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SHORT COMMUNICATION

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Total Synthesis of the Antifungal Natural Product Mollisin

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Mollisin, a bioactive polyketide secondary metabolite of the fungus *Mollisia caesia*, was synthesized in nine linear steps from commercially available 2,6-dimethyl-γ-pyrone. A key transformation in this first total synthesis of mollisin was the *ipso* substitution of an arylstannane, which permitted the otherwise cumbersome introduction of the characteristic dichloroacetyl moiety. The fungal fungicide was obtained in an overall yield of 9 %.

Introduction

Mollisin (**1**) is a fungal secondary metabolite produced by several *Mollisia* species. It was first isolated by Gremmen from *Mollisia caesia* and *Mollisia fallens* in 1956.[1,2] Mollisin has a naphthoquinone core and shows various antifungal activities, for example, against the mold fungus *Heterobasidion annosum*, the poplar pests *Dothichiza populea* and *Pollaccia radiosa*, as well as against the economically relevant *Sclerotinia trifoliorum*, which can affect spruces.[2] The structure of mollisin was elucidated in 1964 by Overeem and van der Kerk,[3,4] who also pursued a first approach towards its total synthesis.[5] Biosynthetically, mollisin is produced through the polyketide pathway and the chlorine atoms are introduced with the aid of chloroperoxidase.[6–10] Despite its astonishingly simple structure (Figure 1), no successful synthesis of **1** has been reported so far.[5,11]

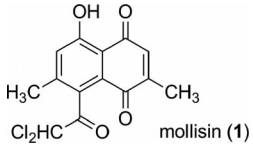
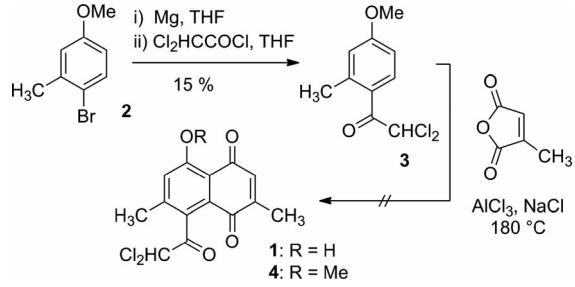


Figure 1. Structure of mollisin.

Results and Discussion

As already described in the literature, the introduction of the CH-acidic, electrophilic, and redox-active dichloroacetyl moiety proved to be particularly cumbersome. All our attempts at direct electrophilic acylation of naphthalene precursors with dichloroacetyl reagents and attempts at late-stage chlorination of acetylated precursors failed.[5,11] However, the Friedel–Crafts-like *ipso* substitution of a stannylated naphthalene building block finally permitted the clean introduction of this characteristic functionality and ultimately the preparation of the natural product (Figure 1).

As a first attempt for the synthesis of **1**, treatment of dichloroacetylated 3-methoxytoluene **3** with citraconic anhydride in a double Friedel–Crafts acylation was envisioned.[12,13] Apart from potential regioselectivity issues, this procedure should allow straightforward assembly of mollisin's naphthoquinone core. Starting from 1-bromo-4-methoxy-2-methylbenzene (**2**),[14] the corresponding Grignard reagent was prepared and treated with dichloroacetyl chloride to give desired ketone **3**, albeit in a disappointing yield of only 15%. The observed concomitant formation of the symmetrical biaryl suggested that the reduction of the activated dichloromethyl group had taken place. Reaction of **3** with citraconic anhydride by using the $AlCl_3$/NaCl system of Laatsch[13] at 180 °C did not produce desired naphthoquinone **4** or its regioisomer or their *O*-demethylated analogues (Scheme 1).



Scheme 1. Attempted synthesis of mollisin by double Friedel–Crafts acylation.

In a second strategy, 3,6-dimethylnaphthalene-1,8-diol (**8**) was chosen as the key intermediate. This oxidation-sensitive compound was synthesized according to the protocol

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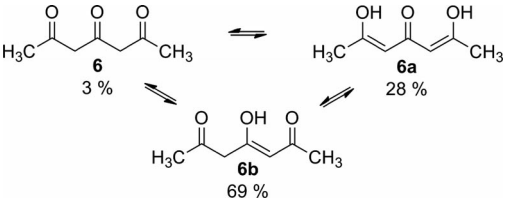
by Overeem and van der Kerk,[5] which involved $Ba(OH)_2$-induced ring opening of 2,6-dimethyl-γ-pyrone (**5**). Hydrolysis of the intermediate Ba^{2+}-chelate complex with hydrochloric acid afforded diacetylacetone (**6**).[15] NMR spectroscopy revealed that this compound exists in three tautomeric forms, **6b** (69%), **6a** (28%), and **6** (3%), in $CDCl_3$ at 25 °C (Scheme 2).



