Ex Chiral Pool Synthesis from a Highly Methyl-branched Wax Ester and Biological Properties of (+)-Capensifuranone

Yana Galeyeva[a], Michael Morr[b], Florenz Sasse[b], Randi Diestel[b], Sabine Laschat[a], Angelika Baro[a], and Wolfgang Frey[a]

[a] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
[b] Abteilung Chemische Biologie, Helmholtz-Zentrum für Infektionsforschung GmbH, Inhoffenstraße 7, 38124 Braunschweig, Germany

Reprint requests to Prof. Dr. S. Laschat. E-mail: sabine.laschat@oc.uni-stuttgart.de

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

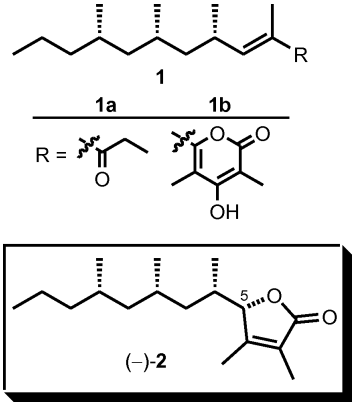
Unnatural (+)-capensifuranone (+)-**2** and its epimer (–)-5-*epi*-capensifuranone **6** were prepared from enantiopure methyl-branched aldehyde **4**, employing cyclisation with 3-bromomethacrylic acid to 4-bromofuranones **5a**,**b** followed by Negishi cross coupling. Compound **4** was obtained from the preen-gland wax-derived ester **3** after ozonolysis and reductive work-up. The configuration of **6** was determined *via* the X-ray crystal structure analysis of a derivative **10**. Compounds (+)-**2**, **5a**,**b** and **6** showed cytotoxic activity against L-929 mouse fibroblasts, and KB-3-1 HeLa and U-937 lymphoma cells.

Key words: Cytotoxic Activity, Ex Chiral Pool Synthesis, Genus *Siphonaria*, Polypropionates, Preen-gland Wax Ester

Introduction

The chemical defense strategy of gastropod mollusks of the genus *Siphonaria*, which are located at the intertidal region of the Mediterranean sea, and the Atlantic and Pacific ocean, relies on a class of structurally related secondary metabolites **1** [1 – 5] containing *syn*-1,3-dimethyl arrays as a common structural motive. Among these compounds is capensifuranone (–)-**2** which was isolated by Davies-Coleman in 1999 from *Siphonaria capensis* from the south east coast of South Africa [6] (Scheme 1).

A vast amount of effort has been spent on the synthesis of these biologically interesting compounds, in particular on the stereoselective formation of the *syn*-1,3-dimethyl arrays. The latter have been prepared by copper-mediated directed allylic substitution [7], asymmetric conjugate addition [8, 9], iterative aldol reactions using Evan's auxiliary [2] or catalytic aldol reactions starting from a chiral ketene dimer [10], iterative alkylations with chiral benzopyranoisoxazolidine [11], or Enders' SAMP methodology [12] and Zr-catalysed asymmetric carboalumination [13, 14]. Recently we reported an *ex chiral pool* strategy for the optical antipodes of two polypropionates, siphonarienone **1a** and pectinatone **1b** [15, 16], using highly methyl-branched wax esters derived from preen-gland wax of the domestic goose *Anser a. f. domesticus* [17]. Along these lines we wanted to extend the methodology to (–)-capensifuranone, (–)-**2**. Based on detailed NMR experiments and correlation with known members of

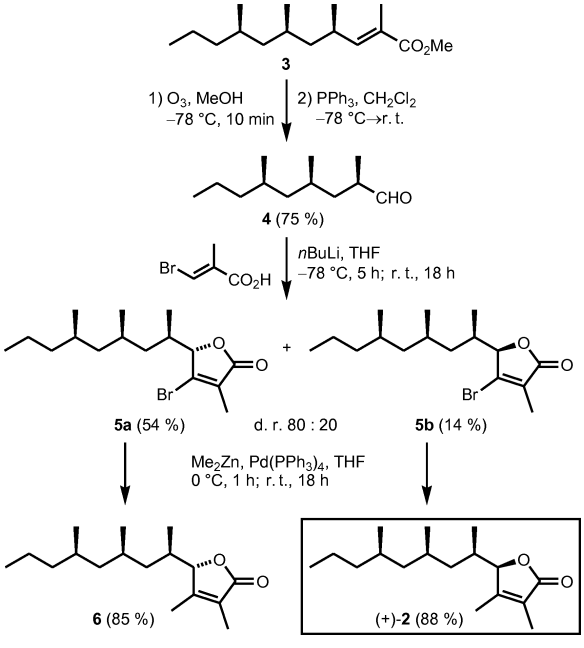


Scheme 1. Structurally related polypropionates such as siphonarienone (**1a**), pectinatone (**1b**) and capensifuranone (**2**).

