpalide (**1**) serving as the calibration point for this comparative study was prepared by total synthesis based on ring-closing metathesis (RCM) as the key step. The chosen route favorably compares to previous approaches to this target and provides further support for the notion that the (*E,Z*)-configuration of a medium-sized cycloalkene can be controlled by proper choice of the catalyst as previously outlined by our group. 9-*epi*-Microcarpalide **26** and furanone **27** as representative examples of the "natural productlike" compounds investigated herein have been characterized by crystal structure analysis.

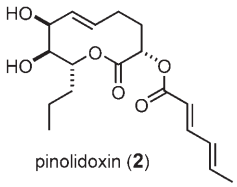
Keywords: actin · lactones · medium-sized rings · metathesis · natural products

Introduction

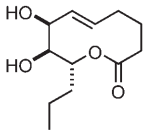
Bioassay-guided fractionation of the culture broth of an unidentified endophytic fungus hosted by a *Ficus microcarpa* L. plant in Hawaii led to the isolation of microcarpalide (**1**).[1] This nonenolide showed antimicrofilament activity at a concentration of $\leq 5\ \mu g\,mL^{-1}$, leading to a 50–75% loss of the regular actin cytoskeleton in A-10 (rat smooth muscle) cells. Thereby, the reported cytotoxicity of **1** is remarkably low, with IC_{50} values for the KB- and LoVo cancer cell lines being as high as 50 and 90 $\mu g\,mL^{-1}$, respectively.[1] This very significant difference in the bioactivity thresholds recommends microcarpalide as a potential lead structure en route to selective, nontoxic antiactin agents[2] for use in chemical biology, medicinal chemistry, and crop protection. Actin is the most abundant protein in eukaryotic cells; it determines their shape and mechanical properties, effects cell locomotion, is responsible for strength development in muscles, and enables motility processes as fundamental as cytokinesis as well as exo- and endocytosis.[3]



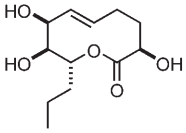
microcarpalide (**1**)



pinolidoxin (**2**)



herbarumin I (**3**)



herbarumin II (**4**)

As part of our ongoing program on the identification, synthesis, chemical modification, and biological evaluation of

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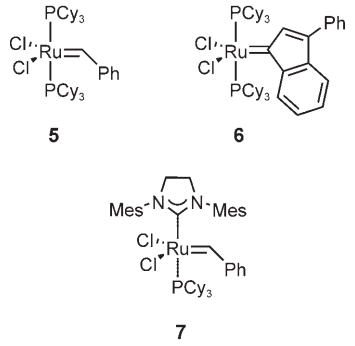
actin-binding small molecules,[4–6] we chose this particular medium-sized lactone as the starting point for further investigations. Our interest was reinforced by the resemblance of **1** to other nonenolides of fungal origin previously prepared in this laboratory (structures **2**–**4**).[7,8] Pinolidoxin **2**[9] and the closely related herbarumins **3** and **4**[10] are promising phytotoxic agents interfering with the defense metabolism of higher plants; they consist of a similar (*E*)-configured nonenolide skeleton decorated with hydroxyl groups and a hydrophobic appendage.[11] Therefore, it seemed appropriate to investigate if **2**–**4** and selected derivatives thereof also exhibit any appreciable microfilament disrupting capacity and, if so, to compare their efficacy with that of microcarpalide (**1**) as the lead compound in this series.

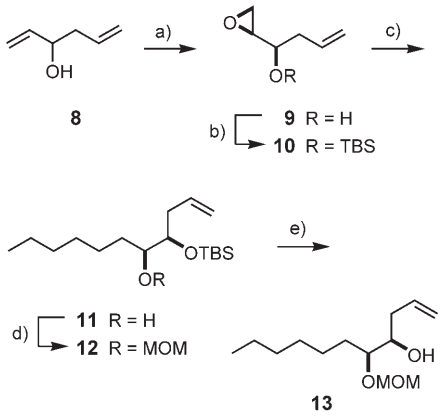
Our approach to herbarumin and pinolidoxin was based on ring-closing olefin metathesis (RCM) for the formation of the strained 10-membered ring.[12] During this synthesis campaign we were able to show that the proper choice of catalyst determines the stereochemical outcome of the cyclization reaction in a predictable fashion.[8,13] Specifically, the use of the first-generation ruthenium carbene complexes **5**[14] or **6**[15] provided the desired (*E*)-alkenes with good to



excellent selectivity, whereas a second-generation catalyst, such as **7**,[16] engenders an equilibration process leading to the thermodynamically more stable (*Z*)-isomers. This concept of "catalyst control"[8] was later successfully extended to a variety of other medium-sized ring derivatives,[17–19] including microcarpalide itself.[20,21] To gain access to sufficient quantities of this lead compound for the planned microfilament assays, it, therefore, sufficed to develop a novel and practical route to the required diene substrate, whereas the final steps of the total synthesis could gravitate toward this validated catalyst-controlled RCM methodology.

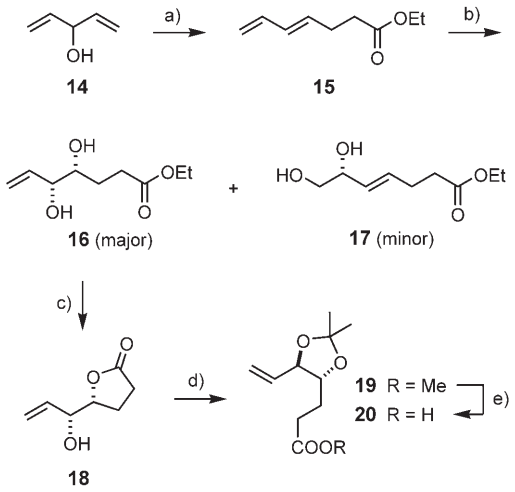
To this end, allyic alcohol **8** underwent a Sharpless kinetic resolution, furnishing multigram quantities of the epoxyalcohol **9** in excellent optical purity (*ee* = 98%) (Scheme 1).[22,23] Temporary protection of the OH group as a TBS-ether followed by copper-mediated opening of the oxirane ring in **10** with pentylmagnesium bromide gave alcohol **11**, which was converted into product **13** by two routine manipulations.

The required acid segment **20** was accessible from cheap divinyl carbinol **14**, which was transformed on a large scale into **15** by a standard Johnson–Claisen rearrangement



Scheme 1. a) L-Dicyclohexyl tartrate, Ti(O*i*Pr)$_4$, *t*BuOOH, MS 4 Å, CH_2Cl_2, 40% (of theoretical 50%, *ee* = 98%); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.; c) pentylmagnesium bromide, CuBr·SMe_2, THF, −78 → −5 °C, 80%; d) MOMCl, (iPr)$_2$NEt, catalytic DMAP, CH_2Cl_2, 85%; e) TBAF, THF, 84%. TBS = *tert*-butyldimethylsilyl; MOM = methoxymethyl; DMAP = 4-dimethylaminopyridine; TBAF = tetrabutylammonium fluoride.

(Scheme 2).[24] Exploiting the inherent preference of osmylation reactions for more electron-rich olefins, the internal double bond of **15** reacted preferentially in the subsequent

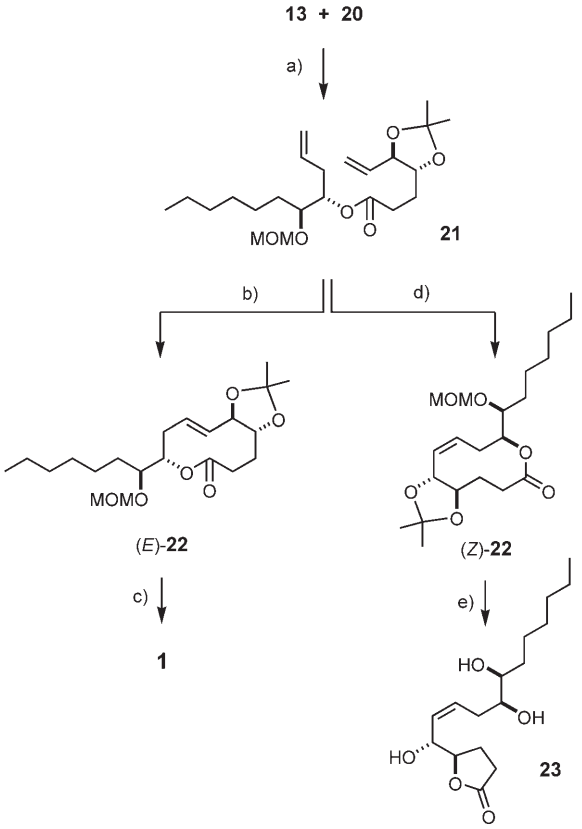


Scheme 2. a) MeC(OEt)$_3$, propionic acid cat., reflux, cf. reference [24c]; b) AD-mix-β, $MeSO_2NH_2$, *t*BuOH/H_2O, 5 °C; c) catalytic *p*TsOH, MeOH, 54% (over two steps, *ee* = 99%); d) $Me_2C(OMe)_2$, catalytic *p*TsOH, MeOH; e) KOH, MeOH, 93% (over two steps).

asymmetric Sharpless dihydroxylation.[25] The undesired terminal diol byproduct **17** could be conveniently removed after the crude reaction mixture had been treated with catalytic amounts of *p*-toluenesulfonic acid in methanol, which converted **16** into lactone **18** but left diol **17** untouched; because of the large difference in the polarity of these compounds, they can be easily separated by flash chromatography. Treatment of lactone **18** with acetone dimethylacetal in methanol under slightly acidic conditions resulted in con-

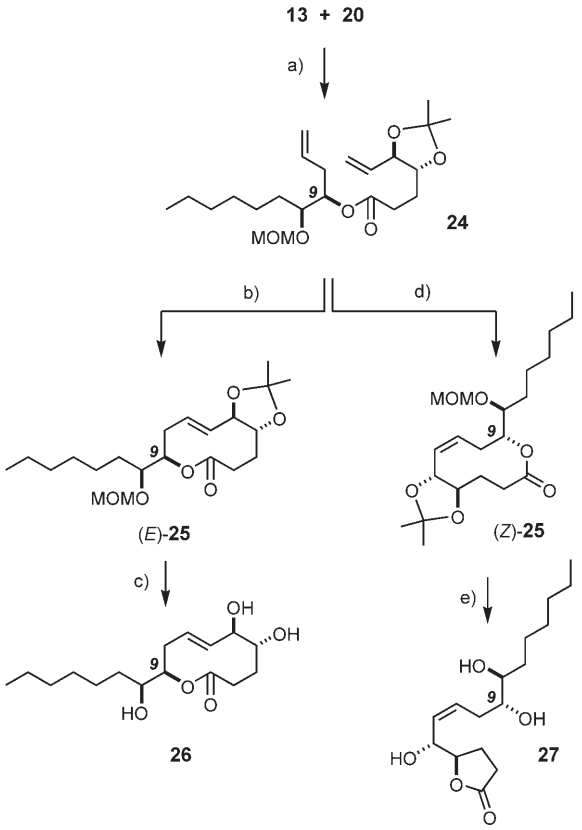
comitant ring opening and acetal formation. Saponification of the resulting ester **19** under standard conditions furnished the required acid **20** in good overall yield.