Scheme 2. Tautomeric equilibrium of diacetylacetone (**6**) in $CDCl_3$ at 298 K.

Crystallization from light petroleum ether gave tautomer **6a**, which was analyzed by X-ray crystallography (Figure 2).

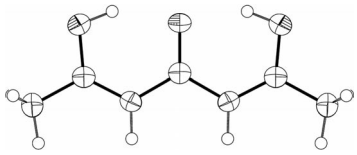


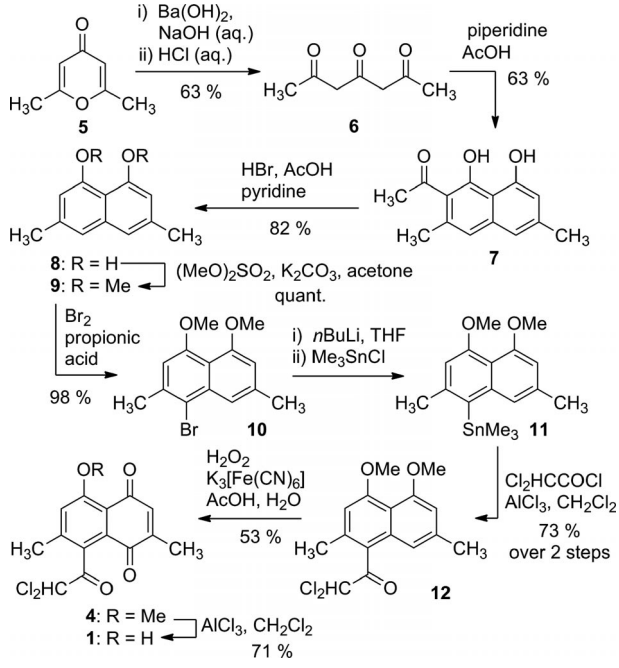
Figure 2. ORTEP plot of diacetylacetone tautomer **6a** at 173 K (ellipsoids drawn at the 50% probability level).

The naphthalene core was established by triple intermolecular Knoevenagel condensation[16] of two molecules of diacetylacetone (**6**). While Overeem[5] used pure piperidine as the catalyst for this reaction, we found a combination of piperidine (0.3 equiv.) and acetic acid (0.03 equiv.) to be more effective. Deacetylation of dimerization product **7** by a retro-Friedel–Crafts reaction[17,18] with hydrobromic acid and acetic acid in pyridine provided symmetrical key intermediate **8**.

For the subsequent transformations, the judicious choice of the O-protecting group was crucial. Whereas diisopropylsilylene protection was too labile under the conditions required for electrophilic aromatic substitution, *O*-allylation led to Claisen rearrangement,[19] even at ambient temperature. Double benzylation was sluggish, and reactions of **8** with *p*-methoxybenzyl chloride (PMBCl)/Bu_4NI as well as with *tert*-butyldimethylsilyl chloride/4-(dimethylamino)pyridine (TBDMSCl/DMAP) did not go to completion. In contrast, double methylation with dimethyl sulfate according to Overeem provided highly stable dimethyl derivative **9** in quantitative yield.[5]

As already described by Matthes,[11] the introduction of the dichloroacetyl group by Friedel–Crafts acylation with dichloroacetyl chloride and various Lewis acids failed, and, for instance, the action of acetyl chloride/$TiCl_4$ even gave the 4,5-diacetylated product. We also found that late-stage chlorination of monoacetyl derivatives was unsuccessful.[11] Therefore, it was decided to introduce the acyl group through a halogen substituent. After optimization, bromination of the 4-position in **9** with Br_2 in propionic acid proceeded with a yield of 98%. Conversion of the bromide into the corresponding Grignard reagent and subsequent treatment with dichloroacetyl chloride did not produce desired ketone **12**.[20] To activate the 4-position for electrophilic attack, stannane **11** was prepared by halogen–lithium exchange on bromide **10** with *n*BuLi and reaction with chlorotrimethylstannane. A small amount of dehalogenated product **9** was formed concomitantly, even under rigorous exclusion of moisture, and was not separated from the stannane.

Although Stille-type coupling of **11** with acyl chloride[21,22] did not provide **12**, the dichloroacetyl group could be introduced by Friedel–Crafts-like acylation.[23] Substitution at the *ipso* position is favored because of the weak C–Sn bond, which makes the trimethylstannyl cation a good leaving group. Upon screening the reaction conditions, we found that the formation of naphthoquinone **4** was best achieved by oxidation of acyl naphthalene **12** with the $H_2O_2/K_3[Fe(CN)_6]$ system.[24] In contrast, Frémy's salt did not effect the oxidation of **12**. Finally, *O*-demethylation with $AlCl_3$ and chromatographic purification provided mollisin (**1**) as yellow crystals in an overall yield of 9% from commercially available 2,6-dimethyl-γ-pyrone (Scheme 3).