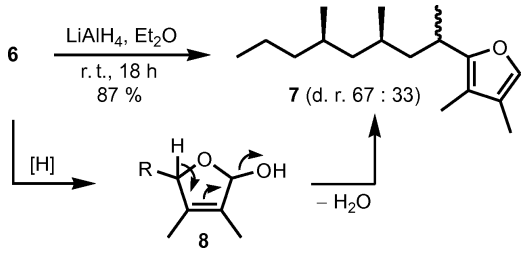
the *Siphonaria* polyketides a structure was assigned for compound (–)-**2** with an unsolved configuration at C-5 [6]. In 2004 Williams reported the first total synthesis of (–)-capensifuranone, (–)-**2**, which confirmed the original assignment [8]. In addition, the (*S*)-configuration at C-5 could be secured. We here report on the total synthesis of the unnatural enantiomer (+)-capensifuranone (+)-**2**.

Results and Discussion

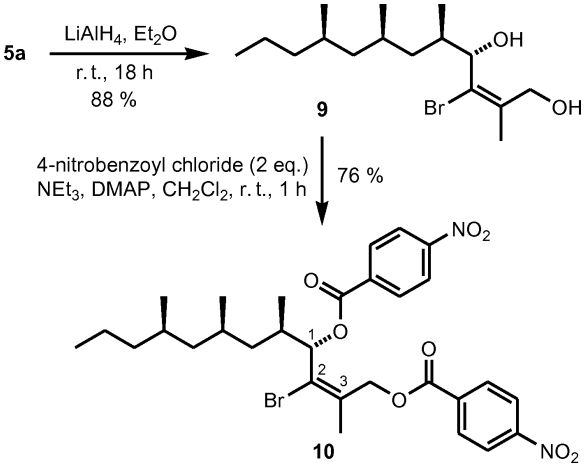
The synthesis commenced with the known preen-gland wax-derived methyl (2*E*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundec-2-enoate **3** [16], which was submitted to ozonolysis with reductive work-up with triphenylphosphine according to the method by Breit [7a] providing the corresponding aldehyde **4** in 75 % yield (Scheme 2). Compound **4** was then treated with (*E*)-3-bromomethacrylic acid [18] in the presence of butyllithium in THF at −78 °C following the procedure by Williams [8] to give an (80 : 20) diastereomeric mixture of 4-bromo-3-methylfuranones **5a** and **5b**. After chromatographic separation, **5a** and **5b** were isolated in 54 % and 14 % yield, respectively. Negishi cross coupling of the latter with dimethylzinc in the presence of $Pd(PPh_3)_4$ in THF [8] finally gave (+)-capensifuranone (+)-**2** and (–)-5-*epi*-capensifuranone **6** in 88 % and 85 % yield, respectively.



Scheme 2. Synthesis of capensifuranone (+)-**2**.



Scheme 3.



Scheme 4.

In order to secure the stereochemical assignment of the final product (+)-**2**, we followed the same approach as described by Williams [8]. Surprisingly, when (–)-5-*epi*-capensifuranone **6** was treated with $LiAlH_4$ in diethyl ether at r. t. no reductive lactone opening was achieved, but a diastereomeric mixture of the furan derivative **7** was obtained (d. r. = 67 : 33) (Scheme 3). Compound **7** is probably formed *via* initial reduction of the lactone **6** to the corresponding lactol **8** and subsequent vinylogous elimination of H_2O (Scheme 3).

Attempts towards lactone opening under various conditions (*e. g.* K_2CO_3, MeOH or NaOMe/MeOH or H_2SO_4) failed. However, when 4-bromo-3-methylfuranone **5a** was reduced with $LiAlH_4$ under similar conditions as described above, clean conversion to the diol **9** was observed without any accompanying reduction of the bromo substituent (Scheme 4).

Next, diol **9** was treated with 4-nitrobenzoyl chloride in CH_2Cl_2 in the presence of NEt_3 and catalytic amounts of DMAP to afford the bis(4-nitrobenzoate) **10** in 76 % yield. Single crystals of **10** were obtained, which were suitable for an X-ray crystal structure analysis (Fig. 1) [19]. The absolute configuration at

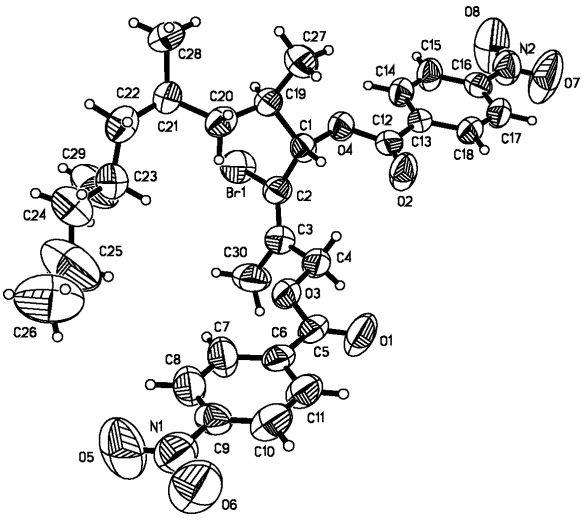


Fig. 1. ORTEP view of the molecular structure of (1*S*,2*E*)-2-bromo-3-methyl-4-[(4-nitrobenzoyl)oxy]-1-[(1*R*,3*R*,5*R*)-1,3,5-trimethyloctyl]but-2-enyl 4-nitrobenzoate **10** in the solid state.