Esterification of **13** and **20** with inversion of configuration[27] at the alcoholic center set the correct stereochemistry for the synthesis of **1** (Scheme 3). In line with our expectations,[8,13,17,20] treatment of the resulting diene **21** with catalytic amounts of the ruthenium carbene complex **5** in dilute CH_2Cl_2 solution resulted in an effective cyclization of the 10-membered ring, delivering (*E*)-**22** as the major product; in contrast, the use of catalyst **7** gave (*Z*)-**22** exclusively. These isomeric lactones were then deprotected with ethane-1,2-dithiol and $BF_3{\cdot}Et_2O$, following a literature protocol.[21a] Under these conditions, compound (*E*)-**22** afforded (−)-microcarpalide **1** in 74% yield as a colorless syrup, the analytical and spectroscopic properties of which matched those of the natural product in every respect.[1,20,21] Its (*Z*)-configured analogue (*Z*)-**22**, however, reacted much less cleanly. Moreover, careful examination of the NMR spectroscopic and MS data of the resulting major product showed that a lactone interconversion had occurred, resulting in the formation of butanolide **23**. This reaction is enabled by the transannular proximity of the substituents on the 10-membered frame and likely driven by the release of ring strain. A similar result was observed in the epimeric series (vide infra).



Scheme 3. a) DEAD, PPh_3, 60%; b) catalyst **5** (20 mol%), CH_2Cl_2 (0.001 M), reflux, 72% (*E*:*Z* 2.3:1); c) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C, 74%; d) catalyst **7** (20 mol%), 66% (+traces of (*E*)-**22**);[18a] e) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C, 32%. DEAD = (*Z*)-1,2-diazene-dicarboxylate

Esterification of **13** and **20** with retention of configuration opened access to 9-*epi*-microcarpalide **26** (Scheme 4). The concept of "kinetic versus thermodynamic control" previously introduced by our group[8,13,17] could also be imposed upon the ring closure of the resulting diene **24**. Thus, the use of complex **5** as the catalyst furnished (*E*)-**25** exclusively, whereas the second generation ruthenium carbene **7**, under otherwise identical conditions, led to the formation of appreciable amounts of (*Z*)-**25**. In line with the results outlined above, the cleavage of the acetal groups with ethane-1,2-dithiol and $BF_3{\cdot}Et_2O$[21a] engendered a *trans*-lactonization of (*Z*)-**25** to furnanone **27**, whereas the 10-membered ring remained intact in the (*E*)-series. The structures assigned to 9-*epi*-microcarpalide **26** and the ring-contracted isomer **27** were confirmed by single-crystal structure analysis (Figures 1 and 2).



Scheme 4. a) DCC, catalytic DMAP, CH_2Cl_2, 84%; b) catalyst **5** (20 mol%), CH_2Cl_2 (0.001 M), reflux, 85% (E only); c) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C, 62%; d) catalyst **7** (20 mol%), 94% (*E*:*Z* 1.1:1); e) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C, 24%.

The preparation of a suitable collection of pinolidoxin analogues for biological testing largely followed the previously established route to the parent compound **2**;[8] however, the synthesis of the required acid segment **32** was improved

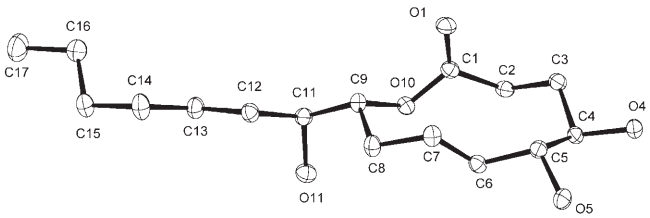


Figure 1. Molecular crystal structure of 9-*epi*-microcarpalide **26** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

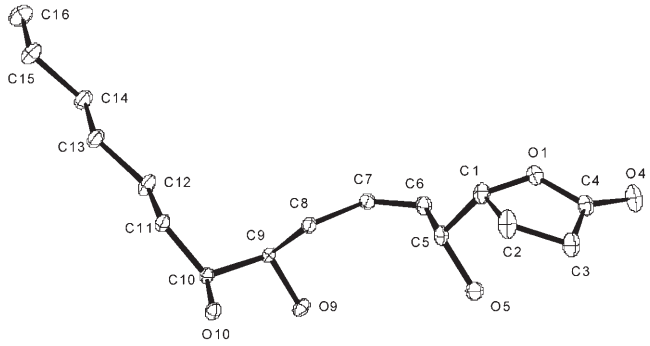


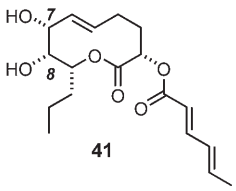
Figure 2. Molecular crystal structure of butanolide **27** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

over prior art (Scheme 5). Formation of the (*E*)-cycloalkene **35** from diene **34** was ensured by the use of the ruthenium indenylidene complex **6**[15,28,29] as a readily available and cheap substitute for the classical Grubbs catalyst **5**. Compound **35** thus obtained was then transformed into the parent nonenolide **2**, the corresponding ether **36**, as well as several esters of different polarity (**38**–**40**).

Evaluation of the actin-binding properties: Microcarpalide **1**, its epimer **26**, the corresponding butanolides **23** and **27**, the naturally occurring nonenolides herbarumin **4** and pinolidoxin **2**, synthetic 7,8-bis-*epi*-pinolidoxin **41**,[8] as well as the collection of newly prepared derivatives **36**–**40** described above, underwent a standardized assay allowing the effect of small molecules on the actin cytoskeleton to be determined.

Specifically, NIH/3T3 fibroblasts were incubated with DMSO solutions of the respective compounds at different concentrations and the induced morphological changes were visualized by staining the actin cytoskeleton of the cells with fluorescene-marked phalloidin. In parallel, the number of living cells were counted after an incubation time of 24 h as an estimate for the toxicity of the compounds at a given concentration.

In accordance with the published data for the A-10 cell line,[1] incubation of the NIH/3T3 fibroblasts with microcarpalide (**1**) at a 5 μM concentration resulted in clearly detectable actin microfilament disruption (Figure 3, micrograph II). Importantly, however, *similar potencies were observed*



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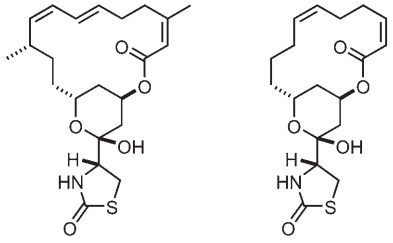


latrunculin A (**42**) **43**

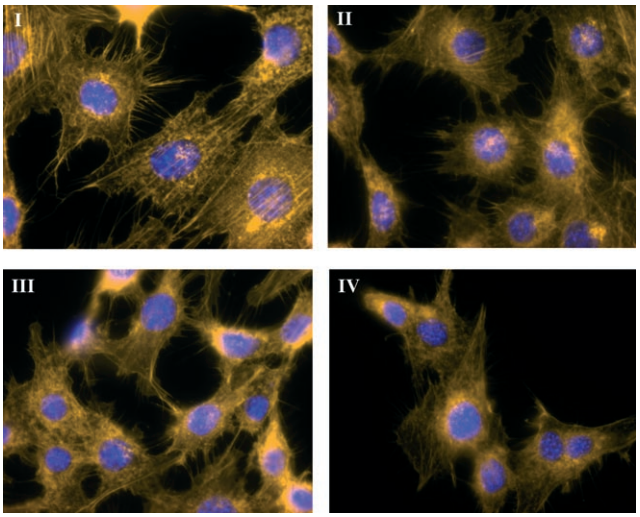
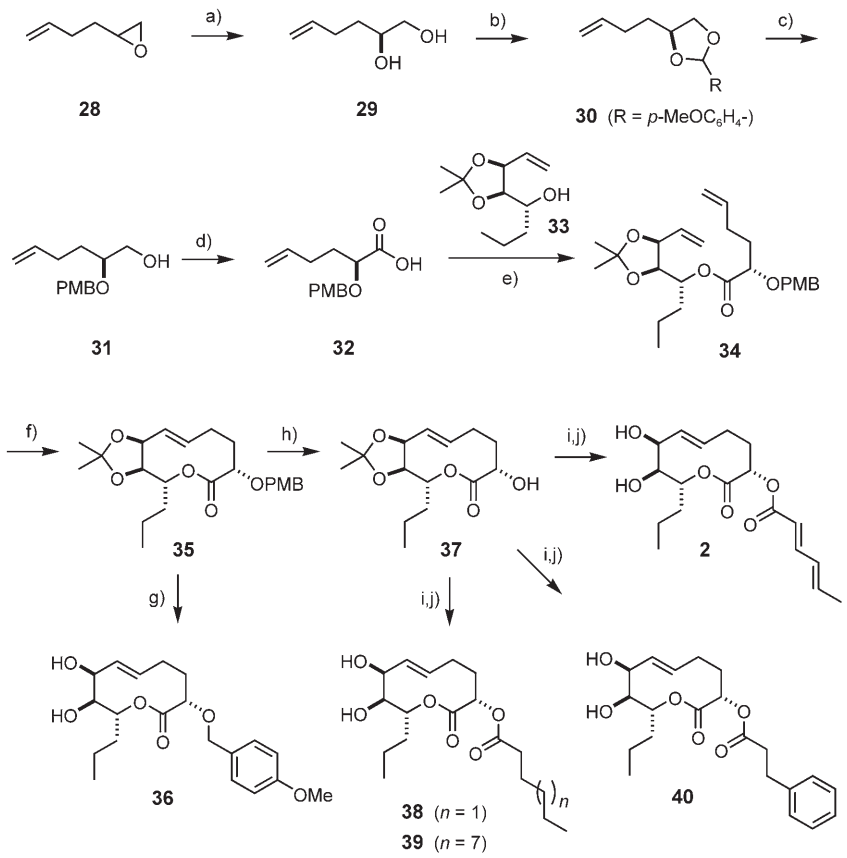


Figure 3. Fluorescence micrographs (250×) of NIH/3T3 fibroblast cells allowing a direct comparison of the microfilament disrupting activity of microcarpalide and related compounds. The actin filament is stained with fluorescence-marked phalloidin, the nuclei with 2-(4-amidinophenyl)-6-indolecarbamidine hydrochloride (DAPI). **I**: untreated cells; **II**: after incubation with **1** (5 μM); **III**: after incubation with **2** (5 μM); **IV**: after incubation with **27** (5 μM).