Scheme 3. Total synthesis of mollisin (**1**).

The target molecule proved to be identical to natural mollisin in all respects. Furthermore, the structures of mollisin and intermediates **4** and **12** were proven by X-ray crystallography (Figure 3, see also the Supporting Information).

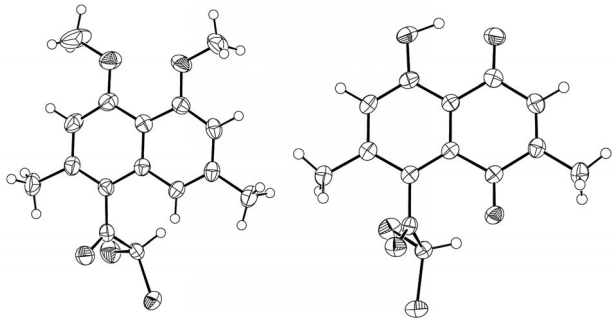


Figure 3. ORTEP plot of the crystal structures of intermediate **12** (left) and mollisin (**1**, right) at 173 K (ellipsoids drawn at the 50% probability level).

Conclusions

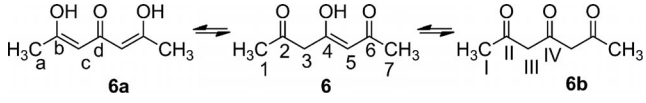
In summary, the first total synthesis of the fungal fungicide mollisin was achieved in nine steps starting from 2,6-dimethyl-γ-pyrone, which was ring opened and subjected to self-condensation to give 3,6-dimethylnaphthalene-1,8-diol. The introduction of the characteristic dichloroacetyl group was accomplished by bromination at the 4-position, halogen–tin exchange, and Friedel–Crafts-like acylation. This reaction sequence circumvented chemoselectivity problems originating from the reactivity of the dichloroacetyl moiety. Final oxidation followed by Lewis-acidic deprotection furnished the naphthoquinone structure of the natural product.

Experimental Section

General Methods: All reactions under anhydrous conditions were performed in dried glassware under an argon atmosphere. Solvents were dried by standard procedures.[25] Reactions at a temperature of 0 °C were performed in a water/ice bath. Elemental analyses were performed in the microanalytical laboratory of the Institute of Organic Chemistry, Johannes Gutenberg University Mainz, with a Vario EL cube (Elementar, Hanau). Flash chromatography was performed on silica gel 60 (0.035–0.070 mm, Acros). Chromatography solvents (petroleum ether, cyclohexane, EtOAc) were distilled prior to use. For analytical TLC, silica gel aluminum sheets (60 F_{254}, Merck) were used. Visualization was accomplished by illuminating with UV light (254 nm) or treatment with Seebach's reagent [$Ce(SO_4)_2{\cdot}4H_2O$ (1.0 g), $H_3PMo_{12}O_{40}$ (2.5 g), H_2O (94 mL), conc. H_2SO_4 (6 mL)]. NMR spectra were recorded with AC 300, AM 400, and AV 400 instruments (Bruker) by using the residual solvent peak as an internal reference ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; [D_6]DMSO: δ_H = 2.50 ppm, δ_C = 39.52 ppm).[26] IR spectra were recorded with a Tensor 27 FTIR spectrometer (Bruker) by using a diamond ATR unit. FD mass spectra were recorded with a MAT 95 spectrometer (Finnigan). ESI mass spectrometry was performed with a LC–MSD Trap ion trap (Bruker/Agilent) by using a C8 core shell column with 2.7 μm particle size (Ascentis Express, 2.1 mm × 30 mm, Agilent). The samples were dissolved in MeCN (c 0.1 mg/mL) and filtered. Melting points were determined with a KSP 1 N (Krüss Optronic) at a heating rate of 1 °C min^{-1}. X-Ray structure determination was performed with a Siemens/Bruker Smart CCD diffractometer. Data collection: APEX2;[27] cell refinement: SAINT;[27] program used to solve the structure: SIR97;[28] program used to refine the structure: SHELXL97;[29] molecular graphics and software used to prepare material for publication: PLATON.[30]

