Supplementary Methods

General Experimental Details

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H2O/ice (0 °C). Reaction temperatures above room temperature were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminum plates precoated with silica gel (0.25 mm, 60-Å pore size, Merck) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution (KMnO4), ceric ammonium molybdate solution (CAM) or p-anisaldehyde solution (Anis), and were developed by heating with a heat gun. Flash-column chromatography on silica gel was performed as described by Still et al., employing silica gel (60 Å, 40–63 μm, Merck KGaA). The yields refer to chromatographically and spectroscopically (1H and 13C NMR) pure material.

Materials

Tetrahydrofuran (THF) and diethyl ether (Et2O) were distilled under N2 atmosphere from sodium and benzophenone prior to use. Dichloromethane (CH2Cl2), triethylamine (Et3N), disopropylamine (DIPA) and Hünig’s base (DIPEA) were distilled under nitrogen atmosphere from CaH2 prior to use. Dimethyl sulfoxide (DMSO), acetonitrile (MeCN), acetone, toluene, chlororform (CHCl3) and methanol (MeOH) were purchased from Acros Organics as ‘extra dry’ reagents and used as received. All other reagents and solvents were purchased from chemical suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, ABCR) and were used as received. Solvents for extraction, crystallization and flash-column chromatography on silica gel were purchased in technical grade and distilled under reduced pressure prior to use. Lithium chloride was dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. The molarity of n-butyllithium and t-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).2

NMR spectroscopy

NMR spectra were measured on a Bruker Avance III HD 400 MHz spectrometer equipped with a CryoProbe™, Bruker AXR300, Varian VXR400 S, Bruker AMX600 or Bruker Avance HD 800. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual proton in the NMR solvent (CHCl3: δ 7.26, C6D6: δ 7.16, CD2Cl2: δ 5.32). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent (CDCl3: δ 77.16, C6D6: δ 128.06, CD2Cl2: δ 54.00). 1H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants J (Hz), integration intensity, assigned proton). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Additionally to 1H and 13C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. Coupling constants J are reported in Hz. All raw fid files were processed and the spectra analyzed using the program MestReNOVA 9.1 from Mestrelab Research S. L.
Mass spectrometry

All mass spectra were measured by the analytic section of the Department of Chemistry, Ludwig-Maximilians-Universität München. Mass spectra were recorded on the following spectrometers (ionisation mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from Thermo Finnigan GmbH. Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section.

IR spectroscopy

IR spectra were recorded on a PerkinElmer Spectrum BX II FT-IR system. If required, substances were dissolved in CH₂Cl₂ prior to direct application on the ATR unit. Data are represented as follows: frequency of absorption (cm⁻¹).

Optical rotation

Optical rotation values were recorded on a PerkinElmer 241 or Anton Paar MCP 200 polarimeter. The specific rotation is calculated according to Supplementary Equation 1.

\[
\left[\alpha\right]_\lambda^\phi = \frac{[\alpha] \cdot 100}{c \cdot d} \tag{1}
\]

Thereby, the wave length \(\lambda\) is reported in nm and the measuring temperature \(\phi\) in °C. \(\alpha\) represents the recorded optical rotation at the apparatus, \(c\) the concentration of the analyte in 10 mg/mL and \(d\) the length of the cuvette in dm. Thus, the specific rotation is given in \(10^{-1}\)-deg·cm²·g⁻¹. Usage of the sodium D line (\(\lambda = 589\) nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

Melting Points

Melting points were determined on a B-450 melting point apparatus from BÜCHI Labortechnik AG. The values are uncorrected.

X-Ray Crystallographic Data

The data collections were performed either on an Oxford Diffraction Xcalibur diffractometer, on a Bruker D8Quest diffractometer or on a Bruker D8Venture at 100 K or at 173 K using MoKα-radiation (\(\lambda = 0.71073\) Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[S8] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97² and refined by least-squares methods against F2 with SHELXL-97.⁴ All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

Antibacterial assays

Overnight cultures of the bacteria were grown aerobically at 37 °C in Müller Hinton broth with added 1% glucose and pH 7.2 for Gram-negative strains, or with Trypticase soy yeast extract medium (TSY – 30 g/l trypticase soy broth, 3 g/L yeast extract, pH 7.2) for Gram-positive strains. The cultures were adjusted to an OD600nm of 0.001, which resulted in a final start OD600nm of 0.0005 in the test. 25 \(\mu\)L of test culture was added to 25 \(\mu\)L of a serial dilution of the test compounds in the appropriate medium for the different strains in accordance with standardized procedures in 384 well plates (DIN 58940-7: Medical microbiology – susceptibility testing of microbial pathogens to antimicrobial agents – determination of the minimum bactericidal concentration (MBC) with the method of micro boullion dilution; text in German and English). Test compounds from stock solutions
in DMSO were used at final concentrations of 100, 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.2 µM. As positive control compounds, Linezolid (both MRSA strains), Ciprofloxacin (*E. faecium, E. coli, A. baumannii, K. pneumonia*), Amikacin (P. aeruginosa) and Amphotericin (C. albicans) were applied. The highest DMSO concentration in the assay was 1%, which had no apparent effect on the growth of the bacteria. After an incubation time of 18 h at 37 °C under moist conditions, the optical density at 600 nm was measured with a Fusion Universal Microplate Analyser (Perkin–Elmer, Waltham, USA). The lowest concentration that completely suppressed growth defined the MIC values. The following bacterial strains were used. Gram-negative: *Acinetobacter baumannii* (DSM 30007), *Escherichia coli* (DSM 1116), *Klebsiella pneumoniae* (DSM 11678) and *Pseudomonas aeruginosa* PA7 (DSM 24068). Gram-positive: *Enterococcus faecium* (DSM 20477), *Staphylococcus aureus* MRSA (clinical isolate, RKI 11-02670) and *Staphylococcus aureus* MRSA (DSM 11822). The EC$_{50}$ and MIC values were determined by curve fitting with Sigma Plot.

**Antiproliferative assays**

The effect of compounds on cell viability was probed with a WST-1 test using the procedure of Ishiyama et al.\textsuperscript{5} as modified by Sasse et al.\textsuperscript{6} The following cell lines were used: mouse fibroblast cell line L929 (DSM ACC 2), human cervix carcinoma cell line KB-3-1 (DSM ACC 158) and human breast cancer cell line MCF-7 (DSM ACC 115). In addition, the conditional immortalized human fibroblast cell line FS4-LTM (InScreenex, Braunschweig, Germany) was used without doxycyclin to induce primary cell-like behavior (Pub. No.: US2011/0189142 A2). The subconfluent cells were briefly washed with Earle's Balanced Salt Solution (Gibco) without Ca and Mg, trypsinized and re-suspended in Dulbecco's modified eagle's medium that contained 5% fetal bovine serum (FBS; L929, KB-31, FS4-LTM) or Roswell Park Memorial Institute medium that contained 5% FBS, 0.5% Minimum Essential Medium Non-Essential Amino Acids, Gibco (MEM NEAA), 0.5% GlutaMAX (Gibco) and insulin at 5 µg/mL (MCF-7). 25 µL of serial dilutions of the test compounds (100–0.2 µM), that were made with a pipetting robot (epMotion, Eppendorf, Hamburg, Germany), were added to 25 µL aliquots of a cell suspension (1500 cells for KB3-1 and L929, 3000 cells for MCF-7 and 7500 cells for FS4-LTM) in 384 well microtiter plates. Blank and solvent controls were incubated under identical conditions. After an incubation period of 5 days (for L929, KB-3-1, and MCF-7) or 24h (for FS4-LTM), 3 µL WST-1 (ready to use solution by Roche) was added. The incubation time of the plates at 37 °C varied between the cell lines from 20 min for KB-3-1, L929 for 30 min, FS4-LTM for 1 h and 2 h for MCF-7 before measuring absorbance at 450 nm (reference 600 nm) with an Infinite 200 PRO plate reader (Tecan, Männedorf, Switzerland). As positive control compounds, Auranofin and Staurosporin were applied. The absorbance of the solvent control was set to 100%. The EC$_{50}$ values were determined with Sigma Plot.
Synthesis of (+)-Stachyflin (1), 38 and 39

Diene 10

![Chemical Structure]

To a suspension of dimedone (S01) (24.8 g, 177 mmol, 1 equiv) in dichloromethane (450 mL) was added hexamethyldisilazane (HMDS) (51.8 mL, 244 mmol, 1.38 equiv) and the resulting solution was stirred at 23 °C. After 23 h, the solution was concentrated and the residue was added dropwise to a solution of lithium diisopropylamine (195 mmol, 1.10 equiv), itself freshly prepared by the addition of n-butyllithium (2.4 M in hexanes, 81.1 mL, 195 mmol, 1.10 equiv) to a solution of diisopropylamine (27.5 mL, 195 mmol, 1.10 equiv) in tetrahydrofuran (350 mL) at −78 °C, over a period of 30 min. After 60 min, chlorotrimethylsilane (21.1 g, 195 mmol, 1.10 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 90 min, the reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in pentane, the so-obtained mixture was filtered through a plug of Celite® and the solvent was removed under reduced pressure. This process was repeated twice, yielding 10 (50.3 g, 99%) as a pale yellow oil. The obtained characterization data were in full agreement with the values previously reported.7
Dimethyl-3,5-dihydroxyphthalate 11

A mixture of dimethyl acetylenedicarboxylate (S02) (12.6 g, 88.4 mmol, 1 equiv) and diene 10 (50.3 g, 177 mmol, 2.00 equiv) was heated to 120 °C. After 17 h, the reaction mixture was diluted with a mixture of ethyl acetate-hexanes (2:3, 400 mL) and the resulting suspension was filtered through a plug of Celite®. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes). The obtained yellowish solid was dissolved in a minimum amount of hot dichloromethane and precipitated by the addition of hexanes to give 11 (17.2 g, 86%) as a white powder.

**TLC** (40% ethyl acetate in hexanes): \( R_f = 0.32 \) (KMnO₄, UV).

**¹H NMR** (CDCl₃, 300 MHz): \( \delta = 10.96 \) (s, 1H), 6.45 (d, \( J = 2.5 \) Hz, 1H), 6.40 (d, \( J = 2.5 \) Hz, 1H), 5.73 (s, 1H), 3.87 (s, 6H).

**¹³C NMR** (CDCl₃, 75 MHz): \( \delta = 169.9, 169.5, 164.1, 161.3, 137.9, 108.4, 105.2, 103.5, 53.2, 53.1 \).

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 3343, 3202, 2952, 1671, 1615, 1588, 1437, 1238, 1194, 1154, 1024, 849, 729 \).

**HRMS** (ESI) calc. for C₁₀H₉O₆⁻ [M–H]⁻: 225.0405; found: 225.0406.

**Melting point**: 125–126 °C.
Dimethyl 3-hydroxy-5-methoxypthalate 12

To a solution of phenol 11 (10.0 g, 44.2 mmol, 1 equiv) in acetone (200 mL) were added potassium carbonate (9.17 g, 66.3 mmol, 1.50 equiv) and dimethyl sulfate (5.58 g, 44.2 mmol, 1.00 equiv). After 3.5 h, the reaction mixture was filtered through a plug of Celite® and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield phthalate 12 (7.79 g, 73%) as a colorless solid

TLC (30% ethyl acetate in hexanes): $R_f = 0.44$ (KMnO₄, UV).

$^{1}H$ NMR (CDCl₃, 300 MHz): $\delta = 11.00$ (s, 1H), 6.48 (d, $J = 2.5$ Hz, 1H), 6.45 (d, $J = 2.5$ Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H).

$^{13}C$ NMR (CDCl₃, 75 MHz): $\delta = 169.7, 169.6, 164.8, 164.2, 137.5, 108.1, 103.0, 102.6, 56.1, 53.0, 52.9$.

IR (Diamond-ATR, neat): $\tilde{\nu}_{\text{max}} = 2954, 1733, 1615, 1501, 1433, 1264, 1197, 1149, 1022, 759$.

HRMS (ESI) calc. for C₁₁H₁₁O₆$^-$ [M–H]$^-$: 239.0561; found: 239.0563.

Melting point: 68–69 °C.
Imide 13

To a solution of 3,4-dimethoxybenzylamine (3,4-DMBNH$_2$) (15.8 mL, 104 mmol, 5.00 equiv) in benzene (13 mL) was added trimethylaluminium (2.0 M in toluene, 51.0 mL, 102 mmol, 4.90 equiv) at 0 °C and the solution was allowed to warm to 23 °C. After 40 min, a solution of diester 12 (5.00 g, 20.8 mmol, 1 equiv) in benzene (24 mL) was added to the yellow suspension. The transfer was quantified with benzene (2 × 3 mL). The reaction mixture was heated to 70 °C. After 3 h, the mixture was allowed to cool to 23 °C and ethyl acetate (400 mL) was added. The organic layer was washed with aqueous hydrochloric acid solution (2 M, 2 × 200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic extract was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give the phthalamide (10.6 g) as a yellow solid.

The crude phthalamide (10.6 g) was placed in a bulb-to-bulb distillation apparatus. (Set up: flask 1 was filled with starting material, flask 2 was in heating device, flask 3 as trap at 23 °C, flask 4 was cooled to −78 °C, Supplementary Figure 1). The oven was carefully heated to 210 °C under high vacuum (1 mbar) for 60 min. The dark orange residue remaining in flask 1 was recrystallized from ethanol (40 mL) to yield 13 (5.05 g, 58% over 2 steps) as pale yellow crystalline solid.

**TLC** (dichloromethane): $R_f = 0.25$ (UV, KMnO$_4$).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.51$ (br s, 1H), 7.00–6.96 (m, 2H), 6.93 (d, $J = 2.0$ Hz, 1H), 6.80 (m, 1H), 6.56 (d, $J = 2.0$ Hz, 1H), 4.70 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta = 169.8, 167.7, 167.0, 156.3, 149.1, 148.8, 134.0, 129.0, 121.3, 112.0, 111.1, 107.7, 105.9, 104.2, 56.4, 56.0, 56.0, 41.4$.

IR (Diamond-ATR, neat): $\tilde{\nu}_{\text{max}} = 3440, 2939, 1693, 1624, 1516, 1400, 1260, 1156, 1026, 758$.

HRMS (EI) calc. for C$_{18}$H$_{17}$NO$_6$ 343.1050 [M]$^+$; found: 343.1046.

**Melting point:** 155–157 °C.
Supplementary Figure 1 Bulb-to-bulb setup: flask 1 was filled with starting material, flask 2 was in heating device, flask 3 as trap at 23 °C, flask 4 was cooled to −78 °C.
To a suspension of phenol 13 (5.05 g, 14.7 mmol, 1 equiv) and iodine (2.24 g, 8.83 mmol, 0.60 equiv) in ethanol (60 mL) was added a solution of periodic acid (671 mg, 2.94 mmol, 0.20 equiv) in water (3.5 mL) and the reaction mixture was heated to 40 °C. After 30 h, dichloromethane (200 mL) was added, the organic layer was washed with saturated aqueous sodium thiosulfate solution (2×150 mL) and saturated sodium chloride solution (150 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% methanol in dichloromethane) to yield 14 (4.70 g, 68%) as an off-white solid.

**TLC** (4% methanol in dichloromethane): \( R_f = 0.70 \) (UV, KMnO₄).

**¹H NMR** (CDCl₃, 400 MHz): \( \delta = 8.11 \) (br s, 1H), 7.00–6.94 (m, 2H), 6.89 (s, 1H), 6.80 (d, \( J = 8.0 \) Hz, 1H), 4.72 (s, 2H), 4.01 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H).

**¹³C NMR** (CDCl₃, 101 MHz): \( \delta = 169.5, 167.5, 165.3, 155.5, 149.2, 149.0, 133.9, 128.8, 121.4, 112.1, 111.3, 108.1, 99.3, 82.0, 57.6, 56.1, 56.1, 41.7.\)

**IR** (Diamond-ATR, neat): \( \tilde{v}_{\text{max}} = 3413, 2940, 1693, 1620, 1393, 1259, 1158, 1061, 1025, 729.\)

**HRMS (EI)** calc. for C₁₈H₁₆I₂7NO₄ [M⁺]: 469.0017; found: 469.0009.

**Melting point**: 214–216 °C.
Isoindolinone S03

To a solution of iodide 14 (810 mg, 1.73 mmol, 1 equiv) in tetrahydrofuran (9 mL) was added a solution of borane tetrahydrofuran complex (1.00 M in tetrahydrofuran, 2.16 mL, 2.16 mmol, 3.00 equiv) at 23 °C. After the gas evolution ceased, sodium borohydride (3.27 mg, 0.09 mmol, 0.05 equiv) was added at 23 °C and the mixture was heated to 70 °C in a pressure flask. After 17 h, the reaction mixture was cooled to 23 °C, diluted with aqueous hydrochloric acid solution (1 M, 75 mL) and extracted with ethyl acetate (4 × 75 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% methanol in dichloromethane) to give S03 (573 mg, 73%) as an off-white powder.

TLC (2% methanol in dichloromethane): \( R_f = 0.23 \) (UV, KMnO₄).

\(^1\)H NMR (CDCl₃, 599 MHz): \( \delta = 6.92 \) (s, 1H), 6.85–6.77 (m, 3H), 6.22 (s, 1H), 4.69 (s, 2H), 4.21 (s, 2H), 3.94 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H).

\(^{13}\)C NMR (CDCl₃, 151 MHz): \( \delta = 168.0, 159.4, 151.0, 149.5, 148.8, 135.3, 129.5, 120.7, 119.7, 111.5, 111.2, 97.9, 82.6, 57.2, 56.1, 56.1, 47.4, 46.6.\)

IR (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 2937, 1649, 1514, 1466, 1350, 1259, 1138, 1082, 1026, 729. \)

HRMS (EI) calc. for C₁₈H₁₈INO₅ [M]⁺: 455.0224; found: 455.0222.

Melting point: 198–200 °C.
Methoxymethyl ether 15

To a solution of amide S03 (550 mg, 1.21 mmol, 1 equiv) in N,N-dimethylformamide (24 mL) was added sodium hydride (60% dispersion in mineral oil, 72.5 mg, 1.81 mmol, 1.50 equiv) at 0 °C. After 1 h, bromomethyl methyl ether (130 µL, 1.57 mmol, 1.30 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 2.5 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (40 mL) and ethyl acetate (40 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (50% ethyl acetate in hexanes) to give 15 (435 mg, 72%) as a white crystalline solid.

TLC (2% methanol in dichloromethane): Rf = 0.31 (UV, KMnO4).

\(^1\)H NMR (CDCl\(_3\), 599 MHz): δ = 7.11 (s, 1H), 6.86–6.79 (m, 3H), 5.12 (s, 2H), 4.71 (s, 2H), 4.32 (s, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.52 (s, 3H).

\(^13\)C NMR (CDCl\(_3\), 151 MHz): δ = 167.6, 160.2, 153.1, 149.5, 148.8, 135.8, 129.4, 124.5, 120.6, 111.4, 111.3, 101.2, 98.1, 88.4, 57.5, 57.2, 56.1, 56.1, 48.0, 46.5.

IR (Diamond-ATR, neat): \(\tilde{\nu}_{\text{max}}\) = 2933, 1678, 1609, 1512, 1461, 1257, 1132, 1045, 1023, 762.

HRMS (El) calc. for C\(_{20}\)H\(_{22}\)Cl\(_2\)NO\(_4\) [M]+: 499.0486; found: 499.0483.

Melting point: 106–108 °C.
(E)-2-Methylbut-2-enoyl chloride (S05)

\[
\text{S04} \quad \xrightarrow{(\text{COCl})_2} \quad \text{S05}
\]

(E)-2,3-Dimethylacrylic acid (S04) (29.3 g, 293 mmol, 1 equiv) was added portionwise to oxalyl chloride (29.5 mL, 304 mmol, 1.30 equiv) followed by one drop of \(N,N\)-dimethylformamide. After 2.5 h, excess oxalyl chloride was removed under reduced pressure to give S05 (34.7 g, 99%) as a colorless liquid. Acid chloride S05 was used directly used in the next step without further purification.

Oxazolidinone 21

\[
\text{S05} \quad + \quad \text{S06} \quad \xrightarrow{n-\text{BuLi}} \quad \text{21}
\]

A solution of \(n\)-butyllithium (2.5 M in hexanes, 99.0 mL, 248 mmol, 1.10 equiv) was added dropwise to a solution of S06 (29.1 g, 225 mmol, 1 equiv) in tetrahydrofuran (600 mL) at \(-78 \, ^\circ\text{C}\). After 15 min, S05 (34.7 g, 293 mmol, 1.30 equiv) was slowly added to the reaction mixture via cannula at \(-78 \, ^\circ\text{C}\). After 30 min, the reaction mixture was allowed to warm to 23 \, ^\circ\text{C}. After 14 h, aqueous hydrochloric acid (2 M, 1 L) was added to the reaction mixture, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 \times 300 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield 21 (45.1 g, 95%) as a yellow solid. The obtained analytical data were in full agreement with those previously reported.\(^8\)

2,2-Dimethyl-1,3-cyclohexadione (16)

\[
\text{S07} \quad \xrightarrow{\text{Mel}, K_2\text{CO}_3, \text{acetone}, 60 \, ^\circ\text{C}} \quad \text{16}
\]

A suspension of 1,3-cyclohexadione (S07) (38.0 g, 340 mmol, 1 equiv), potassium carbonate (93.7 g, 680 mmol, 2.00 equiv) and iodomethane (61.0 mL, 980 mmol, 2.90 equiv) in acetone (300 mL) was heated to 60 \, ^\circ\text{C}. After 3 h, excess iodomethane was removed by distillation into a cooling finger (cooled to \(-78 \, ^\circ\text{C}\)). The residue was diluted with chloroform (300 mL) and water (150 mL). The layers were separated, the aqueous layer was extracted with chloroform (2 \times 150 mL) and the combined organic extracts were dried over sodium
sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to yield 16 (18.5 g, 39%) as a yellow oil. The obtained analytical data were in full agreement with those values reported in literature.\(^9\)

**Tributyl(vinyl)tin (S09)**

\[
\begin{array}{c}
\text{Bu}_3\text{SnCl} \quad \text{MgBr} \\
\text{THF, 70 °C} \\
\text{(92%)} \\
\text{SnBu}_3
\end{array}
\]

A solution of tributyltin chloride (S08) (42.0 mL, 155 mmol, 1 equiv) in tetrahydrofuran (50 mL) was slowly added to a solution of vinylmagnesium bromide (1.0 M in tetrahydrofuran, 310 mL, 310 mmol, 2.00 equiv) via a dropping funnel over a period of 2 h. Upon complete addition, the reaction mixture was heated to 70 °C. After 18 h, the reaction mixture was cooled to 23 °C and saturated aqueous ammonium chloride solution (100 mL) was carefully added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were concentrated and the residue was purified by vacuum distillation (10 mbar, 128 °C) to yield S09 (45.1 g, 92%) as a colorless oil. The obtained analytical data were in full agreement with those values reported in literature.\(^10\)

**\((R)-(+)\)-2-Methyl-CBS-oxazaborilidine (S11)**

\[
\begin{array}{c}
\text{(R)-(+) diphenyl-2-pyrrolidinemethanol (S10)} \\
toluene, 125 °C \\
\text{(98%)} \\
\text{S11}
\end{array}
\]

\((R)-(+)\)-2-Methyl-CBS-oxazaborilidine (S11) was prepared according to the procedure described by E. J. Grabowski.\(^11\) A solution of \((R)-(+)\)-diphenyl-2-pyrrolidinemethanol (S10) (5.25 g, 20.7 mmol, 1 equiv) and butylboronic acid (2.10 g, 20.7 mmol, 1 equiv) in toluene (250 mL) in a two-necked, round-bottomed flask equipped with an additional funnel (containing a cotton plug and 100 g of 4 Å molecular sieves) was heated to 125 °C. After 16 h, the reaction mixture was allowed to cool to 23 °C and the solvent was removed to give S11 (6.80 g, 98%) as a colorless oil. The obtained analytical data were in full agreement with those values reported in literature.\(^11\)
Alcohol 17

To a solution of \((R)-(-)-2\text{-methyl-CBS-oxazaborilidine (S11) (6.80 g, 22.3 mmol, 0.10 equiv)}\), \(N,N\)-diethylaniline (DEA) (14.8 mL, 92.7 mmol, 0.500 equiv) and 2,2-dimethyl-1,3-cyclohexadione (16) (26.0 g, 185 mmol, 1 equiv) in toluene (200 mL) was added a solution of catecholborane (19.8 mL, 185 mmol, 1.00 equiv) in toluene (200 mL) via a dropping funnel over a period of 2.5 h at \(-60^\circ C\). Upon complete addition, methanol (50 mL) was added and the mixture was diluted with diethyl ether (100 mL). The organic layer was washed with a 1:1 mixture of saturated sodium bicarbonate solution (50 mL) and aqueous sodium hydroxide solution (1 M, 50 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (300 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield 17 (16.7 g, 63%, 83% ee) as a yellow oil. The obtained analytical data were in full agreement with those values reported in literature.12

Mosher ester S13

The enantiomeric excess of alcohol 17 was determined as 83% by \(^1H\)-NMR analysis of its corresponding-MTPA ester S13 according to the procedure described by E. J. Corey.12

To a solution of alcohol 17 (10.0 mg, 70.0 µmol, 1 equiv) in dichloromethane (1 mL) were added 4-dimethylaminopyridine (34.4 mg, 28.0 µmol, 4.00 equiv) and \((R)-(-)-\alpha\text{-methoxy-}\alpha\text{-}(\text{trifluoromethyl})\text{phenylacetyl chloride (S12) (20.0 µL, 110 µmol, 1.50 equiv)}\) at 23 °C. After 1 h, water (2 mL) and dichloromethane (3 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 3 mL) and the combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to give S13 as a yellow oil. The obtained analytical data were in full agreement with those values reported in literature.
Benzyl ether 18

To a solution of alcohol 17 (14.0 g, 98.5 mmol, 1 equiv) in tetrahydrofuran (360 mL) was added sodium hydride (60% mineral oil dispersion, 4.33 g, 108 mmol, 1.10 equiv) at 0 °C. After 30 min, tetrabutylammonium iodide (TBAI) (72.7 g, 197 mmol, 2.00 equiv) and benzyl bromide (29.4 mL, 246 mmol, 2.5 equiv) were added subsequently and the resulting suspension was heated to 66 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C, saturated aqueous ammonium chloride solution (300 mL) and diethyl ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 5% ethyl acetate in hexanes) to yield 18 (12.7 g, 56%) as a colorless oil.