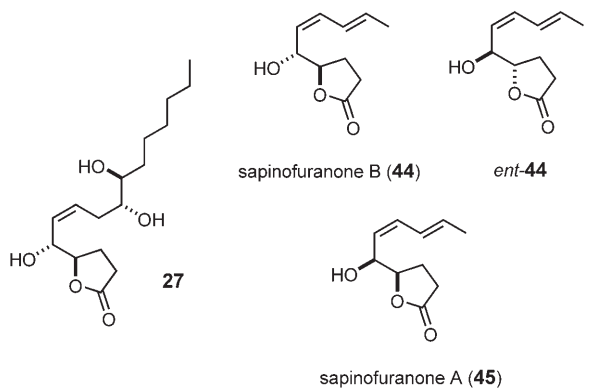
for the entire series, except for **38** and **41** which were only marginally active at this concentration. As can be seen from Figure 3 (micrograph III), pinolidoxin **2** elicits a similar or even stronger response than **1**. Particularly noteworthy, however, is our finding that even the rearranged products **23** and **27** remain functional and exhibit an appreciable potency (Figure 3, micrograph IV). This result shows that an intact 10-membered frame is not necessary to induce severe actin malformation and raises the question whether other butanolides might share this particular biological profile. Potential candidates are the sapinofuranones **44** and **45**:[31] much like microcarpalide and pinolidoxin, these compounds are secondary metabolites of a phytopathogenic fungus that instigates a wide range of disease symptoms of conifers and causes



Scheme 5. a) Hydrolytic kinetic resolution, cf. reference [30]; b) p-$MeOC_6H_4CH(OMe)_2$, camphorsulfonic acid (10%), CH_2Cl_2, 59%; c) DIBAL-H, toluene, 0°C→RT, 83% (+17% of regioisomer); d) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C→RT; ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $tBuOH/H_2O$, quant.; e) 2,4,6-trichlorobenzoyl chloride, Et_3N, catalytic DMAP, toluene, then alcohol **33**, 89%; f) complex **6** (10 mol%), CH_2Cl_2, reflux, 77% (+18% of Z isomer); g) HCl (1 M), MeOH/H_2O, 60°C, 87%; h) DDQ, CH_2Cl_2, 90%; i) carboxylic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, catalytic DMAP, toluene, then alcohol **37**; j) HCl (1 M), MeOH/H_2O, 60°C, 94% (**38**), 86% (**39**), 94% (**40**). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIBAL-H = diisobutylaluminum hydride.

considerable damage in *Pinus* plantations around the world. Not only is their structural resemblance to **23** and **27** striking, but it is also noteworthy that they exist in both enantiomeric forms in nature, although in different fungal strains.[31]

Compared with the well-known actin-binding macrolides latrunculin A (**42**) and its equipotent synthetic congener **43**,[4,5,32] the compounds investigated herein are less effective microfilament disrupting agents. However, they have the bonus of being much less toxic than **42**; only for **39** was the number of living cells reduced to approximately 40% after 24 h of treatment. In all other cases investigated, the entire fibroblast cell population continues to grow and metabolize even upon incubation with 10 μM of the respective agent. This finding corroborates the significant differential between antimicrofilament activity and cytotoxicity previously noted for the parent compound **1**,[1] and shows that this favorable profile is retained throughout a sizable number of analogues.



Conclusion

The first comparative investigation of the actin-binding properties of microcarpalide (**1**) and other naturally occurring nonenolides is reported. Although their effects on actin are less pronounced than those of the latrunculins, which represent the standard in the field,[4,32] their toxicity index is more favorable. Moreover, it is demonstrated that the basic nonenolide frame accommodates significant structural changes without noticeable alterations of the microfilament disrupting capacity. Therefore microcarpalide and its at least equipotent congener pinolidoxin (**2**) constitute validated leads in the quest for nontoxic actin-binding agents. Most remarkable with regard to structure/activity relationships is the finding that even the rearrangement of the medium-sized lactone to a butanolide scaffold, as found in compounds **23** and **27**, does not engender loss of bioactivity. As the latter skeleton is readily accessible by more direct routes, an evaluation of this new hit is warranted and should be straightforward. It also remains to be seen if closely related butanolides produced by other phytopathogenic fungi, such as the sapinofuranones, are endowed with similar actin-disrupting properties.

Experimental Section

General methods: All reactions were carried out in flame-dried glassware under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, 1,4-dioxane (Mg/anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N, pyridine (CaH_2), MeOH (Mg), DMF (Desmodur, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR spectra were recorded on a Bruker DPX 300 or AV 400 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C= 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H=7.24 ppm; CD_2Cl_2: δ_C= 53.8 ppm; residual CH_2Cl_2 in CD_2Cl_2: δ_H=5.32 ppm). IR: Nicolet FT-7199 spectrometer, wavenumbers (λ) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESIMS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

***tert*-Butyl(dimethyl)({(1*R*)-1-[(2*S*)-oxiranyl]-3-butenyl}oxy)silane (10)**: A solution of 2,6-lutidine (1.55 g, 14.5 mmol) and TBS-OTf (3.06 g, 11.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of alcohol **9** (1.04 g, 7.24 mmol)[22] in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 5 min, the reaction was quenched with water, the mixture was repeatedly extracted with EtOAc, the combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by flash chromatography (hexanes/EtOAc 30:1) to give product **10** as a colorless liquid (1.64 g, quant.). $[\alpha]_D^{20}=-27.4°$ (c=1.08 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.87 (tdd, J=17.2, 10.2, 7.2 Hz, 1H), 5.14–5.07 (m, 2H), 3.63 (dd, J=11.1, 4.9 Hz, 1H), 2.91 (dt, J=4.3, 2.7 Hz, 1H), 2.69 (ddd, J=8.1, 5.4, 3.3 Hz, 2H), 2.43–2.28 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 134.2, 117.4, 71.0, 54.3, 44.9, 40.0, 25.8, 25.8, 25.7, 18.2, −4.5, −4.8 ppm; IR (film): $\tilde{\nu}$=3078, 2956, 2930, 2858, 1642, 1473, 1253, 1111, 999, 914, 837, 777 cm^{-1}; MS (EI): m/z (%): 187 (14), 171 (7), 141 (24), 129 (23), 115 (14), 101 (32), 99 (23), 75 (100), 73 (79), 59 (27); elemental analysis calcd (%) for $C_{12}H_{24}O_2Si$: C 63.10, H 10.59; found: C 63.18, H 10.52.

(4*R*,5*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-undecen-5-ol (11): CuBr·Me_2S (4.43 g, 21.5 mmol) was added to a solution of pentylmagnesium bromide (2 M in Et_2O, 10.8 mL, 21.5 mmol) at −78 °C and the resulting mixture was stirred at that temperature for 15 min. A solution of oxirane **10** (1.64 g, 7.18 mmol) in THF (30 mL) was introduced and the mixture was stirred at −20 °C for 30 min and at −5 °C for 19 h. The reaction was then quenched with aq saturated NH_4Cl, the aqueous phase was extracted with EtOAc (3×20 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography (hexanes/EtOAc 20:1) gave product **11** as a colorless liquid (1.72 g, 80%). $[\alpha]_D^{20}=-0.9°$ (c=1.13 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.83 (tdd, J=17.2, 10.2, 7.2 Hz, 1H), 5.10–5.02, (m, 2H), 3.65 (ddd, J=9.0, 6.4, 4.0 Hz, 1H), 3.61–3.51 (m, 1H), 2.35–2.16 (m, 2H), 2.10 (br s, 1H), 1.52–1.47 (m, 1H), 1.41 (dd, J=13.4, 6.7 Hz, 2H), 1.35–1.26 (m, 6H), 0.92–0.87 (m, 13H), 0.07 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.6, 116.8, 75.1, 74.6, 35.9, 31.9, 31.8, 29.4, 26.1, 25.9 (2C), 25.8, 22.6, 18.1, 14.1, −4.3, −4.5 ppm; IR (film): $\tilde{\nu}$= 3578, 3462, 3077, 2955, 2929, 2858, 1642, 1471, 1463, 1361, 1256, 1083, 1005, 913, 837, 776, 676 cm^{-1}; MS (EI): m/z (%): 285 (1), 259 (8), 243 (84), 225 (5), 199 (5), 185 (70), 145 (41), 129 (13), 95 (32), 75 (100), 67 (18); HRMS (ESI-pos): m/z: calcd for $C_{17}H_{36}O_2Si$+Na: 323.2377 [M^++Na]; found: 323.2376; elemental analysis calcd (%) for $C_{17}H_{36}O_2Si$: C 76.94, H 12.07; found: C 76.78, H 12.15.