C-1 of derivative **10** is clearly confirmed by anomalous dispersion, as indicated by the Flack parameter of −0.014(14). The crystal structure shows *trans* configuration at the C-2–C-3 double bond identified by the distance of 1.324(9) Å. It is also remarkable that the 4-nitrobenzoyl moieties have a nearly coplanar orientation.

Both (+)-capensifuranone (+)-**2**, (–)-5-*epi*-capensifuranone **6** as well as the corresponding bromo precursors **5a**,**b** were submitted to an antimicrobial agar diffusion assay (20 μg/6 mm paper disc) employing Gram-negative (*E. coli tolC*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) and Gram-positive bacteria (*Staphylococcus aureus, Micrococcus luteus*, *Mycobacterium phlei*), yeasts (*Candida albicans*, *Hansenula anomala*, *Saccharomyces cerevisiae*) as well as hyphal fungi (*Aspergillus fumigatus*, *Botrytis cinerarea*, *Pythium debaryanum*). No antimicrobial activity could be detected, however, all compounds displayed cytotoxic activity against L-929 mouse fibroblasts, and KB-3-1 HeLa and U-937 lymphoma cells (Table 1). In general, the cytotoxic activities of (+)-capensifuranone (+)-**2** and (–)-5-*epi*-capensifuranone **6** are slightly higher than that of the corresponding 3-bromo-furanones **5a**,**b**. There is almost no difference in cytotoxicity between compound (+)-**2** and its C-5-epimer **6** which further supports our previous assumption that the polypropionate backbone induces the cytotoxicity [16].

Table 1. Results of cytotoxicity assays of compounds (+)-**2**, **5a**,**b**, **6**[a].

Cell line	Origin	**5a**	**5b**	(+)-**2**	**6**
L-929	Murine connective tissue	11	19	4.5	6
KB-3-1	Human cervix carcinoma	18	14	11	11
U-937	Human histiocytic lymphoma	18	9.5	6.5	5

[a] For details see Experimental Section. Cells were cultivated at 37 °C and 10 % CO_2 in media with 10 % fetal calf serum; activity is given as IC_{50} values in $\mu g\,mL^{-1}$.

Published data on the biological activities of polypropionate compounds from *Siphonaria* [4b] show cytotoxic activities with IC_{50} values between 5 to 10 $\mu g\,mL^{-1}$ and above, which is in the same range we found with capensifuranones. Whereas we did not find antibiotic activity, other polypropionates were reported to be active against Gram-positive bacteria and yeasts, too [3].

In conclusion, (+)-capensifuranone (+)-**2** and (–)-5-*epi*-capensifuranone **6** have been prepared by a three-step *ex chiral pool* synthesis starting from the wax ester **3**. After reductive ring opening of 5-*epi*-capensifuranone precursor **5a** to diol **9** and subsequent derivatization, an X-ray crystal structure analysis of **10** allowed to determine the absolute configuration to be *S*. Both (+)-capensifuranone (+)-**2** and its 5-epimer **6** display cytotoxic activities with IC_{50} values of 4 – 11 $\mu g\,mL^{-1}$, in the range of other polypropionates.

Experimental Section

General information

All cell lines were from DMSZ and grown in DME medium with high glucose (L-929, KB-3-1) or RPMI 1640 (U-937) from GIBCO. All solvents were dried, and reactions were performed in dried glassware. (*E*)-3-Bromomethacrylic acid was prepared as described [18]. The following spectroscopic and analytical instruments were used. IR: Bruker Vector 22 FTIR. – NMR: Bruker ARX 300 or Bruker ARX 500. For ^1H spectra, TMS was used as internal standard. – Mass spectrometry: Finnigan MAT 90 and Bruker Daltonics micrO-TOF Q or Varian MAT 711. – Optical rotations: Perkin Elmer Polarimeter 241 in 1 mL-cuvettes (l = 0.1 dm). – Flash chromatography: Silica gel 60, 40 – 63 μm (Fluka). – GC: Hewlett-Packard HP 6890, column HP-5 (30 m × 0.32 mm) with H_2 as carrier gas (flow 2 mL min^{-1}); temperature program: 8 °C min^{-1} gradient from 80 °C to 280 °C. PE = petroleum ether.