**TLC** (5% ethyl acetate in hexanes): \( R_f = 0.18 \) (UV, KMnO₄).

**\( ^1H \) NMR** (400 MHz, CDCl₃): \( \delta = 7.29–7.25 \) (m, 4H), \( 7.23–7.18 \) (m, 1H), \( 4.56 \) (d, \( J = 11.8 \) Hz, 1H), \( 4.34 \) (d, \( J = 11.8 \) Hz, 1H), \( 3.37–3.31 \) (m, 1H), \( 2.33 \) (td, \( J = 6.4, 1.9 \) Hz, 2H), \( 2.01–1.90 \) (m, 2H), \( 1.88–1.78 \) (m, 1H), \( 1.61–1.51 \) (m, 1H), \( 1.13–1.11 \) (m, 6H).

**\( ^{13}C \) NMR** (101 MHz, CDCl₃): \( \delta = 213.9, 138.4, 128.1, 127.3, 127.3, 84.4, 71.1, 50.8, 37.1, 24.3, 23.2, 20.3, 20.3 \).

**IR** (Diamond-ATR, neat): \( \tilde{v}_{max} = 2943, 2870, 1706, 1453, 1118, 1090, 1074, 1066, 1028, 737 \).

**HRMS** (El) calc. for C₁₅H₂₀O₂ [M]+: 232.1458; found: 232.1463.

\[ [\alpha]_D^{20} = +9.1^\circ \] (c = 6.80, CH₂Cl₂).
Triflate 19

To a solution of benzyl ether 18 (12.0 g, 51.7 mmol, 1 equiv) in tetrahydrofuran (200 mL) was added lithium bis(trimethylsilyl)amide solution (1.00 M in tetrahydrofuran, 67.1 mL, 67.1 mmol, 1.30 equiv) at –78 °C. After 1 h, N-phenylbis(trifluoromethanesulfonimide) (24.0 g, 67.1 mmol, 1.30 equiv) was added portionwise. Upon complete addition, the reaction mixture was allowed to warm to 23 °C. After 2.5 h, saturated aqueous ammonium chloride solution (200 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (2% ethyl acetate in hexanes) to yield 19 (15.1 g, 80%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): Rf = 0.50 (UV, CAM).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.42–7.37\) (m, 4H), 7.35–7.30 (m, 1H), 5.69 (t, \(J = 4.1\) Hz, 1H), 4.71 (d, \(J = 11.8\) Hz, 1H), 4.50 (d, \(J = 11.8\) Hz, 1H), 3.40 (dd, \(J = 9.0, 2.7\) Hz, 1H), 2.38–2.25 (m, 1H), 2.24–2.11 (m, 1H), 2.00–1.89 (m, 1H), 1.84–1.73 (m, 1H), 1.28–1.16 (m, 6H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)): \(\delta = 153.9, 138.6, 128.5, 127.7, 127.6, 118.5\) (q, \(J = 319.3\) Hz), 115.5, 82.0, 71.7, 40.6, 24.7, 21.8, 21.1, 20.7.

\(\text{IR (Diamond-ATR, neat)}: \tilde{v}_{\text{max}} = 2978, 2945, 2874, 1411, 1208, 1143, 1025, 983, 874, 698.\)

\(\text{HRMS (EI)}\) calc. for C\(_{16}\)H\(_{19}\)F\(_3\)O\(_4\)S \([\text{M}]^+\): 364.0951; found: 364.0947.

\([\alpha]_{D}^{20} = +22.1^\circ\) (c = 1.07, CH\(_2\)Cl\(_2\)).
Diene 20

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

To a mixture of lithium chloride (6.98 g, 165 mmol, 5.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (1.90 g, 1.65 mmol, 5.00 mol%) in degassed tetrahydrofuran (235 mL) was added triflate 19 (13.6 g, 35.0 mmol, 1 equiv) and tributyl(vinyl)tin (S09) (20.5 mL, 70.0 mmol, 2.00 equiv) at 23 °C in an Ace® pressure tube. After complete addition, the tube was sealed and the mixture was heated to 75 °C. After 18 h, aqueous ammonia solution (10%, 100 mL) was added to the dark brown reaction mixture and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to yield diene 20 (6.83 g, 86%) as a colorless oil.

**TLC** (10% ethyl acetate in hexanes): $R_f = 0.69$ (UV, CAM).

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta = 7.40–7.27$ (m, 5H), 6.38–6.20 (m, 1H), 5.81–5.68 (m, 1H), 5.36–5.27 (m, 1H), 5.01–4.91 (m, 1H), 4.71 (d, $J = 11.7$ Hz, 1H), 4.47 (d, $J = 11.7$ Hz, 1H), 3.32–3.23 (m, 1H), 2.29–2.19 (m, 1H), 2.13–2.02 (m, 1H), 1.94–1.84 (m, 1H), 1.77–1.66 (m, 1H), 1.14–1.08 (m, 6H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$): $\delta = 143.9$, 139.2, 136.4, 128.2, 127.5, 127.3, 121.6, 113.6, 83.0, 71.3, 38.6, 26.2, 23.8, 22.3, 22.1.

**IR** (Diamond-ATR, neat): $\tilde{\nu}_{max} = 3028, 2965, 2940, 2869, 1454, 1359, 1096, 907, 735, 697$.

**HRMS** (EI) calc. for C$_{17}$H$_{22}$O [M]: 242.1665; found: 242.1677.

$[\alpha]_D^{20} = +29.0^\circ$ (c = 1.45, CH$_2$Cl$_2$).
A solution of dimethylaluminium chloride (1.00 M in hexanes, 82.9 mL, 82.9 mmol, 3.00 equiv) was added dropwise to a solution of dienophile 21 (7.59 g, 35.9 mmol, 1.30 equiv) in 1,2-dichloroethane (100 mL) at −40 °C in an oven dried Ace® round-bottom pressure flask (Sigma Aldrich, product number: Z567205) under nitrogen over a period of 30 min. After 30 min, a solution of diene 20 (6.70 g, 27.6 mmol, 1 equiv) in 1,2-dichloroethane (65 mL) was added dropwise over a period of 20 min to the reaction mixture. The transfer was quantitated with 1,2-dichloroethane (2 × 5 mL). After complete addition, the pressure tube was sealed and the reaction mixture was allowed to warm to 23 °C. After 40 h, the reaction mixture was cooled to 0 °C and aqueous hydrochloric acid (2 M, 200 mL) was carefully added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (4% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to yield the 22 (6.43 g, 51%) as colorless solid and S14 (483 mg, 4%) as colorless solid. Recrystallization from ethyl acetate gave crystals of both epimers 22 and S14 suitable for single-crystal X-ray diffraction.

**Major diastereomer 22:**

TLC (20% ethyl acetate in hexanes): R_f = 0.69 (UV, CAM).

^1H NMR (599 MHz, CDCl3): δ = 7.32 (dd, J = 3.9, 1.4 Hz, 4H), 7.26–7.23 (m, 1H), 5.56–5.48 (m, 1H), 4.61–4.53 (m, 2H), 4.35 (d, J = 12.3 Hz, 1H), 4.29 (t, J = 8.7 Hz, 1H), 4.26–4.18 (m, 1H), 3.45 (d, J = 12.7 Hz, 1H), 3.22–3.11 (m, 2H), 2.41–2.31 (m, 1H), 2.02–1.93 (m, 1H), 1.91–1.83 (m, 1H), 1.83–1.74 (m, 2H), 1.73–1.65 (m, 1H), 1.15 (s, 3H), 1.08 (s, 3H), 1.07–1.03 (m, 4H), 0.94–0.90 (m, 6H), 0.80 (d, J = 6.8 Hz, 3H).

^13C NMR (151 MHz, CDCl3): δ = 178.0, 153.1, 142.4, 139.5, 128.3, 127.6, 127.3, 118.2, 83.1, 70.4, 62.9, 61.2, 53.6, 41.2, 36.8, 31.4, 29.8, 29.0, 28.3, 25.8, 23.7, 22.4, 18.6, 16.5, 14.6, 12.4.

IR (Diamond-ATR, neat): ν_max = 2963, 2874, 1777, 1682, 1454, 1383, 1240, 1196, 1117, 747.

HRMS (ESI) calc. for: C_{28}H_{43}N_{2}O_{4} 471.3217 [M+NH_4]^+; found: 471.3225.

[a]_D^{20} = +46.6° (c = 0.56, CH_2Cl_2).

Melting point: 133–141 °C
Minor diastereomer S14:

TLC (20% ethyl acetate in hexanes): Rf = 0.69 (UV, CAM).

$^1$H NMR (800 MHz, CDCl$_3$): $\delta = 7.36$–$7.31$ (m, 4H), 7.27–$7.25$ (m, 1H), 5.59 (d, $J = 6.0$ Hz, 1H), 4.63 (d, $J = 12.1$ Hz, 1H), 4.56 (d, $J = 8.2$ Hz, 1H), 4.43 (d, $J = 12.1$ Hz, 1H), 4.32–4.27 (m, 1H), 4.21 (dd, $J = 9.2$, 2.3 Hz, 1H), 3.38–3.32 (m, 1H), 3.21–3.14 (m, 1H), 2.93 (dd, $J = 11.5$, 4.2 Hz, 1H), 2.38–2.31 (m, 1H), 2.02–1.97 (m, 1H), 1.97–1.92 (m, 1H), 1.76–1.70 (m, 1H), 1.54–1.47 (m, 1H), 1.40–1.35 (m, 1H), 1.24–1.20 (m, 1H), 1.18 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93–0.90 (m, 6H), 0.80 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (201 MHz, CDCl$_3$): $\delta = 177.8$, 153.0, 144.3, 139.5, 128.3, 127.5, 127.4, 117.9, 84.4, 71.6, 62.9, 61.1, 53.3, 42.5, 36.9, 31.2, 29.6, 28.3, 26.3, 26.2, 24.6, 22.5, 18.6, 16.4, 14.6, 12.6.

IR (Diamond-ATR, neat): $\tilde{\nu}_{\text{max}}$ = 2963, 2873, 1772, 1679, 1381, 1358, 1192, 1090, 1062, 914, 732.

HRMS (ESI) calc. for: C$_{28}$H$_{43}$N$_2$O$_4$ 471.3217 [M+NH$_4$]$^+$; found: 471.3226.

$[\alpha]_{D}^{20} = +18.7^\circ$ (c = 1.19, CH$_2$Cl$_2$).

Melting point: 126–132 °C
A solution of \(\text{n-butyllithium (2.22 M in hexanes, 27.5 mL, 61.1 mmol, 4.70 equiv)}\) was added dropwise to a solution of ethanethiol (4.82 mL, 65.0 mmol, 5.00 equiv) in tetrahydrofuran (200 mL) at 0 °C. After complete addition, the reaction mixture was allowed to warm to 23 °C. After 30 min, a solution of oxazolidinone 22 (5.90 g, 13.0 mmol, 1 equiv) in tetrahydrofuran (60 mL) was slowly added. The transfer was quantitated with tetrahydrofuran (2 × 5 mL). After 21 h, saturated aqueous ammonium chloride solution (200 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to yield 23 (4.20 g, 84%) as a colorless oil.

**TLC (9% ethyl acetate in hexanes):** \(R_f = 0.32\) (UV, CAM).

**\(^1\text{H NMR (599 MHz, CDCl}_3\):** \(\delta = 7.34–7.30\) (m, 4H), 7.28–7.24 (m, 1H), 5.51–5.45 (m, 1H), 4.57 (d, \(J = 12.1\) Hz, 1H), 4.34 (d, \(J = 12.1\) Hz, 1H), 3.17–3.13 (m, 1H), 2.92–2.82 (m, 3H), 2.05–1.91 (m, 2H), 1.89–1.76 (m, 2H), 1.74–1.63 (m, 2H), 1.29–1.22 (m, 4H), 1.16 (s, 3H), 1.08–1.02 (m, 6H), 0.81 (d, \(J = 6.7\) Hz, 3H).

**\(^{13}\text{C NMR (151 MHz, CDCl}_3\):** \(\delta = 208.2, 142.7, 139.4, 128.3, 127.6, 127.3, 117.9, 82.8, 70.3, 56.8, 42.9, 40.9, 36.9, 31.6, 29.4, 25.9, 23.2, 23.2, 21.0, 15.9, 14.9, 9.6.

**IR (Diamond-ATR, neat):** \(\tilde{\nu}_{\text{max}} = 2963, 2929, 2872, 1669, 1453, 1383, 1113, 950, 909, 731\).

**HRMS (ESI) calc. for \(\text{C}_{24}\text{H}_{38}\text{NO}_{2}\text{S}^+ [M+NH}_4^+\):** 404.2618; found: 404.2607.

\([\alpha]_D^{20} = +3.22^\circ\) (c = 3.29, CHCl\(_3\)).
Alcohol 24

Lithium aluminium hydride (1.96 g, 51.1 mmol, 5.00 equiv) was added portionwise to a solution of thioester 23 (4.00 g, 10.3 mmol, 1 equiv) at 0 °C. After complete addition, the reaction mixture was heated to 45 °C. After 3 h, the reaction mixture was cooled to 0 °C, diluted with diethyl ether (100 mL) and saturated aqueous potassium sodium tartrate solution (400 mL) was carefully added. After stirring vigorously for 1 h, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield 24 (3.40 g, 99%) as a colorless oil.

**TLC** (15% ethyl acetate in hexanes): R<sub>f</sub> = 0.15 (CAM).

**<sup>1</sup>H NMR** (599 MHz, CDCl<sub>3</sub>): δ = 7.34–7.30 (m, 4H), 7.26–7.23 (m, 1H), 5.52–5.49 (m, 1H), 4.59 (d, J = 12.5 Hz, 1H), 4.36 (d, J = 12.4 Hz, 1H), 3.55–3.50 (m, 1H), 3.49–3.41 (m, 1H), 3.18–3.13 (m, 1H), 2.51–2.42 (m, 1H), 1.93–1.81 (m, 3H), 1.76–1.67 (m, 2H), 1.56–1.49 (m, 2H), 1.23 (s, 1H), 1.15 (s, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.57 (s, 3H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>): δ = 143.6, 139.6, 128.3, 127.7, 127.3, 118.3, 83.0, 70.3, 65.8, 41.1, 39.5, 37.4, 32.0, 31.6, 29.1, 26.0, 23.7, 20.5, 15.1, 11.5.

**IR** (Diamond-ATR, neat): ν<sub>max</sub> = 3359, 2952, 2873, 1453, 1380, 1102, 1061, 1039, 733, 696.

**HRMS** (EI) calc. for C<sub>22</sub>H<sub>32</sub>O<sub>2</sub> [M]+: 328.2397; found: 328.2403.

\[ [\alpha]_{D}^{20} = +50.9^\circ \ (c = 0.89, \text{CH}_2\text{Cl}_2). \]
Methanesulfonyl chloride (1.63 mL, 21.0 mmol, 3.00 equiv) was added to a solution of alcohol 24 (2.30 g, 7.00 mmol, 1 equiv) and triethylamine (5.84 mL, 42.0 mmol, 6.00 equiv) in dichloromethane (45 mL) at 0 °C. After 30 min, the orange, turbid reaction mixture was allowed to warm to 23 °C. After 3 h, dichloromethane (50 mL) and pH 7 phosphate buffer (100 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 60 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to give mesylate S15 as an orange oil. The so-obtained mesylate was directly used in the following reaction without further purification.

To a solution of crude mesylate S15 (2.85 g, 7.00 mmol, 1 equiv) in N,N-dimethylformamide (60 mL) was added sodium iodide (8.39 g, 56.0 mmol, 8.00 equiv) and the resulting orange suspension was heated to 100 °C. After 39 h, the reaction mixture was cooled to 23 °C and saturated, aqueous sodium thiosulfate solution (200 mL) and diethyl ether (200 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (pentane initially, grading to 40% diethyl ether in pentane) to yield iodide 25 (2.30 g, 75% over 2 steps) as a brown oil and unreacted starting alcohol 24 (379 mg, 17%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.33 (CAM).

1H NMR (800 MHz, CDCl3): δ = 7.36–7.32 (m, 4H), 7.28–7.25 (m, 1H), 5.52–5.47 (m, 1H), 4.61 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 12.3 Hz, 1H), 3.45 (d, J = 10.3 Hz, 1H), 3.23 (d, J = 10.3 Hz, 1H), 3.19–3.17 (m, 1H), 2.46–2.39 (m, 1H), 1.95–1.88 (m, 2H), 1.79–1.72 (m, 2H), 1.63–1.57 (m, 1H), 1.55–1.50 (m, 1H), 1.40–1.36 (m, 1H), 1.17 (s, 3H), 0.87 (s, 3H), 0.83 (d, J = 6.7 Hz, 3H).

13C NMR (201 MHz, CDCl3): δ = 143.2, 139.5, 128.3, 127.6, 127.3, 118.1, 82.9, 70.3, 41.1, 41.0, 37.4, 35.2, 31.6, 29.3, 25.9, 23.4, 22.2, 19.9, 14.6, 12.4.

IR (Diamond-ATR, neat): 𝜈_{max} = 2960, 2871, 1453, 1380, 1231, 1182, 1110, 970, 732.

HRMS (EI) calc. for C_{22}H_{31}{^{127}I}O [M]^+: 438.1414; found: 438.1419.

[a]_{D}^{20} = +6.25° (c = 0.80, CH₂Cl₂).
Cyclization precursor 26

![Cyclization precursor 26 diagram]

**Supplementary Table 1** Conditions investigated for the sp²–sp³ Negishi cross coupling. n.r.: no reaction; ¹ isolated yield of analytically pure product, ² 60 µmol (15) scale, ³ 870 µmol (15) scale

| Entry | Catalyst (20 mol%) | Additive | Solvent | Temperature | Yield |
|-------|--------------------|----------|---------|-------------|-------|
| 1     | Pd(dba)₂, SPhos    | -        | THF     | 23 °C to 60 °C | n.r.  |
| 2     | Pd(dba)₂, SPhos    | DMA (25 vol%) | THF     | 23 °C to 60 °C | n.r.  |
| 3     | Pd(PPh₃)₄          | -        | THF     | 23 °C to 60 °C | n.r.  |
| 4     | Pd(PPh₃)₄          | DMA (25 vol%) | THF     | 23 °C to 60 °C | n.r.  |
| 5     | Pd-SPhos-G2, SPhos | -        | THF     | 60 °C        | n.r.  |
| 6     | Pd-SPhos-G2, SPhos | DMA (25 vol%) | THF     | 60 °C        | 37%¹  |
| 7     | Pd-SPhos-G2, SPhos | -        | THF     | 23 °C        | n.r.  |
| 8     | Pd-SPhos-G2, SPhos | DMA (25 vol%) | THF     | 40 °C        | 61%¹² |}

1, 2, 3
Tetrahydrofuran was dried according to the procedure described by B. Williams prior to use.\textsuperscript{13}

To a mixture of alkyl iodide \textbf{25} (554 mg, 1.26 mmol, 1.45 equiv) and a solution of zinc chloride (1.00 M in tetrahydrofuran, 1.39 mL, 1.39 mmol, 1.60 equiv) in tetrahydrofuran (1.2 mL) was added dropwise a solution of tert-butyllithium (1.50 M in pentane, 1.80 mL, 2.70 mmol, 3.10 equiv) at –78 °C. After 50 min, the mixture was allowed to warm to 23 °C. After 20 min, the mixture was added to a mixture of aryl iodide \textbf{15} (435 mg, 870 µmol, 1 equiv), SPhos (71.3 mg, 174 µmol, 0.20 equiv) and SPhos-Pd-G2 (125 mg, 174 µmol, 0.20 equiv) in tetrahydrofuran (2.2 mL) and freshly distilled (over CaH\textsubscript{2}) \textit{N,N}-dimethylacetamide (2.2 mL) and the reaction mixture was directly placed in a preheated oil bath at 40 °C. After 7 h, the reaction mixture was allowed to cool to 23 °C, and ethyl acetate (50 mL) and saturated aqueous ammonium chloride solution (60 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 60 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (70 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in benzene) to yield \textbf{26} (332 mg, 56%) as a yellow foam.

\textbf{TLC} (50% ethyl acetate in hexanes): \textit{R}_f = 0.14 (UV, CAM).

\textbf{\textsuperscript{1}H NMR} (599 MHz, CDCl\textsubscript{3}): δ = 7.30–7.26 (m, 4H), 7.24–7.21 (m, 1H), 7.15 (s, 1H), 6.88–6.86 (m, 2H), 6.84–6.82 (m, 1H), 5.46–5.41 (m, 1H), 4.99 (s, 2H), 4.76–4.69 (m, 2H), 4.48 (d, \textit{J} = 12.5 Hz, 1H), 4.36–4.27 (m, 2H), 4.25 (d, \textit{J} = 12.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.49 (s, 3H), 3.03–3.01 (m, 1H), 2.92 (d, \textit{J} = 12.9 Hz, 1H), 2.66 (d, \textit{J} = 12.9 Hz, 1H), 2.59–2.55 (m 1H), 1.91–1.85 (m, 2H), 1.61–1.56 (m, 1H), 1.55–1.51 (m, 1H), 1.44–1.35 (m, 1H), 1.22–1.14 (m, 1H), 1.07 (s, 3H), 1.01 (d, \textit{J} = 6.7 Hz, 3H), 0.96 (s, 3H), 0.85–0.78 (m, 1H), 0.76 (s, 3H).

\textbf{\textsuperscript{13}C NMR} (151 MHz, CDCl\textsubscript{3}): δ = 168.4, 160.1, 152.4, 149.4, 148.7, 144.5, 139.4, 132.6, 129.9, 128.2, 127.8, 127.3, 126.6, 123.8, 120.7, 117.5, 111.6, 111.3, 100.5, 97.6, 82.7, 70.2, 57.1, 56.1, 56.1, 55.9, 48.6, 46.5, 42.0, 41.4, 41.3, 38.9, 35.4, 32.0, 28.5, 25.8, 24.5, 23.8, 16.5, 14.4.

\textbf{IR} (Diamond-ATR, neat): ʋ\textsubscript{max} = 2933, 1686, 1514, 1464, 1259, 1259, 1237, 1152, 1055, 735.

\textbf{HRMS} (El) calc. for C\textsubscript{42}H\textsubscript{53}NO\textsubscript{7} [M\textsuperscript{+}]: 683.3817; found: 683.3800.

[\textit{a}]\textsubscript{D}\textsuperscript{29} = +22.4° (c = 0.19, CH\textsubscript{2}Cl\textsubscript{2}).
A solution of hydrochloric acid (~1.25 M in methanol, 10 mL) was added to a solution of 26 (290 mg, 424 µmol, 1 equiv) in dichloromethane (5 mL) and the reaction mixture was heated to 40 °C. After 1 h, the reaction mixture was diluted with dichloromethane (30 mL) and saturated aqueous sodium bicarbonate solution (70 mL) was added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 60 mL) and the combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to yield S17 as a yellow foam that was directly used in the following step without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 1.11 mL, 4.24 mmol, 10.0 equiv) was added dropwise to a solution of the crude phenol S17 (271 mg, 424 µmol, 1 equiv) in dichloromethane (40 mL) at −40 °C and the reaction mixture was allowed to slowly warm to −15 °C over a period of 1 h. After 5 h, saturated aqueous sodium bicarbonate solution (50 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica to yield a mixture of S18 (83%) and rearranged S19 (17%) as a colorless foam that was used in the following step without further purification.