Compound 12: A solution of alcohol **11** (1.72 g, 5.72 mmol), MOM-Cl (1.38 g, 17.2 mmol), $EtN(iPr)_2$ (2.22 g, 17.2 mmol) and DMAP (ca. 50 mg) in CH_2Cl_2 (15 mL) was stirred for 18 h. For work up, the solution was partitioned between water and *tert*-butyl methyl ether, the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give product **12** as a colorless liquid (1.67 g, 85%). $[\alpha]_D^{20}=-35.3°$ (c=1.02 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.80 (ddt, J=17.3, 8.7, 5.3 Hz, 1H), 5.07–4.97 (m, 2H), 4.75 (d, J=6.7 Hz, 1H), 4.58 (d, J= 6.6 Hz, 1H), 3.67 (ddd, J=8.3, 5.7, 3.3 Hz, 1H), 3.49–3.46 (m, 1H), 3.35 (s, 3H), 2.36–2.12 (m, 2H), 1.50–1.40 (m, 3H), 1.25–1.21 (m, 7H), 0.85–0.83 (m, 12H), 0.06 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.8, 116.7, 96.2, 80.2, 74.3, 55.8, 37.6, 31.9, 30.7, 29.4, 29.4, 25.9, 25.9, 25.9, 22.6, 18.1, 14.1, −4.4, −4.5 ppm; IR (film): $\tilde{\nu}$=3077, 2955, 2929, 2857, 2822, 1642, 1472, 1464, 1361, 1255, 1152, 1102, 1040, 915, 836, 776 cm^{-1}; MS (EI): m/z (%): 303 (8), 287 (13), 257 (67), 225 (5), 201 (26), 185 (83), 159 (14), 129 (15), 119 (27), 89 (70), 73 (75), 45 (100); HRMS (EI): m/z: calcd for $C_{19}H_{40}O_3Si$+Na: 367.2639 [M^++Na]; found: 367.2637; elemental analysis calcd (%) for $C_{19}H_{40}O_3Si$: C 66.22, H 11.70; found: C 66.18, H 11.64.

(4*R*,5*S*)-5-(Methoxymethoxy)-1-undecen-4-ol (13): A solution of compound **12** (357 mg, 1.04 mmol) and TBAF (1 M in THF, 1.25 mL, 1.25 mmol) in THF (3 mL) was stirred for 24 h. For work up, the solution was partitioned between water (5 mL) and EtOAc (5 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 10:1) to give product **13** as a colorless liquid (202 mg, 84%). $[\alpha]_D^{20}$=+ 21.5° (c=0.98 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.90 (tdd, J= 17.2, 10.2, 7.0 Hz, 1H), 5.16–5.09 (m, 2H), 4.75 (d, J=6.8 Hz, 1H), 4.65 (d, J=6.9 Hz, 1H), 3.69–3.65 (m, 1H), 3.57–3.53 (m, 1H), 3.43 (s, 3H), 2.77 (br s, 1H), 2.27–2.20 (m, 2H), 1.59–1.43 (m, 3H), 1.33–1.24 (m, 7H), 0.89 ppm (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.5, 117.2, 97.3, 83.5, 72.4, 55.8, 36.4, 31.8, 30.4, 29.3, 25.8, 22.6, 14.1 ppm; IR (film): $\tilde{\nu}$=3460, 3076, 2930, 1642, 1212, 1152, 1100, 1037, 916 cm^{-1}; MS (EI): m/z (%): 199 (0.3), 189 (3), 185 (5), 157 (14), 115 (9), 97 (13), 71 (14), 55 (16), 45 (100); HRMS (EI): m/z: calcd for $C_{13}H_{26}O_3$+Na: 253.1774 [M^++Na]; found: 253.1773; elemental analysis calcd (%) for $C_{13}H_{26}O_3$: C 67.79, H 11.38; found: C 67.86, H 11.43.

Ethyl 4,6-heptadienoate (15): Ethyl formiate (22.55 g, 0.3 mol) was added to a solution of vinylmagnesium bromide (1 M in THF, 800 mL, 0.8 mol) at 10 °C and the resulting mixture was stirred for 16 h at ambient temperature once the addition was complete. The reaction was quenched with aq HCl (2 M, 300 mL), the aqueous phase was extracted with Et_2O (3× 300 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was distilled off by using a Vigreux column. Triethyl orthoacetate (239 g, 1.5 mol) and propionic acid (0.8 mL, 10.8 mmol) were added to a solution of the resulting crude divinyl carbinol **14** in benzene (200 mL) and the resulting mixture was refluxed for 16 h. For work up, the solvent was distilled off at ambient pressure followed by removal of most of the residual triethyl orthoacetate under reduced pressure (12 mbar). The residue (ca. 75–80% pure by GC) was then purified by fractional distillation using a 50 cm column under reduced pressure to give ester **15** in analytically pure form (>99%, GC) as a colorless liquid (13.2 g, 29%); b.p. 73–74 °C (10 mbar). The analytical data are in accord with those previously reported in the literature.[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.24 (dt, J= 17, 10 Hz, 1H), 6.04 (dd, J=15, 10 Hz, 1H), 5.70–5.60 (m, 1H), 5.06 (d, J=17 Hz, 1H), 4.94 (d, J=10 Hz, 1H), 4.09 (q, J=7.2 Hz, 2H), 2.37 (m, 4H), 1.21 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.7, 136.7, 132.5, 131.8, 115.5, 60.2, 33.7, 27.7, 14.1 ppm; MS (EI): m/z (%): 154 (59) [M^+], 117 (19), 109 (29), 81 (100), 80 (73), 79 (64), 67 (99), 61 (16), 53 (15), 41 (42), 29 (37).

(5*R*)-5-[(1*R*)-1-Hydroxy-2-propenyl]dihydro-2(3*H*)furanone (18): Ester **15** (2.00 g, 13.0 mmol) was added to a cooled (5 °C) solution of AD-mix-β (18.2 g) and methanesulfonamide (1.23 g, 13.0 mmol) in *t*BuOH/H_2O (1:1, 120 mL) and the resulting mixture was stirred at that temperature for 4 h. For work up, Na_2SO_3 (19.7 g, 156 mmol) was added in solid form and stirring was continued for 1 h at 5 °C and for 2 h at ambient temperature. Enough water was then added to dissolve all salts, the resulting aqueous phase was extracted with EtOAc (3×50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (15 mL) before *p*TsOH (100 mg, 0.53 mmol) was introduced, and the resulting solution was stirred for 15 h at ambient temperature. All volatile materials were then evaporated and the crude product was purified by flash chromatography (hexanes/EtOAc gradient) to give lactone **18** as a colorless liquid (994 mg, 54%). The ana-

lytical and spectroscopic data agree with those published in the literature.[26] $[\alpha]_D^{20} = -30.0°$ ($c = 1.03$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 5.90 (ddd, $J = 16.9$, 10.5, 6.2 Hz, 1H), 5.38 (dd, $J = 33.1$, 13.9 Hz, 2H), 4.48 (dt, $J = 7.3$, 5.3 Hz, 1H), 4.19–4.15 (m, 1H), 2.68–2.48 (m, 2H), 2.28–2.11 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.2$, 135.1, 118.3, 82.4, 74.6, 28.4, 23.5 ppm.

3-[(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]propanoic acid (20): A solution of lactone **18** (994 mg, 6.99 mmol), 2,2-dimethoxypropane (8.5 g, 82 mmol), and *p*TsOH (150 mg, 0.79 mmol) in MeOH (10 mL) was stirred for 24 h at ambient temperature. The reaction was quenched with water (10 mL) and the resulting aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give crude methyl ester **19** which was used in the next step without further purification.

A solution of KOH (25% w/w in MeOH, 5 mL) was added to a solution of crude **19** in MeOH (15 mL) and the resulting mixture was stirred for 3 d at ambient temperature. The solution was diluted with water (15 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (4×20 mL), and the combined organic layers were discarded. The aqueous phase was then acidified with aq HCl (3 M) to pH ≈3, before it was extracted again with *tert*-butyl methyl ether (5×15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give acid **20** as pale yellow oil (1.30 g, 93% over both steps). $[\alpha]_D^{20} = +3.4°$ ($c = 0.89$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.81$ (ddd, $J = 17.5$, 10.2, 7.4 Hz, 1H), 5.38 (dd, $J = 17.1$, 1.0 Hz, 1H), 5.28 (dd, $J = 10.3$, 0.7 Hz, 1H), 4.04–3.99 (m, 1H), 3.71 (dt, $J = 8.3$, 3.7 Hz, 1H), 2.65–2.43 (m, 2H), 2.03–1.76 (m, 2H), 1.41 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.7$, 134.9, 119.3, 109.0, 82.4, 79.3, 30.4, 27.2, 27.0, 26.5 ppm; IR (film): $\tilde{\nu} = 3086$, 2987, 2935, 2875, 1739, 1712, 1380, 1372, 1242, 1167, 1114, 1069, 989, 934, 873 cm^{-1}; MS (EI): *m*/*z* (%): 200 (0.1) [M^+], 185 (39), 167 (1), 144 (3), 125 (71), 98 (75), 83 (37), 69 (25), 55 (23), 43 (100); HRMS (EI): *m*/*z*: calcd for $C_{10}H_{16}O_4$: 199.0977; found: 199.0976; elemental analysis calcd (%) for $C_{10}H_{16}O_4$: C 59.98, H 8.05; found: C 59.70, H 8.11.

(1*S*)-1-[(1*S*)-1-(Methoxymethoxy)heptyl]-3-butenyl 3-[(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]propanoate (21): PPh_3 (92.0 mg, 0.35 mmol) was added to a solution of alcohol **13** (41.0 mg, 0.18 mmol) and acid **20** (35.3 mg, 0.18 mmol) in toluene (1.5 mL), followed by the dropwise addition of diethyl (*Z*)-1,2-diazene-dicarboxylate (DEAD, 61.4 mg, 0.35 mmol). After stirring for 1.5 h, additional PPh_3 (46.0 mg, 0.18 mmol) and DEAD (30.7 mg, 0.18 mmol) were introduced and stirring was continued for 18 h. A standard extractive workup followed by flash chromatography (hexanes/EtOAc, 10:1) of the crude product furnished ester **21** as a colorless liquid (43.6 mg, 60%).[20] $[\alpha]_D^{20} = +4.2°$ ($c =$ 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.86$–5.68 (m, 2H), 5.37 (br d, $J = 16.7$ Hz, 1H), 5.26 (br d, $J = 10.4$ Hz, 1H), 5.13–5.03 (m, 3H), 4.70 (d, $J = 6.9$ Hz, 1H), 4.67 (d, $J = 6.9$ Hz, 1H), 4.02–3.97 (m, 1H), 3.69 (dt, $J = 8.3$, 3.8 Hz, 1H), 3.58 (dt, $J = 6.3$, 4.3 Hz, 1H), 3.40 (s, 3H), 2.59–2.28 (m, 4H), 2.01–1.75 (m, 2H), 1.52–1.47 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.35–1.27 (m, 8H), 0.88 ppm (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.6$, 135.0, 133.9, 119.2, 117.7, 108.8, 96.6, 82.4, 79.5, 78.0, 73.6, 55.9, 34.7, 31.7, 30.7, 30.5, 29.4, 27.2, 26.9, 26.8, 25.3, 22.6, 14.1 ppm; IR (film): $\tilde{\nu} = 3080$, 2931, 2859, 1737, 1644, 1379, 1370, 1241, 1165, 1103, 1069, 1039, 989, 920, 875 cm^{-1}; MS (EI): *m*/*z* (%): 397 (6), 283 (2), 253 (1), 229 (17), 213 (4), 183 (10), 143 (6), 125 (100), 113 (6), 98 (64), 45 (57); HRMS (EI): *m*/*z*: calcd for $C_{23}H_{40}O_6Na$: 435.2717 [M^++Na]; found: 435.2714; elemental analysis calcd (%) for $C_{23}H_{40}O_6$: C 66.96, H 9.77; found C 66.87, H 9.81.