*(2R,4R,6R)-2,4,6-Trimethylnonanal (**4**)*

Unsaturated ester **3** (100 mg, 0.39 mmol) was dissolved in dry methanol (5 mL), and O_3 was bubbled through the reac-

tion mixture at −78 °C for 10 min. After complete removal of O_3 with N_2, a solution of PPh_3 (124 mg, 0.47 mmol) in dry CH_2Cl_2 (0.3 mL) was added dropwise at −78 °C. The reaction mixture was warmed to r. t. and hydrolysed with water (3 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* (10 mbar) at 30 °C. Chromatography on SiO_2 with PE/EtOAc (40 : 1) gave **4** as a colourless oil (54 mg, 0.29 mmol, 75 %). – R_f = 0.27. – $[\alpha]_D^{20}$ = −7.3 (*c* = 1.00, $CHCl_3$). – IR (ATR): ν = 2956.3, 2913.9, 2872.1, 2845.1, 1727.8, 1458.7, 1378.3, 1075.7, 1056.8, 945.8 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3 H, 6-Me), 0.87 (d, *J* = 6.6 Hz, 3 H, 4-Me), 0.88 (t, *J* = 7.1 Hz, 3 H, 9-H), 0.91 – 1.06 (m, 2 H, 5-H), 1.08 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.09 – 1.39 (m, 5 H, 3-H, 7-H, 8-H_a), 1.40 – 1.62 (m, 2 H, 6-H, 8-H_b), 1.65 – 1.79 (m, 1 H, 4-H), 2.37 – 2.53 (m, 1 H, 2-H), 9.57 (d, *J* = 2.6 Hz, 1 H, 1-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.2 (C-9), 14.4 (Me-2), 19.9 (C-8), 20.2 (Me-4), 20.4 (Me-6), 27.9 (C-6), 29.7 (C-4), 38.4 (C-2), 38.9 (C-7), 44.1 (C-5), 45.1 (C-3), 202.5 (C-1). – HRMS (EI): *m/z* = 184.1812 (calcd. 184.1827 for $C_{12}H_{24}O$, $[M]^+$). – MS (EI): *m/z* (%) = 184.2 (2), 154.2 (10), 126.2 (20), 111.1 (80), 85.1 (70), 69.1 (100), 57.1 (50), 43.1 (90).

*(5R)- and (5S)-4-Bromo-3-methyl-5-[(1R,3R,5R)-1,3,5-trimethyloctyl]furan-2(5H)-one (**5a**,**b**)*

To a solution of (*E*)-3-bromo-2-methyl-2-propionic acid (55 mg, 0.334 mmol) in dry THF (3 mL) was added at −78 °C a solution of *n*-butyllithium (2.5 M in THF, 267 µL, 0.668 mmol), and the mixture was stirred for 3 h. A solution of **4** (28 mg, 0.152 mmol) in dry THF (1.5 mL) was added dropwise at −78 °C and the mixture stirred for a further 2 h at −78 °C. After warming up to r. t. over 18 h, the reaction was quenched with brine (5 mL) and diluted with Et_2O (10 mL). The aqueous layer was separated and extracted with Et_2O (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 with PE/EtOAc (50 : 1) to give in a first fraction **5a** (27 mg, 81.4 µmol, 54 %) and in a second fraction **5b** (7 mg, 21.1 µmol, 14 %) as colourless oils.

*Compound **5a**:* R_f = 0.24 (PE/EtOAc 20 : 1). – $[\alpha]_D^{20}$ = −37.8 (*c* = 1.00, $CHCl_3$). – IR (ATR): ν = 2955.2, 2925.2, 2871.0, 1765.2, 1662.5, 1457.6, 1379.9, 1271.0, 1080.8, 984.3, 744.3 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.66 (d, *J* = 6.8 Hz, 3 H, 9-Me), 0.79 (d, *J* = 6.8 Hz, 3 H, 7-Me), 0.88 (t, *J* = 7.1 Hz, 3 H, 12-H), 0.91 (d, *J* = 6.8 Hz, 3 H, 5-Me), 0.93 – 1.06 (m, 2 H, 6-H), 1.12 – 1.45 (m, 6 H, 8-H, 10-H, 11-H), 1.50 – 1.70 (m, 2 H, 7-H, 9-H), 1.92 (d, *J* = 1.9 Hz, 3 H, 2-H), 2.14 – 2.27 (m, 1 H, 5-H), 4.17 – 4.25 (m, 1 H, 4-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2 (Me-2), 12.0 (Me-5), 14.4 (C-12), 20.0 (C-11), 20.2 (Me-9), 20.3 (Me-7), 27.2 (C-7), 29.6 (C-9), 31.7 (C-5), 39.0 (C-10), 40.7 (C-8), 45.2 (C-6), 85.2 (C-4), 129.4 (C-2), 143.9 (C-3), 171.5 (C-1). – HRMS (ESI): *m/z* = 331.1263 and 333.1257 (calcd. 331.1274 and 333.1254 for $C_{16}H_{28}BrO_2$, $[M+H]^+$). – MS (EI): *m/z* (%) = 330.1 (10), 251.2 (25), 205.0 (15), 181.1 (10), 167.1 (15), 155.2 (75), 113.1 (15), 101.1 (45), 85.1 (90), 71.1 (100), 57.1 (90), 43.1 (75).