Analytically pure samples of S18 and S19 were obtained by normal-phase semi-preparative HPLC purification using 5% i-propanol in n-heptane as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention times: 21.9 min for S18 and 23.3 min for S19) to give S18 as colorless foam and S19 as colorless solid. Recrystallization of S19 from diethyl ether gave crystals suitable for single-crystal X-ray diffraction.
For S18:

TLC (50% ethyl acetate in benzene): Rf = 0.30 (UV, CAM).

$^1$H NMR (400 MHz, CDCl₃): δ = 7.36–7.32 (m, 4H), 7.30–7.26 (m, 1H), 6.91 (s, 1H), 6.86–6.79 (m, 3H), 4.95 (d, J = 14.8 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 14.8 Hz, 1H), 4.36 (d, J = 12.1 Hz, 1H), 4.21–4.08 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.23–3.07 (m, 2H), 2.27–2.10 (m, 4H), 2.06–1.99 (m, 1H), 1.85–1.69 (m, 3H), 1.66–1.58 (m, 1H), 1.56–1.50 (m, 1H), 1.32 (d, J = 13.5 Hz, 1H), 1.10 (d, J = 7.4 Hz, 3H), 1.00–0.94 (m, 6H), 0.86 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl₃): δ = 169.2, 158.6, 149.4, 148.6, 147.3, 139.7, 131.7, 130.2, 128.3, 127.2, 127.2, 121.0, 120.4, 114.0, 111.3, 111.1, 95.9, 84.1, 82.4, 71.7, 56.1, 56.1, 55.9, 47.6, 46.4, 45.0, 39.8, 38.6, 37.7, 32.3, 30.7, 28.0, 27.1, 24.4, 23.8, 21.0, 20.4, 17.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max} = 2958, 1688, 1606, 1515, 1464, 1368, 1263, 1121, 1084, 737$.

HRMS (EI) calc. for C₄₀H₄₉NO₆ [M]⁺: 639.3554; found: 639.3557.

$[\alpha]_D^{20} = +90.1°$ (c = 0.69, CH₂Cl₂).

For S19:

TLC (50% ethyl acetate in benzene): Rf = 0.30 (UV, CAM).

$^1$H NMR (400 MHz, CDCl₃): δ = 6.91 (s, 1H), 6.87–6.84 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 4.69 (s, 2H), 4.10 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.96 (d, J = 18.1 Hz, 1H), 2.83–2.72 (m, 1H), 2.46–2.38 (m, 1H), 2.37–2.31 (m, 1H), 2.28 (d, J = 18.1 Hz, 1H), 2.23–2.09 (m, 2H), 2.08–2.00 (m, 1H), 1.79–1.69 (m, 1H), 1.66–1.61 (m, 1H), 1.47 (d, J = 12.6 Hz, 1H), 1.30–1.25 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.78 (s, 3H), 0.75 (d, J = 6.8 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl₃): δ = 169.2, 158.6, 149.3, 148.9, 148.6, 143.4, 131.9, 131.6, 130.3, 121.8, 120.8, 113.6, 111.6, 111.0, 96.1, 95.2, 56.1, 56.0, 56.0, 47.4, 46.5, 37.7, 32.0, 31.6, 30.5, 29.3, 28.0, 27.1, 22.4, 22.2, 20.7, 16.0, 15.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max} = 2930, 1680, 1602, 1466, 1365, 1258, 1144, 1106, 1024, 764$.

HRMS (EI) calc. for C₃₃H₄₁NO₅ [M]⁺: 531.2979; found: 531.2976.

$[\alpha]_D^{20} = -54.3°$ (c = 0.47, CH₂Cl₂).

Melting point: 175 °C
Neopentylic alcohol 30

A crude mixture of S18 and S19 (424 µmol, 1 equiv) in ethanol (20 mL) was treated with palladium on carbon (10 wt.%, 451 mg, 424 µmol, 1.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 2 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 14 h, the reaction mixture was filtered through a pad of Celite® and the filter cake was thoroughly rinsed with dichloromethane (70 mL). The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in benzene initially, grading to 50% ethyl acetate in benzene) to give alcohol 30 (145 mg, 62% over 3 steps) as a colorless foam and S19 (59 mg, 26% over 2 steps) as a colorless foam. The obtained analytical data for 30 were in full agreement with those values previously reported.¹⁴

TLC (benzene with 50% EtOAc): R_f = 0.32 (UV, CAM).

¹H NMR (400 MHz, CDCl₃): δ = 6.91 (s, 1H), 6.87–6.79 (m, 3H), 4.94 (d, J = 14.8 Hz, 1H), 4.47 (d, J = 14.8 Hz, 1H), 4.21–4.07 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.52 (s, 1H), 3.14 (d, J = 18.2 Hz, 1H), 2.48–2.35 (m, 1H), 2.30–2.21 (m, 1H), 2.22–2.16 (m, 1H), 2.12–1.97 (m, 2H), 1.81–1.71 (m, 2H), 1.69–1.59 (m, 2H), 1.59–1.57 (m, 1H), 1.57–1.52 (m, 1H), 1.33 (d, J = 12.2 Hz, 1H), 1.12 (d, J = 7.5 Hz, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.90–0.85 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 169.1, 158.4, 149.3, 148.5, 147.1, 131.7, 130.0, 120.8, 120.3, 113.8, 111.2, 111.1, 95.9, 83.8, 74.6, 56.0, 55.9, 55.8, 47.5, 46.3, 44.7, 39.5, 37.9, 37.6, 32.2, 30.3, 28.1, 26.3, 25.9, 24.1, 23.7, 20.2, 17.1.

IR (Diamond-ATR, neat): v_max = 3447, 2935, 2871, 1673, 1606, 1515, 1463, 1260, 1120, 974.

HRMS (EI) calc. for C₃₃H₄₃NO₆ [M]+: 549.3085; found: 549.3093.

[a]_D⁰ = +106.0° (c = 0.20, CHCl₃); lit. [α]_D⁰ = +71.7° (c = 2.82, CHCl₃)¹⁴
Phenyliodine(III) bis(trifluoroacetate) (PIFA) (1.19 g, 2.77 mmol, 16.0 equiv) was added in small portions (1 equiv every 30 min) to a solution of 30 (95.0 mg, 173 µmol, 1 equiv) in benzene (24 mL). After 10 h, saturated aqueous sodium thiosulfate solution was added (60 mL) and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution. The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% methanol in dichloromethane initially, grading to 5% methanol in dichloromethane) to give S20 (39.0 mg, 57%) as a colorless solid. The obtained analytical data for 30 were in full agreement with those previously reported.14
(+)-Stachyflin (1)

Potassium tert-butoxide (25.3 mg, 225 µmol, 3.00 equiv) was added to a solution of O-methyl-stachyflin (S20) (30.0 mg, 75.1 µmol, 1 equiv) and 1-dodecanethiol (71.9 µL, 30.0 µmol, 4.00 equiv) in N,N-dimethylformamide (3 mL) at 23 °C. After 5 min, the bright yellow solution was heated to 140 °C. After 75 min, the dark orange reaction mixture was allowed to cool to 23 °C and saturated aqueous ammonium chloride solution (50 mL) was added. The mixture was extracted with ethyl acetate (4 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 40 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% methanol in dichloromethane initially, grading to 5% methanol in dichloromethane) to yield (+)-stachyflin (1) (22.1 mg, 76%) as a colorless solid.

**TLC** (5% methanol in dichloromethane): R<sub>T</sub> = 0.19 (UV, CAM).

**<sup>1</sup>H NMR** (599 MHz, DMSO-<sub>d6</sub>): δ = 9.65 (s, 1H, Ar-<OH>), 8.26 (s, 1H, N-H), 6.60 (s, 1H, H-20), 4.43 (s, 1H), 4.16 (dd, <sup>2</sup>J<sub>23A/23B</sub> = 17.0 Hz, <sup>3</sup>J<sub>23A/NH</sub> = 1.1 Hz, 1H, H-23A), 4.05 (dd, <sup>2</sup>J<sub>23B/23A</sub> = 17.0 Hz, <sup>3</sup>J<sub>23B/NH</sub> = 1.1 Hz, 1H, H-23B), 3.07 (d, <sup>2</sup>J<sub>15A/15B</sub> = 17.8 Hz, 1H, H-15A), 3.33 (m, 1H, H-3; re-assigned based on HSQC correlations), 2.37–2.30 (m, 1H, H-2α), 2.25–2.18 (m, 1H, H-1α), 2.18–2.11 (m, 1H, H-6α), 2.09 (d, <sup>2</sup>J<sub>15B/15A</sub> = 17.8 Hz, 1H, H-15B), 2.01–1.93 (m, 1H, H-7α), 1.75–1.71 (m, 1H, H-8), 1.67–1.61 (m, 1H, H-6β), 1.59–1.51 (m, 2H, H-1β, H-2β), 1.46 (dd, <sup>3</sup>J<sub>6α/6β</sub> = 13.0 Hz, <sup>3</sup>J<sub>6α/6β/6α/6β</sub> = 3.9 Hz, 1H, H-5), 1.27–1.24 (m, 1H, H-7β), 1.09 (d, <sup>3</sup>J<sub>13B</sub> = 7.5 Hz, 3H, H-13), 0.92 (s, 3H, H-14), 0.88 (s, 3H, H-12), 0.83 (s, 3H, H-11).

**<sup>13</sup>C NMR** (101 MHz, DMSO-<sub>d6</sub>): δ = 170.4 (C-22), 155.9 (C-21), 147.2 (C-17), 131.6 (C-19), 120.8 (C-18), 112.1 (C-16), 99.1 (C-20), 83.3 (C-10), 72.2 (C-3), 44.4 (C-5), 42.6 (C-23), 39.1 (C-8; re-assigned based on HSQC correlations), 37.5 (C-4), 37.1 (C-9), 32.0 (C-15), 30.1 (C-11), 27.6 (C-7), 27.1 (C-12), 25.8 (C-2), 23.5 (C-1), 23.5 (C-6), 20.0 (C-14), 17.0 (C-13).

**IR** (Diamond-ATR, neat): ν<sub>max</sub> = 3350, 2927, 2356, 2334, 1693, 1600, 1478, 1358, 1066, 974.

**HRMS** (EI) calc. for C<sub>23</sub>H<sub>31</sub>NO<sub>4</sub> [M]+: 385.2248; found: 385.2250.

[α]<sub>D</sub><sup>20</sup> = +129.3° (c = 0.53, MeOH); lit. [α]<sub>D</sub><sup>24.5</sup> = +138.7° (c = 1.0, MeOH) (+)-stachyflin.<sup>15</sup>
**Supplementary Table 2** Comparison of $^1$H NMR data for synthetic and natural (+)-stachyflin (1).

| Proton | Synthetic (599 MHz, DMSO-$d_6$) | Natural (600 MHz, DMSO-$d_6$)$^{15}$ | Δ: δ (ppm) |
|--------|---------------------------------|----------------------------------------|------------|
| 1A     | 2.25–2.18 (m, 1H)               | 2.21 (m, 1H)                           | + 0.01     |
| 1B     | 1.59–1.51 (m, 2H)               | 1.57 (m, 1H)                           | – 0.01     |
| 2A     | 2.37–2.30 (m, 1H)               | 2.34 (m, 1H)                           | – 0.01     |
| 2B     | 1.59–1.51 (m, 2H)               | 1.54 (m, 1H)                           | ± 0.00     |
| 3      | 3.33 (m, 1H)                    | 3.34 (m, 1H)                           | – 0.01     |
| 5      | 1.46 (dd, J = 13.0, 3.9 Hz, 1H) | 1.46 (dd, J = 13.0, 3.0 Hz, 1H)        | ± 0.00     |
| 6A     | 2.18–2.11 (m, 1H)               | 2.12 (m, 1H)                           | + 0.03     |
| 6B     | 1.67–1.61 (m, 1H)               | 1.64 (m, 1H)                           | ± 0.00     |
| 7A     | 2.01–1.93 (m, 1H)               | 1.97 (m, 1H)                           | ± 0.00     |
| 7B     | 1.27–1.24 (m, 1H)               | 1.25 (m, 1H)                           | ± 0.01     |
| 8      | 1.75–1.71 (m, 1H)               | 1.73 (m, 1H)                           | ± 0.00     |
| 11     | 0.83 (s, 3H)                    | 0.83 (s, 3H)                           | ± 0.00     |
| 12     | 0.88 (s, 3H)                    | 0.89 (s, 3H)                           | – 0.01     |
| 13     | 1.09 (d, J = 7.5 Hz, 3H)        | 1.09 (d, J = 7.5 Hz, 3H)               | ± 0.00     |
| 14     | 0.92 (s, 3H)                    | 0.92 (s, 3H)                           | ± 0.00     |
| 15A    | 3.07 (d, J = 17.8 Hz, 1H)       | 3.07 (d, J = 17.9 Hz, 1H)              | ± 0.00     |
| 15B    | 2.09 (d, J = 17.8 Hz, 1H)       | 2.09 (d, J = 17.9 Hz, 1H)              | ± 0.00     |
| 20     | 6.60 (s, 1H)                    | 6.61 (s)                               | – 0.01     |
| 23A    | 4.16 (dd, J = 17.0, 1.1 Hz, 1H) | 4.16 (d, J = 16.8 Hz, 1H)              | ± 0.00     |
| 23B    | 4.05 (dd, J = 17.0, 1.1 Hz, 1H) | 4.06 (d, J = 16.8 Hz, 1H)              | – 0.01     |
| Alk-OH | 4.43 (s, 1H)                    | 4.46 (d, J = 3.0 Hz, 1H)               | – 0.03     |
| Ar-OH  | 9.65 (s, 1H)                    | 9.70 (s)                               | – 0.05     |
| NH     | 8.26 (s, 1H)                    | 8.29 (s)                               | – 0.03     |
Supplementary Table 3  Comparison of $^{13}$C NMR data for synthetic and natural (+)-stachyflin (1).

| Carbon | Synthetic (101 MHz, DMSO-$d_6$) | Natural (150 MHz, DMSO-$d_6$) | $\Delta: \delta$ (ppm) |
|--------|-------------------------------|-------------------------------|------------------------|
| 1      | 23.5                          | 23.4                          | + 0.1                  |
| 2      | 25.8                          | 25.6                          | + 0.1                  |
| 3      | 72.2                          | 72.1                          | + 0.1                  |
| 4      | 37.5                          | 37.3                          | + 0.2                  |
| 5      | 44.4                          | 44.2                          | + 0.2                  |
| 6      | 23.5                          | 23.3                          | + 0.2                  |
| 7      | 27.6                          | 27.5                          | + 0.1                  |
| 8      | 39.1                          | 39.0                          | + 0.1                  |
| 9      | 37.1                          | 37.0                          | + 0.1                  |
| 10     | 83.3                          | 83.2                          | + 0.1                  |
| 11     | 30.1                          | 30.0                          | + 0.1                  |
| 12     | 27.1                          | 26.9                          | + 0.2                  |
| 13     | 17.0                          | 16.9                          | + 0.1                  |
| 14     | 20.0                          | 19.8                          | + 0.2                  |
| 15     | 32.0                          | 31.8                          | + 0.2                  |
| 16     | 112.1                         | 111.9                         | + 0.2                  |
| 17     | 147.2                         | 147.1                         | + 0.1                  |
| 18     | 120.8                         | 120.7                         | + 0.1                  |
| 19     | 131.6                         | 131.5                         | + 0.1                  |
| 20     | 99.1                          | 99.0                          | + 0.1                  |
| 21     | 155.9                         | 155.8                         | + 0.1                  |
| 22     | 170.4                         | 170.4                         | ± 0.0                  |
| 23     | 42.6                          | 42.4                          | + 0.2                  |
Phenyliodine(III) bis(trifluoroacetate) (228 mg, 530 µmol, 10.0 equiv) was added to a solution of S18 (28.2 mg, 53.0 µmol, 1 equiv) in benzene (5 mL). After 18 h, additional phenyliodine(III) bis(trifluoroacetate) (PIFA) (182 mg, 424 µmol, 8.00 equiv) was added in small portions over a period of 4 h (2 equiv/h). After 1 h, saturated aqueous sodium thiosulfate solution (50 mL) was added and the biphasic mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 80 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica, the filtercake was rinsed with a mixture of 5% methanol in dichloromethane and used without further purification. An analytically pure sample of 38 was obtained by normal-phase semi-preparative HPLC purification using 10% iso-propanol in n-heptane as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention time: 13.7 min).

**TLC** (5% methanol in dichloromethane): $R_f = 0.31$ (UV, CAM).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 6.89$ (s, 1H), 6.23 (s, 1H), 4.29 (s, 2H), 3.87 (s, 3H), 2.99 (d, $J = 18.1$ Hz, 1H), 2.86–2.75 (m, 1H), 2.51–2.42 (m, 1H), 2.42–2.34 (m, 1H), 2.31 (d, $J = 18.1$ Hz, 1H), 2.27–2.13 (m, 2H), 2.12–2.03 (m, 1H), 1.82–1.75 (m, 1H), 1.72–1.64 (m, 1H), 1.56–1.46 (m, 1H), 1.36–1.24 (m, 1H), 1.06 (d, $J = 6.9$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.81 (s, 3H), 0.77 (d, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 172.2, 158.7, 149.2, 143.4, 132.0, 130.7, 124.3, 114.1, 95.8, 95.2, 56.0, 43.4, 37.7, 32.1, 31.6, 30.5, 29.3, 28.0, 27.1, 22.5, 22.2, 20.8, 16.1, 15.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max} = 2926, 2971, 1697, 1583, 1573, 1427, 1378, 1174, 1001, 934$.

HRMS (EI) calc. for C$_{24}$H$_{31}$NO$_3$ [M]$^+$: 381.2298; found: 381.2296.

$[\alpha]_D^{20} = -14.6^\circ$ (c = 0.27, CH$_2$Cl$_2$).

Melting point: 143–150 °C
Phenol 39

Potassium tert-butoxide (29.7 mg, 265 µmol, 5.00 equiv) was added to a solution of crude 38 (20.2 mg, 53.0 µmol, 1 equiv) and 1-dodecanethiol (76.2 µL, 318 µmol, 6.00 equiv) in N,N-dimethylformamide (0.9 mL) at 23 °C. After 5 min, the bright yellow suspension was heated to 140 °C. After 45 min, the dark orange reaction mixture was allowed to cool to 23 °C and saturated aqueous ammonium chloride solution (30 mL) was added and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 40 mL), the washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica, the filtercake was rinsed with a mixture of 5% methanol in dichloromethane and was purified by normal-phase semi-preparative HPLC purification using 5% iso-propanol in n-heptane grading to 15% iso-propanol in n-heptane over 30 min as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention times: 14.3 min) to give 39 (9.0 mg, 49% over 2 steps) as a colorless solid.

TLC (5% methanol in dichloromethane): Rf = 0.28 (UV, CAM).

$^1$H NMR (599 MHz, CDCl$_3$): δ = 7.07 (s, 1H), 6.41 (s, 1H), 4.28 (s, 2H), 3.01 (d, J = 17.8 Hz, 1H), 2.85–2.76 (m, 1H), 2.52–2.42 (m, 1H), 2.42–2.34 (m, 2H), 2.26–2.15 (m, 2H), 2.11–2.05 (m, 1H), 1.86–1.76 (m, 1H), 1.73–1.67 (m, 1H), 1.56–1.46 (m, 1H), 1.35–1.24 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.81 (s, 3H), 0.77 (d, J = 6.9 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ = 172.5, 155.4, 149.5, 143.5, 132.0, 130.5, 123.4, 113.3, 100.9, 95.4, 43.6, 37.8, 32.1, 31.6, 30.5, 29.3, 27.9, 27.1, 22.5, 22.2, 20.8, 16.1, 15.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{\text{max}}$ = 3234, 2935, 2959, 1683, 1609, 1465, 1360, 1240, 1076, 934.

HRMS (El) calc. for C$_{23}$H$_{28}$NO$_3$ [M]+: 367.2142; found: 367.246.

$[\alpha]_D^{20} = -85.3^\circ$ (c = 0.15, CH$_2$Cl$_2$).

Melting point: 156–161 °C
Synthesis of Aldehyde 33

2,2-Dimethylcyclohexan-1-one (S22)

Note: The alkylation was carried out in three parallel 12.3 g batches.

Potassium \( \text{tert}-\text{butoxide} \) (29.6 g, 263 mmol, 2.10 equiv) was added to a solution of cyclohexanone (S21) (12.3 g, 125 mmol, 1 equiv) and methyl iodide (37.3 g, 263 mmol, 2.10 equiv) in tetrahydrofuran (600 mL) at \(-20^\circ\text{C}\). After 15 h, saturated aqueous ammonium chloride solution (200 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with diethyl ether (3 \( \times \) 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% diethyl ether in pentane) to yield S22 (7.67 g, 48%) as a colorless oil. The obtained analytical data were in full agreement with those previously reported.\(^{16}\)

2,2-Dimethyl-1-vinylcyclohexan-1-ol (S23)

A solution of S22 (23.0 g, 182 mmol, 1 equiv) in tetrahydrofuran (90 mL) was added dropwise to a solution of vinylmagnesium bromide (1 M in tetrahydrofuran, 219 mL, 219 mmol, 1.20 equiv) over a period of 45 min at 0 \(^\circ\text{C}\). After 1.5 h, saturated aqueous ammonium chloride solution (500 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 \( \times \) 300 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield crude S23 as a yellow oil. The residue was used without further purification in the next step.

Diene 31

Note: CuSO\(_4\)•5H\(_2\)O was dried over night in a 140 \(^\circ\text{C}\) oven.
To a solution of crude \textbf{S23} (28.1 g, 182 mmol, 1 equiv) in benzene (400 mL) was added anhydrous copper(II) sulfate (63.9 g, 400 mmol, 2.20 equiv) and the reaction mixture was heated to 90 °C under Dean-Stark conditions. After 16 h, the reaction mixture was allowed to cool to 23 °C, filtered through a pad of Celite® and was washed thoroughly with \textit{n}-pentane. The filtrate was carefully concentrated (>220 mbar, 30 °C) and the residue was purified by flash-column chromatography on silica gel (\textit{n}-pentane) to yield \textbf{31} as a yellow oil (17.7 g, 71% over 2 steps). The obtained analytical data were in full agreement with those previously reported.\textsuperscript{17}

\textbf{5,6-Dehydrodecalin S24}

\[ \text{31} \quad \text{+} \quad \text{21} \quad \xrightarrow{\text{Me2AlCl}} \quad \text{S24} \]

\textbf{5,6-Dehydrodecalin S24} was prepared according to the procedure described by A. J. Minnaard\textsuperscript{18}:

A solution of dimethylaluminium chloride (1 M in hexanes, 93.0 mL, 93.0 mmol, 2.20 equiv) was added dropwise to a solution of \textbf{21} (9.83 g, 46.5 mmol, 1.10 equiv) in 1,2-dichloroethane (250 mL) over a period of 15 min at -40 °C. After 20 min, a solution of \textbf{30} (8.00 g, 42.3 mmol, 1 equiv) in 1,2-dichloroethane (100 mL) was added over a period of 15 min to the reaction mixture. After complete addition, the reaction mixture was allowed to warm to 23 °C. After 36 h, aqueous hydrogen chloride solution (1 M, 100 mL) was carefully added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (14% diethyl ether in \textit{n}-pentane) to yield \textbf{S24} as a yellow highly viscous oil (9.02 g, 61%). The obtained analytical data were in full agreement with those previously reported.