2,2-Dichloro-1-(4-methoxy-2-methylphenyl)ethanone (3): According to a modified synthesis of Tishchenko,[31] a portion (100 μL) of 1-bromo-4-methoxy-2-methylbenzene (**2**; 1.01 g, 5.02 mmol, 1.0 equiv.) in dry THF (2 mL) was added to a suspension of magnesium turnings (122 mg, 5.02 mmol, 1.0 equiv., stored several hours over iodine before use) in dry THF (2 mL). After the suspension turned cloudy, the residual amount (1.9 mL) of the solution of the aryl bromide was added slowly. The reaction mixture was cooled to –78 °C, and a solution of dichloroacetyl chloride (460 μL, 704 mg, 4.77 mmol, 0.95 equiv.) in dry THF (2 mL) was added dropwise. After stirring for 30 min at –78 °C, the reaction mixture was warmed to 0 °C. For hydrolysis, 1 N hydrochloric acid (15 mL) was added, and the mixture was extracted with Et_2O (2 × 15 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (1 × 20 mL) and water (1 × 20 mL) and then dried with $MgSO_4$. The solvent was removed in vacuo. After purification by column chromatography on silica gel (cyclohexane/EtOAc, 20:1), the title compound (180 mg, 770 μmol, 15%) was obtained as a yellow oil. R_f = 0.20 (cyclohexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.6 Hz, 1 H, H-6′), 6.84–6.77 (m, 2 H, H-3′, H-4′), 6.68 (s, 1 H, $CHCl_2$), 3.87 (s, 3 H, OCH_3), 2.58 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 186.4 (CO), 163.2 (C-4′), 145.2 (C-2′), 132.2 (C-6′), 123.9 (C-1′), 118.3 (C-3′), 111.0 (C-5′), 69.0 ($CHCl_2$), 55.6 (OCH_3), 22.7 (CH_3) ppm. MS (FD+): m/z (%) = 232.0 (100.0) [M (2 ^{35}Cl)]$^+$, 234.0 (65.3) [M (^{35}Cl,^{37}Cl)]$^+$. MS (ESI+): m/z (%) = 233.2 (100.0) [M (2 ^{35}Cl) + H]$^+$, 235.1 (68.2) [M (^{35}Cl,^{37}Cl) + H]$^+$. IR (ATR): $\tilde{\nu}$ = 2931, 2843, 1693, 1602, 1565, 1454, 1327, 1251, 1128, 1052, 1041, 824, 755 cm^{-1}.

Diacetylacetone (6):[32]



$Ba(OH)_2{\cdot}8H_2O$ (100.0 g, 317.0 mmol, 2.0 equiv.) was dissolved almost completely in boiling water (1.3 L) under an argon atmosphere. The resulting suspension was added directly to a 50 °C warm solution of 2,6-dimethyl-γ-pyrone (19.67 g, 158.5 mmol, 1.0 equiv.) in aqueous NaOH (8 wt.-%, 40 mL). A yellow precipitate formed immediately. The solution was cooled slowly to 0 °C. The crystals were filtered off, washed with aqueous NaOH (4 wt.-%), and then dissolved under ice cooling in aqueous HCl (15 wt.-%, 200 mL). The solution was stirred for 1 h, extracted with Et_2O (3 × 200 mL), and dried with $MgSO_4$. The solvent was removed by distillation in vacuo. The product was recrystallized from petroleum ether to afford the title compound (14.16 g, 99.61 mmol, 63%) as a colorless, crystalline solid. R_f = 0.50 (cyclohexane/EtOAc, 3:5), m.p. (petroleum ether): 48.0–49.0 °C (ref.[32] 49 °C). Tautomeric equilibrium of **3** in $CDCl_3$: **6b**: 69%, **6a**: 28%, **6**: 3%. ^{1}H NMR, NOESY (400 MHz, $CDCl_3$): δ = 15.20 (s, 1 H, OH-4), 14.17 (s, 2 H, OH-b), 5.55 (s, 1 H, H-5), 5.12 (s, 1 H, H-c), 3.69 (s, 4 H, H-III), 3.40 (s, 2 H, H-3), 2.24 (s, 3 H, H-1), 2.23 (s, 6 H, H-I), 2.06 (s, 3 H, H-7), 1.96 (s, 3 H, H-a) ppm. ^{13}C NMR, ^{13}C-DEPT, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 202.4 (C-II), 202.1 (C-2), 198.4 (C-IV), 193.9 (C-d), 191.2 (C-6), 187.0 (C-4), 178.6 (C-b), 101.2 (C-5), 98.7 (C-c), 57.8 (C-III), 54.0 (C-3), 31.1 (C-1), 24.7 (C-7), 21.9 (C-a) ppm. MS (FD+): m/z (%) = 142.07 (100.0) [M]$^+$. $C_7H_{10}O_3$ (142.15): calcd. C 59.14, H 7.09; found C 58.80, H 7.16.

IR (ATR): $\tilde{\nu}$ = 3726, 2963, 2922, 1647, 1596, 1542, 1389, 1354, 1238, 1183, 1141, 1034, 896, 821, 754 cm^{-1}.