(1*R*)-1-[(1*S*)-1-(Methoxymethoxy)heptyl]-3-butenyl 3-[(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]propanoate (24): A solution of DCC (92 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added to a solution of alcohol **13** (69 mg, 0.3 mmol), acid **20** (90 mg, 0.4 mmol), and DMAP (ca. 5 mg) and the resulting mixture was stirred at ambient temperature for 18 h. CH_2Cl_2 (2 mL) was then added, the precipitates were filtered off through a short pad of silica, and the filtrate was evaporated. The residue was suspended in water (10 mL) and extracted with *tert*-butyl methyl ether (3× 15 mL), the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 10:1) to give ester **24** as a colorless liquid (104 mg, 84%). $[\alpha]_D^{20} = -17.0°$ ($c = 1.02$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.84$–5.69 (m, 2H), 5.38 (dd, $J = 17.1$, 1.2 Hz, 1H), 5.26 (dd, $J = 10.3$, 1.3 Hz, 1H), 5.11–5.02 (m, 3H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.60 (d, $J = 6.9$ Hz, 1H), 4.00 (dd, $J = 8.2$, 7.5 Hz, 1H), 3.69 (dt, $J = 8.4$, 3.7 Hz, 1H), 3.64 (dd, $J = 8.1$, 3.2 Hz, 1H), 3.39 (s, 3H), 2.57–2.33 (m, 4H), 1.99–1.91 (m, 1H), 1.85–1.76 (m, 1H), 1.56–1.47 (m, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.33–1.29 (br m, 7H), 0.89 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.6$, 135.0, 134.0, 119.2, 117.5, 108.8, 96.0, 82.5, 79.5, 77.8, 74.1, 55.8, 34.2, 31.8, 30.8, 30.6, 29.3, 27.2, 26.9, 26.8, 25.6, 22.6, 14.1 ppm; IR (film): $\tilde{\nu} = 3080$, 2954, 1737, 1644, 1379, 1371, 1241, 1166, 1101, 1069, 1038, 989, 920, 875 cm^{-1}; MS (EI): *m*/*z* (%): 397 (4), 283 (2), 229 (19), 183 (9), 125 (100), 98 (65), 45 (61); HRMS (EI): *m*/*z*: calcd for $C_{23}H_{40}O_6$+Na: 435.2717 [M^++Na]; found: 435.2717; elemental analysis calcd (%) for $C_{23}H_{40}O_6$: C 66.96, H 9.77; found: C 66.85, H 9.70.

Ring-closing metathesis: preparation of the nonenolides 22: A solution of diene **21** (300 mg, 0.73 mmol) in CH_2Cl_2 (18 mL) was added over 1 h to a refluxing solution of complex **5** (120 mg, 0.15 mmol) in CH_2Cl_2 (710 mL) and reflux was continued for 24 h once the addition was complete. For workup, all volatile materials were evaporated and the residue was purified by flash chromatography (hexanes/EtOAc 10:1) to give (*E*)-**22** as a colorless syrup (139 mg, 50%) and (*Z*)-**22** as a pale-yellow syrup (61 mg, 22%).

*Compound (*E*)-**22**:*[20] $[\alpha]_D^{20} = -31.2°$ ($c = 0.85$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.96$–5.72 (m, 1H), 5.33 (dd, $J = 15.6$, 9.2 Hz, 1H), 5.11–4.91 (m, 1H), 4.71 (d, $J = 7.0$ Hz, 1H), 4.68 (d, $J = 7.0$ Hz, 1H), 3.93 (t, $J = 8.8$ Hz, 1H), 3.67–3.59 (m, 2H), 3.41 (s, 3H), 2.69–2.61 (m, 1H), 2.54 (dt, $J = 13.0$, 4.4 Hz, 1H), 2.45–2.40 (m, 1H), 2.37–2.27 (m, 1H), 2.11–2.05 (m, 1H), 2.04–1.93 (m, 1H), 1.57 ppm (br s, 2H), 1.41 (s, 6H), 1.29 (br s, 8H), 0.89 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 171.7, 130.1, 129.3, 108.8, 96.4, 84.4, 79.8, 79.2, 73.5, 56.0, 34.2, 31.7, 30.8, 30.5, 29.4, 27.1, 26.9, 25.5, 25.3, 22.6, 14.1 ppm; IR (film): $\tilde{\nu} =$ 2931, 2859, 1732, 1666, 1447, 1379, 1237, 1166, 1066, 1040, 977, 919 cm^{-1}; MS (EI): *m*/*z* (%): 384 (5) [M^+], 352 (1), 327 (1), 282 (4), 237 (14), 157 (7), 139 (10), 123 (17), 110 (23), 85 (37), 79 (12), 45 (100); HRMS (EI): *m*/*z*: calcd for $C_{21}H_{36}O_6$+Na: 407.2404 [M^++Na]; found: 407.2407.

*Compound (*Z*)-**22**:*[18a] $[\alpha]_D^{20} = +20.2°$ ($c = 0.89$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.75$ (dt, $J = 10.4$, 7.0 Hz, 1H), 5.51 (t, $J = 10.3$ Hz, 1H), 5.05 (ddd, $J = 11.9$, 4.2, 2.0 Hz, 1H), 4.69 (s, 2H), 4.53–4.48 (m, 1H), 3.69–3.62 (m, 2H), 3.41 (s, 3H), 2.71–2.62 (m, 2H), 2.40–2.06 (m, 4H), 1.61–1.52 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H), 1.37–1.22 (br m, 8H), 0.88 ppm (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.7$, 130.9, 130.3, 107.7, 96.5, 81.4, 78.3, 76.7, 72.9, 55.9, 32.2, 31.7, 30.9, 29.4, 29.3, 28.2, 27.1, 26.9, 25.1, 22.6, 14.1 ppm; IR (film): $\tilde{\nu} = 3020$, 2932, 2858, 1737, 1661, 1379, 1369, 1242, 1179, 1100, 1056, 1031, 919, 885 cm^{-1}; MS (EI): *m*/*z* (%): 384 (5) [M^+], 369 (7), 282 (4), 265 (4), 252 (3), 237 (14), 220 (18), 199 (3), 179 (3), 157 (6), 110 (22), 85 (33), 45 (100); HRMS (EI): *m*/*z*: calcd for $C_{21}H_{36}O_6$+Na: 407.2404 [M^++Na]; found: 407.2405.

Nonenolide (*E*)-25: Prepared according to the procedure for the ring-closing alkene metathesis described above, using diene **24** (80.0 mg, 0.19 mmol) and catalyst **5** (32 mg, 0.04 mmol); only traces of the (*Z*)-isomer were formed which could be removed by flash chromatography with hexanes/EtOAc 10:1 as the eluent; colorless liquid (63.5 mg, 85%). $[\alpha]_D^{20} = +4.8°$ ($c = 0.94$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.71$ (ddd, $J = 15.5$, 11.2, 4.4 Hz, 1H), 5.31 (dd, $J = 15.3$, 9.6 Hz, 1H), 5.08 (dt, $J = 11.4$, 3.5 Hz, 1H), 4.75 (d, $J = 6.9$ Hz, 1H), 4.68 (d, $J = 6.8$ Hz, 1H), 3.94 (t, $J = 8.9$ Hz, 1H), 3.70 (dt, $J = 8.0$, 3.9 Hz, 1H), 3.53 (td, $J = 8.4$, 3.2 Hz, 1H), 3.41 (s, 3H), 2.53–2.42 (m, 2H), 2.26–2.05 (m, 4H), 1.59–1.46 (m, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.29 (br m, 7H), 0.89 ppm (t, $J =$ 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.9$, 135.1, 129.6, 108.0, 96.4, 82.4, 82.1, 77.8, 75.0, 55.9, 34.5, 32.2, 31.7, 31.2, 29.3, 27.2, 27.0, 27.0, 25.4, 22.6, 14.1 ppm; IR (film): $\tilde{\nu} = 2932$, 1733, 1669, 1378, 1367, 1239, 1212, 1181, 1152, 1066, 1043, 975, 920, 861 cm^{-1}; MS (EI): *m*/*z* (%): 384 (6) [M^+], 369 (8), 382 (4), 365 (3), 237 (16), 220 (22), 157 (7), 139 (13), 110 (28), 85 (37), 45 (100); HRMS (EI): *m*/*z*: calcd for $C_{21}H_{36}O_6$+Na: 407.2404 [M^++Na]; found: 407.2407; elemental analysis calcd (%) for $C_{21}H_{36}O_6$: C 65.60, H 9.44; found: C 65.48, H 9.38.

Nonenolide (*Z*)-25: Prepared according to the procedure for the ring-closing alkene metathesis described above, using diene **24** (104 mg,

0.25 mmol) and catalyst **7** (43 mg, 0.05 mmol). Flash chromatography (hexanes/EtOAc 10:1) of the crude product afforded (*E*)-**25** (49 mg, 50%) and (*Z*)-**25** (43 mg, 44%).