*Compound **5b**:* R_f = 0.22 (PE/EtOAc 20 : 1). – $[\alpha]_D^{20}$ = +25.3 (*c* = 0.60, $CHCl_3$). – IR (ATR): ν = 2955.6, 2925.0, 2871.3, 1764.5, 1662.1, 1458.1, 1379.4, 1272.2, 1084.2, 990.0, 743.6 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.5 Hz, 3 H, 9-Me), 0.85 (d, *J* = 6.5 Hz, 3 H, 7-Me), 0.87 (t, *J* = 7.0 Hz, 3 H, 12-H), 0.91 – 1.01 (m, 3 H, 6-H, 8-H_a), 1.13 (d, *J* = 6.9 Hz, 3 H, 5-Me), 1.15 – 1.35 (m, 5 H, 10-H, 11-H, 8-H_b), 1.44 – 1.54 (m, 2 H, 7-H, 9-H), 1.91 (d, *J* = 1.9 Hz, 3 H, 2-H), 2.16 – 2.28 (m, 1 H, 5-H), 4.85 (t, *J* = 2.0 Hz, 1 H, 4-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.1 (Me-2), 14.4 (C-12), 17.1 (Me-5), 19.8 (C-11), 20.7 (Me-9), 21.2 (Me-7), 27.6 (C-7), 29.8 (C-9), 32.3 (C-5), 36.2 (C-10), 38.4 (C-8), 44.3 (C-6), 87.7 (C-4), 129.8 (C-2), 143.2 (C-3), 171.3 (C-1). – HRMS (ESI): *m/z* = 331.1268 and 333.1265 (calcd. 331.1274 and 333.1254 for $C_{16}H_{28}BrO_2$, $[M+H]^+$). – MS (EI): *m/z* (%) = 330.1 (2), 251.2 (10), 192.2 (30), 189.0 (90), 167.1 (100), 155.2 (10), 125.1 (12), 85.1 (15), 71.1 (12), 57.1 (12), 43.0 (55).

*(5R)-3,4-Dimethyl-5-[(1R,3R,5R)-1,3,5-trimethyloctyl]-furan-2(5H)-one [(+)-capensifuranone (+)-**2**]*

To a solution of **5b** (17 mg, 51.3 µmol) and $Pd(PPh_3)_4$ (6 mg, 5.1 µmol) in dry THF (1.5 mL) was added under argon at 0 °C a solution of Me_2Zn (2.0 M in toluene, 128 µL, 0.256 mmol), and the reaction mixture was stirred at r. t. for 18 h. The mixture was diluted with Et_2O (4 mL) and quenched with water (1.5 mL) and 1 M HCl (2 mL). The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 with PE/EtOAc (10 : 1) afforded (+)-**2** as a colourless oil (12 mg, 45.0 µmol, 88 %). – R_f = 0.25. – $[\alpha]_D^{20}$ = +14.8 (*c* = 0.40, $CHCl_3$). – IR (ATR): ν = 2955.9, 2922.8, 2871.7, 1748.6, 1458.1, 1380.0, 1338.4, 1285.1, 1092.2, 988.3, 750.6 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, 3 H, 9-Me), 0.84 (d, *J* = 6.8 Hz, 3 H, 7-Me), 0.87 (t, *J* = 7.0 Hz, 3 H, 12-H), 0.90 – 1.00 (m, 3 H, 6-H, 8-H_a), 1.09 (d, *J* = 6.9 Hz, 3 H, 5-Me), 1.12 – 1.38 (m, 5 H, 10-H, 11-H, 8-H_b), 1.42 – 1.52 (m, 2 H, 7-H, 9-H), 1.81 – 1.83 (m, 3 H, 3-H), 1.92 – 1.94 (m, 3 H, 2-H), 1.99 – 2.07 (m, 1 H, 5-H), 4.67 – 4.69 (m, 1 H, 4-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.45 (Me-3), 12.4 (Me-2), 14.4 (C-12), 17.5 (Me-5), 19.8 (C-11), 20.7 (Me-7), 21.2 (Me-9), 27.5 (C-7), 29.7 (C-9), 32.0 (C-5), 36.5 (C-10), 38.3 (C-8), 44.4 (C-6), 87.8 (C-4), 124.5 (C-2), 158.1 (C-3), 174.9 (C-1). – HRMS (EI): *m/z* = 266.2248 (calcd. 266.2246 for

$C_{17}H_{31}O_2$, $[M]^+$). – MS (EI): *m/z* (%) = 266.2 (30), 252.2 (3), 155.2 (10), 139.1 (15), 112.0 (100), 85.1 (25), 71.1 (30), 57.1 (30), 43.0 (20).