1-(1,8-Dihydroxy-3,6-dimethylnaphthalen-2-yl)ethanone (7): According to a modified synthesis of Overeem,[5] a mixture of AcOH (170 μL, 2.97 μmol, 0.03 equiv.) and piperidine (2.29 mL, 2.51 g, 29.5 mmol, 0.30 equiv.) was added to molten diacetylacetone (**6**; 14.0 g, 98.4 mmol, 1.00 equiv.) under an argon atmosphere, and the mixture was stirred for 2–4 h at 90 °C (TLC control). The reaction mixture was concentrated in vacuo, coevaporated with toluene, and recrystallized from EtOAc. The product was washed with 1 N HCl, half-saturated aqueous $NaHCO_3$, water, and EtOAc, and the title compound (7.14 g, 31.0 mmol, 63%) was obtained as a yellow, crystalline solid. R_f = 0.40 (cyclohexane/EtOAc, 3:1), m.p. (EtOAc): 180.2–181.6 °C [ref.[5] 183–184 °C (AcOH)]. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.99, 6.98 (2 s, 2 H, H-4′, H-5′), 6.60 (s, 1 H, H-7′), 2.53 (s, 3 H, CH_3CO), 2.33 (s, 3 H, CH_3-3′), 2.24 (s, 3 H, CH_3-6′) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 204.2 (CO), 153.8, 153.3 (C-1′, C-8′), 138.0, 136.4 (C-3′, C-6′), 133.3 (C-2′), 122.1 (C-4a′), 118.6, 117.9 (C-4′, C-5′), 110.8 (C-8a′), 110.3 (C-7′), 32.2 (CH$_3$CO), 21.4, 19.9 (CH_3-6′, CH_3-3′) ppm. MS (FD+): *m*/*z* (%) = 460.1 (100.0) [2M]$^+$, 297.0 (51.5) [M + 3Na – 2H]$^+$, 230.0 (23.5) [M]$^+$. $C_{14}H_{14}O_3$ (230.26): calcd. C 73.03, H 6.13; found C 72.93, H 6.18. IR (ATR): $\tilde{\nu}$ = 3726, 3709, 3628, 1637, 1541, 1404, 1374, 985, 874, 846, 669, 650 cm^{-1}.

3,6-Dimethylnaphthalene-1,8-diol (8):[5] Ac_2O (15 mL), aqueous HBr (48 wt.-%, 7.5 mL), and pyridine (0.45 mL) were added to **7** (1.48 g, 6.43 mmol, 1.0 equiv.) under an argon atmosphere. The brown suspension dissolved upon heating to 105 °C. After 1 h, the solution was slowly cooled to room temperature and then cooled by using an ice bath. After the addition of water (150 mL), the resulting black precipitate was absorbed with cotton wool and dissolved in Et_2O (300 mL). The organic phase was washed with aqueous HCl (1 N, 1 × 100 mL) and dried with $MgSO_4$. The solvent was removed by distillation in vacuo. The product was recrystallized from benzene/petroleum ether to obtain the title compound (997 mg, 5.29 mmol, 82%) as a colorless, crystalline solid. R_f = 0.36 (cyclohexane/EtOAc, 2:1), m.p. (benzene/petroleum ether): 125.0–127.2 °C (ref.[5] 127–128 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.65 (s, 2 H, OH-1, OH-8), 6.94 (s, 2 H, H-4, H-5), 6.48 (s, 1 H, H-2, H-7), 2.31 (s, 6 H, CH_3-6, CH_3-3) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 153.8 (C-1, C-8), 136.8 (C-4a), 136.4 (C-3, C-6), 117.5 (C-4, C-5), 111.1 (C-8a), 109.5 (C-2, C-7), 21.4 (CH_3-3, CH_3-6) ppm. MS (FD+): *m*/*z* (%) = 188.0 (100.0) [M]$^+$. $C_{12}H_{12}O_2$ (188.23): calcd. C 76.57, H 6.43; found C 76.34, H 6.65. IR (ATR): $\tilde{\nu}$ = 3734, 3250, 1646, 1626, 1578, 1368, 1340, 1283, 1153, 1081, 1010, 842, 669 cm^{-1}.