*Compound (Z)-**25***: Pale yellow oil; $[\alpha]_D^{20}=+17.1°$ (c=1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=5.87$ (dt, $J=10.5$, 7.3 Hz, 1H), 5.57 (t, $J=10.4$ Hz, 1H), 4.96 (t, $J=5.6$ Hz, 1H), 4.68 (s, 2H), 4.25–4.21 (m, 1H), 3.86 (ddd, $J=8.1$, 4.8, 2.9 Hz, 1H), 3.65 (dd, $J=11.2$, 6.1 Hz, 1H), 3.41 (s, 3H), 2.76–2.63 (m, 2H), 2.43–2.34 (m, 2H), 2.18 (ddt, $J=14.4$, 11.6, 2.6 Hz, 1H), 2.07–1.99 (m, 1H), 1.55–1.49 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.38–1.24 (m, 8H), 0.88 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.7$, 130.4, 129.2, 107.8, 96.3, 79.6, 76.3, 74.0, 73.4, 55.0, 31.7, 31.5, 29.4, 29.4, 27.2, 27.0, 25.6, 25.4, 24.4, 22.6, 14.1 ppm; IR (film): $\tilde{\nu}=$ 3021, 2932, 1734, 1657, 1379, 1370, 1244, 1161, 1096, 1038, 933, 883 cm^{-1}; MS (EI): *m/z* (%): 384 ([M^+] 9), 369 (12), 339 (2), 309 (3), 282 (8), 265 (7), 237 (27), 220 (39), 193 (5), 157 (10), 110 (40), 85 (47), 55 (18), 45 (100); HRMS (EI): *m/z*: calcd for $C_{21}H_{36}O_6+$Na: 407.2404 [M^++Na]; found: 407.2404; elemental analysis calcd (%) for $C_{21}H_{36}O_6$: C 65.60, H 9.44; found: C 65.46, H 9.38.

(−)-Microcarpalide (1): $BF_3{\cdot}Et_2O$ (51.4 mg, 0.36 mmol) and 1,2-ethanedithiol (136 mg, 1.45 mmol) were added to a solution of compound (*E*)-**22** (139 mg, 0.36 mmol) in CH_2Cl_2 (15 mL) at 0°C. After stirring for 1.5 h, the reaction was quenched with saturated aq $NaHCO_3$ (20 mL), the organic phase was carefully extracted with EtOAc (3×20 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 10:1→0:1) to give product **1** as a colorless oil (80.6 mg, 74%).[1,20,21] $[\alpha]_D^{20}=-27.2°$ (*c*=0.83, MeOH); ^1H NMR (400 MHz, CD_3CN; mixture of two conformers): $\delta=5.70$ (dd, $J=15.8$, 1.6 Hz, 1H), 5.55–5.47 (m, 1H), 4.81 (ddd, $J=11.2$, 4.3, 3.6 Hz, 1H), 4.11 (brs, 1H), 3.78 (brs, 1H), 3.55 (brm, 1H), 3.12 (brs, 1H), 2.86 (brm, 2H), 2.56–2.34 (m, 1H), 2.26–2.21 (m, 1H), 2.08–2.03 (m, 3H), 1.81–1.69 (m, 1H), 1.43 (brm, 2H), 1.29 (brm, 8H), 0.89 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN; mixture of two conformers): $\delta=176.3$, 173.4, 134.4, 133.7, 129.9, 126.6, 79.4, 76.9, 76.4, 73.7, 72.7, 72.3, 36.6, 35.9, 34.1, 33.8, 32.5, 32.2, 32.1, 29.9, 26.4, 26.0, 23.3, 14.3 ppm; IR (film): $\tilde{\nu}=$ 3398, 3035, 2928, 1710, 1435, 1225, 1157, 1064, 983 cm^{-1}; MS (EI): *m/z* (%): 282 (1), 230 (1), 198 (3), 180 (38), 141 (7), 129 (20), 95 (23), 84 (73), 70 (100), 55 (48), 43 (49); HRMS (EI): *m/z*: calcd for $C_{16}H_{28}O_5+$Na: 323.1829 [M^++Na]; found: 323.1828; elemental analysis calcd (%) for $C_{16}H_{28}O_5$: C 63.97, H 9.40; found: C 63.88, H 9.37.

Furanone 23: Prepared from compound (*Z*)-**22** (77 mg, 0.2 mmol) by following the procedure described above; colorless oil (19 mg, 32%). $[\alpha]_D^{20}=+61.9°$ (*c*=0.95, MeOH); ^1H NMR (400 MHz, CD_3CN): $\delta=5.55$ (ddd, $J=10.3$, 10.0, 7.1 Hz, 1H), 5.39 (t, $J=10.6$ Hz, 1H), 4.69 (ddd, $J=11.6$, 3.7, 1.7, 1H), 4.33 (t, $J=9.4$ Hz, 1H), 3.56–3.55 (m, 2H), 3.30 (brs, 1H), 3.19 (brs, 1H), 2.97 (brs, 1H), 2.69–2.60 (m, 1H), 2.57–2.51 (m, 1H), 2.18–2.04 (m, 3H), 1.79–1.72 (m, 1H), 1.42 (brm, 3H), 1.29 (brs, 7H), 0.88 ppm (t, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=175.1$, 133.3, 129.6, 76.1, 75.6, 72.9, 70.3, 34.2, 32.4, 31.0, 30.0, 29.9, 29.6, 26.2, 23.2, 14.3 ppm; IR (film): $\tilde{\nu}=3406$, 3011, 2954, 2927, 2856, 1734, 1714, 1663, 1250, 1144, 1056 cm^{-1}; MS (EI): *m/z* (%): 300 (0.5) [M^+], 282 (2), 264 (0.4), 215 (1), 197 (47), 179 (20), 167 (58), 150 (22), 138 (96), 122 (25), 110 (29), 95 (38), 85 (76), 55 (100), 43 (73); HRMS (EI): *m/z*: calcd for $C_{16}H_{28}O_5+$Na: 323.1829 [M^++Na]; found: 323.1831; elemental analysis calcd (%) for $C_{16}H_{28}O_5$: C 63.97, H 9.40; found: C 63.75, H 9.27.

9-*epi*-Microcarpalide (26): Prepared as described above from lactone (*E*)-**25** (47 mg, 0.12 mmol) in the form of colorless crystals (23 mg, 62%). M.p.=104–105°C; $[\alpha]_D^{20}=+47.3°$ (*c*=0.51, MeOH); ^1H NMR (400 MHz, CD_3CN): $\delta=5.51$ (ddd, $J=15.5$, 10.6, 5.0 Hz, 1H), 5.25 (dd, $J=15.4$, 9.7 Hz, 1H), 4.77 (ddd, $J=11.3$, 5.3, 3.3, 1H), 3.61–3.52 (m, 2H), 3.32–3.27 (m, 3H), 2.93 (d, $J=5.6$ Hz, 1H), 2.46–2.39 (m, 2H), 2.12–1.98 (m, 2H), 1.92–1.82 (m, 2H), 1.54–1.44 (m, 2H), 1.35–1.29 (br m, 8H), 0.89 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=175.9$, 134.5, 133.2, 78.3, 77.7, 77.1, 72.7, 35.2, 34.0, 32.7, 32.4, 31.7, 30.0, 26.2, 23.2, 14.3 ppm; IR (film): $\tilde{\nu}=3398$, 2929, 2857, 1730, 1710, 1666, 1431, 1383, 1239, 1149, 1057, 977 cm^{-1}; MS (EI): *m/z* (%): 301 (0.1) [M^+], 282 (0.1), 213 (0.5), 198 (2), 180 (26), 141 (6), 129 (24), 95 (21), 84 (100), 70 (66), 55 (44), 43 (38); HRMS (EI): *m/z*: calcd for $C_{16}H_{28}O_5+$Na: 323.1829 [M^++Na]; found: 323.1828; elemental analysis calcd (%) for $C_{16}H_{28}O_5$: C 63.97, H 9.40; found: C 64.11, H 9.49.

Furanone 27: Prepared as described above from lactone (*Z*)-**25** (38 mg, 0.1 mmol) as a colorless solid (7 mg, 24%); crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2. M.p.=104–105°C; $[\alpha]_D^{20}=-54.4°$ (*c*=0.31, MeOH); ^1H NMR (400 MHz, CD_3CN): $\delta=5.77$–5.70 (m, 1H), 5.62–5.57 (m, 1H), 4.45–4.39 (m, 2H), 3.56 (brd, $J=2.6$ Hz, 1H), 3.39 (brs, 2H), 3.03 (brd, $J=2.9$ Hz, 1H), 2.78 (brd, $J=4.4$ Hz, 1H), 2.48–2.42 (m, 2H), 2.38–2.18 (m, 2H), 2.12–1.97 (m, 2H), 1.57–1.41 (m, 2H), 1.36–1.18 (brm, 8H), 0.89 ppm (t, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=178.4$, 132.4, 130.5, 83.5, 74.8, 74.4, 69.4, 33.2, 32.5, 31.4, 30.1, 28.9, 26.5, 24.3, 23.3, 14.3 ppm; IR (film): $\tilde{\nu}=3400$, 2951, 2928, 1763, 1658, 1188, 1036 cm^{-1}; MS (EI): *m/z* (%): 282 (2), 264 (1), 215 (1), 197 (73), 186 (10), 179 (25), 167 (94), 138 (78), 122 (32), 95 (42), 85 (82), 79 (36), 67 (37), 55 (100), 43 (69); HRMS (EI): *m/z*: calcd for $C_{16}H_{28}O_5+$Na: 323.1829 [M^++Na]; found: 323.1829; elemental analysis calcd (%) for $C_{16}H_{28}O_5$: C 63.97, H 9.40; found: C 64.10, H 9.36.

Acetal 30: A solution of diol **29** (1.40 g, 12.1 mmol),[30] *p*-methoxybenzaldehyde dimethyl acetal (4.40 g, 24.2 mmol) and camphorsulfonic acid (279 mg, 1.20 mmol) in CH_2Cl_2 (40 mL) was refluxed for 14 h. The reaction was quenched with Et_3N before all volatiles were evaporated and the residue was purified by flash chromatography (hexane/EtOAc 19:1) to afford product **30** as a colorless liquid (1.67 g, 59%); mixture of diastereomers (*dr*=57:43). ^1H NMR (400 MHz, C_6D_6): $\delta=7.51$–7.46 (m, 4H), 6.80–6.76 (m, 4H), 5.92 (s, 1H of minor isomer), 5.77 (s, 1H of major isomer), 5.73–5.62 (m, 2H), 4.99–4.91 (m, 4H), 3.97–3.83 (m, 3H), 3.71 (dd, $J=7.5$, 6.9 Hz, 1H of major isomer), 3.41 (dd, $J=7.5$, 6.9 Hz, 1H of major isomer), 3.27 (dd, $J=7.7$, 7.0 Hz, 1H of minor isomer), 3.26 (s, 3H of minor isomer), 3.25 (s, 3H of major isomer), 2.08–1.91 (m, 4H), 1.69–1.56 (m, 2H), 1.43–1.22 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2; mixture of isomers): $\delta=161.3$, 161.1, 138.8, 131.7, 131.1, 128.8, 128.6, 115.5, 114.3, 104.6, 103.7, 77.3, 76.7, 56.0, 33.7, 33.4, 30.8, 30.7 ppm; IR (film): $\tilde{\nu}=3076$, 2937, 1716, 1641, 1615, 1517, 1249, 1171, 1079, 1034, 915, 830 cm^{-1}; MS (EI): *m/z* (%): 234 (10), 233 (21), 135 (100), 121 (20), 108 (31), 81 (16), 77 (12), 41 (11); HRMS (EI): *m/z*: calcd for $C_{14}H_{18}O_3+$Na: 257.11481 [M^++Na]; found 257.11483; elemental analysis calcd (%) for $C_{14}H_{18}O_3$: C 71.77, H 7.74; found C 71.86, H 7.70.