*(5S)-3,4-Dimethyl-5-[(1R,3R,5R)-1,3,5-trimethyloctyl]-furan-2(5H)-one [(–)-5-epi-capensifuranone] (**6**)*

To a solution of **5a** (44 mg, 0.133 mmol) and $Pd(PPh_3)_4$ (15 mg, 13.3 μmol) in dry THF (2 mL) was added under argon at 0 °C a solution of Me_2Zn (2.0 M in toluene, 332 μL, 0.664 mmol), and the reaction mixture was stirred at r. t. for 18 h. The mixture was diluted with Et_2O (5 mL) and quenched with water (2 mL) and 1 M HCl (3 mL). The aqueous layer was separated and extracted with Et_2O (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 with PE/EtOAc (10 : 1) afforded **6** as a colourless oil (30 mg, 0.113 mmol, 85 %). – R_f = 0.26. – $[\alpha]_D^{20}$ = −29.6 (*c* = 0.50, $CHCl_3$). – IR (ATR): ν = 2956.1, 2923.5, 2871.7, 1749.0, 1457.8, 1380.4, 1302.4, 1087.6, 988.4, 752.5 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.61 (d, *J* = 6.8 Hz, 3 H, 9-Me), 0.85 (d, *J* = 6.8 Hz, 3 H, 7-Me), 0.87 (t, *J* = 7.1 Hz, 3 H, 12-H), 0.89 (d, *J* = 6.8 Hz, 3 H, 5-Me), 0.91 – 1.05 (m, 2 H, 6-H), 1.12 – 1.40 (m, 5 H, 8-H, 10-H, 11-H_a), 1.50 – 1.62 (m, 3 H, 7-H, 9-H, 11-H_b), 1.81 – 184 (m, 3 H, 2-H), 1.91 – 1.94 (m, 3 H, 3-H), 1.96 – 2.04 (m, 1 H, 5-H), 4.74 (s, 1 H, 4-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.4 (Me-3), 12.0 (Me-2), 12.3 (Me-5), 14.4 (C-12), 20.0 (C-11), 20.3 (Me-7), 20.4 (Me-9), 27.2 (C-7), 29.6 (C-9), 31.4 (C-5), 38.9 (C-10), 41.2 (C-8), 45.3 (C-6), 85.0 (C-4), 124.0 (C-2), 158.6 (C-3), 175.1 (C-1). – HRMS (ESI): *m/z* = 267.2319 (calcd. 267.2326 for $C_{17}H_{31}O_2$, $[M]^+$). – MS (EI): *m/z* (%) = 266.2 (15), 251.2 (3), 155.2 (15), 139.0 (20), 112.0 (100), 85.1 (25), 71.1 (25), 57.1 (25), 43.0 (10).

*3,4-Dimethyl-2-[(3R,5R)-1,3,5-trimethyloctyl]furan (**7**)*

To a solution of **6** (27 mg, 0.101 mmol) in dry Et_2O (2 mL) was added at 0 °C a solution of $LiAlH_4$ (1.0 M in Et_2O, 91 μL, 91.2 μmol). The reaction mixture was stirred at 0 °C for 10 min and then at r. t. for 18 h. After addition of Et_2O (7 mL), the reaction was quenched with water (1 mL) and 1 M NaOH (3 mL). The aqueous layer was separated and extracted with Et_2O (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on SiO_2 with PE/EtOAc (30 : 1) gave a diastereomeric mixture (d. r. 33 : 67) of **7** as a colourless oil (22 mg, 87.8 μmol, 87 %). – R_f = 0.88. – IR (ATR): ν = 2958.6, 2925.4, 2871.1, 2162.1, 2010.7, 1456.2, 1377.5, 1259.6, 1091.8, 1014.8, 798.8 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.81* (d, *J* = 6.4 Hz, 3 H, 10-Me), 0.82 (d, *J* = 6.5 Hz, 3 H, 10-Me), 0.84 (d, *J* = 6.6 Hz, 3 H, 8-Me), 0.85* (t, *J* = 7.2 Hz, 3 H, 13-H), 0.87 (t, *J* = 7.2 Hz, 3 H, 13-H), 0.92 – 1.07 (m, 2 H, 7-H), 1.08 – 1.15 (m, 2 H, 9-H), 1.16* (d, *J* = 6.7 Hz, 3 H, 6-Me), 1.18 (d, *J* = 6.7 Hz, 3 H, 6-Me), 1.19 – 1.36 (m, 4 H, 11-H, 12-H), 1.37 – 1.57 (m, 1 H, 10-H), 1.74 – 1.81 (m, 1 H, 8-H), 1.87 – 1.88 (m, 3 H, 4-Me), 1.91 – 1.92 (m, 3 H, 3-Me), 2.81 – 2.89 (m, 1 H, 6-H), 7.02 – 7.04 (m, 1 H, 2-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.8 (Me-3), 7.9* (Me-3), 8.3* (Me-4), 8.4 (Me-4), 14.4 (C-13), 19.4* (Me-6), 19.8* (C-12), 19.9 (C-12), 20.3* (Me-8), 20.4 (Me-8), 20.5* (Me-10), 20.6 (Me-10), 27.9 (C-8), 28.0* (C-8), 29.1* (C-6), 29.2 (C-6), 29.6 (C-10), 29.7* (C-10), 38.9* (C-11), 39.5 (C-11), 42.7 (C-7), 43.2* (C-7), 45.2* (C-9), 45.5 (C-9), 113.1* (C-4), 113.7 (C-4), 120.6 (C-3), 120.8 (C-3), 136.0* (C-2), 136.1 (C-2), 154.3 (C-5), 155.1* (C-5). – HRMS (ESI): *m/z* = 251.2370 (calcd. 251.2377 for $C_{17}H_{31}O$, $[M+H]^+$). – MS (EI): *m/z* (%) = 250.2 (15), 235.2 (3), 205.1 (2), 137.1 (15), 123.1 (100), 109.1 (5), 97.1 (3), 79.0 (3), 67.1 (3), 55.1 (3), 41.0 (4).