1,8-Dimethoxy-3,6-dimethylnaphthalene (9):[5] A suspension of **8** (340 mg, 1.81 mmol, 1.0 equiv.), K_2CO_3 (1.50 g, 10.9 mmol, 6.0 equiv.), and dimethyl sulfate (210 μL, 2.17 mmol, 1.2 equiv.) in dry acetone (5 mL) was heated under reflux for 16 h. After cooling to room temperature, the reaction was stopped by adding a few milliliters of dilute aqueous NH_3, and the mixture was stirred for 15 min. The reaction mixture was neutralized with dilute aqueous HCl and extracted with Et_2O (3 × 30 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was again treated with K_2CO_3 (1.50 g, 10.9 mmol, 6.0 equiv.) and dimethyl sulfate (210 μL, 2.17 mmol, 1.2 equiv.) in dry acetone (5 mL) for 16 h under reflux. After cooling to room temperature, the reaction was stopped by adding a few milliliters of dilute aqueous NH_3, and the mixture was stirred for 15 min. After neutralization with dilute aqueous HCl, the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed in vacuo. The product was recrystallized from ethanol to afford the title compound (391 mg, 1.81 mmol, quant.) as a yellow, crystalline solid. R_f = 0.23 (cyclohexane/EtOAc, 8:1), m.p. (ethanol): 134.0–135.5 °C (ref.[5] 135–137 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (s, 2 H, H-4, H-5), 6.60 (s, 1 H, H-2, H-7), 3.95 (s, 6 H, CH_3-1, CH_3-8), 2.44 (s, 6 H, CH_3-6, CH_3-3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.9 (C-1, C-8), 137.8 (C-4a), 136.3 (C-3, C-6), 119.6 (C-4, C-5), 114.0 (C-8a), 107.6 (C-2, C-7), 56.4 (OCH_3-1, OCH_3-8), 21.9 (CH_3-3, CH_3-6) ppm. MS (FD+): *m*/*z* (%) = 216.1 (100.0) [M]$^+$. IR (ATR): $\tilde{\nu}$ = 2964, 2848, 1627, 1577, 1466, 1382, 1367, 1355, 1272, 1173, 1123, 1102, 822, 737 cm^{-1}.

1-Bromo-4,5-dimethoxy-2,7-dimethylnaphthalene (10): 1,8-Dimethoxy-3,6-dimethylnaphthalene (**9**; 200 mg, 925 μmol, 1.0 equiv.) was dissolved in propionic acid (10 mL) under an argon atmosphere and cooled to 0 °C. Portions (0.2–0.5 mL) of a stock solution of Br_2 (500 μL) in propionic acid (31.4 mL) were added at 0 °C (stirring) under TLC monitoring until the starting material was consumed (ca. 2.5 h). Careful addition was required to prevent dibromination. After addition of ice (20 g) and saturated aqueous $NaHCO_3$ (5 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and water (1 × 20 mL) and then dried with $MgSO_4$. The solvent was removed in vacuo. After purification by column chromatography on silica gel (cyclohexane/EtOAc, 10:1), the title compound (267 mg, 905 μmol, 98%) was obtained as a yellow, amorphous solid. R_f = 0.20 (cyclohexane/EtOAc, 10:1), m.p. 114.0–115.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (s, 1 H, H-8), 6.70 (s, 1 H, H-3), 6.67 (s, 1 H, H-6), 3.96 (s, 3 H, OCH_3-4), 3.94 (s, 3 H, OCH_3-5), 2.57 (s, 3 H, CH_3-2), 2.50 (s, 3 H, CH_3-7) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.2 (C-4), 156.4 (C-5), 137.9 (C-2), 136.8 (C-7), 135.5 (C-8a), 119.3 (C-8), 115.2 (C-4a), 114.9 (C-1), 108.5 (C-3), 108.4 (C-6), 56.7 (OCH_3-4), 56.6 (OCH_3-5), 24.8 (CH_3-2), 22.4 (CH_3-7) ppm. MS (FD+): *m*/*z* (%) = 294.3 (100.0) [M (^{79}Br)]$^+$, 296.3 (94.0) [M (^{81}Br)]$^+$. IR (ATR): $\tilde{\nu}$ = 3004, 2914, 2841, 1623, 1601, 1566, 1380, 1259, 1176, 1102, 823 cm^{-1}. $C_{14}H_{15}BrO_2$ (295.18): calcd. C 56.97, H 5.12; found C 56.83, H 5.01.