Alcohol 31: To a solution of compound **30** (1.06 g, 4.52 mmol) in toluene (40 mL) was added DIBAL-H (1 M in toluene, 9.0 mL, 9.0 mmol) at 0°C. The mixture was allowed to warm to room temperature over 3 h. The reaction mixture was filtered through a short pad of silica to remove the aluminum salts, the filtrate was adsorped on silica and the product eluted with hexane/EtOAc (10:1→4:1) to give product **31** as a colorless liquid (885 mg, 83%). ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.29$ (d, $J=8.6$ Hz, 2H), 6.91 (d, $J=8.6$ Hz, 2H), 5.83 (ddt, $J=17.1$, 10.2, 6.6 Hz, 1H), 5.07–4.99 (m, 2H), 4.57 (d, $J=11.2$ Hz, 1H), 4.50 (d, $J=11.2$ Hz, 1H), 3.83 (s, 3H), 3.72 (dd, $J=13.8$, 5.8, 1H), 3.57–3.52 (m, 2H), 2.18–2.13 (m, 2H), 1.86 (br, 1H), 1.80–1.71 (m, 1H), 1.66–1.59 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.0$, 137.8, 130.2, 129.0 (2C), 114.5, 113.6 (2C), 78.4, 70.9, 63.8, 54.9, 29.8, 29.2 ppm; IR (film): $\tilde{\nu}=3429$, 2998, 2935, 1640, 1612, 1514, 1248, 1036, 99 8, 912, 822 cm^{-1}; MS (EI): *m/z* (%): 236 (1), 205 (9), 121 (100), 77 (5); HRMS (EI): *m/z*: calcd for $C_{14}H_{20}O_3+$Na: 259.13049 [M^++Na]; found 259.13022. Small amounts of the regioisomeric PMB-ether could be separated (178 mg, 17%), which showed the following spectroscopic properties: ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.10$ (d, $J=8.6$ Hz, 2H), 6.74 (d, $J=8.6$ Hz, 2H), 5.67 (ddt, $J=17.1$, 10.3, 6.6 Hz, 1H), 4.91–4.79 (m, 2H), 4.33 (s, 2H), 3.66 (m, 1H), 3.65 (s, 3H), 3.33 (dd, $J=9.4$, 3.1 Hz, 1H), 3.16 (dd, $J=9.4$, 7.8 Hz, 1H), 2.06–1.96 (m, 3H), 1.43–1.36 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.0$, 137.9, 129.7, 129.0 (2C), 114.5, 113.5 (2C), 73.8, 72.7, 69.5, 54.9, 32.0, 29.4 ppm; IR (film): $\tilde{\nu}=3452$, 2999, 2934, 1640, 1612, 1586, 1514, 1248, 1092, 997, 912, 821 cm^{-1}; MS (EI): *m/z* (%): 236 (5), 137 (12), 122 (19), 121 (100), 77 (5); HRMS (EI): *m/z*: calcd for $C_{14}H_{20}O_3+$Na: 259.13047 [M^++Na]; found 259.13023.

Carboxylic acid 32: Oxalyl chloride (0.26 mL, 3.0 mmol) was added dropwise to a solution of DMSO (0.43 mL, 6.0 mmol) in CH_2Cl_2 (10 mL) at −78°C and the resulting mixture was stirred for 15 min at that temperature. A solution of alcohol **31** (473 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) was

added and the resulting suspension was stirred for 45 min, at which point Et_3N (1.1 mL, 8.0 mmol) was introduced. The mixture was then allowed to reach 0 °C over 3 h before it was quenched with saturated aq NH_4Cl (10 mL). The aqueous layer was repeatedly extracted with Et_2O (3× 10 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated.

The resulting crude aldehyde (481 mg, quant.) was dissolved in *t*BuOH (15 mL). A solution of NaH_2PO_4 (380 mg, 3.2 mmol) in water (2.5 mL), 2-methyl-2-butene (1.1 mL) and $NaClO_2$ (570 mg, 6.3 mmol) were successively added and the resulting mixture was stirred at room temperature for 2.5 h. All volatile materials were removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL). The solution was dried over Na_2SO_4 and the solvent was evaporated to give carboxylic acid **32** (504 mg, quant.) which could be used in the next step without further purification. The spectroscopic data of **32** are in full agreement with those previously reported in the literature.[8]

Ester 34: Et_3N (0.61 mL, 4.4 mmol) and 2,4,6-trichlorobenzoyl chloride (0.32 mL, 2.0 mmol) were added to a solution of acid **32** (504 mg, 2.0 mmol) in toluene (19 mL). The resulting suspension was stirred for 1.5 h before a solution of alcohol **33** (407 mg, 2.0 mmol)[8] and DMAP (122 mg, 1.0 mmol) in toluene (11 mL) was introduced and the resulting mixture was stirred at ambient temperature for 2 h. The precipitate formed was filtered off through a pad of silica, the filtrate was evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc 19:1) to give ester **34** as a colorless oil (764 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.81–5.64 (m, 2H), 5.31–5.13 (m, 2H), 4.98–4.89 (m, 2H), 4.57–4.53 (m, 2H), 4.21 (d, J = 11.0 Hz, 1H), 4.14 (dd, J = 7.5, 6.5 Hz, 1H), 3.81–3.78 (m, 1H), 3.73 (s, 3H), 2.15–2.07 (m, 2H), 1.76–1.71 (m, 2H), 1.67–1.56 (m, 2H), 1.42 (s, 3H), 1.31 (s, 3H), 1.29 (m, 3H), 0.85 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 159.1, 137.1, 132.8, 129.4, 129.2 (2C), 118.3, 115.0, 113.5 (2C), 108.4, 78.4, 77.7, 71.9, 71.6, 54.9, 33.0, 31.8, 29.2, 27.2, 26.6, 24.9, 17.5, 13.7 ppm; IR (film): $\tilde{\nu}$ = 3077, 1959, 1750, 1641, 1613, 1514, 1381, 1372, 124 9, 1214, 1109, 1037, 995, 927, 872, 822 cm^{-1}; MS (EI): *m*/*z* (%): 249 (11), 197 (27), 137 (14), 125 (14), 121 (100), 98 (22), 69 (11), 55 (12); HRMS (EI): *m*/*z*: calcd for $C_{25}H_{36}O_6$+Na: 455.24041 [M^++Na]; found 455.24074.

Nonenolide 35: A solution of diene **34** (543 mg, 1.26 mmol) and the ruthenium catalyst **6** (120 mg, 0.13 mmol) in CH_2Cl_2 (700 mL) was refluxed for 15 h. The reaction was quenched with ethyl vinyl ether (1.8 mL) before the solvent was evaporated and the residue was purified by flash chromatography (hexane/EtOAc 19:1) to afford (*E*)-**35** (392 mg, 77 %) and small amounts of the *Z* isomer (92 mg, 18 %) as colorless syrups each.

Compound (E)-***35***: ^{1}H NMR (400 MHz, $CDCl_3$; mixture of two conformers): δ = 7.22–7.15 (m, 4H), 6.83–6.79 (m, 4H), 5.80–5.37 (m, 4H), 5.02–4.86 (m, 2H), 4.70–4.59 (m, 4H), 4.48–4.23 (m, 2H), 4.07–3.89 (m, 4H), 3.74 (s, 3H of major conformer), 3.73 (s, 3H of minor conformer), 2.40–2.20 (m, 2H), 2.09–1.50 (m, 10H), 1.47 (s, 3H of major conformer), 1.39 (s, 3H of minor conformer), 1.36–1.29 (m, major and minor conformer overlapping, 7H), 0.88 (t, J = 7.4 Hz, 3H of minor conformer), 0.87 (t, J = 7.4 Hz, 3H of major conformer); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two conformers): δ = 174.8, 172.3, 159.1, 159.0, 132.0, 131.8, 129.8, 129.1, 128.8, 128.4, 127.1, 122.7, 113.5, 113.5, 108.7, 108.6, 78.0, 77.7, 77.6, 75.8, 75.7, 75.3, 71.6, 71.2, 71.1, 54.9, 33.8, 33.6, 31.6, 29.7, 28.2, 27.6, 26.8, 26.6, 25.8, 25.4, 24.9, 17.8, 17.6, 13.6, 13.6 ppm; IR (film): $\tilde{\nu}$ = 2933, 1725, 1613, 1586, 1514, 1381, 1249, 1221, 1221, 1120, 1053, 822 cm^{-1}; MS (EI): *m*/*z* (%): 404 (1), 283 (9), 225 (5), 121 (100), 95 (5), 77 (4); HRMS (EI): *m*/*z*: calcd for $C_{23}H_{32}O_6$+Na: 427.20911 [M^++Na]; found 427.20929.