*(2E,4S,5R,7R,9R)-3-Bromo-2,5,7,9-tetramethyldodec-2-ene-1,4-diol (**9**)*

To a solution of **5a** (9 mg, 27.1 μmol) in dry Et_2O (1.5 mL) was added at 0 °C a solution of $LiAlH_4$ (1.0 M in Et_2O, 22 μL, 21.7 μmol). The reaction mixture was stirred at 0 °C for 10 min and then at r. t. for 18 h. After addition of Et_2O (5 mL), the reaction was quenched with water (1 mL) and 1 M NaOH (1 mL). The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on SiO_2 with PE/EtOAc (2 : 1) gave **9** as a colourless oil (8 mg, 23.8 μmol, 88 %). – R_f = 0.26. – $[\alpha]_D^{20}$ = +40.4 (*c* = 0.70, $CHCl_3$). – IR (ATR): ν = 3330.2, 2954.8, 2922.5, 2870.6, 1457.3, 1376.7, 1215.7, 1121.5, 997.0, 757.2 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.71 – 0.81 (m, 2 H, 10-H), 0.84 (d, *J* = 6.7 Hz, 3 H, 9-Me), 0.85 (d, *J* = 6.7 Hz, 3 H, 7-Me), 0.88 (t, *J* = 7.1 Hz, 3 H, 12-H), 0.92 – 1.02 (m, 1 H, 7-H), 1.17 (d, *J* = 6.4 Hz, 1 H, 5-Me), 1.18 – 1.40 (m, 4 H, 8-H, 10-H), 1.42 – 1.50 (m, 2 H, 6-H), 1.52 – 1.60 (m, 1 H, 5-H), 2.04 (s, 3 H, 2-Me), 2.20 (bs, 2 H, 2 × OH), 4.06 – 4.16 (m, 2 H, 1-H), 4.35 (d, *J* = 12.0 Hz, 1 H, 4-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 (C-12), 16.1 (Me-2), 19.8 (C-11), 20.7 (Me-5), 21.5 (Me-7), 22.1 (Me-9), 27.6 (C-7), 29.8 (C-9), 36.1 (C-5), 38.3 (C-10), 41.2 (C-6), 44.0 (C-8), 63.0 (C-1), 75.9 (C-4), 131.6 (C-3), 136.9 (C-2). – HRMS (ESI): *m/z* = 357.1400 and 359.1381 (calcd. 357.1405 and 359.1385 for $C_{16}H_{31}BrNaO_2$, $[M+Na]^+$). – MS (EI): *m/z* (%) = 334.1 (2), 316.1 (50), 303.1 (47), 179.0 (100), 163.0 (30), 155.2 (10), 133.0 (15), 111.1 (5), 85.1 (30), 71.1 (35), 57.1 (35), 43.1 (40).

*(1S,2E)-2-Bromo-3-methyl-4-[(4-nitrobenzoyl)oxy]-1-[(1R,3R,5R)-1,3,5-trimethyloctyl]but-2-enyl 4-nitrobenzoate (**10**)*

To a solution of diol **9** (9 mg, 26.8 μmol) in dry CH_2Cl_2 (2 mL) were added at r. t. DMAP (0.7 mg, 5.4 μmol), Et_3N