(4,5-Dimethoxy-2,7-dimethylnaphthalen-1-yl)trimethylstannane (11): 1-Bromo-4,5-dimethoxy-2,7-dimethylnaphthalene (**10**; 292 mg, 990 μmol, 1.0 equiv.) was dissolved in dry THF (6 mL), cooled to –78 °C, and *n*BuLi (1.6 M in hexane, 0.74 mL, 1.19 mmol, 1.2 equiv.) was added dropwise. After 15 min, Me_3SnCl (1 M in THF, 1.09 mL, 1.09 mmol, 1.1 equiv.) was added, and the reaction solution was warmed to 25 °C within 16 h. Et_2O (7 mL) was added to the mixture, and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and water (1 × 10 mL) and then dried with Na_2SO_4. The solvent was removed in vacuo. The crude product was obtained as a mixture with 1,8-dimethoxy-3,6-dimethylnaphthalene (**9**) (**11**/**9** = 9:1) as a yellow, amorphous solid and used without further purification. The analytical data derives from measurements on the mixture. R_f = 0.36 (cyclohexane/EtOAc, 2:1), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (s, 1 H, H-8′), 6.65 (s, 2 H, H-3′, H-6′), 3.96 (s, 6 H, 2 OCH_3′), 2.56 (s, 3 H, CH_3-2′), 2.54 (s, 3 H, CH_3-7′), 0.46 [s, 9 H, Sn(CH_3)$_3$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = [ppm] = 157.6, 157.5 (C-4′, C-5′), 144.7 (C-2′), 143.2 (C-7′), 138.2 (C-4a′), 135.7 (C-8′), 130.7 (C-1′), 122.3 (C-3′), 110.7 (C-8a′), 108.6 (C-6′), 56.7 (OCH_3-4′), 56.3 (OCH_3-5′), 28.3 (CH_3-2′), 26.2 (CH_3-7′) ppm. MS (FD+): *m*/*z* (%) = 380.4 (100.0) [M (^{120}Sn)]$^+$, 378.4 (68.7) [M (^{118}Sn)]$^+$, 376.4 (40.9) [M (^{116}Sn)]$^+$. IR (ATR): $\tilde{\nu}$ = 2916, 2839, 1587, 1454, 1364, 1347, 1330, 1257, 1124, 1105, 827, 771 cm^{-1}.

2,2-Dichloro-1-(4,5-dimethoxy-2,7-dimethylnaphthalen-1-yl)-ethanone (12): On the basis of a procedure outlined by Neumann,[33] a solution of crude **11**, synthesized from **10** (2.33 g, 7.91 mmol, 1.0 equiv.), in dry CH_2Cl_2 (30 mL) was added to $AlCl_3$ (1.58 g, 11.9 mmol, 1.5 equiv.). The reaction mixture was cooled to –30 °C, and a solution of dichloroacetyl chloride (1.14 mL, 11.9 mmol, 1.5 equiv.) in dry CH_2Cl_2 (30 mL) was added dropwise. The reaction mixture was warmed to 25 °C within 16 h and ice (50 g) was added. The aqueous layer was extracted with CH_2Cl_2 (2× 50 mL), and the combined organic extract was washed with half-saturated aqueous $NaHCO_3$ (2× 40 mL) and water (1× 50 mL) and then dried with Na_2SO_4. The solvent was removed in vacuo. After purification by column chromatography on silica gel (petroleum ether/EtOAc, 20:1), the title compound (2.12 g, 6.50 mmol, 73% over two steps from **7**) was obtained as a yellow, crystalline solid. R_f = 0.35 (cyclohexane/EtOAc, 2:1), m.p. 109.0–111.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (s, 1 H, H-8′), 6.67 (s, 1 H, H-6′), 6.61 (s, 1 H, H-3′), 6.46 (s, 1 H, $CHCl_2$), 3.99 (s, 3 H, OCH_3-4′), 3.96 (s, 3 H, OCH_3-5′), 2.45 (s, 3 H, CH_3-2′), 2.45 (s, 3 H, CH_3-7′) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 193.0 (CO), 159.3 (C-4′), 157.8 (C-5′), 139.0 (C-2′), 137.3 (C-7′), 134.3 (C-8a′), 124.3 (C-1′), 116.0 (C-8′), 114.0 (C-4a′), 108.3 (C-6′), 107.4 (C-3′), 70.7 ($CHCl_2$), 56.4 (OCH_3), 56.3 (OCH_3), 22.3 (CH_3-7′), 20.6 (CH_3-2′) ppm. MS (FD+): *m/z* (%) = 326.3 (100.0) [M (2 ^{35}Cl)]$^+$, 328.3 (65.1) [M (^{35}Cl,^{37}Cl)]$^+$, 330.3 (9.4) [M (2 ^{37}Cl)]$^+$. $C_{16}H_{16}Cl_2O_3$ (327.21): calcd. C 58.73, H 4.93; found C 58.92, H 5.01, IR (ATR): $\tilde{\nu}$ = 3425, 3001, 2933, 2849, 1713, 1625, 1594, 1466, 1390, 1344, 1270, 1201, 1114, 1086, 1042, 829, 801, 738 cm^{-1}.