Compound (Z)-***35***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.32 (m, 2H), 4.98–4.94 (m, 1H), 4.78–4.73 (m, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.26–4.22 (m, 2H), 3.97 (t, J = 3.4 Hz, 1H), 3.74 (s, 3H), 2.59 (m, 1H), 2.04–2.00 (m, 1H), 1.90–1.75 (m, 2H), 1.64–1.55 (m, 2H), 1.43 (s, 3H), 1.37 (m, 2H), 1.32 (m, 3H), 0.89 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 159.1, 133.4, 129.3, 129.0 (2C), 127.6, 113.6 (2C), 109.8, 78.7, 76.1, 74.4, 72.8, 71.4, 54.9, 35.4, 32.6, 27.9, 25.5, 21.3, 17.8, 13.8 ppm; IR (film): $\tilde{\nu}$ = 2959, 1737, 1612, 1514, 1381, 1370, 1250, 1082, 1042, 869, 827 cm^{-1}; MS (EI): *m*/*z* (%): 404 (2), 283 (11), 137 (13), 121 (100), 95 (7), 77 (4); HRMS (EI): *m*/*z*: calcd for $C_{23}H_{32}O_6$+Na: 427.20911 [M^++Na]; found: 427.20906.

Compound 36: A solution of (*E*)-**35** (60 mg, 0.15 mmol) in MeOH (5 mL), water (2.4 mL) and aq HCl (1 M, 1 mL) was stirred at 60 °C for 1 h. The reaction mixture was neutralized with aq NaOH (1 M) and the organic solvents were evaporated. The remaining aqueous layer was extracted with EtOAc (3×10 mL), the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the residue by flash chromatography (hexane/EtOAc 1:1) provided product **36** as a colorless syrup (49 mg, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.68 (d, J = 15.7 Hz, 1H), 5.45–5.38 (m, 1H), 5.03 (dt, J = 9.5, 2.4 Hz, 1H), 4.60 (d, J = 11.0 Hz, 1H), 4.38 (br m, 1H), 4.31 (d, J = 4.3 Hz, 1H), 3.89 (dd, J = 5.2, 2.5 Hz, 1H), 3.74 (s, 3H), 3.56 (br s, 1H), 2.42–2.33 (m, 2H), 2.30 (br s, 1H), 2.04–1.81 (m, 4H), 1.62–1.56 (m, 1H), 1.36–1.18 ppm (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 159.0, 131.9, 129.7, 128.7 (2C), 122.8, 113.5 (2C), 75.3, 73.0, 72.8, 71.7, 70.7, 54.9, 33.5, 31.0, 26.5, 17.8, 13.6 ppm; IR (film): $\tilde{\nu}$ = 3470, 2997, 2958, 1724, 1612, 1586, 1514, 1250, 1056, 821 cm^{-1}; MS (EI): *m*/*z* (%): 364 (1), 278 (1), 137 (9), 121 (100), 113 (2), 77 (3), 55 (2); HRMS (EI): *m*/*z*: calcd for $C_{20}H_{28}O_6$+Na: 387.17781 [M^++Na]; found 387.17748.

Compound 37: A solution of product **35** (80 mg, 0.20 mmol) and DDQ (48 mg, 0.21 mmol) in CH_2Cl_2 (7.0 mL) and water (0.4 mL) was stirred for 15 h at room temperature. For work up, all volatile materials were evaporated and the residue was purified by flash chromatography (hexane/EtOAc 9:1→6:1) to give alcohol **37** as a colorless syrup (51 mg, 90 %). The analytical and spectroscopic data were in full agreement with those previously reported in the literature.[8]

Product 38: Et_3N (56 μL, 0.40 mmol) and 2,4,6-trichlorobenzoyl chloride (28 μL, 0.18 mmol) were added to a solution of hexanoic acid (21 mg, 0.18 mmol) in toluene (2.0 mL) and the resulting suspension was stirred for 1.5 h before a solution of alcohol **37** (51 mg, 0.18 mmol) and DMAP (11 mg, 0.09 mmol) in toluene (1.0 mL) was introduced. Stirring was continued for 2 h, the precipitated salts were filtered off through a short pad of silica, the filtrate was evaporated, and the residue was purified by flash chromatography (hexane/EtOAc 19:1) to afford the corresponding ester. This product was dissolved in MeOH (5 mL), water (2.4 mL), and aq HCl (1 M, 1 mL) and the resulting mixture was stirred at 60 °C for 1 h. The reaction was then neutralized with aq NaOH (1 M), the aqueous layer was extracted with EtOAc (3×5 mL), the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography (hexane/EtOAc 2:1) to give product **38** as a colorless syrup (58 mg, 94 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (d, J = 15.8 Hz, 1H), 5.48–5.44 (m, 1H), 5.13 (dd, J = 5.4, 1.6 Hz, 1H), 4.97 (dt, J = 9.5, 2.6 Hz, 1H), 4.37 (m, 1H), 3.45–3.42 (m, 1H), 2.35–2.33 (m, 3H), 2.17–2.11 (m, 4H), 1.90–1.61 (m, 4H), 1.50–1.40(m, 1H), 1.32–1.12 (m, 6H), 0.86 (t, J = 7.0 Hz, 3H), 0.82 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 171.4, 132.0, 122.6, 73.1, 72.7, 71.0, 69.3, 33.8, 33.4, 30.8, 29.5, 27.0, 24.3, 22.0, 17.2, 13.5, 13.4 ppm; IR (film): $\tilde{\nu}$ = 3460, 2959, 1740, 1258, 1078, 986 cm^{-1}; MS (EI): *m*/*z* (%): 426 (2), 323 (2), 285 (5), 244 (20), 183 (100), 141 (83), 124 (10), 113 (32), 86 (15), 71 (21), 57 (59), 55 (41), 43 (39), 41 (20), 29 (10); HRMS (EI): *m*/*z*: calcd for $C_{18}H_{30}O_6$+Na: 365.19346 [M^++Na]; found: 365.19314.

Compound 39: Prepared analogously as a colorless syrup (53 mg, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (dd, J = 15.8, 1.2 Hz, 1H), 5.48–5.40 (m, 1H), 5.14 (dd, J = 5.5, 2.0 Hz, 1H), 4.96 (dt, J = 9.6, 2.7 Hz, 1H), 4.37 (m, 1H), 3.43 (dd, J = 9.8, 2.7 Hz, 1H), 2.38–2.27 (m, 3H), 2.18–1.17 (m, 27H), 0.82 (t, J = 7.4 Hz, 3H), 0.81 ppm (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 171.4, 132.0, 122.6, 73.1, 72.7, 71.0, 69.3, 33.8, 33.4, 31.5, 29.4, 29.2, 29.2, 29.1, 28.9 (2C), 28.7, 27.0, 24.7, 22.3, 17.2, 13.7, 13.5 ppm; IR (film): $\tilde{\nu}$ = 3530, 3414, 3038, 2957, 1743, 1723, 1259, 1060 cm^{-1}; MS (EI): *m*/*z* (%): 342 (1), 257 (2), 141 (49), 113 (23), 99 (100), 86 (11), 71 (29), 67 (10), 57 (18), 55 (25), 43 (41), 41 (14), 29 (11); HRMS (EI): *m*/*z*: calcd for $C_{24}H_{42}O_6$+Na: 449.28736 [M^++Na]; found 449.28750.

Compound 40: Prepared analogously as a colorless syrup (66 mg, 94 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.14 (m, 5H), 5.53–5.49 (m, 1H), 5.45–5.38 (m, 1H), 5.13 (dd, J = 5.5, 1.8 Hz, 1H), 4.94 (dt, J = 9.4, 2.5 Hz, 1H), 4.34 (m, 1H), 3.36 (dd, J = 9.8, 2.6 Hz, 1H), 2.94 (t, J = 7.8 Hz, 2H), 2.69 (t, J = 7.8 Hz, 2H), 2.32–2.21 (m, 1H), 2.15–2.01 (m, 4H), 1.89–1.81 (m, 1H), 1.78–1.70 (m, 1H), 1.42–1.13 (m, 3H), 0.82 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 171.2, 139.8, 132.0, 128.2 (2C), 127.8 (2C), 126.1, 122.5, 72.9, 72.7, 71.0, 69.6, 35.1, 33.3, 30.5, 29.4, 26.9, 17.2, 13.5 ppm; IR (film): $\tilde{\nu}$ = 3467, 3028, 2959, 1736, 1604, 1497, 1454, 1259, 1078, 1078, 752, 699 cm^{-1}; MS (EI): m/z (%): 376 (3), 291 (10), 244 (13), 141 (5 9), 133 (90), 113 (25), 105 (100), 91 (70), 86 (12), 70 (12), 67 (12), 55 (26), 41 (11); HRMS (EI): m/z: calcd for $C_{21}H_{28}O_6$+Na: 399.17781 [M^++Na]; found 399.17811.

X-ray crystal structure analysis of 9-*epi*-microcarpalide (26): Empirical formula = $C_{16}H_{28}O_5$; M_r = 300.38 g mol^{-1}; colorless block; crystal size = 0.18 × 0.06 × 0.04 mm; orthorhombic; space group = $P2_12_12_1$; a = 5.2184(6), b = 7.4547(7), c = 42.045(13) Å; V = 1635.6(5) Å^3; T = 100 K; Z = 4; ρ_{calcd} = 1.220 g cm^{-3}; λ = 0.71073 Å, μ($Mo_{K\alpha}$) = 0.089 mm^{-1}; multiscan absorption correction; Nonius KappaCCD diffractometer; $5.15 < \theta < 33.09$; 15611 measured reflections; 3044 independent reflections; 2748 reflections with $I > 2\sigma(I)$, Structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.042 [$I > 2\sigma(I)$], wR_2 = 0.094; 203 parameters; OH atoms refined other H atoms riding; S = 1.062; residual electron density = +0.4/−0.2 e Å^{-3}.

X-ray crystal structure analysis of butanolide 27: Empirical formula = $C_{16}H_{28}O_5$; M_r = 300.38 g mol^{-1}; colorless plate; crystal size = 0.18 × 0.06 × 0.04 mm; orthorhombic; space group = $P2_12_12_1$; a = 5.13100(10), b = 6.0500(3), c = 19.8385(3) Å; V = 1633.75(5) Å^3; T = 100 K; Z = 4; ρ_{calcd} = 1.221 g·cm^3; λ = 0.71073 Å; μ($Mo_{K\alpha}$) = 0.089 mm^{-1}; multiscan absorption correction; Nonius KappaCCD diffractometer; $3.27 < \theta < 33.18$; 50586 measured reflections; 3557 independent reflections; 3241 reflections with $I > 2\sigma(I)$; structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.043 [$I > 2\sigma(I)$], wR_2 = 0.099; 203 parameters; OH atoms refined other H atoms riding; S = 1.095; residual electron density = +0.3/−0.2 e Å^{-3}.

CCDC-620214 and -620215 contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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