\textbf{Thioester 32}

A solution of \textit{n}-butyllithium (2.40 M in hexanes 50.8 mL, 122 mmol, 4.70 equiv) was added dropwise to a solution of ethanethiol (11.3 mL, 153 mmol, 5.90 equiv) in tetrahydrofuran (250 mL) at 0 °C. After complete addition, the reaction mixture was slowly allowed to warm to 23 °C. After 30 min, a solution of \textbf{S24} (9.02 g,}
26.0 mmol, 1 equiv) in tetrahydrofuran (70 mL) was added. After 7 h, diethyl ether (100 mL) and saturated aqueous ammonium chloride solution (100 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (2% diethyl ether in n-pentane) to yield 32 as a yellow oil (7.10 g, 98%). The obtained analytical data were in full agreement with those previously reported.18

Aldehyde 33

Triethylsilane (1.07 g, 9.20 mmol, 1.20 equiv) was added to a solution of thioester 32 (2.15 g, 7.67 mmol, 1 equiv) and palladium(II) acetate (103 mg, 460 µmol, 0.060 equiv) in acetone (60 mL). After 2.5 h, the dark brown solution was filtered through a plug of silica, the filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (2% ethyl acetate in hexanes) to provide 33 (1.43 g, 85%) as a colorless solid. The obtained analytical data were in full agreement with those previously reported.18 Recrystallization from diethyl ether gave crystals suitable for single-crystal X-ray diffraction.
Synthesis of (+)-Aureol (2) and 5-epi-Aureol (9)

Benzylic alcohol (S25)

To a solution of 34 (1.16 g, 5.85 mmol, 1.60 equiv) in tetrahydrofuran (8.5 mL) and freshly distilled N,N,N′,N′-tetramethylethane-1,2-diamine (TMEDA) (over CaH₂, 1.65 mL, 11.0 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.40 M in hexanes, 2.28 mL, 5.48 mmol, 1.50 equiv) at –78 °C. After complete addition, the solution was allowed to warm to –30 °C. After 1.5 h, the reaction mixture was cooled to –78 °C and a solution of aldehyde 33 (805 mg, 3.65 mmol, 1 equiv) in tetrahydrofuran (3.5 mL) was added. The reaction mixture was allowed to warm to –30 °C over a period of 2 h, then diethyl ether (40 mL) and saturated aqueous ammonium chloride solution (40 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield S25 (1.32 g, 86%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

**TLC** (10% ethyl acetate in hexanes): \( R_f = 0.29 \) (CAM).

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 3496, 2952, 1492, 1381, 1218, 1188, 1150, 1078, 1004, 922 \).

**HRMS** (EI) calcd for C_{25}H_{38}O_{5} [M]+: 418.2714; found: 418.2708.
A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 15.4 mL, 15.4 mmol, 5.00 equiv) was added dropwise to a solution of S25 (1.29 g, 3.08 mmol, 1 equiv) in tetrahydrofuran (24 mL) at −78 °C. After 30 min, carbon disulfide (3.72 mL, 61.6 mmol, 20.0 equiv) was added dropwise to the orange solution and the resulting red solution was allowed to warm to −65 °C. After 1 h, methyl iodide (3.84 mL, 61.6 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

A solution of the xanthogenate (1.57 g, 3.08 mmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (253 mg, 1.54 mmol, 0.500 equiv) and tributyltin hydride (6.72 g, 23.1 mmol, 7.50 equiv) in benzene (50 mL) was heated to 90 °C. After 1.5 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 3% ethyl acetate in hexanes) to yield 35 as a colorless oil (1.05 g, 84% over 2 steps).

TLC (10% ethyl acetate in hexanes): Rf = 0.53 (CAM).

1H NMR (599 MHz, CDCl3): δ = 7.04 (d, J = 8.9 Hz, 1H), 6.91 (d, J = 3.0 Hz, 1H), 6.83 (d, J = 8.9 Hz, 1H), 5.39–5.36 (m, 1H), 5.15 (d, J = 6.6 Hz, 1H), 5.10 (s, 2H), 5.09 (d, J = 6.6 Hz, 1H), 3.49 (s, 3H), 3.47 (s, 3H), 2.82 (d, J = 13.6 Hz, 1H), 2.55 (d, J = 13.6 Hz, 1H), 2.13 (m, 1H), 1.96 (m, 1H), 1.80 (m, 2H), 1.55–1.47 (m, 2H), 1.47–1.42 (m, 1H), 1.39–1.34 (m, 1H), 1.17 m, 1H), 1.04 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.95 (m, 1H), 0.90 (s, 3H), 0.78 (s, 3H).

13C NMR (151 MHz, CDCl3): δ = 152.0, 151.6, 146.8, 130.5, 120.5, 115.4, 115.0, 114.8, 95.7, 95.4, 56.1, 56.0, 41.5, 40.3, 39.9, 37.5, 36.5, 34.7, 31.8, 29.9, 29.9, 28.3, 22.7, 16.8, 16.4.

IR (Diamond-ATR, neat): νmax = 2926, 1495, 1455, 1219, 1189, 1149, 1075, 1010, 922, 81.

HRMS (El) calcd for C25H38O4 [M]+: 402.2765; found: 402.2757.

[α]D² = + 28.68° (c = 0.96, CH2Cl2).
A solution of hydrochloric acid (~1.25 M in methanol, 9 mL) was added to a solution of 35 (300 mg, 744 μmol, 1 equiv) in dichloromethane (3 mL) and the resulting solution was heated to 30 °C. After 5 h, the reaction mixture was diluted with dichloromethane (25 mL) and saturated aqueous sodium bicarbonate solution (25 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield S26 as a colorless foam that was directly used in the following step.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 1.95 mL, 7.44 mmol, 10.0 equiv) was added dropwise to a solution of the crude para-hydroquinone S26 (234 mg, 744 μmol, 1 equiv) in dichloromethane (30 mL) at −78 °C. After complete addition, the reaction mixture was allowed to warm to −10 °C over a period of 1.5 h. After 2 h at −10 °C, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield (+)-aureol (2) (193 mg, 83% over two steps) as a colorless foam.

**TLC** (20% ethyl acetate in hexanes): Rf = 0.43 (CAM).

**1H NMR** (800 MHz, CDCl3): δ = 6.61 (d, 3J18/19 = 8.6 Hz, 1H, H-18), 6.56 (dd, 3J15A/15B = 8.6 Hz, 4J18/21 = 3.0 Hz, 1H, H-19), 6.49 (d, 4J21/19 = 3.0 Hz, 1H), 4.32 (s, 1H, O-H), 3.38 (d, 2J15A/15B = 17 Hz, 1H, H-15A), 2.10–1.99 (m, 2H, 1α, 2α), 1.97 (d, 2J15B/15A = 17 Hz, 1H, H-15A), 1.84–1.75 (m, 2H, H-7), 1.71–1.64 (m, 2H, H-6A, H-8), 1.60–1.53 (m, 1H, H-6B), 1.50–1.45 (m, 1H, H-2b), 1.45–1.40 (m, 2H, H-3A, H-5), 1.37–1.33 (m, 1H, H-1b), 1.20–1.17 (m, 1H, H-3b), 1.11 (d, 3J13/17 = 7.5 Hz, 3H, H-17), 1.06 (s, 3H, H-11), 0.92 (s, 3H, H-14), 0.78 (s, 3H, H-14).

**13C NMR** (201 MHz, CDCl3): δ = 148.3 (C-20), 145.8 (C-17), 122.2 (C-16), 117.2 (C-18), 115.0 (C-19), 114.0 (C-21), 82.3 (C-10), 44.0 (C-5), 39.3 (C-8), 38.1 (C-9), 37.3 (C-15), 33.9 (C-4), 33.8 (C-3), 31.9 (C-12), 29.8 (C-11), 29.3 (C-7), 27.9 (C-1), 22.2 (C-6), 20.2 (C-14), 18.3 (C-2), 17.3 (C-13).

**IR** (Diamond-ATR, neat): νmax = 3344, 2933, 1494, 1450, 1231, 1185, 1171, 1158, 952, 907, 733.

**HRMS** (EI) calcd for C21H38O2 [M]+: 314.2240; found: 314.2234.

[α]D20 = +73.5° (c = 1.19, CCl4); lit. [α]D25 = +65.0° (c = 2.00, CCl4) (+)-aureol.20
Supplementary Table 4 Comparison of \(^1\)H NMR data for natural and synthetic (+)-aureol (2).

| Proton | Synthetic (800 MHz, CDCl\(_3\)) | Natural (n.a., CDCl\(_3\)) | \(\Delta: \delta\) (ppm) |
|--------|---------------------------------|----------------------------|-------------------------|
| 1A     | 2.10–1.99 (m, 2H)               |                            |                         |
| 1B     | 1.37–1.33 (m, 1H)               |                            |                         |
| 2A     | 2.10–1.99 (m, 2H)               |                            |                         |
| 2B     | 1.50–1.45 (m, 1H)               |                            |                         |
| 3A     | 1.45–1.40 (m, 2H)               |                            |                         |
| 3B     | 1.20–1.17 (m, 1H)               |                            |                         |
| 5      | 1.45–1.40 (m, 2H)               |                            |                         |
| 6A     | 1.71–1.64 (m, 2H)               |                            |                         |
| 6B     | 1.60–1.53 (m, 1H)               |                            |                         |
| 7      | 1.84–1.75 (m, 2H)               |                            |                         |
| 8      | 1.71–1.64 (m, 2H)               |                            |                         |
| 11     | 1.06 (s, 3H)                    | 1.06 (s, 3H)               | ± 0.00                  |
| 12     | 0.78 (s, 3H)                    | 0.78 (s, 3H)               | ± 0.00                  |
| 13     | 1.11 (d, \(J = 7.5\) Hz, 3H)   | 1.11 (d, \(J = 7\) Hz, 3H) | ± 0.00                  |
| 14     | 0.92 (s, 3H)                    | 0.92 (s, 3H)               | ± 0.00                  |
| 15A    | 3.38 (d, 1H)                    | 3.38 (d, \(J = 16\) Hz, 1H) | + 0.00                 |
| 15B    | 1.97 (d, \(J = 17.0\) Hz, 1H), | 1.96 (d, \(J = 16\) Hz, 1H) | + 0.01                 |
| 18     | 6.61 (d, \(J = 8.6\) Hz, 1H),  |                            |                         |
| 19     | 6.56 (dd, \(J = 8.6, 3.0\) Hz, 1H), |                            |                         |
| 21     | 6.49 (d, \(J = 3.0\) Hz, 1H),  | 6.50 (br s, 1H)            | – 0.01                 |
| OH     | 4.32 (s, 1H)                    | Not reported               |                         |
Supplementary Table 5 Comparison of $^{13}$C NMR data for natural and synthetic (+)-aureol (2).

| Carbon | Synthetic (201 MHz, CDCl$_3$) | Natural (n.a., CDCl$_3$) | Δ: δ (ppm) |
|--------|-------------------------------|--------------------------|------------|
| 1      | 27.9                          | 27.9                     | ± 0.0      |
| 2      | 18.3                          | 18.4                     | − 0.1      |
| 3      | 33.8                          | 33.9                     | − 0.1      |
| 4      | 33.9                          | 33.9                     | ± 0.0      |
| 5      | 44.0                          | 44.0                     | ± 0.0      |
| 6      | 22.2                          | 22.2                     | ± 0.0      |
| 7      | 29.3                          | 29.3                     | ± 0.0      |
| 8      | 39.3                          | 39.3                     | ± 0.0      |
| 9      | 38.1                          | 38.1                     | ± 0.0      |
| 10     | 82.3                          | 82.4                     | − 0.1      |
| 11     | 29.8                          | 29.8                     | ± 0.0      |
| 12     | 31.9                          | 31.9                     | ± 0.0      |
| 13     | 17.3                          | 17.3                     | ± 0.0      |
| 14     | 20.2                          | 20.2                     | ± 0.0      |
| 15     | 37.3                          | 37.4                     | − 0.1      |
| 16     | 122.2                         | 122.2                    | ± 0.0      |
| 17     | 145.8                         | 145.8                    | ± 0.0      |
| 18     | 117.2                         | 117.2                    | − 0.1      |
| 19     | 115.0                         | 115.2                    | − 0.2      |
| 20     | 148.3                         | 148.2                    | + 0.1      |
| 21     | 114.0                         | 114.2                    | − 0.2      |
A solution of hydroiodic acid (57 wt.% in H$_2$O, 63.0 µL, 477 µmol, 10.0 equiv) was added to a solution of (+)-aureol (2) (15.0 mg, 47.7 µmol, 1 equiv) in benzene (4 mL) in a pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 24 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield 5-epi-aureol (9) (13.0 mg, 87% over two steps) as a colorless foam. The obtained analytical data were in full agreement with those values reported in literature.$^{21}$
Synthesis of (+)-Strongylin A (4), 5-epi-Strongylin A (45), 46, 47, 3-Hydroxy-strongylin A (48) and 49

Arene Unit S28

To a solution of S27²² (675 mg, 4.28 mmol, 1 equiv) in N,N-dimethylformamide (25 mL) was added in small portions sodium hydride (60% mineral oil dispersion, 482 mg, 12.0 mmol, 2.50 equiv) at 0 °C. After 30 min, bromomethyl methylether (1.51 g, 12.0 mmol, 2.50 equiv) was added dropwise to the dark green suspension and the resulting mixture was allowed to warm to 23 °C. After 13 h, saturated aqueous ammonium chloride solution (60 mL) and diethyl ether (80 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 60 mL). The combined organic extracts were washed with aqueous saturated sodium chloride solution (50 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to provide S28 (879 mg, 80%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): \(R_f = 0.23\) (UV, CAM).

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.06\) (d, \(J = 8.8\) Hz, 1H), 6.78 (d, \(J = 2.9\) Hz, 1H), 6.47 (dd, \(J = 8.8, 2.9\) Hz, 1H), 5.21 (s, 2H), 5.14 (s, 2H), 3.76 (s, 3H), 3.52 (s, 3H), 3.51 (s, 3H).

\(^1^3^C\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 155.5, 148.5, 141.3, 118.4, 106.2, 104.2, 96.5, 95.5, 56.3, 56.2, 55.8\).

IR (Diamond-ATR, neat): \(\tilde{\nu}_{\text{max}} = 2902, 2829, 1609, 1506, 1259, 1219, 1150, 1072, 1039, 984, 921\).

HRMS (El) calcd for: C\(_{11}\)H\(_{16}\)O\(_5\) [M]: 228.0992; found: 228.0989.
Benzylic alcohol S29

To a solution of S28 (109 mg, 478 µmol, 1.40 equiv) in tetrahydrofuran (2 mL) and freshly distilled N,N,N',N'-tetramethylethane-1,2-diamine (over CaH₂, 150 µL, 1.02 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.44 M in hexanes, 128 µL, 443 µmol, 1.30 equiv) at −78 °C. After 10 min, the reaction mixture was allowed to warm to −30 °C. After 1.5 h, the reaction mixture was cooled to −78 °C and a solution of aldehyde 33 (75.2 mg, 341 µmol, 1 equiv) in tetrahydrofuran (1 mL) was added. The reaction mixture was allowed to warm to −30 °C over a period of 2 h. Diethyl ether (15 mL) and saturated aqueous ammonium chloride solution (15 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield S29 (153 mg, 88%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (10% ethyl acetate in hexanes): \( R_f = 0.23 \) (CAM).

IR (Diamond-ATR, neat): \( \tilde{\nu}_{max} = 3552, 2925, 1591, 1483, 1357, 1251, 1152, 1069, 977, 924, 805 \).

HRMS (El) calcd for C_{26}H_{40}O_6 [M]^+: 448.2819; found: 448.2816.
A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.53 mL, 1.53 mmol, 5.00 equiv) was added dropwise to a solution of S29 (137 mg, 305 µmol, 1 equiv) in tetrahydrofuran (2 mL) at −78 °C. After 30 min, carbon disulfide (370 µL, 610 µmol, 20.0 equiv) was slowly added and the reaction mixture was allowed to warm to −65 °C. After 1 h, methyl iodide (380 µL, 6.10 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL) were added to the reaction mixture, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

A degassed solution of the xanthogenate (164 mg, 305 µmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (25.0 mg, 152 µmol, 0.50 equiv) and tributyltin hydride (666 mg, 2.29 mmol, 7.50 equiv) in benzene (6 mL) was heated to 90 °C. After 4 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 3% ethyl acetate in hexanes) to yield S30 as a colorless oil (57.0 mg, 43% over 2 steps).

**TLC** (20% ethyl acetate in hexanes): Rf = 0.35 (CAM).

**1H NMR** (800 MHz, C6D6): δ = 6.99 (d, J = 8.9 Hz, 1H), 6.28 (d, J = 8.9 Hz, 1H), 5.61–5.54 (m, 1H), 5.15–5.09 (m, 2H), 4.92–4.88 (m, 2H), 3.41 (s, 3H), 3.35 (s, 3H), 3.24 (d, J = 12.9 Hz, 1H), 3.22 (s, 3H), 2.97 (d, J = 12.9 Hz, 1H), 2.90–2.86 (m, 1H), 2.01–1.97 (m, 2H), 1.79–1.74 (m, 1H), 1.61–1.54 (m, 1H), 1.51–1.47 (m, 1H), 1.46–1.40 (m, 2H), 1.27–1.22 (m, 1H), 1.21 (s, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 0.94–0.88 (m, 1H).

**13C NMR** (201 MHz, C6D6): δ = 154.7, 148.6, 147.7, 144.5, 125.0, 115.8, 115.6, 105.5, 99.6, 96.4, 57.5, 55.8, 55.1, 42.6, 41.9, 41.2, 39.4, 36.9, 35.9, 32.3, 31.5, 30.2, 28.4, 23.4, 16.8, 14.8.

**IR** (Diamond-ATR, neat): νmax = 2928, 2837, 1483, 1464, 1250, 1154, 1069, 1038, 983, 951, 801.

**HRMS** (EI) calcd for C26H40Os [M]+: 432.2870; found: 432.2865.

[α]D20° = +13.1° (c = 5.38, CH2Cl2).
(+)-Strongylin A (4)

A solution of hydrochloric acid (~1.25 M in methanol, 4 mL) was added to a solution of S30 (33.0 mg, 76.0 µmol, 1 equiv) in dichloromethane (2 mL) and the resulting solution was heated to 30 °C. After 6.5 h, the reaction mixture was diluted with dichloromethane (5 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield S31 as a colorless solid that was directly used in the following step.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 140 µL, 534 µmol, 7.00 equiv) was added dropwise to a solution of crude hydroquinone S31 (26.0 mg, 76.0 µmol, 1 equiv) in dichloromethane (3 mL) at −78 °C and the reaction mixture was allowed to warm to −30 °C over a period of 30 min. After 1.5 h, saturated aqueous ammonium chloride solution (10 mL) and dichloromethane (5 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield (+)-strongylin A (4) (16.6 mg, 63% over two steps) as a colorless foam.

TLC (20% ethyl acetate in hexanes): Rₗ = 0.50 (CAM).

\(^1\)H NMR (400 MHz, \(\text{C}_6\text{D}_6\)): \(\delta = 6.96\) (d, \(^3\)J₁₉/₂₀ = 8.6 Hz, 1H, H-19), 6.13 d, \(^3\)J₂₀/₁₉ = 8.6 Hz, 1H, H-20), 5.12 (s, 1H, O-H), 3.42 (s, 3H, H-22), 3.23 (d, \(^2\)J₁₅A/₁₅B = 17.7 Hz, 1H, H-15A), 2.33 (d, \(^2\)J₁₅B/₁₅A = 17.7 Hz, 1H, H-15B), 1.93–1.78 (m, 2H, H-2ₐ, H7ₐ), 1.69–1.51 (m, 3H, H-1ₐ, H-1ₕ, H-8), 1.45–1.36 (m, 2H, H-5, H-6ₐ), 1.33–1.18 (m, 3H, H-2ₕ, H-3ₐ, H-6ₕ). 1.12–1.04 (m, 5H, H-3ₕ, H-7ₕ, H-12), 0.88 (d, \(^3\)J₁₃/₈ = 7.6 Hz, 3H, H-1₃), 0.82 (s, 3H, H-1₄), 0.64 (s, 3H, H-1₁).

\(^1\)C NMR (101 MHz, \(\text{C}_6\text{D}_6\)): \(\delta = 151.4\) (C-2₁), 139.8 (C-1₇), 139.6 (C-1₈), 111.5 (C-1₉), 110.7 (C-1₆), 100.9 (C-2₀), 83.9 (C-1₀), 55.0 (C-2₂), 44.0 (C-5), 39.8 (C-₈), 38.3 (C-₉), 34.0 (C-₃), 33.5 (C-₄), 32.9 (C-₁₅), 32.2 (C-₁₁), 29.5 (C-₁), 29.3 (C-₁₂), 28.0 (C-₇), 22.7 (C-₆), 20.3 (C-₁₄), 18.9 (C-₂), 17.4 (C-₁₃).

IR (Diamond-ATR, neat): \(\tilde{\nu}_{\text{max}} = 3567, 2953, 1490, 1384, 1264, 1182, 1107, 1089, 946\).

HRMS (El calcd for \(\text{C}_{22}\text{H}_{3ₐ}\text{O}_{₃}\) [M⁺]: 344.2346; found: 344.2346.

[\(\alpha\)]\text{D}^{20} = +66.3° (c = 1.46, CH₂Cl₂); lit. [\(\alpha\)]\text{D}^{20} = +72.0° (c = 0.012, CH₂Cl₂) (+)-strongylin A.²³
Supplementary Table 6 Comparison of $^1$H NMR data for natural and synthetic (+)-strongylin A (4).

| Proton | Synthetic (400 MHz, C$_6$D$_6$) | Natural (360 MHz, C$_6$D$_6$) | $\Delta$: $\delta$ (ppm) |
|--------|---------------------------------|-------------------------------|---------------------------|
| 1      | 1.69–1.51 (m, 3H)               | 1.66 (2H, m, 2H)              |                           |
| 2A     | 1.93–1.78 (m, 2H)               | 1.86 (m, 2H)                  | ± 0.00                    |
| 2B     | 1.33–1.18 (m, 3H)               | 1.32 (m, 1H)                  |                           |
| 3A     | 1.33–1.18 (m, 3H)               | 1.25 (m, 2H)                  |                           |
| 3B     | 1.12–1.04 (m, 5H)               | 1.12 (m, 2H)                  |                           |
| 5      | 1.45–1.36 (m, 2H)               | 1.43 (m, 1H)                  |                           |
| 6A     | 1.45–1.36 (m, 2H)               | 1.41 (m, 1H)                  |                           |
| 6B     | 1.33–1.18 (m, 3H)               | 1.25 (m, 2H)                  | ± 0.00                    |
| 7A     | 1.93–1.78 (m, 2H)               | 1.86 (m, 2H)                  | ± 0.00                    |
| 7B     | 1.12–1.04 (m, 5H)               | 1.12 (m, 2H)                  |                           |
| 8      | 1.69–1.51 (m, 3H)               | 1.60 (m, 1H)                  |                           |
| 11     | 0.64 (s, 3H)                    | 0.65 (s, 3H)                  | – 0.01                    |
| 12     | 1.12–1.04 (m, 5H)               | 1.09 (s, 3H)                  |                           |
| 13     | 0.88 (d, $J$ = 7.6 Hz, 3H)      | 0.90 (d, $J$ = 7.6 Hz, 3H)    | – 0.02                    |
| 14     | 0.82 (s, 3H)                    | 0.82(s, 3H)                   | ± 0.00                    |
| 15A    | 3.23 (d, $J$ = 17.7 Hz, 1H)     | 3.20 (d, $J$ = 7.7 Hz, 1H)    | + 0.03                    |
| 15B    | 2.33 (d, $J$ = 17.7 Hz, 1H)c    | 2.30 (d, $J$= 7.7 Hz, 1H)     | + 0.03                    |
| 19     | 6.96 (d, $J$ = 8.6 Hz, 1H)      | 6.91 (d, $J$ = 8.6 Hz, 1H)    | + 0.05                    |
| 20     | 6.13 (d, $J$ = 8.6 Hz, 1H)      | 6.13 (d, $J$ = 8.6, 1H)       | ± 0.00                    |
| 22     | 3.42 (s, 3H)                    | 3.44 (s, 3H)                  | – 0.02                    |
| OH     | 5.12 (s, 1H)                    | 5.12 (s, 1H)                  | ± 0.00                    |
**Supplementary Table 7** Comparison of $^{13}$C NMR data for natural and synthetic (+)-strongylin A (4).

| Carbon | Synthetic (101 MHz, C$_6$D$_6$) | Natural (90 MHz, C$_6$D$_6$)$^{23}$ | Δ: δ (ppm) |
|--------|--------------------------------|-----------------------------------|-------------|
| 1      | 29.5                           | 29.5                              | ± 0.0       |
| 2      | 18.9                           | 18.9                              | ± 0.0       |
| 3      | 34.0                           | 34.0                              | ± 0.0       |
| 4      | 33.5                           | 33.5                              | ± 0.0       |
| 5      | 44.0                           | 44.0                              | ± 0.0       |
| 6      | 22.7                           | 22.7                              | ± 0.0       |
| 7      | 28.0                           | 27.9                              | + 0.1       |
| 8      | 39.8                           | 39.8                              | ± 0.0       |
| 9      | 38.3                           | 38.3                              | ± 0.0       |
| 10     | 83.9                           | 83.8                              | + 0.1       |
| 11     | 32.2                           | 32.1                              | + 0.1       |
| 12     | 29.3                           | 29.2                              | + 0.1       |
| 13     | 17.4                           | 17.4                              | ± 0.0       |
| 14     | 20.3                           | 20.5                              | - 0.2       |
| 15     | 32.9                           | 32.8                              | + 0.1       |
| 16     | 110.7                          | 110.7                             | ± 0.0       |
| 17     | 139.8                          | 139.7                             | + 0.1       |
| 18     | 139.6                          | 139.4                             | + 0.2       |
| 19     | 111.5                          | 111.5                             | ± 0.0       |
| 20     | 100.9                          | 100.8                             | + 0.1       |
| 21     | 151.4                          | 151.3                             | + 0.1       |
| 22     | 55.0                           | 55.0                              | ± 0.0       |
5-epi-strongylin A (45)

A solution of hydrochloric acid (~1.25 M in methanol, 9 mL) was added to a solution of S30 (117 mg, 270 µmol, 1 equiv) in dichloromethane (7 mL) at 23 °C and the mixture was heated to 30 °C. After 6 h, the reaction mixture was diluted with dichloromethane (30 mL) and saturated aqueous sodium bicarbonate solution (20 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield S31 as a colorless solid that was directly used in the following reaction.