8-(2,2-Dichloroacetyl)-5-methoxy-2,7-dimethylnaphthalene-1,4-dione (4): On the basis of a procedure outlined by Shinnaka,[24] a solution of **12** (380 mg, 1.17 mmol) and potassium ferricyanide (800 µg, 23.0 µmol, 2 mol-%) in a mixture of AcOH/water (10:1, 5 mL) was heated to 45 °C. H_2O_2 (35 wt.-% in water, 380 µL, 4.43 mmol, 3.8 equiv.) was added to the solution over a period of 1 h. After stirring for 1 h, the reaction was quenched with water (20 mL) and extracted with Et_2O (2× 20 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2× 20 mL) and water (1× 20 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. After recrystallization from MeOH, the title compound (202 mg, 617 µmol, 53%) was obtained as an orange, crystalline solid. R_f = 0.30 (cyclohexane/EtOAc, 1:1), m.p. (MeOH, decomp.): 162.8–164.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (s, 1 H, H-6), 6.73 (s, 1 H, H-3), 6.30 (s, 1 H, $CHCl_2$), 4.01 (s, 3 H, OCH_3), 2.46 (s, 3 H, CH_3-7), 1.96 (s, 3 H, CH_3-2) ppm. ^{13}C NMR, HMBC, HMQC (100.6 MHz, $CDCl_3$): δ = 191.9 (Cl_2HCCO), 187.1 (C-1), 183.3 (C-4), 160.4 (C-5), 144.8 (C-7), 144.6 (C-2), 138.5 (C-3), 133.0 (C-8a), 129.4 (C-8), 120.0 (C-6), 117.7 (C-4a), 71.3 ($CHCl_2$), 56.8 (OCH_3), 20.9 (CH_3-7), 15.8 (CH_3-2) ppm. MS (ESI+): *m/z* (%) = 348.9 (100.0) [M – 2 ^{35}Cl + Na]$^+$, 351.0 (52.8) [M – ^{35}Cl,^{37}Cl + Na]$^+$. $C_{15}H_{12}Cl_2O_4$ (327.16): C 55.07, H 3.70; found C 54.71, H 4.04, IR (ATR): $\tilde{\nu}$ = 1719, 1655, 1587, 1307, 1260, 1218, 1077, 731 cm^{-1}.

8-(2,2-Dichloroacetyl)-5-hydroxy-2,7-dimethylnaphthalene-1,4-dione (mollisin, 1): A mixture of **4** (260 mg, 795 µmol, 1.0 equiv.) and $AlCl_3$ (530 mg, 3.97 mmol, 5.0 equiv.) was suspended in dry CH_2Cl_2 (10 mL). The suspension was stirred for 5 min. A mixture of ice water/NaCl/conc. HCl (1:1, 10 mL) was added at 0 °C, and the reaction mixture was extracted with Et_2O (3× 25 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (1× 20 mL) and water (1× 20 mL) and then dried with $MgSO_4$. The solvent was removed by distillation in vacuo. After purification by column chromatography on silica gel (petroleum ether/EtOAc, 4:1) the title compound (178 mg, 568 µmol, 71%) was obtained as a yellow, crystalline solid. R_f = 0.35 (petroleum ether/EtOAc, 4:1), m.p. (petroleum ether/EtOAc, 5:1, decomp.): 198.3–199.7 °C. ^{1}H NMR, NOESY (400 MHz, $CDCl_3$): δ = 12.08 (s, 1 H, OH), 7.18 (s, 1 H, H-6), 6.84 (q, ^4J = 1.6 Hz, 1 H, H-3), 6.31 (s, 1 H, $CHCl_2$), 2.42 (s, 3 H, CH_3-7), 2.17 (d, ^4J = 1.6 Hz, 3 H, CH_3-2) ppm. ^{13}C NMR, HMBC, HMQC (100.6 MHz, $CDCl_3$): δ = 192.0 ($COCHCl_2$), 189.4 (C-4), 186.2 (C-1), 162.3 (C-5), 148.8 (C-2), 146.5 (C-7), 136.2 (C-3), 130.4 (C-8), 130.2 (C-8a), 126.2 (C-6), 112.9 (C-4a), 71.0 ($CHCl_2$), 20.7 (CH_3-7), 16.6 (CH_3-2) ppm. MS (FD+): *m/z* (%) = 312.4 (100.0) [M]$^+$. $C_{14}H_{10}Cl_2O_4$ (313.14): calcd. C 53.70, H 3.22; found C 53.41, H 3.35. IR (ATR): $\tilde{\nu}$ = 3330, 2925, 1723, 1644, 1613, 1460, 1371, 1287, 1123, 668 cm^{-1}.

CCDC-945345 (for **1**), -945346 (for **4**), -945347 (for **6a**), and -945348 (for **12**) contain the supplementary crystallographic data 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.

Supporting Information (see footnote on the first page of this article): Copies of the 1D and 2D NMR spectra for all new compounds.

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