(8 μL, 53.6 μmol) and *p*-nitrobenzoyl chloride (12 mg, 61.6 μmol). The reaction mixture was stirred for 1 h, diluted with CH_2Cl_2 (5 mL) and quenched with 1 M HCl (2 mL). The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on SiO_2 with PE/EtOAc (10 : 1) gave **10** as a crystalline solid (13 mg, 20.5 μmol, 76 %). – R_f = 0.30. – M. p. 93 – 94 °C. – $[\alpha]_D^{20}$ = +102.1 (*c* = 0.70, $CHCl_3$). – IR (ATR): ν = 3112.4, 3080.9, 2955.7, 2924.6, 2870.6, 2188.1, 1975.2, 1722.3, 1526.5, 1346.1, 1262.3, 1097.1, 945.7, 753.8, 717.1 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.5 Hz, 3 H, 9-Me), 0.86 (d, *J* = 6.4 Hz, 3 H, 7-Me), 0.88 (t, *J* = 7.0 Hz, 3 H, 12-H), 0.87 – 0.91 (m, 1 H, 8-H_a), 0.92 – 1.00 (m, 1 H, 8-H_b), 1.05 (d, *J* = 6.5 Hz, 3 H, 5-Me), 1.10 – 1.40 (m, 6 H, 7-H, 9-H, 10-H, 11-H), 1.44 – 1.54 (m, 1 H, 6-H_b), 1.56 – 1.68 (m, 1 H, 6-H_a), 2.10 (s, 3 H, 2-Me), 2.30 – 2.40 (m, 1 H, 5-H), 5.06 (d, *J* = 12.2 Hz, 1 H, 1-H_b), 5.36 (d, *J* = 12.2 Hz, 1 H, 1-H_a), 5.56 (d, *J* = 9.5 Hz, 1 H, 4-H), 8.20 – 8.25 (m, 4 H, Ar-H), 8.27 – 8.31 (m, 4 H, Ar-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 (C-12), 16.1 (Me-2), 19.8 (C-11), 20.7 (Me-5), 21.4 (Me-7), 27.4 (C-7), 29.8 (C-9), 33.8 (C-5), 38.2 (C-10), 40.3 (C-6), 43.7 (C-8), 65.1 (C-1), 78.4 (C-4), 123.6, 123.7 (C-3′), 130.8, 130.9 (C-2′), 135.3, 135.7 (C-1′), 150.5, 150.6 (C-4′), 163.9, 164.2 (C=O). – HRMS (ESI): *m/z* = 655.1625 and 657.1610 (calcd. 655.1633 and 657.1613 for $C_{30}H_{37}BrN_2NaO_8$, $[M+Na]^+$). – MS (EI): *m/z* (%) = 553.1 (2), 386.1 (8), 260.0 (13), 219.1 (15), 150.0 (100), 134.0 (5), 104.0 (10), 57.1 (8), 43.0 (10).

X-Ray structure determination of ***10***

Crystal size: 1.0 × 0.2 × 0.15 mm^3, monoclinic crystal system, space group $P2_1$, *a* = 7.9536(17), *b* = 11.386(3), *c* = 17.681(3) Å, β = 92.722(15)°, *V* = 1599.4(6) $Å^3$, *Z* = 2, *T* = 293 K, μ(MoK_α) = 1.334 mm^{-1}, θ range for data collection 2.13 – 25.00°, index ranges (*h*, *k*, *l*) = +9, ±13, ±21, 6079 measured reflections, 5649 independent reflections, R_{int} = 0.0301, GOF (F^2) = 1.049, *R*1/w*R*2 [$I \geq 2\sigma(I)$] = 0.0694/0.1189, *R*1/*wR*2 (all data) = 0.1356/0.1360, *x*(Flack) = −0.014(14), $\Delta\rho_{fin}$ (max/min) = 0.253/−0.234 e $Å^{-3}$. Remarks: Data collection was performed using a Nicolet P3 diffractometer with MoK_α radiation. The structure was solved with Direct Methods and refined against F^2 with SHELXL-97 [20]. All non-hydrogen atoms were refined anisotropically. H atoms were located on difference Fourier maps but refined with fixed individual displacement parameters using a riding model with *d*(C–H) ranging from 0.93 – 0.98 Å [19].

Cytotoxicity assays

MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (Sigma) was used to measure the metabolic activity of cells which are capable of reducing it by dehydrogenases to a violet formazan product. 60 μL aliquots of serial dilutions of the test compounds were added to 120 μL aliquots of a cell suspension (50000/mL) in 96-well microplates. Solvent controls were incubated under identical conditions. After 5 days, 20 μL MTT in phosphate-buffered saline (PBS) were added to a final concentration of 0.5 mg mL^{-1}. After 2 h, the precipitate of formazan crystals was centrifuged, and the supernatant discarded. The precipitate was washed with 100 μL PBS and dissolved in 100 μL of isopropanol containing 0.4 % hydrochloric acid. The microplates were gently shaken for 20 min to ensure a complete dissolution of the formazan and finally measured at 590 nm using an ELISA plate reader. All experiments were carried out in pairs, the percentage of viability at a certain compound concentration was calculated as the mean with respect to the controls set to 100 %. With U-937 the cytotoxicity was measured in a homogeneous assay using WST-1 from Roche instead of MTT. The developing colour was directly measured at 450 nm.

Agar diffusion assays

Agar plates containing 15 mL of medium were inoculated with bacterial or yeast suspensions in liquid broth to give a final O. D. of 0.01 (bacteria) or 0.1 (yeasts). The microorganisms were from the HZI collection and grown on standard medium. In the case of molds, spores were collected from well-grown Petri dishes which were rinsed with 10 mL of sterile *aqua dest*. 1 mL of the spore suspension was added to 100 mL of molten agar medium. 20 μL of test samples in methanol (1 mg mL^{-1}) were applied to 6-mm cellulose discs, which were then placed onto the agar plates. The diameters of resulting growth inhibition zones were determined after 24 h of incubation at 30 °C.

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