A solution of hydroiodic acid (57 wt.% in water, 357 µL, 2.70 mmol, 10.0 equiv) was added to a solution of the crude hydroquinone S31 (93.2 mg, 270 µmol, 1 equiv) in benzene (10 mL) in an Ace® pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 16 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield epi-strongylin A (45) (59.0 mg, 63% over two steps) as a colorless foam.

**TLC** (20% ethyl acetate in hexanes): \( R_f = 0.47 \) (CAM).

**\(^1H\) NMR** (800 MHz, C\(_6\)D\(_6\)): \( \delta = 6.99 \) (d, \( J = 8.6 \) Hz, 1H), 6.13 (d, \( J = 8.6 \) Hz, 1H), 5.38 (s, 1H), 3.40 (s, 3H), 2.98 (d, \( J = 17.8 \) Hz, 1H), 2.30 (dd, \( J = 17.8, 1.0 \) Hz, 1H), 1.69–1.61 (m, 2H), 1.60–1.51 (m, 2H), 1.40–1.35 (m, 1H), 1.32–1.25 (m, 3H), 1.14–1.06 (m, 2H), 1.04 (s, 3H), 1.03–0.96 (m, 2H), 0.81 (s, 3H), 0.74 (s, 3H), 0.68 (d, \( J = 6.8 \) Hz, 3H).

**\(^{13}C\) NMR** (201 MHz, C\(_6\)D\(_6\)): \( \delta = 149.8, 138.88, 138.86, 109.9, 109.2, 100.0, 81.5, 53.7, 44.5, 40.1, 35.9, 31.8, 31.1, 30.6, 29.1, 27.0, 27.0, 21.3, 20.6, 16.7, 15.7, 15.0.

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{max} = 3557, 2938, 1618, 1489, 1390, 1264, 1170, 1083, 918, 788. $$

**HRMS** (EI) calcd for C\(_{22}\)H\(_{32}\)O\(_3\) [M\(^+\)]: 344.2346; found: 344.2336.

[\( \alpha \)]\(_D\)\(^{20} \) = −8.7° (\( c = 0.21, \text{CH}_2\text{Cl}_2 \)).
Quinone 46

A solution of diammonium cerium(IV) nitrate (28.2 mg, 51.5 µmol, 2.50 equiv) in water (2.5 mL) was added dropwise to a solution of strongylin A (4) (7.10 mg, 21.0 µmol, 1 equiv) in acetonitrile (2.5 mL) over a period of 40 min at 0 °C. After 2 h, the bright yellow solution was diluted with water (10 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (7% diethyl ether in pentane) to yield 46 (5.10 mg, 75%) as a yellow oil.

**TLC** (10% ethyl acetate in hexanes): \( R_f = 0.25 \) (UV, CAM).

**\(^1\H NMR**** (599 MHz, CDCl₃): \( \delta = 6.64 \) (d, \( J = 10.2 \) Hz, 1H), 6.57 (d, \( J = 10.2 \) Hz, 1H), 2.86 (d, \( J = 18.7 \) Hz, 1H), 2.17–2.06 (m, 1H), 2.05–1.97 (m, 1H), 1.94 (d, \( J = 18.7 \) Hz, 1H), 1.89–1.80 (m, 2H), 1.80–1.72 (m, 2H), 1.60–1.51 (m, 2H), 1.44–1.35 (m, 3H), 1.25–1.21 (m, 1H), 1.09 (d, \( J = 7.5 \), 1.2 Hz, 3H), 0.99 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H).

**\(^{13}\C NMR** (151 MHz, CDCl₃): \( \delta = 187.4, 181.6, 150.6, 137.0, 134.0, 117.9, 87.5, 45.1, 39.2, 38.1, 33.9, 33.6, 32.1, 30.9, 29.8, 29.1, 27.9, 22.6, 20.3, 18.4, 17.3.

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 2931, 2360, 1675, 1646, 1598, 1393, 1220, 1048, 839, 733.

**HRMS** (EI) calcd for C₂₁H₂₆O₃ [M]⁺: 328.2033; found: 328.2043.

\[ [\alpha]_D^{20} = +22.3^\circ \ (c = 1.20, \text{CH}_2\text{Cl}_2). \]
Quinone 47

A solution of diammonium cerium(IV) nitrate (35.8 mg, 65.3 µmol, 2.50 equiv) in water (3 mL) was added dropwise to a solution of *epi*-strongylin A (45) (9.00 mg, 26.0 µmol, 1 equiv) in acetonitrile (3 mL) over a period of 30 min at 0 °C. After 2 h, the bright yellow solution was diluted with water (10 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield 47 (6.30 mg, 73%) as a yellow solid.

**TLC** (20% ethyl acetate in hexanes): \( R_f = 0.50 \) (UV, CAM).

**\(^1\)H NMR** (599 MHz, CDCl\(_3\)): \( \delta = 6.63 \) (d, \( J = 10.1 \) Hz, 1H), 6.58 (d, \( J = 10.1 \) Hz, 1H), 2.55 (d, \( J = 19.2 \) Hz, 1H), 1.99 (d, \( J = 19.2 \) Hz, 1H), 1.70–1.64 (m, 1H), 1.64–1.58 (m, 3H), 1.53–1.41 (m, 4H), 1.39–1.33 (m, 2H), 1.31–1.27 (m, 1H), 1.23–1.18 (m, 1H), 1.16 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.78 (d, \( J = 6.7 \) Hz, 3H).

**\(^{13}\)C NMR** (151 MHz, CDCl\(_3\)): \( \delta = 187.2, 181.6, 152.1, 137.0, 134.2, 117.8, 86.2, 45.8, 41.8, 37.3, 33.6, 32.61, 32.60, 30.4, 29.4, 26.9, 22.3, 22.0, 18.0, 17.0, 16.5.

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{max} = 2942, 1677, 1645, 1595, 1387, 1344, 1202, 1162, 1041, 898, 839, 731.\)

**HRMS** (EI) calcd for C\(_{21}\)H\(_{28}\)O\(_3\): 328.2033 [M]\(^+\); found: 328.2035.

\( [\alpha]_D^{20} = -1.9^\circ \) (c = 0.17, CH\(_2\)Cl\(_2\)).

**Melting point:** 138–143 °C
2-Hydroxy-3-iodo-4-methoxybenzaldehyde (S33) was synthesized according to a procedure described by U. Schilde.\textsuperscript{24}

Aluminum trichloride (1.17 g, 8.81 mmol, 1 equiv) was added to a solution of aldehyde S32 (1.34 g, 8.81 mmol, 1 equiv) in dichloromethane (40 mL) at –20 °C. After 15 min, N-iodosuccinimide (NIS) (2.18 g, 9.96 mmol, 1.10 equiv) was added to the bright orange solution and the reaction mixture was allowed to warm to 23 °C. After 13 h, aqueous hydrochloric acid solution (2 m, 100 mL) and dichloromethane (60 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield aldehyde S33 (1.72 g, 70%) as a colorless solid. The obtained analytical data were in full agreement with those previously reported.
3-Iodo-4-methoxy-2-(methoxymethoxy)benzaldehyde (S34)

To a solution of S33 (1.05 g, 3.78 mmol, 1 equiv) in N,N-dimethylformamide (40 mL) was added sodium hydride (60% mineral oil dispersion, 196 mg, 4.91 mmol, 1.30 equiv) at 0 °C. After 60 min, bromomethyl methylether (339 µL, 4.15 mmol, 1.10 equiv) was added dropwise to the dark brown suspension that became clear upon addition. After 1 h, saturated aqueous ammonium chloride solution (60 mL) was added and the mixture was extracted with diethyl ether (3 × 60 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (25% ethyl acetate in hexanes) to provide S34 (1.08 g, 89%) as a colorless solid.

**TLC** (30% ethyl acetate in hexanes): R<sub>f</sub> = 0.38 (UV, KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (599 MHz, CDCl<sub>3</sub>): δ = 10.18 (d, J = 0.8 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 6.76 (dd, J = 8.7, 0.8 Hz, 1H), 5.18 (s, 2H), 3.98 (s, 3H), 3.63 (s, 3H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>): δ = 189.1, 164.5, 162.2, 130.6, 125.1, 107.6, 101.7, 85.2, 58.6, 57.1.

**IR** (Diamond-ATR, neat): ν<sub>max</sub> = 2940,1683, 1583, 1376, 1283, 1248, 1120, 1059, 962, 900.

**HRMS** (EI) calc. for C<sub>10</sub>H<sub>11</sub>O<sub>4</sub>I<sup>127</sup>I [M]+: 321.9697; found: 321.9695.

**Melting point**: 67 °C.
2-Iodo-1-methoxy-3,4-bis(methoxymethoxy)benzene (S36)

Sodium percarbonate (143 mg, 914 µmol, 1 equiv) was added to a solution of S34 (254 mg, 914 µmol, 1 equiv) in tetrahydrofuran (20 mL) and water (8 mL). After 1.5 h, saturated aqueous sodium thiosulfate solution (20 mL) and diethyl ether (20 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was directly used in the following reaction without further purification.

Sodium hydride (60% mineral oil dispersion, 84.0 mg, 2.10 mmol, 2.30 equiv) was added to a solution of crude S35 (283 mg, 914 µmol, 1 equiv) in N,N-dimethyl formamide (5 mL) at 0 °C. After 1 h, bromomethyl methylether (153 µL, 1.87 µmol, 2.05 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 1 h, water (40 mL) and diethyl ether (40 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (70 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (25% ethyl acetate in hexanes) to provide S36 (147 mg, 71% over 2 steps) as a colorless oil.

**TLC** (20% ethyl acetate in hexanes): R\textsubscript{f} = 0.23 (UV, CAM).

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3})\textbf{:} \(\delta = 7.11\) (d, \(J = 9.0\) Hz, 1H), 6.55 (d, \(J = 9.0\) Hz, 1H), 5.21 (s, 2H), 5.11 (s, 2H), 3.84 (s, 3H), 3.68 (s, 3H), 3.50 (s, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\textsubscript{3})\textbf{:} \(\delta = 154.8, 148.4, 144.3, 118.2, 106.4, 99.2, 96.4, 85.7, 58.6, 57.0, 56.4.\)

IR (Diamond-ATR, neat): \(\tilde{\nu}_{\text{max}} = 2954, 2900, 2833, 1477, 1436, 1251, 1154, 1069, 971, 923.\)

HRMS (El) calc. for C\textsubscript{11}H\textsubscript{15}\textsuperscript{127}I\textsubscript{5}[M]\textsuperscript{+}: 353.9959; found: 353.9960.
Note: Tetrahydrofuran was dried according to the procedure described by B. Williams prior to use.\textsuperscript{13}

To a solution of alkyl iodide \textbf{25} (278 mg, 634 µmol, 1.50 equiv) and a solution of zinc chloride (1.00 M in tetrahydrofuran, 676 µL, 676 µmol, 1.6 equiv) in tetrahydrofuran (6 mL) was added dropwise a solution of tert-butyllithium (1.50 M in pentane, 902 µL, 1.35 mmol, 3.2 equiv) at \(-78\) °C. After 50 min, the mixture was allowed to warm to 23 °C. After 20 min, the mixture was transferred into a mixture of aryl iodide \textbf{S36} (150 mg, 423 µmol, 1 equiv), SPhos (17.4 mg, 42.3 µmol, 0.100 equiv) and SPhos-Pd-G2 (30.5 mg, 42.3 µmol, 0.100 equiv) in tetrahydrofuran (3 mL) and \(N, N\)-dimethylacetamide (3 mL) and the reaction mixture was directly placed in a preheated oil bath (35 °C). Diethyl ether (50 mL) and saturated aqueous ammonium chloride solution (50 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (80 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (9% ethyl acetate in hexanes) to yield \textbf{S37} (178 mg, 78%) as a yellow oil.

**TLC** (20% ethyl acetate in hexanes): \(R_f = 0.60\) (UV, CAM).

\textbf{\(^1H\) NMR} (599 MHz, CDCl\textsubscript{3}): \(\delta = 7.31–7.26\) (m, 4H), 7.24–7.21 (m, 1H), 6.95 (d, \(J = 8.9\) Hz, 1H), 6.53 (d, \(J = 8.9\) Hz, 1H), 5.48–5.39 (m, 1H), 5.13–5.09 (m, 2H), 5.07 (s, 2H), 4.50 (d, \(J = 12.4\) Hz, 1H), 4.26 (d, \(J = 12.4\) Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H), 3.51 (s, 3H), 3.03 (d, \(J = 2.7\) Hz, 1H), 2.94 (d, \(J = 12.9\) Hz, 1H), 2.68–2.62 (m, 2H), 1.94–1.82 (m, 2H), 1.65–1.59 (m, 1H), 1.56–1.51 (m, 1H), 1.50–1.44 (m, 1H), 1.23–1.14 (m, 1H), 1.08 (s, 3H), 1.03 (d, \(J = 6.8\) Hz, 3H), 0.99 (s, 3H), 0.91–0.87 (m, 1H), 0.79 (s, 3H).

\textbf{\(^{13}C\) NMR} (151 MHz, CDCl\textsubscript{3}): \(\delta = 154.5, 148.0, 144.8, 143.8, 139.6, 128.2, 127.9, 127.2, 124.9, 117.5, 115.5, 105.4, 99.3, 96.4, 82.9, 70.2, 57.9, 56.4, 55.5, 41.7, 41.3, 40.9, 39.1, 35.4, 32.1, 28.6, 25.8, 24.5, 23.8, 16.4, 14.2.

**IR** (Diamond-ATR, neat): \(\tilde{\nu}_{max} = 2950, 1483, 1252, 1154, 1068, 1038, 984, 951, 736, 698.

**HRMS** (EI) calc. for C\textsubscript{33}H\textsubscript{46}O\textsubscript{cc} [M]+: 538.3289; found: 538.3303.

\([\alpha]_D^{20} = +18.1^\circ\) (\(c = 0.85, \text{CH}_2\text{Cl}_2\)).
A solution of hydrochloric acid (~1.25 M in methanol, 12 mL) was added to a solution of S37 (145 mg, 269 µmol, 1 equiv) in dichloromethane (6 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (25 mL) and saturated aqueous sodium bicarbonate solution (25 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated to yield S38 as a yellow oil that was directly used in the following reaction without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 707 µL, 2.69 mmol, 10.0 equiv) was added dropwise to a solution of the crude S38 (83.4 mg, 269 µmol, 1 equiv) in dichloromethane (35 mL) at –50 °C. After 15 min, the reaction mixture was allowed to warm to –15 °C. After 30 min, saturated aqueous sodium bicarbonate solution (50 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes with 5% ethyl acetate) to yield S39 (71.4 mg, 59% over 2 steps) as a colorless, highly viscous oil.

**TLC** (20% ethyl acetate): R_f = 0.61 (UV, CAM).

**^1H NMR** (400 MHz, CDCl₃): δ = 7.40–7.33 (m, 4H), 7.32–7.26 (m, 1H), 6.69 (d, J = 8.6 Hz, 1H), 6.27 (d, J = 8.6 Hz, 1H), 4.94 (s, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 3.78 (s, 3H), 3.23–3.11 (m, 2H), 2.34–2.21 (m, 2H), 2.20–2.10 (m, 2H), 2.09–1.99 (m, 1H), 1.96–1.88 (m, 1H), 1.82–1.71 (m, 3H), 1.63–1.56 (m, 1H), 1.35–1.29 (m, 1H), 1.13 (d, J = 7.5 Hz, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H).

**^13C NMR** (101 MHz, CDCl₃): δ = 151.0, 139.8, 139.2, 138.6, 128.3, 127.2, 127.1, 110.7, 110.7, 100.3, 84.4, 82.4, 71.8, 55.5, 44.4, 39.7, 38.4, 38.1, 32.0, 30.2, 28.0, 27.2, 24.4, 23.8, 21.4, 20.3, 17.3.

**IR** (Diamond-ATR, neat): ν_max = 3564, 2938, 2874, 1490, 1384, 1264, 1185, 1085, 908, 732.

**HRMS** (EI) calc. for C_{29}H_{38}O_{4} [M]⁺: 450.2765; found: 450.2762.

[a]_{D}^{20} = +73.6° (c = 1.48, CH₂Cl₂).
A solution of S39 (62.0 mg, 138 µmol, 1 equiv) in ethanol (5 mL) was treated with palladium on carbon (10 wt.%, 146 mg, 138 µmol, 1 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 2 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 14 h, the reaction mixture was filtered through a pad of Celite®. The filtercake was thoroughly rinsed with dichloromethane (40 mL). The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to give 3-hydroxy-strongylin A (47) (40.0 mg, 80%) as a colorless solid. Recrystallization from ethyl acetate gave crystals suitable for single-crystal X-ray diffraction.

**TLC** (30% ethyl acetate in hexanes): R<sub>f</sub> = 0.27 (UV, CAM).

**<sup>1</sup>H NMR** (400 MHz, CD<sub>6</sub>D<sub>6</sub>): δ = 6.95 (d, J = 8.6 Hz, 1H), 6.12 (d, J = 8.6 Hz, 1H), 4.99 (s, 1H), 3.41 (s, 3H), 3.28 (d, J = 17.5 Hz, 1H), 3.18–3.12 (m, 1H), 2.35 (d, J = 17.5 Hz, 1H), 2.24–2.04 (m, 3H), 1.90–1.78 (m, 1H), 1.62–1.50 (m, 3H), 1.50–1.42 (m, 1H), 1.37–1.27 (m, 1H), 1.19–1.10 (m, 1H), 1.00–0.95 (m, 6H), 0.87 (s, 3H), 0.76 (s, 1H), 0.74 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CD<sub>6</sub>D<sub>6</sub>): δ = 151.4, 139.6, 139.5, 111.5, 110.9, 100.8, 84.2, 74.3, 55.0, 44.2, 40.0, 38.2, 37.8, 32.7, 30.0, 28.3, 26.7, 26.5, 24.3, 24.1, 20.4, 17.2.

**IR** (Diamond-ATR, neat): ν<sub>max</sub> = 3472, 3157, 2986, 2963, 1605, 1464, 1265, 1096, 979.

**HRMS** (EI) calc. for C<sub>22</sub>H<sub>32</sub>O<sub>4</sub> [M]: 360.2295; found: 360.2302.

[α]<sub>D</sub><sup>20</sup> = +66.8° (c = 0.79, CH<sub>2</sub>Cl<sub>2</sub>).

**Melting point**: 187 °C.
A solution of diammonium cerium(IV) nitrate (35.7 mg, 65.2 µmol, 2.50 equiv) in water (2.5 mL) was added dropwise to a solution of 3-hydroxy-strongylin A (47) (9.40 mg, 26.1 µmol, 1 equiv) in acetonitrile (2.5 mL) over a period of 1 h at 0 °C. After 2 h, the bright yellow solution was diluted with water (10 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield 48 (5.50 mg, 61%) as a yellow oil.

**TLC** (30% ethyl acetate in hexanes): \( R_f = 0.37 \) (UV, CAM).

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \( \delta = 6.65 \) (d, \( J = 10.1 \) Hz, 1H), 6.57 (d, \( J = 10.1 \) Hz, 1H), 3.56 (s, 1H), 2.87 (d, \( J = 19.0 \) Hz, 1H), 2.62–2.50 (m, 1H), 2.25 (td, \( J = 13.6, 3.9 \) Hz, 1H), 2.08 (td, \( J = 13.6, 4.9 \) Hz, 1H), 2.01–1.86 (m, 2H), 1.82–1.72 (m, 3H), 1.71–1.63 (m, 1H), 1.61–1.50 (m, 1H), 1.49–1.42 (m, 1H), 1.37–1.30 (m, 1H), 1.11 (d, \( J = 7.4 \) Hz, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H).

**\(^{13}\)C NMR** (101 MHz, CDCl\(_3\)): \( \delta = 187.3, 181.6, 150.3, 137.1, 133.9, 118.1, 87.6, 74.3, 45.3, 39.3, 38.1, 38.1, 30.7, 30.4, 28.2, 26.6, 26.0, 24.3, 23.6, 20.4, 17.1.

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 3540, 2928, 2876, 1675, 1645, 1596, 1394, 1193, 1050, 970.\)

**HRMS** (El) calcd for C\(_{21}\)H\(_{26}\)O\(_4\) [M\(^+\)]: 344.1982; found: 344.1981.

\([\alpha]_D^{30} = +112.0^\circ \) (c = 0.10, CHCl\(_3\)).
Synthesis of 5-epi-Cyclosmenospongine (49), (+)-Smenoqualone (3) & 5-epi-Smenoqualone (50)

Bromide S42

Benzaldehyde S40\textsuperscript{24,25} (1.48 g, 5.38 mmol, 1 equiv) was added to a solution of selenium dioxide (47.8 mg, 430 µmol, 8.0 mol%) and hydrogen peroxide (30% in water, 1.21 mL, 11.8 mmol, 2.20 equiv) in dichloromethane (30 mL). After 14 h, saturated aqueous ammonium chloride solution (40 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was dissolved in methanol (40 mL) and an aqueous solution of potassium carbonate (14%, 10 mL) was added. After 1 h, the reaction mixture was extracted with dichloromethane (3 × 30 mL), the combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated to give crude S41 (924 mg) as a yellow oil that was used without further purification.

To a solution of crude S41 (924 mg, 3.51 mmol, 1 equiv) in N,N-dimethylformamide (12 mL) was added sodium hydride (60% mineral oil dispersion, 211 g, 5.27 mmol, 1.50 equiv) at 0 °C. After 1 h, bromomethyl methyl ether (344 µL, 4.21 mmol, 1.20 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 1.5 h, water (20 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20 ethyl acetate in hexanes) to provide S42 (510 mg, 48% over 2 steps) as a yellow oil. The obtained analytical data were in full agreement with those previously reported.\textsuperscript{26}
A mixture of aryl bromide \textbf{S42} (503 mg, 1.64 mmol, 1 equiv), sodium methoxide (177 mg, 3.28 mmol, 2.00 equiv), copper(I) chloride (6.49 mg, 65.5 µmol, 0.04 equiv) and formic acid methyl ester (40.6 µL, 65.5 µmol, 0.40 equiv) in methanol (1 mL) was heated to 120 °C in a pressure tube. After 13 h, the reaction mixture was cooled to 23 °C, dichloromethane (10 mL) and saturated aqueous ammonium chloride solution (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes) to provide \textbf{S43} (350 mg, 83%) as a colorless oil.

\textbf{TLC} (20% ethyl acetate in hexanes): $R_f = 0.22$ (UV, CAM).

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}): $\delta = 6.79$ (s, 2H), 5.14 (s, 4H), 3.83 (s, 6H), 3.53 (s, 6H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}): $\delta = 144.6, 141.2, 104.2, 96.9, 56.7, 56.4$.

\textbf{IR} (Diamond-ATR, neat): $\tilde{\nu}_{\text{max}} = 2937, 2830, 1512, 1465, 1384, 1214, 1191, 1151, 1009, 908, 729$.

\textbf{HRMS} (El) calcd for C\textsubscript{12}H\textsubscript{18}O\textsubscript{6} [M]$^+$: 258.1098; found: 258.1098.
Benzylic alcohol (S44)

To a solution of S43 (327 mg, 1.27 mmol, 1.40 equiv) in tetrahydrofuran (6 mL) and freshly distilled N,N,N′,N′-tetramethylethane-1,2-diamine (over CaH₂, 409 µL, 2.71 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.44 M in hexanes 0.45 mL, 1.13 mmol, 1.25 equiv) at −78 °C. The reaction mixture was allowed to warm to −60 °C. After 1.5 h, the yellow suspension was cooled to −78 °C and a solution of aldehyde 33 (199 mg, 904 µmol, 1 equiv) in tetrahydrofuran (4 mL) was added to give a clear yellow solution. The reaction mixture was warmed to −30 °C over a period of 2 h. Diethyl ether (30 mL) and saturated aqueous ammonium chloride solution (40 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield S44 (391 mg, 90%) as a colorless oil. The mixture of inseparable diastereoisomers was partially characterized by HRMS and IR spectroscopy.

**TLC** (30% ethyl acetate in hexanes): \( R_f = 0.35 \) (CAM).

**IR** (Diamond-ATR, neat): \( \tilde{v}_{\text{max}} = 3559, 2928, 1592, 1482, 1435, 1227, 1153, 1035, 948 \).

**HRMS** (EI) calcd for \( C_{27}H_{42}O_7 \) [M]+: 478.2925; found: 478.2925.
A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 3.90 mL, 3.90 mmol, 5.00 equiv) was added dropwise to a solution of S44 (373 mg, 779 µmol, 1 equiv) in tetrahydrofuran (10 mL) at −78 °C. After 30 min, carbon disulfide (940 µL, 15.6 mmol, 20.0 equiv) was slowly added and the reaction mixture was allowed to warm to −65 °C. After 1 h, methyl iodide (970 µL, 15.6 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (25 mL) and ethyl acetate (30 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica and the obtained crude xanthogenate was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

A degassed solution of the xanthogenate (420 mg, 779 µmol, 1 equiv), 2,2′-azobis(2-methylpropionitrile) (AIBN) (64.0 mg, 390 µmol, 0.50 equiv) and tributyltin hydride (1.04 mL, 3.90 mmol, 5.00 equiv) in benzene (25 mL) was heated to 90 °C. After 7.5 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to yield S45 as a colorless oil (202 mg, 56% over 2 steps).

**TLC** (20% ethyl acetate in hexanes): \( R_f = 0.34 \) (CAM).

**1H NMR** (800 MHz, CDCl3): \( \delta = 6.66 \) (s, 1H), 5.41–5.36 (m, 1H), 5.17–5.12 (m, 2H), 5.02–4.98 (m, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 3.59 (s, 3H), 3.52 (s, 3H), 2.85 (d, \( J = 12.8 \) Hz, 1H), 2.60 (d, \( J = 12.8 \) Hz, 1H), 2.59–2.55 (m, 1H), 1.97–1.90 (m, 1H), 1.84–1.78 (m, 1H), 1.56–1.52 (m, 1H), 1.44–1.37 (m, 1H), 1.34–1.28 (m, 2H), 1.19–1.14 (m, 1H), 1.11–1.06 (m, 1H), 1.03–0.99 (m, 9H), 0.75 (s, 3H), 0.72–0.66 (m, 1H).

**13C NMR** (201 MHz, CDCl3): \( \delta = 149.2, 147.7, 145.8, 143.8, 140.9, 129.8, 114.7, 101.6, 99.5, 96.5, 60.4, 57.8, 56.5, 56.3, 42.1, 41.7, 40.9, 38.9, 36.7, 36.2, 31.8, 31.1, 30.0, 28.1, 23.0, 16.6, 14.8.

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 2973, 2840, 1593, 1483, 1338, 1239, 1154, 1049, 956, 731.\)

**HRMS** (El) calcd for C_{27}H_{42}O_6 [M]^+: 462.2976; found: 462.2972.

[\( \alpha \)]\_D\(^{20} \) = +24.3° (c = 0.41, CH\_2Cl\_2).
A solution of hydrochloric acid (~1.25 M in methanol, 3 mL) was added to a solution of S45 (24.4 mg, 52.7 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 30 °C. After 4 h, the reaction mixture was diluted with dichloromethane (5 mL) and saturated aqueous sodium bicarbonate solution (3 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield S46 as a yellow foam that was directly used in the following step.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 138 µL, 527 µmol, 10.0 equiv) was added dropwise to a solution of the crude hydroquinone S46 (19.7 mg, 52.7 µmol, 1 equiv) in dichloromethane (3 mL) at −78 °C. After complete addition, the reaction mixture was allowed to warm to −10 °C over a period of 30 min. After 1.5 h, saturated aqueous ammonium chloride solution (5 mL) and dichloromethane (5 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield S47 (19.0 mg, 96% over two steps) as an amorphous solid.

**TLC** (20% ethyl acetate in hexanes): R_f = 0.58 (UV, KMnO_4).

**¹H NMR** (400 MHz, C_6D_6): δ = 6.64 (s, 1H), 5.26 (s, 1H), 3.78 (s, 3H), 3.37 (s, 3H), 3.28 (d, J = 17.6 Hz, 1H), 2.26 (d, J = 17.6 Hz, 1H), 1.91–1.75 (m, 2H), 1.67–1.58 (m, 2H), 1.54–1.48 (m, 1H), 1.46–1.39 (m, 2H), 1.31–1.21 (m, 3H), 1.12 (s, 4H), 1.09–1.05 (m, 1H), 0.89 (d, J = 7.5 Hz, 3H), 0.82 (s, 3H), 0.67 (s, 3H).

**¹³C NMR** (101 MHz, C_6D_6): δ = 146.3, 140.9, 140.5, 132.8, 116.1, 99.9, 83.4, 60.1, 56.2, 44.1, 39.7, 38.4, 34.1, 33.6, 33.1, 32.2, 29.5, 29.3, 27.9, 22.7, 20.2, 18.9, 17.4.

**IR** (Diamond-ATR, neat): υ max = 2934, 2279, 1618, 1492, 1329, 1259, 1188, 1049, 811.

**HRMS** (EI) calcd for C_{23}H_{34}O_{4} [M]^+: 374.2452; found: 374.2449.

[α]_D^{20} = +45.8° (c = 1.46, CH_2Cl_2).
A solution of ammonium cerium(IV) nitrate (55.1 mg, 100 µmol, 2.20 equiv) in water (3 mL) was added dropwise over a period of 40 min to a solution of phenol S47 (17.1 mg, 45.7 µmol, 1 equiv) in acetonitrile (3 mL) at 0 °C. After 3 h, the bright yellow solution was diluted with water (5 mL) and diethyl ether (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% diethyl ether in pentane initially, grading to 30% diethyl ether in pentane) to provide (+)-smenoqualone (3) (12.4 mg, 76%) as a bright yellow foam.

TLC (30% ethyl acetate in hexanes): Rf = 0.35 (UV, CAM).

$^1$H NMR (800 MHz, CDCl$_3$): δ = 5.73 (s, 1H, H-19), 3.81 (s, 3H, H-3), 2.85 (d, $^2$J$_{15A/15B}$ = 18.3 Hz, 1H, H-15A), 2.15–2.07 (m, 1H, H-2A), 2.04–1.98 (m, 1H, H-7A), 1.95 (d, $^2$J$_{15B/15A}$ = 18.3 Hz, 1H, H-15B), 1.89–1.85 (m, 1H, H-1A), 1.84–1.79 (m, 1H, H-1B), 1.79–1.76 (m, 1H, H-8), 1.76–1.72 (m, 1H, H-6A), 1.59–1.55 (m, 1H, H-6B), 1.54–1.50 (m, 1H, H-2B), 1.42–1.35 (m, 3H, H-3A), 1.25–1.22 (m, 1H, H-3B), 1.09 (d, $^3$J$_{13/8}$ = 7.6 Hz, 3H, H-13), 1.00 (s, 3H, H-12), 0.85 (s, 3H, H-14), 0.82 (s, 3H, H-11).

$^{13}$C NMR (201 MHz, CDCl$_3$): δ = 181.53 (C-21), 181.47 (C-18), 159.5 (C-20), 151.1 (C-17), 115.2 (C-16), 104.6 (C-19), 87.8 (C-10), 56.3 (C-22), 45.1 (C-5), 39.0 (C-8), 38.0 (C-9), 33.7 (C-4), 33.4 (C-3), 31.9 (C-11), 30.7 (C-15), 29.7 (C-12), 28.9 (C-1), 27.7 (C-7), 22.4 (C-6), 20.1 (C-14), 18.3 (C-2), 17.1 (C-13).

IR (Diamond-ATR, neat): $\tilde{v}_{\text{max}}$ = 2938, 1665, 1646, 1602, 1457, 1342, 1276, 1220, 1037, 842.

HRMS (EI) calcd for C$_{22}$H$_{30}$O$_4$ [M]+: 358.2139; found: 358.2139.

$[\alpha]_D^{20}$ = +84.3° (c 0.37, CHCl$_3$); $[\alpha]_D^{20}$ = +70° (c = 0.001, CHCl$_3$) for (+)-smenoqualone.\(^{27}\) n.a.: Temperature not available
**Supplementary Table 8** Comparison of $^1$H NMR data for natural and synthetic (+)-smenoqualone (3).

| Proton | Synthetic (800 MHz, CDCl$_3$) | Natural | $\Delta$: $\delta$ (ppm) |
|--------|-------------------------------|---------|--------------------------|
| 1A     | 1.89–1.85 (m, 1H)             |         |                          |
| 1B     | 1.84–1.79 (m, 1H)             |         |                          |
| 2A     | 2.15–2.07 (m, 1H)             |         |                          |
| 2B     | 1.54–1.50 (m, 1H)             |         |                          |
| 3A     | 1.42–1.35 (m, 3H)             |         |                          |
| 3B     | 1.25–1.22 (m, 1H)             |         |                          |
| 5      | 1.42–1.35 (m, 3H)             |         |                          |
| 6A     | 1.76–1.72 (m, 1H)             |         |                          |
| 6B     | 1.59–1.55 (m, 1H)             |         |                          |
| 7A     | 2.04–1.98 (m, 1H)             |         |                          |
| 7B     | 1.42–1.35 (m, 3H)             |         |                          |
| 8      | 1.79–1.76 (m, 1H)             |         |                          |
| 11     | 0.82 (s, 3H).                 |         |                          |
| 12     | 1.00 (s, 3H)                  |         |                          |
| 13     | 1.09 (d, $J$ = 7.6 Hz, 3H)    |         |                          |
| 14     | 0.85 (s, 3H)                  |         |                          |
| 15A    | 2.85 (d, $J$ = 18.3 Hz, 1H)   |         |                          |
| 15B    | 1.95 (d, $J$ = 18.3 Hz, 1H)   |         |                          |
| 19     | 5.73 (s, 1H)                  |         |                          |
| 22     | 3.81 (s, 3H)                  |         |                          |
**Supplementary Table 9** Comparison of $^{13}$C NMR data for natural and synthetic (+)-smenoqualone (3).

| Carbon | Synthetic (201 MHz, CDCl$_3$) | Natural (75 MHz, CDCl$_3$) | $\Delta$: $\delta$ (ppm) |
|--------|-------------------------------|-----------------------------|--------------------------|
| 1      | 28.9                          | 28.9                        | ± 0.0                    |
| 2      | 18.3                          | 18.3                        | ± 0.0                    |
| 3      | 33.4                          | 33.4                        | ± 0.0                    |
| 4      | 33.7                          | 33.7                        | ± 0.0                    |
| 5      | 45.1                          | 45.1                        | ± 0.0                    |
| 6      | 22.4                          | 22.5                        | −0.1                     |
| 7      | 27.7                          | 27.7                        | ± 0.0                    |
| 8      | 39.0                          | 39.0                        | ± 0.0                    |
| 9      | 38.0                          | 37.9                        | +0.1                     |
| 10     | 87.8                          | 87.8                        | ± 0.0                    |
| 11     | 31.9                          | 31.9                        | ± 0.0                    |
| 12     | 29.7                          | 29.7                        | ± 0.0                    |
| 13     | 17.1                          | 17.1                        | ± 0.0                    |
| 14     | 20.1                          | 20.1                        | ± 0.0                    |
| 15     | 30.7                          | 30.7                        | ± 0.0                    |
| 16     | 115.2                         | 115.3                       | −0.1                     |
| 17     | 151.1                         | 151.1                       | ± 0.0                    |
| 18     | 181.5                         | 181.5                       | ± 0.0                    |
| 19     | 104.6                         | 104.7                       | −0.1                     |
| 20     | 159.5                         | 159.5                       | ± 0.0                    |
| 21     | 181.5                         | 181.5                       | +0.0                     |
| 22     | 56.3                          | 56.3                        | ± 0.0                    |
5-Epi-cyclosmenosponge (49)

To a solution of (+)-smenoqualone (3) (6.70 mg, 18.7 µmol, 1 equiv) and pyridine (600 µL) in aqueous methanol (50%, 6 mL) was added aqueous ammonia (25%, 600 µL) at 23 °C. After 14 h, the reaction mixture was concentrated, water (5 mL) was added and the aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Sephadex® LH-20 (9% ethanol in chloroform) to yield 5-epi-cyclosmenosponge (50) (4.30 mg, 67%) as a dark red oil.

TLC (30% ethyl acetate in hexanes): Rf = 0.19 (UV, KMnO₄).

¹H NMR (800 MHz, CDCl₃): δ = 5.53 (s, 1H), 5.10 (s, 2H), 2.83 (d, J = 18.1 Hz, 1H), 2.18–2.09 (m, 1H), 2.05–1.98 (m, 1H), 1.92–1.86 (m, 2H), 1.85–1.79 (m, 1H), 1.78–1.71 (m, 2H), 1.57–1.55 (m, 1H), 1.53–1.49 (m, 1H), 1.44–1.39 (m, 2H), 1.39–1.35 (m, 1H), 1.26–1.22 (m, 1H), 1.09 (d, J = 7.6 Hz, 3H), 1.03 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H).

¹³C NMR (201 MHz, CDCl₃): δ = 182.8, 180.3, 153.2, 147.7, 113.0, 99.2, 88.0, 45.3, 39.2, 38.1, 33.9, 33.6, 32.1, 30.7, 29.9, 29.1, 27.9, 22.6, 20.2, 18.5, 17.3.

IR (Diamond-ATR, neat): ʋmax = 3448, 3338, 1936, 2873, 2360, 2340, 1593, 1373, 1226, 943.

HRMS (EI) calcd for C₂₁H₂₉NO₃ [M]⁺: 343.2142; found: 343.2135.

[α]D²⁰ = +492.3° (c = 0.16, CH₂Cl₂).
A solution of hydrochloric acid (~1.25 M in methanol, 4 mL) was added to a solution of S45 (64.0 mg, 138 µmol, 1 equiv) in dichloromethane (2 mL) and the mixture was heated to 40 °C. After 2 h, the reaction mixture was diluted with dichloromethane (20 mL) and saturated aqueous sodium bicarbonate solution (30 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield S46 as a yellow oil that was directly used in the following reaction.

A solution of hydroiodic acid (57 wt.% in H₂O, 183 µL, 1.38 mmol, 10.0 equiv) was added to a solution of crude S46 (51.7 mg, 138 µmol, 1 equiv) in benzene (5 mL) in an Ace® pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 20 h, the reaction mixture was cooled to 23 °C, saturated aqueous sodium bicarbonate chloride solution (15 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield 5-epi-smenoqualone (51) (34.2 mg, 69% over two steps) as a bright yellow solid. The obtained analytical data were in full agreement with those values previously reported by our group.²¹
Synthetic Analogues 40, 41, 42, 43 and 44

Olefin S48

Note: Tetrahydrofuran was dried according to the procedure described by B. Williams prior to use.\textsuperscript{13}

To a mixture of alkyl iodide 25 (120 mg, 274 \( \mu \)mol, 1.50 equiv) and a solution of zinc chloride (1.00 M in tetrahydrofuran, 292 \( \mu \)L, 292 \( \mu \)mol, 1.6 equiv) in tetrahydrofuran (3 mL) was added dropwise a solution of \textit{tert}-butyllithium (1.50 M in pentane, 389 \( \mu \)L, 584 \( \mu \)mol, 3.20 equiv) at \(-78\) °C. After 50 min, the mixture was allowed to warm to 23 °C. After 20 min, the mixture was added to a mixture of aryl iodide S47 (435 mg, 870 \( \mu \)mol, 1 equiv), SPhos (71.3 mg, 174 \( \mu \)mol, 0.20 equiv) and SPhos-Pd-G2 (125 mg, 174 \( \mu \)mol, 0.20 equiv) in tetrahydrofuran (2.2 mL) and freshly distilled (over CaH\(_2\)) \( N,N \)-dimethylacetamide (2.2 mL) and the reaction mixture was directly placed in a preheated oil bath at 40 °C. After 15 min, the reaction mixture was allowed to cool to 23 °C and ethyl acetate (20 mL) and saturated aqueous ammonium chloride solution (20 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 \( \times \) 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% ethyl acetate in hexanes) to yield methoxymethyl-ether S48 (46.1 mg, 56%) as a colorless oil.

**TLC** (10% ethyl acetate in hexanes): \( R_f = 0.47 \) (UV, CAM).

\( ^1\text{H NMR} \) (800 MHz, CDCl\(_3\)): \( \delta = 7.34–7.29 \) (m, 4H), 7.26–7.23 (m, 1H), 7.20 (dd, \( J = 7.6, 1.7 \) Hz, 1H), 7.16–7.13 (m, 1H), 7.10 (dd, \( J = 8.2, 1.3 \) Hz, 1H), 6.92 (td, \( J = 7.6, 1.3 \) Hz, 1H), 5.42 (d, \( J = 5.7 \) Hz, 1H), 5.21 (d, \( J = 6.6 \) Hz, 1H), 5.15 (d, \( J = 6.6 \) Hz, 1H), 4.57 (d, \( J = 12.4 \) Hz, 1H), 4.33 (d, \( J = 12.4 \) Hz, 1H), 3.50 (s, 3H), 3.08 (s, 1H), 2.87 (d, \( J = 13.7 \) Hz, 1H), 2.61 (d, \( J = 13.7 \) Hz, 1H), 2.22–2.17 (m, 1H), 1.98–1.92 (m, 1H), 1.90–1.84 (m, 1H), 1.84–1.78 (m, 1H), 1.58–1.51 (m, 3H), 1.49–1.44 (m, 1H), 1.09 (s, 3H), 1.07 (d, \( J = 6.7 \) Hz, 3H), 0.88 (s, 3H), 0.83 (s, 3H).

\( ^{13}\text{C NMR} \) (201 MHz, CDCl\(_3\)): \( \delta = 156.7, 139.6, 132.1, 129.2, 128.2, 128.2, 127.8, 127.8, 127.3, 127.3, 121.3, 117.5, 114.3, 95.1, 83.0, 70.3, 70.3, 56.2, 56.2, 41.2, 39.9, 39.7, 37.2, 34.8, 32.0, 28.6, 25.8, 24.4, 22.7, 16.7.

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_\text{max} = 2952, 1493, 1453, 1232, 1154, 1077, 1051, 1004, 754, 697.\)

**HRMS** (EI) calc. for C\(_{30}\)H\(_{40}\)O\(_3\) [M]: 448.2972; found: 448.2933.

\( [\alpha]_D^{20} = +55.2^\circ \) (c = 0.91, CHCl\(_3\)).
A solution of hydrochloric acid (~1.25 M in methanol, 1.5 mL) was added to a solution of S48 (36.0 mg, 80.2 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated yielding a yellow foam that was directly used in the following reaction.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 211 µL, 802 µmol, 10.0 equiv) was added dropwise to a solution of the crude phenol (32.2 mg, 80.2 µmol, 1 equiv) in dichloromethane (5 mL) at –40 °C and the reaction mixture was allowed to warm to –10 °C. After 0.5 h, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was directly used in the following step.

A solution of crude S49 (32.2 mg, 80.2 µmol, 1 equiv) in ethanol (3 mL) was treated with oalladium on carbon (10 wt.%, 85.4 mg, 80.2 µmol, 1 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 2 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 14 h, the reaction mixture was filtered through a pad of Celite®. The filtercake was thoroughly rinsed with dichloromethane (50 mL). The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (6% ethyl acetate in hexanes) to give 40 (17.0 mg, 67% over 3 steps) as a colorless oil.

TLC (10% ethyl acetate in hexanes): Rf = 0.28 (UV, CAM).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.10–7.03 (m, 1H), 7.00 (d, $J$ = 7.3 Hz, 1H), 6.81 (t, $J$ = 7.3 Hz, 1H), 6.69 (d, $J$ = 8.1 Hz, 1H), 3.60–3.53 (m, 1H), 3.44 (d, $J$ = 17.0 Hz, 1H), 2.62–2.50 (m, 1H), 2.30–2.19 (m, 1H), 2.16–2.01 (m, 2H), 2.00–1.90 (m, 1H), 1.79–1.61 (m, 4H), 1.58–1.45 (m, 2H), 1.39–1.29 (m, 1H), 1.14 (d, $J$ = 7.5 Hz, 3H), 1.05 (s, 3H), 0.99–0.93 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ = 151.6, 129.2, 126.8, 121.6, 119.5, 116.6, 82.9, 75.0, 44.7, 39.6, 38.3, 38.2, 37.1, 30.8, 28.3, 26.5, 26.0, 24.1, 23.9, 20.3, 17.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3434, 2960, 2872, 1589, 1455, 1257, 974, 908, 732.

HRMS (EI) calc. for C$_{21}$H$_{30}$O$_2$ [M]$^+$: 314.2240; found: 314.2245.
$[\alpha]_D^{20} = +18.9^\circ$ (c = 0.55, CHCl$_3$).
Benzylic alcohol S50

To a solution of iodide S47 (168 mg, 635 µmol, 1.40 equiv) in tetrahydrofuran (1.5 mL) and freshly distilled N,N,N,N′,N′-tetramethylethane-1,2-diamine (over CaH₂, 192 µL, 1.27 mmol, 2.80 equiv) was added a solution of n-butyllithium (2.22 M in hexanes, 266 µL, 590 µmol, 1.30 equiv) at −78 °C and the reaction mixture was allowed to warm to −30 °C. After 45 min, the reaction mixture was cooled to −78 °C and a solution of aldehyde 33 (100 mg, 454 µmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to warm to 23 °C over a period of 30 min. Diethyl ether (10 mL) and saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash-column chromatography on silica gel (9% ethyl acetate in hexanes) to yield S50 (148 mg, 91%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

**TLC** (10% ethyl acetate in hexanes): \( R_f = 0.44 \) (CAM).

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 3480, 2954, 2924, 1488, 1452, 1229, 1153, 997, 923, 755 \).

**HRMS** (ESI) calcd for C₂₃H₃₅O₃⁺ [M+H]⁺: 359.2581; found: 359.2586.
A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 2.02 mL, 2.02 mmol, 5.00 equiv) was added dropwise to a solution of S50 (145 mg, 404 µmol, 1 equiv) in tetrahydrofuran (5 mL) at −78 °C. After 30 min, carbon disulfide (488 µL, 8.09 mmol, 20.0 equiv) was added dropwise to the orange solution and the resulting red solution was allowed to warm to −65 °C. After 1 h, methyl iodide (504 µL, 8.09 mmol, 20.0 equiv) was added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained crude product was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

A degassed solution of the xanthogenate (145 mg, 404 µmol, 1 equiv), 2,2’-azobis(2-methylpropionitrile) (AIBN) (33.2 mg, 202 µmol, 0.50 equiv) and tributyltin hydride (817 µL, 3.03 mmol, 7.50 equiv) in benzene (6.5 mL) was heated to 90 °C. After 1.5 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to yield S51 as a colorless oil (119 mg, 86% over 2 steps).

TLC (5% ethyl acetate in hexanes): Rf = 0.37 (CAM).

$^1$H NMR (599 MHz, CDCl₃): δ = 7.19 (dd, J = 7.6, 1.7 Hz, 1H), 7.16–7.10 (m, 2H), 6.94–6.90 (m, 1H), 5.39–5.36 (m, 1H), 5.22 (d, J = 6.7 Hz, 1H), 5.16 (d, J = 6.7 Hz, 1H), 3.51 (s, 3H), 2.85 (d, J = 13.7 Hz, 1H), 2.60 (d, J = 13.7 Hz, 1H), 2.14–2.10 (m, 1H), 2.01–1.95 (m, 1H), 1.85–1.77 (m, 2H), 1.56–1.52 (m, 1H), 1.52–1.48 (m, 1H), 1.46–1.41 (m, 1H), 1.39–1.35 (m, 1H), 1.17 (td, J = 13.2, 4.5 Hz, 1H), 1.05 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.97–0.93 (m, 1H), 0.89 (s, 3H), 0.79 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl₃): δ = 156.7, 146.8, 132.1, 129.1, 127.2, 121.2, 121.1, 115.0, 114.2, 95.1, 56.2, 41.6, 40.3, 39.8, 37.3, 36.6, 34.8, 31.8, 30.0, 29.9, 28.3, 22.8, 16.8, 16.5.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2956, 2928, 1493, 1453, 1232, 1155, 1078, 1008, 923, 754.

HRMS (EI) calcd for C₂₃H₃₄O₂ [M]⁺: 342.2553; found: 342.2553.

$[\alpha]_D^{20} = +35.6^\circ$ (c = 1.53, CH₂Cl₂).
Tetracycle 41

A solution of hydrochloric acid (~1.25 M in methanol, 1.5 mL) was added to a solution of S51 (27.0 mg, 78.8 µmol, 1 equiv) in dichloromethane (0.5 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide S52 as a colorless foam that was used in the following reaction without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 207 µL, 788 µmol, 10.0 equiv) was added dropwise to a solution of crude phenol S52 (23.5 mg, 78.8 µmol, 1 equiv) in dichloromethane (2 mL) at −40 °C and the reaction mixture was allowed to warm to −10 °C over a period of 2.5 h. After 0.5 h, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexane) to yield 41 (8.3 mg, 35% over two steps) as a colorless oil.

**TLC** (5% ethyl acetate in hexanes): Rf = 0.68 (CAM).

**1H NMR** (400 MHz, CDCl3): δ = 7.06 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.80 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 3.43 (d, J = 16.9 Hz, 1H), 2.19–1.99 (m, 3H), 1.88–1.76 (m, 2H), 1.75–1.65 (m, 2H), 1.64–1.55 (m, 1H), 1.54–1.42 (m, 3H), 1.40–1.33 (m, 1H), 1.25–1.17 (m, 1H), 1.12 (d, J = 7.5 Hz, 3H), 1.08 (s, 3H), 0.92 (s, 3H), 0.79 (s, 3H).

**13C NMR** (101 MHz, CDCl3): δ = 151.9, 129.2, 126.8, 121.5, 119.4, 116.7, 82.8, 44.5, 39.5, 38.2, 37.2, 34.1, 33.9, 32.1, 30.0, 29.4, 28.0, 22.4, 20.3, 18.5, 17.5.

**IR** (Diamond-ATR, neat): νmax = 2932, 2872, 2362, 2335, 1590, 1492, 1456, 1260, 960, 750.

**HRMS** (EI) calcd for C21H30O [M]+: 298.2291; found: 298.2299.

[α]D20 = +101.1° (c = 0.12, CH2Cl2)
A solution of hydrochloric acid (~1.25 M in methanol, 1.5 mL mmol, equiv) was added to a solution of S51 (26.5 mg, 77.4 µmol, 1 equiv) in dichloromethane (0.5 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated to yield S52 as a colorless foam that was directly used in the following reaction without further purification.

A solution of hydroiodic acid (57 wt.% in water 102 µL, 774 µmol, 10.0 equiv) was added to a solution of the crude phenol S52 (23.1 mg, 77.4 µmol, 1 equiv) in benzene (2 mL) in an Ace® pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 16 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (10 mL) was added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (n-heptane) to yield 42 (11.8 mg, 51% over two steps) as a colorless oil.

**TLC** (5% ethyl acetate in hexanes): R_t = 0.76 (CAM).

**¹H NMR** (400 MHz, CDCl₃): δ = 7.12–7.07 (m, 1H), 7.00–6.96 (m, 1H), 6.84–6.78 (m, 2H), 2.59 (d, J = 4.0 Hz, 2H), 1.79–1.63 (m, 4H), 1.61–1.54 (m, 1H), 1.52–1.26 (m, 6H), 1.25–1.16 (m, 1H), 1.14 (s, 3H), 0.93 (s, 3H), 0.93 (s, 3H), 0.76 (d, J = 6.8 Hz, 3H).

**¹³C NMR** (101 MHz, CDCl₃): δ = 152.9, 129.5, 127.2, 121.3, 119.6, 117.0, 81.6, 45.8, 42.1, 37.4, 33.6, 33.6, 32.8, 31.9, 30.7, 29.0, 22.6, 22.0, 18.0, 17.1, 16.4.

**IR** (Diamond-ATR, neat): ν_max = 2949, 1586, 1488, 1456, 1387, 1254, 1171, 1036, 935, 750.

**HRMS** (EI) calcd for C₂₁H₂₆O [M]: 298.2291; found: 298.2291.

[α]_D^20 = +25.5° (c = 0.13, CH₂Cl₂).
Benzylic alcohol S54

To a solution of S53 (178 mg, 672 µmol, 1.40 equiv) in tetrahydrofuran (1.5 mL) was added a solution of iso-propylmagnesium chloride lithium chloride complex (1.30 M in tetrahydrofuran, 517 µL, 672 µmol, 1.40 equiv) at −40 °C. After 15 min, a solution of aldehyde 33 (106 mg, 480 µmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added and the reaction mixture was allowed to warm to 23 °C. After 24 h, diethyl ether (10 mL) and saturated aqueous ammonium chloride solution (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield S54 (133 mg, 91%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

**TLC** (10% ethyl acetate in hexanes): \( R_f = 0.11 \) (CAM).

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 3468, 2955, 2925, 1448, 1408, 1265, 1154, 1082, 1040, 986 \).

**HRMS** (ESI) calcd for \( \text{C}_{22}\text{H}_{34}\text{NO}_3^+ \) [M+H]^+: 360.2533; found: 360.2533.
A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.78 mL, 1.78 mmol, 5.00 equiv) was added dropwise to a solution of 54 (128 mg, 356 µmol, 1 equiv) in tetrahydrofuran (5 mL) at −78 °C. After 35 min, carbon disulfide (430 µL, 7.12 mmol, 20.0 equiv) was added dropwise to the orange solution and the resulting red solution was allowed to warm to −65 °C. After 1 h, methyl iodide (443 µL, 7.12 mmol, 20.0 equiv) was added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

A degassed solution of the xanthogenate (160 mg, 356 µmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (29.2 mg, 178 µmol, 0.500 equiv) and tributyltin hydride (720 µL, 2.67 mmol, 7.50 equiv) in benzene (6.5 mL) was heated to 90 °C. After 2 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 5% ethyl acetate in hexanes) to yield S55 as a colorless oil (64.0 mg, 52% over 2 steps).

**TLC** (10% ethyl acetate in hexanes): Rf = 0.38 (UV, KMnO₄).

**¹H NMR** (599 MHz, CDCl₃): δ = 8.19 (dd, J = 4.7, 1.5 Hz, 1H), 7.38 (dd, J = 8.2, 1.5 Hz, 1H), 7.04 (dd, J = 8.2, 4.7 Hz, 1H), 5.40 (dt, J = 5.7, 2.1 Hz, 1H), 5.21 (d, J = 6.9 Hz, 1H), 5.17 (d, J = 6.9 Hz, 1H), 3.50 (s, 3H), 3.00 (d, J = 13.4 Hz, 1H), 2.79 (d, J = 13.4 Hz, 1H), 2.38 (d, J = 12.6 Hz, 1H), 1.95–1.87 (m, 1H), 1.82–1.76 (m, 1H), 1.66 (d, J = 12.2 Hz, 1H), 1.62–1.56 (m, 1H), 1.51–1.46 (m, 1H), 1.46–1.40 (m, 1H), 1.38–1.34 (m, 1H), 1.20–1.14 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.98–0.92 (m, 1H), 0.91 (s, 3H), 0.81 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃): δ = 152.7, 151.4, 146.7, 141.8, 121.7, 120.7, 115.5, 95.0, 56.4, 41.5, 41.0, 40.6, 39.6, 36.4, 35.4, 31.9, 29.9, 29.6, 28.5, 22.8, 16.4, 16.0.

**IR** (Diamond-ATR, neat): νmax = 2929, 1584, 1446, 1380, 1260, 1156, 1081, 1065, 995, 799.

**HRMS** (ESI) calcd for C₂₂H₃₄NO₂⁺ [M+H⁺⁺]: 344.2584; found: 344.2584.

[α]D² = +45.4° (c = 0.55, CH₂Cl₂).
A solution of hydrochloric acid (4 M in 1,4-dioxane, 0.5 mL, 2.00 mmol, 43.0 equiv) was added to a solution of S55 (16.0 mg, 46.6 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 40 °C. After 6 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to yield S56 as a colorless foam that was directly used in the following reaction without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 122 µL, 466 µmol, 10.0 equiv) was added dropwise to a solution of the crude phenol S56 (14.0 mg, 46.6 µmol, 1 equiv) in dichloromethane (2.5 mL) at −40 °C and the reaction mixture was allowed to warm to 23 °C over a period of 2.5 h. After 7 h, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in n-heptane) to yield 43 (9.5 mg, 68% over two steps) as an amorphous solid.

**TLC** (20% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM).

**1H NMR** (800 MHz, DMSO-d6): δ = 9.56 (s, 1H), 7.92 (dd, J = 4.5, 1.5 Hz, 1H), 7.06 (dd, J = 8.1, 1.6 Hz, 1H), 6.97 (dd, J = 8.1, 4.6 Hz, 1H), 2.96 (d, J = 13.3 Hz, 1H), 2.68 (d, J = 13.2 Hz, 1H), 2.27–2.20 (m, 1H), 1.98–1.90 (m, 1H), 1.92–1.82 (m, 3H), 1.82–1.76 (m, 1H), 1.56–1.49 (m, 2H), 1.43–1.37 (m, 1H), 1.37–1.32 (m, 1H), 1.29–1.25 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H), 0.76 (d, J = 6.8 Hz, 3H).

**13C NMR** (201 MHz, DMSO-d6): δ = 151.9, 148.0, 138.9, 133.8, 132.4, 121.6, 120.9, 41.9, 39.2, 38.5, 33.9, 33.2, 28.4, 28.1, 26.1, 25.9, 21.8, 21.2, 19.6, 15.8.

**IR** (Diamond-ATR, neat):  v_max = 2926, 2612, 1576, 1456, 1378, 1359, 1287, 1173, 1115, 798.

**HRMS** (El) calcd for C_{20}H_{29}NO [M]^+: 299.2244; found: 299.2243.

[α]_{D}^{20} = +51.6° (c = 0.17, CH_{2}Cl_{2})
A solution of hydroiodic acid (57 wt.% in water, 154 µL, 1.16 mmol, 40.0 equiv) was added to a solution of S55 (10.0 mg, 29.1 µmol, 1 equiv) in benzene (1.5 mL) in an Ace® pressure tube. The tube was sealed and heated to 90 °C. After 17 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (8 mL) and saturated aqueous sodium thiosulfate (2 mL) were added. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in n-heptane) to yield 44 (6.20 mg, 71%) as colorless amorphous solid. Recrystallization from ethyl acetate gave crystals suitable for single-crystal X-ray diffraction.

**TLC** (20% ethyl acetate in hexanes): R_f = 0.27 (UV, CAM).

**^1H NMR** (599 MHz, CDCl_3): δ = 8.09 (dd, J = 4.6, 1.5 Hz, 1H), 7.09 (dd, J = 8.2, 1.5 Hz, 1H), 7.04 (dd, J = 8.2, 4.6 Hz, 1H), 2.86 (d, J = 18.0 Hz, 1H), 2.70 (d, J = 18.0 Hz, 1H), 1.74–1.57 (m, 5H), 1.53–1.48 (m, 1H), 1.47–1.38 (m, 3H), 1.34–1.28 (m, 2H), 1.21 (td, J = 13.5, 3.5 Hz, 1H), 1.10 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.80 (d, J = 6.8 Hz, 3H).

**^13C NMR** (151 MHz, CDCl_3): δ = 149.2, 143.5, 141.2, 124.0, 122.5, 82.6, 45.7, 41.9, 38.3, 36.7, 33.6, 32.7, 32.4, 30.6, 29.0, 22.5, 21.9, 17.9, 17.1, 16.4.

**IR** (Diamond-ATR, neat): ν_max = 2948, 1438, 1258, 1170, 1107, 1016, 931, 908, 805, 720.

**HRMS** (ESI) calcd for C_{20}H_{30}NO^+ [M+H]^+: 300.2322; found: 300.2321.

[α]_D^{20} = +54.9° (c = 0.12, CH_2Cl_2).
Synthesis of (−)-Mamanuthaquinone (6)

Arene 36

Selenium dioxide (233 mg, 2.10 mmol, 0.0800 equiv) was added to a solution of iso-vanillin (S57) (4.00 g, 26.3 mmol, 1 equiv) and hydrogenperoxide (30% in water, 5.91 mL, 57.8 mmol, 2.20 equiv) in dichloromethane (70 mL). After 16 h, water (30 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield S58 (1.32 g, 36%) as a clear, colorless solid. The obtained analytical data were in full agreement with those values reported in the literature.

Sodium hydride (60% mineral oil dispersion, 771 mg, 19.3 mmol, 2.50 equiv) was slowly added to a solution of bisphenol S58 (1.08 g, 7.71 mmol, 1 equiv) in N,N-dimethylformamide (30 mL) at 0 °C. After 1 h, bromomethyl methyl ether (1.29 mL, 15.8 mmol, 2.05 equiv) was added to the dark brown suspension and the reaction mixture was allowed to warm to 23 °C. After 5 h, water (40 mL) was carefully added and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to yield 36 (1.23 g, 70%) as a colorless oil.

**TLC** (20% ethyl acetate in hexanes): Rf = 0.20 (CAM).

**1H NMR** (599 MHz, CDCl₃): δ = 6.90 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 6.67 (dd, 8.9, 2.8 Hz, 1H), 5.21 (s, 2H), 5.10 (s, 2H), 3.83 (s, 3H), 3.51 (s, 3H), 3.48 (s, 3H).

**13C NMR** (151 MHz, CDCl₃): δ = 151.5, 147.1, 145.1, 112.4, 109.0, 106.8, 95.5, 95.2, 56.4, 56.2, 55.9.

**IR** (Diamond-ATR, neat): νmax = 2902, 2363, 1596, 1505, 1226, 1150, 1130, 1074, 998, 922.

**HRMS** (EI) calcd for C_{11}H_{16}O_{5} [M]^+: 228.0992; found: 228.0984.
To a solution of 36 (224 mg, 981 µmol, 1.40 equiv) in tetrahydrofuran (4 mL) and freshly distilled (over CaH$_2$) $N,N,N,N'$-tetramethylethene-1,2-diamine (317 µL, 2.10 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.44 M in hexanes 362 µL, 911 µmol, 1.30 equiv) at −78 °C. The reaction mixture was allowed to warm to −30 °C. After 1.5 h, the reaction mixture was cooled to −78 °C and aldehyde 33 (154 mg, 700 µmol, 1 equiv) in tetrahydrofuran (2 mL) was added. The reaction mixture was warmed to −30 °C over a period of 2 h, then diethyl ether (30 mL) and saturated aqueous ammonium chloride solution (30 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield S59 (313 mg, 99%) as a colorless oil. The mixture of inseparable diastereoisomers was characterized by HRMS and IR spectroscopy.

**TLC** (20% ethyl acetate in hexanes): $R_f = 0.18$ (CAM).

**IR** (Diamond-ATR, neat): $\tilde{\nu}_{\text{max}} = 3565, 2953, 1508, 1484, 1256, 1229, 1154, 1077, 1027, 924$.

**HRMS** (El) calcd for C$_{26}$H$_{40}$O$_6$ [M]$^+$: 448.2819; found: 448.2841.
A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 3.49 mL, 3.49 mmol, 5.00 equiv) was added dropwise to a solution of S59 (313 mg, 698 µmol, 1 equiv) in tetrahydrofuran (7 mL) at −78 °C. After 30 min, carbon disulfide (842 µL, 14.0 mmol, 20.0 equiv) was slowly added and the reaction mixture was allowed to warm to −65 °C. After 1 h, methyl iodide (869 µL, 14.0 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (25 mL) and ethyl acetate (30 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

A degassed solution of the xanthogenate (376 mg, 698 µmol, 1 equiv), 2,2’-azobis(2-methylpropionitrile) (AIBN) (56.6 mg, 344 µmol, 0.500 equiv) and tributyltin hydride (1.50 g, 5.17 mmol, 7.50 equiv) in benzene (25 mL) was heated to 90 °C. After 6 h, the reaction mixture was directly purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to yield 37 as a colorless oil (190 mg, 63% over 2 steps).

TLC (20% ethyl acetate in hexanes): RF = 0.34 (CAM).

1H NMR (800 MHz, C6D6): δ = 6.94 (d, J = 8.9 Hz, 1H), 6.48 (d, J = 8.9 Hz, 1H), 5.62–5.56 (m, 1H), 5.13 (q, J = 5.8 Hz, 2H), 4.98–4.88 (m, 2H), 3.42 (s, 3H), 3.30 (s, 3H), 3.26 (d, J = 12.9 Hz, 1H), 3.23 (s, 3H), 3.00 (d, J = 12.9 Hz, 1H), 2.96–2.91 (m, 1H), 2.04–1.99 (m, 2H), 1.84–1.77 (m, 1H), 1.67–1.58 (m, 1H), 1.53–1.48 (m, 1H), 1.46–1.40 (m, 2H), 1.28–1.23 (m, 1H), 1.22 (s, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 0.97–0.89 (m, 1H).

13C NMR (201 MHz, C6D6): δ = 151.9, 147.8, 147.7, 147.5, 126.0, 115.5, 111.3, 109.7, 99.5, 95.8, 57.4, 56.0, 55.8, 42.6, 41.9, 41.2, 39.6, 36.9, 36.3, 32.3, 31.5, 30.3, 28.4, 23.4, 16.8, 15.0.

IR (Diamond-ATR, neat): ν̃max = 2930, 1484, 1251, 1152, 1075, 1038, 982, 925, 801, 720.

HRMS (EI) calcd for C26H40O5 [M]+: 432.2870; found: 432.2868.

[α]D20 = +1.61° (c = 0.66, CH2Cl2)
A solution of hydrochloric acid (~1.25 M in methanol, 3 mL) was added to a solution of 37 (33.0 mg, 76.3 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 30°C. After 5 h, the reaction mixture was diluted with dichloromethane (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield S60 as a brown foam that was directly used in the following reaction.

\( \text{N,N-} \text{Bis(salicylidene)ethylenediaminocobalt(II)} \) (19.8 mg, 61.0 mmol, 0.800 equiv) was added to a solution of crude phenol S60 (26.3 mg, 76.3 µmol, 1 equiv) in \( \text{N,N-} \text{dimethylformamide} \) (6 mL) at 23°C and oxygen was passed through the reaction mixture for 20 min. After 60 min, water (20 mL) was added and the mixture was extracted with diethyl ether (4 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (40% ethyl acetate in hexanes with 0.5% acetic acid) to give \((-\)mamanuthaquinoxine (6) (12.0 mg, 44% over 2 steps) as a bright yellow oil.

**TLC** (40% ethyl acetate in hexanes with 0.5% acetic acid), \( R_f = 0.21 \) (UV, CAM).

**\(^1\)H NMR** (599 MHz, CDCl\(_3\)): \( \delta = 7.43 \) (s, 1H, O-H), 5.87 (s, 1H, H-19), 5.44–5.34 (m, 1H, H-6), 3.87 (s, 3H, H-22), 2.61 (d, \( ^3\)J\( \text{H}_1\)/\( \text{H}_5\)\( = 13.2 \) Hz, 1H, H-15\( A \)), 2.48 (d, \( ^3\)J\( \text{H}_1\)/\( \text{H}_5\)\( = 13.2 \) Hz, 1H, H-15\( B \)), 2.11 (br d, \( ^3\)J\( \text{H}_1\)/\( \text{H}_{10} \) = 12.4 Hz, 1H, H-10), 2.02–1.96 (m, 1H, H-7\( A \)), 1.83 (d, \( ^3\)J\( \text{H}_1\)/\( \text{H}_{10} \) = 12.4 Hz, 1H, H-1\( A \)), 1.80–1.74 (m, 1H, H-7\( B \)), 1.51–1.48 (m, 1H, H-2\( A \)), 1.46–1.35 (m, 3H, H-2\( B \), H-3\( A \), H-8), 1.17–1.13 (m, 1H, H-3\( B \)), 1.03 (s, 3H, H-11), 1.00 (d, \( ^3\)J\( \text{H}_1\)/\( \text{H}_{13} \) = 7.0 Hz, 3H, H-13), 0.97–0.94 (m, 4H, H-1\( A \), H-12), 0.75 (s, 3H, H-14).

**\(^13\)C NMR** (201 MHz, CDCl\(_3\)) \( \delta = 182.6 \) (C-18), 182.4 (C-21), 161.8 (C-20), 153.0 (C-17), 146.5 (C-5), 118.5 (C-16), 115.1 (C-6), 102.2 (C-19), 57.0 (C-22), 41.9 (C-10), 41.5 (C-3), 41.1 (C-9), 36.7 (C-8), 36.6 (C-4), 32.9 (C-15), 31.7 (C-7), 30.8 (C-1), 29.9 (C-11), 28.2 (C-12), 22.9 (C-2), 16.8 (C-13), 16.2 (C-14).

**IR** (Diamond-ATR, neat): \( \tilde{\nu}_{\text{max}} = 3344, 2924, 2891, 2363, 1645, 1608, 1446, 1350, 1234, 1035 \).

**HRMS** (El) calcd for \( \text{C}_{22}\text{H}_{30}\text{O}_4 \)[M]: 358.2139; found: 358.2145.

\( \left[ \alpha \right]_{D}^{19} = -258.4^\circ \) (c = 0.16, CH\(_2\)Cl\(_2\)); lit. \( \left[ \alpha \right]_{D}^{19} = -31^\circ \) (c = 0.058, CHCl\(_3\)). n.a. not available\(^{31}\)*

* This lamp (\( \lambda = 546 \) nm) was not accessible in our laboratory.
**Supplementary Table 10** Comparison of $^1$H NMR data for natural and synthetic (−)-mamanuthaquionone (6).

| Proton | Synthetic (599 MHz, CDCl$_3$) | Natural (500 MHz, CDCl$_3$) | $\Delta$ δ (ppm) |
|--------|-------------------------------|-----------------------------|------------------|
| 1A     | 1.83 (d, $J = 12.4$ Hz, 1H)  | 1.79 (br d, 1H)             | +0.04            |
| 1B     | 0.97–0.94 (m, 4H)             | 0.90 (s, 1H)                |                  |
| 2A     | 1.51–1.48 (m, 1H)             |                             |                  |
| 2B     | 1.46–1.35 (m, 3H)             |                             |                  |
| 3A     | 1.46–1.35 (m, 3H)             |                             |                  |
| 3B     | 1.17–1.13 (m, 1H)             | 1.12 (dd, $J = 13.5$, 13.5 Hz, 1H) | + 0.03 |
| 4      | 5.44–5.34 (m, 1H)             | 5.35 (br s, 1H)             | + 0.04           |
| 7A     | 1.99 (d, $J = 17.8$ Hz, 1H)   | 1.95 (dd, $J = 18$, 17.5 Hz, 4.5 Hz, 1H) | +0.04 |
| 7B     | 1.80–1.74 (m, 1H)             | 1.73 (m, 1H)                | + 0.04           |
| 8      | 1.46–1.35 (m, 3H)             | 1.33–1.45 (m, 4H)           |                  |
| 10     | 2.11 (d, $J = 12.4$ Hz, 1H)   | 2.08 (br d, $J = 13$ Hz, 1H) | +0.03            |
| 11     | 1.03 (s, 3H),                 | 0.99 (s, 3H)                | +0.04            |
| 12     | 0.97–0.94 (m, 4H)             | 0.92 (s, 3H)                |                  |
| 13     | 1.00 (d, $J = 7.0$ Hz, 3H)    | 0.96 (d, $J = 7$ Hz, 3H)    | +0.04            |
| 14     | 0.75 (s, 3H),                 | 0.73 (s, 3H)                | +0.02            |
| 15A    | 2.61 (d, $J = 13.2$ Hz, 1H)   | 2.58 (d = 13.0 Hz, 1H)       | +0.03            |
| 15B    | 2.48 (d, $J = 13.1$ Hz, 1H)   | 2.45 (d, $J = 13.0$ Hz, 1H)  | +0.03            |
| 19     | 5.87 (s, 1H)                  | 5.84 (s, 1H)                | +0.03            |
| 22     | 3.87 (s, 3H)                  | 3.84 (s, 3H)                | +0.03            |
| OH     | 7.43 (s, 1H)                  | 7.45 (s, 1H)                | −0.02            |
Supplementary Table 11 Comparison of $^{13}$C NMR data for natural and synthetic (−)-mamanuthaquinone (6). n.a. not available

| Carbon | Synthetic (201 MHz, CDCl$_3$) | Natural (n.a., CDCl$_3$)$^3$ | Δ: δ (ppm) |
|--------|-------------------------------|-----------------------------|-------------|
| 1      | 30.8                          | 30.6                        | + 0.2       |
| 2      | 22.9                          | 22.7                        | + 0.2       |
| 3      | 41.5                          | 41.2                        | + 0.3       |
| 4      | 36.6                          | 36.3                        | + 0.3       |
| 5      | 146.5                         | 146.3                       | + 0.2       |
| 6      | 115.1                         | 114.8                       | + 0.3       |
| 7      | 31.7                          | 31.5                        | + 0.2       |
| 8      | 36.7                          | 36.4                        | + 0.3       |
| 9      | 41.1                          | 40.9                        | + 0.2       |
| 10     | 41.9                          | 41.7                        | + 0.2       |
| 11     | 29.9                          | 29.7                        | + 0.2       |
| 12$^a$ | 28.2                          | 27.9                        | + 0.3       |
| 13$^a$ | 16.8                          | 16.5                        | + 0.3       |
| 14     | 16.2                          | 16.0                        | + 0.2       |
| 15     | 32.9                          | 32.7                        | + 0.2       |
| 16     | 118.5                         | 118.3                       | + 0.2       |
| 17     | 153.0                         | 152.8                       | + 0.2       |
| 18     | 182.6                         | 182.4                       | + 0.2       |
| 19     | 102.2                         | 102.0                       | + 0.2       |
| 20     | 161.8                         | 161.5                       | + 0.3       |
| 21     | 182.4                         | 182.0                       | + 0.4       |
| 22     | 57.0                          | 56.8                        | + 0.2       |

$^a$ Carbon was reassigned by us on the basis of 2D-NMR studies
Supplementary Figure 2 $^1$H and $^{13}$C NMR Spectra for 11 in CDCl$_3$. 
Supplementary Figure 3 $^1$H and $^{13}$C NMR Spectra for 12 in CDCl$_3$. 
Supplementary Figure 4 $^1\text{H}$ and $^{13}\text{C}$ NMR Spectra for 13 in CDCl$_3$. 

Solvent CDCl$_3$

MHz 400

Nucleus 1H

Solvent CDCl$_3$

MHz 101

Nucleus 13C
Supplementary Figure 5 $^1$H and $^{13}$C NMR Spectra for 14 in CDCl$_3$. 

Solvent CDCl$_3$
MHz 400
Nucleus $^1$H

Solvent CDCl$_3$
MHz 101
Nucleus $^{13}$C
Supplementary Figure 6 $^1$H and $^{13}$C NMR Spectra for S03 in CDCl$_3$. 
Supplementary Figure 7 $^1$H and $^{13}$C NMR Spectra for 15 in CDCl$_3$. 

Solvent CDCl$_3$ 
MHz 599 
Nucleus 1H
Supplementary Figure 8 $^1$H and $^{13}$C NMR Spectra for 18 in CDCl$_3$. 
Supplementary Figure 9 $^1$H and $^{13}$C NMR Spectra for 19 in CDCl$_3$. 
Supplementary Figure 10 $^1$H and $^{13}$C NMR Spectra for 20 in CDCl$_3$. 
Supplementary Figure 11 ¹H and ¹³C NMR Spectra for 22 in CDCl₃.
Supplementary Figure 12: $^1$H and $^{13}$C NMR Spectra for S14 in CDCl$_3$. 

Solvent: CDCl$_3$

MHz: 600

Nucleus: $^1$H

Solvent: CDCl$_3$

MHz: 201

Nucleus: $^{13}$C
Supplementary Figure 13 $^1$H and $^{13}$C NMR Spectra for 23 in CDCl$_3$. 

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Supplementary Figure 14 $^1$H and $^{13}$C NMR Spectra for 24 in CDCl₃.
Supplementary Figure 15 $^1$H and $^{13}$C NMR Spectra for 25 in CDCl$_3$. 
Supplementary Figure 16 $^1$H and $^{13}$C NMR Spectra for 26 in CDCl$_3$. 
Supplementary Figure 17 $^1$H and $^{13}$C NMR Spectra for S18 in CDCl$_3$. 
Supplementary Figure 18 $^1$H and $^{13}$C NMR Spectra for S19 in CDCl$_3$. 
Supplementary Figure 19 $^1$H and $^{13}$C NMR Spectra for 30 in CDCls.
Supplementary Figure 20 $^1$H and $^{13}$C NMR Spectra for 1 in DMSO-d6.
Supplementary Figure 21 HSQC and HMBC NMR Spectra for 1 in DMSO-d6.
Supplementary Figure 22. $^1$H and $^{13}$C NMR Spectra for 38 in CDCl$_3$. 
Supplementary Figure 23 \(^1\)H and \(^{13}\)C NMR Spectra for 39 in CDCl₃.
Supplementary Figure 24 $^1$H and $^{13}$C NMR Spectra for 35 in CDCl$_3$. 

Solvent CDCl$_3$

MHz 999

Nucleus 1H

Solvent CDCl$_3$

MHz 151

Nucleus 13C
Supplementary Figure 25 $^1$H and $^{13}$C NMR Spectra for 2 in CDCl$_3$. 
Supplementary Figure 26 HSQC NMR Spectra for 2 in CDCl₃.
Supplementary Figure 27 $^1$H and $^{13}$C NMR Spectra for S28 in CDCl₃.
Supplementary Figure 28 $^1$H and $^{13}$C NMR Spectra for S30 in C$_6$D$_6$. 
Supplementary Figure 29 $^1$H and $^{13}$C NMR Spectra for 4 in CD$_6$.
Supplementary Figure 30 HSQC NMR Spectra for 4 in C₆D₆.
Supplementary Figure 31 $^1$H and $^{13}$C NMR Spectra for 45 in CDCl$_3$. 

5-epi-strongylin A (45)
Supplementary Figure 32 $^1$H and $^{13}$C NMR Spectra for 46 in CDCl$_3$. 
Supplementary Figure 33 $^1$H and $^{13}$C NMR Spectra for 47 in CDCl$_3$. 
Supplementary Figure 34 $^1$H and $^{13}$C NMR Spectra for S34 in CDCl$_3$. 
Supplementary Figure 35 $^1$H and $^{13}$C NMR Spectra for S36 in CDCl$_3$. 
Supplementary Figure 36: $^1$H and $^{13}$C NMR Spectra for S37 in CDCl$_3$. 
Supplementary Figure 37 $^1$H and $^{13}$C NMR Spectra for S39 in CDCl$_3$. 
Supplementary Figure 38 $^1$H and $^{13}$C NMR Spectra for 48 in C$_6$D$_6$. 
Supplementary Figure 39 $^1$H and $^{13}$C NMR Spectra for 49 in CDCl$_3$. 
Supplementary Figure 40 $^1$H and $^{13}$C NMR Spectra for S43 in CDCl₃.
Supplementary Figure 41 \(^1\)H and \(^{13}\)C NMR Spectra for S45 in CDCl\(_3\).
Supplementary Figure 42 $^1$H and $^{13}$C NMR Spectra for S47 in C$_6$D$_6$. 
Supplementary Figure 43 \(^1\)H and \(^{13}\)C NMR Spectra for 3 in CDCl\(_3\).
Supplementary Figure 44 HSQC C NMR Spectra for 3 in CDCl₃.
Supplementary Figure 45 $^1$H and $^{13}$C NMR Spectra for 50 in CDCl$_3$. 
Supplementary Figure 46 $^1$H and $^{13}$C NMR Spectra for S48 in CDCl$_3$. 
Supplementary Figure 47 $^1$H and $^{13}$C NMR Spectra for 40 in CDCl$_3$. 
Supplementary Figure 48 $^1$H and $^{13}$C NMR Spectra for S51 in CDCl$_3$. 
Supplementary Figure 49 $^1$H and $^{13}$C NMR Spectra for 41 in CDCl$_3$. 
Supplementary Figure 50 $^1$H and $^{13}$C NMR Spectra for 42 in CDCl$_3$. 
Supplementary Figure 51 $^1$H and $^{13}$C NMR Spectra for S55 in CDCl$_3$. 
Supplementary Figure 52 $^1$H and $^{13}$C NMR Spectra for 43 in DMSO-d6.
Supplementary Figure 53 $^1$H and $^{13}$C NMR Spectra for 44 in CDCl$_3$. 
Supplementary Figure 54 $^1$H and $^{13}$C NMR Spectra for 36 in CDCl$_3$. 
Supplementary Figure 55 $^1$H and $^{13}$C NMR Spectra for 37 in C$_6$D$_6$. 

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Supplementary Figure 56 ¹H and ¹³C NMR Spectra for 6 in CDCl₃.
Supplementary Figure 57 HSQC NMR Spectra for 2 in CDCl₃.
X-Ray Crystallographic Data

Supplementary Figure 58  CCDC 1534418 contains the supplementary crystallographic data for isoindole 15. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 59 CCDC 1534416 contains the supplementary crystallographic data for oxazolidone 22. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 60  CCDC 1534417 contains the supplementary crystallographic data for oxazolidone S14. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 61  CCDC 1534419 contains the supplementary crystallographic data for pentacycle S19. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 62 CCDC 1534618 contains the supplementary crystallographic data for aldehyde 33. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 63  CCDC 1534421 contains the supplementary crystallographic data for pyridine 44. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 64  CCDC 1509377 contains the supplementary crystallographic data for 5-epi-strongylin A (45). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 65  CCDC 1534420 contains the supplementary crystallographic data for 3-hydroxy-strongylin A (48). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Figure 66  CCDC 1534580 contains the supplementary crystallographic data for 5-epi-smenoqualone (51). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supplementary Table 12 Crystallographic data for isoindole 15.

| Property                                      | Value                        |
|-----------------------------------------------|------------------------------|
| net formula                                   | C_{20}H_{22}INO_{6}          |
| $M$/g mol$^{-1}$                              | 499.28                       |
| crystal size/mm                               | 0.100 × 0.070 × 0.050        |
| $T/K$                                         | 100.2(2)                     |
| radiation                                     | MoKα                         |
| diffractometer                                | 'Bruker D8 Venture TXS'      |
| crystal system                                | monoclinic                   |
| space group                                   | 'P 1 21/c 1'                 |
| $a$/Å                                         | 11.5389(3)                   |
| $b$/Å                                         | 10.9523(3)                   |
| $c$/Å                                         | 15.9781(4)                   |
| $\alpha$/°                                    | 90                           |
| $\beta$/°                                     | 100.7260(10)                 |
| $\gamma$/°                                    | 90                           |
| $V$/Å$^3$                                      | 1983.99(9)                   |
| $Z$                                           | 4                            |
| calc. density/g cm$^{-3}$                     | 1.672                        |
| $\mu$/mm$^{-1}$                               | 1.651                        |
| absorption correction                         | Multi-Scan                   |
| transmission factor range                     | 0.6975–0.7461                |
| refls. measured                               | 25091                        |
| $R_{int}$                                     | 0.0469                       |
| mean $\sigma(I)/I$                            | 0.0427                       |
| $\theta$ range                                | 3.193–30.504                 |
| observed refls.                               | 4958                         |
| $x$, $y$ (weighting scheme)                   | 0.0187, 1.1451               |
| hydrogen refinement                           | constr                       |
| refls in refinement                           | 6066                         |
| parameters                                    | 257                          |
| restraints                                    | 0                            |
| $R(F_{obs})$                                   | 0.0284                       |
| $R_w(F^2)$                                     | 0.0624                       |
| $S$                                           | 1.046                        |
| shift/error$\text{max}$                       | 0.002                        |
| max electron density/e Å$^{-3}$                | 0.642                        |
| min electron density/e Å$^{-3}$                | -0.549                       |
Supplementary Table 13 Crystallographic data for oxazolidone 22.

| Property                        | Value                        |
|---------------------------------|------------------------------|
| net formula                     | C_{28}H_{39}NO_{4}           |
| M/g mol^{-1}                    | 453.60                       |
| crystal size/mm                 | 0.100 × 0.030 × 0.020        |
| T/K                             | 100.2                        |
| radiation                       | MoKα                         |
| diffractometer                  | 'Bruker D8 Venture TXS'       |
| crystal system                  | orthorhombic                 |
| space group                     | 'P 21 21 21'                 |
| a/Å                             | 10.5044(2)                   |
| b/Å                             | 13.8351(3)                   |
| c/Å                             | 34.2367(8)                   |
| α°                             | 90                           |
| β°                             | 90                           |
| γ°                             | 90                           |
| V/Å³                            | 4975.60(18)                  |
| Z                               | 8                            |
| calc. density/g cm^{-3}         | 1.211                        |
| μ/mm^{-1}                       | 0.080                        |
| absorption correction           | Multi-Scan                   |
| transmission factor range       | 0.8985–0.9705                |
| refls. measured                | 21786                        |
| $R_{int}$                       | 0.0375                       |
| mean σ(I)/I                     | 0.0688                       |
| θ range                         | 3.176–28.282                 |
| observed refls.                | 9666                         |
| x, y (weighting scheme)         | 0.0342, 1.3785               |
| hydrogen refinement             | constr                       |
| Flack parameter                 | 0.5(5)                       |
| refls in refinement             | 11844                        |
| parameters                      | 607                          |
| restraints                      | 0                            |
| $R(F_{obs})$                    | 0.0494                       |
| $R_w(F^2)$                      | 0.1085                       |
| S                               | 1.025                        |
| shift/error_{max}               | 0.001                        |
| max electron density/e Å^{-3}   | 0.288                        |
| min electron density/e Å^{-3}   | -0.246                       |
**Supplementary Table 14 Crystallographic data for oxazolidone S13.**

| Parameter                      | Value                       |
|--------------------------------|-----------------------------|
| net formula                    | C_{28}H_{39}NO_{4}          |
| $M$/g mol$^{-1}$               | 453.60                      |
| crystal size/mm                | 0.100 $\times$ 0.060 $\times$ 0.020 |
| $T$/K                          | 100.2                       |
| radiation                      | MoKα                        |
| diffractometer                 | 'Bruker D8 Venture TXS'     |
| crystal system                 | monoclinic                  |
| space group                    | 'C 1 2 1'                   |
| $a$/Å                          | 21.1557(11)                 |
| $b$/Å                          | 6.9835(3)                   |
| $c$/Å                          | 18.5788(10)                 |
| $\alpha$/°                     | 90                          |
| $\beta$/°                      | 113.077(2)                  |
| $\gamma$/°                     | 90                          |
| $V$/Å$^3$                      | 2525.2(2)                   |
| $Z$                            | 4                           |
| calc. density/g cm$^{-3}$      | 1.193                       |
| $\mu$/mm$^{-1}$               | 0.079                       |
| absorption correction          | Multi-Scan                  |
| transmission factor range      | 0.8764–0.9705               |
| refls. measured               | 11053                       |
| $R_{int}$                      | 0.0308                      |
| mean $\sigma(I)/I$            | 0.0629                      |
| $\theta$ range                | 3.362–28.280                |
| observed refls.               | 5097                        |
| $x$, $y$ (weighting scheme)    | 0.0364, 0.7835              |
| hydrogen refinement            | constr                      |
| Flack parameter               | $-0.8(6)$                   |
| refls in refinement            | 6217                        |
| parameters                    | 304                         |
| restraints                     | 1                           |
| $R(F_{obs})$                   | 0.0475                      |
| $R_w(F^2)$                     | 0.0986                      |
| $S$                            | 1.022                       |
| shift/error$^\text{max}$       | 0.001                       |
| max electron density/e Å$^{-3}$| 0.247                       |
| min electron density/e Å$^{-3}$| $-0.184$                   |
| Property                                      | Value                        |
|----------------------------------------------|------------------------------|
| **net formula**                              | $\text{C}_{33}\text{H}_{41}\text{NO}_5$ |
| $M$/g mol$^{-1}$                             | 531.67                       |
| crystal size/mm                              | $0.080 \times 0.070 \times 0.030$ |
| $T$/K                                        | 100.2                        |
| radiation                                    | MoKα                         |
| diffractometer                               | 'Bruker D8 Venture TXS'       |
| crystal system                               | orthorhombic                  |
| space group                                  | 'P 21 21 21'                 |
| $a$/Å                                        | 9.2680(3)                    |
| $b$/Å                                        | 13.5377(6)                   |
| $c$/Å                                        | 22.8966(10)                  |
| $\alpha/^\circ$                              | 90                           |
| $\beta/^\circ$                               | 90                           |
| $\gamma/^\circ$                              | 90                           |
| $V$/Å$^3$                                     | 2872.8(2)                    |
| $Z$                                          | 4                            |
| calc. density/g cm$^{-3}$                    | 1.229                        |
| $\mu$/mm$^{-1}$                              | 0.082                        |
| absorption correction                        | Multi-Scan                   |
| transmission factor range                    | 0.9145–0.9705                |
| refls. measured                             | 22538                        |
| $R_{\text{int}}$                             | 0.0659                       |
| mean $\sigma(I)/I$                           | 0.0688                       |
| $\theta$ range                               | 3.138–26.360                 |
| observed refls.                              | 4535                         |
| $x$, $y$ (weighting scheme)                  | 0.0462, 0.6830               |
| hydrogen refinement                          | constr                       |
| Flack parameter                              | 0.6(8)                       |
| refls in refinement                          | 5852                         |
| parameters                                   | 359                          |
| restraints                                   | 0                            |
| $R(F_{\text{obs}})$                          | 0.0516                       |
| $R_w(F^2)$                                   | 0.1189                       |
| $S$                                          | 1.042                        |
| shift/error$\text{max}$                      | 0.001                        |
| max electron density/e Å$^{-3}$              | 0.231                        |
| min electron density/e Å$^{-3}$              | −0.239                       |
| Property                              | Value                  |
|--------------------------------------|------------------------|
| net formula                          | C15H24O                |
| $M$ / g mol$^{-1}$                    | 220.34                 |
| crystal size / mm                    | 0.100 x 0.070 x 0.050  |
| $T$ / K                              | 153.2                  |
| radiation                            | MoKα                   |
| diffractometer                       | 'Bruker D8 Venture TXS' |
| crystal system                       | monoclinic             |
| space group                          | 'P 1 21 1'             |
| $a$ / Å                              | 7.1180(3)              |
| $b$ / Å                              | 8.2644(3)              |
| $c$ / Å                              | 11.4134(5)             |
| $\alpha^\circ$                       | 90                     |
| $\beta^\circ$                        | 94.5133(16)            |
| $\gamma^\circ$                       | 90                     |
| $V$ / Å$^3$                           | 669.32(5)              |
| $Z$                                   | 2                      |
| calc. density / g cm$^{-3}$           | 1.093                  |
| $\mu$ / mm$^{-1}$                    | 0.066                  |
| absorption correction                | Multi-Scan             |
| transmission factor range            | 0.9195–0.9593          |
| refls. measured                     | 7512                   |
| $R_{int}$                            | 0.0204                 |
| mean $\sigma(I)/I$                   | 0.0292                 |
| $\theta$ range                       | 3.262–28.255           |
| observed refls.                      | 2940                   |
| $x$, $y$ (weighting scheme)          | 0.0457, 0.1045         |
| hydrogen refinement                  | constr                 |
| Flack parameter                      | $-0.2(4)$              |
| refls in refinement                  | 3068                   |
| parameters                           | 149                    |
| restraints                            | 1                      |
| $R(F_{\text{obs}})$                  | 0.0328                 |
| $R_w(F^2)$                            | 0.0910                 |
| $S$                                   | 1.068                  |
| $\text{shift/error}_{\text{max}}$    | 0.001                  |
| max electron density / e Å$^{-3}$     | 0.223                  |
| min electron density / e Å$^{-3}$     | $-0.160$               |
**Supplementary Table 17 Crystallographic data for pyridine 43.**

| Property                        | Value                      |
|---------------------------------|----------------------------|
| net formula                     | C_{20}H_{29}NO             |
| $M$/g mol$^{-1}$                 | 299.44                     |
| crystal size/mm                 | 0.100 × 0.030 × 0.020      |
| $T$/K                           | 100.(2)                    |
| radiation                       | MoKα                       |
| diffractometer                  | 'Bruker D8 Venture TXS'     |
| crystal system                  | orthorhombic               |
| space group                     | 'P 21 21 21'               |
| $a$/Å                           | 6.5144(10)                 |
| $b$/Å                           | 15.165(2)                  |
| $c$/Å                           | 16.776(2)                  |
| $α$/°                           | 90                         |
| $β$/°                           | 90                         |
| $γ$/°                           | 90                         |
| $V$/Å$^3$                       | 1657.3(4)                  |
| $Z$                             | 4                          |
| calc. density/g cm$^{-3}$       | 1.200                      |
| $μ$/mm$^{-1}$                   | 0.072                      |
| absorption correction          | Multi-Scan                 |
| transmission factor range       | 0.7177–0.9705              |
| refls. measured                | 13220                      |
| $R_{int}$                       | 0.0975                     |
| mean $σ(I)/I$                   | 0.0852                     |
| $θ$ range                       | 3.355–25.328               |
| observed refls.                | 2336                       |
| $x$, $y$ (weighting scheme)     | 0.0453, 0.7034             |
| hydrogen refinement            | constr                     |
| Flack parameter                | 0.3(10)                    |
| refls in refinement            | 3019                       |
| parameters                     | 203                        |
| restraints                      | 0                          |
| $R(F_{obs})$                    | 0.0576                     |
| $R_w(F^2)$                      | 0.1354                     |
| $S$                             | 1.062                      |
| shift/error$_{max}$             | 0.001                      |
| max electron density/e Å$^{-3}$ | 0.182                      |
| min electron density/e Å$^{-3}$ | −0.274                     |
Supplementary Table 18 Crystallographic data for 5-epi-strongylin A (44).

| Property                                      | Value                              |
|-----------------------------------------------|------------------------------------|
| net formula                                   | C_{22}H_{32}O_{3}                   |
| \(M/\text{g mol}^{-1}\)                       | 344.47                             |
| crystal size/mm                               | 0.100 × 0.040 × 0.030              |
| \(T/\text{K}\)                                | 153.2                              |
| radiation                                     | MoKα                               |
| diffractometer                                | 'Bruker D8 Venture TXS'            |
| crystal system                                | orthorhombic                       |
| space group                                   | 'P 21 21 21'                       |
| \(a/\text{Å}\)                                | 9.7896(4)                          |
| \(b/\text{Å}\)                                | 10.6910(5)                         |
| \(c/\text{Å}\)                                | 18.2352(10)                        |
| \(\alpha^\circ\)                              | 90                                 |
| \(\beta^\circ\)                               | 90                                 |
| \(\gamma^\circ\)                              | 90                                 |
| \(V/\text{Å}^3\)                              | 1908.51(16)                        |
| \(Z\)                                         | 4                                  |
| calc. density/\text{g cm}^{-3}                 | 1.199                              |
| \(\mu/\text{mm}^{-1}\)                        | 0.078                              |
| absorption correction                         | Multi-Scan                         |
| transmission factor range                    | 0.9329–0.9705                      |
| refls. measured                              | 22500                              |
| \(R_{int}\)                                   | 0.0375                             |
| mean \(\sigma(I)/I\)                         | 0.0317                             |
| \(\theta\) range                             | 3.600–28.276                       |
| observed refls.                              | 4252                               |
| \(x, y\) (weighting scheme)                  | 0.0464, 0.3655                      |
| hydrogen refinement                           | C-H constr, O-H refall             |
| Flack parameter                               | 0.3(4)                             |
| refls in refinement                           | 4731                               |
| parameters                                    | 235                                |
| restraints                                    | 0                                  |
| \(R(F_{\text{obs}})\)                        | 0.0395                             |
| \(R_{w}(F^2)\)                                | 0.0985                             |
| \(S\)                                        | 1.042                              |
| shift/errormax                                | 0.001                              |
| max electron density/\text{e Å}^{-3}          | 0.249                              |
| min electron density/\text{e Å}^{-3}          | −0.216                             |
| Property                      | Value                                      |
|-------------------------------|--------------------------------------------|
| net formula                   | C_{25}H_{35}O_{4}                          |
| $M$/g mol$^{-1}$              | 399.53                                     |
| crystal size/mm               | 0.080 × 0.060 × 0.020                      |
| $T$/K                         | 173.2(2)                                   |
| radiation                     | MoKα                                       |
| diffractometer                | 'Bruker D8 Venture TXS'                    |
| crystal system                | monoclinic                                 |
| space group                   | 'P 1 2 1 1'                                |
| $a$/Å                         | 13.5556(9)                                 |
| $b$/Å                         | 13.8798(11)                                |
| $c$/Å                         | 15.6721(14)                                |
| $α$°                          | 90                                         |
| $β$°                          | 103.108(4)                                 |
| $γ$°                          | 90                                         |
| $V$/Å$^3$                     | 2871.9(4)                                  |
| $Z$                           | 4                                          |
| calc. density/g cm$^{-3}$     | 0.924                                      |
| $μ$/mm$^{-1}$                 | 0.061                                      |
| absorption correction         | Multi-Scan                                 |
| transmission factor range     | 0.7873–0.9705                              |
| refls. measured              | 8128                                       |
| $R_{int}$                     | 0.1132                                     |
| mean $σ(I)/I$                 | 0.1198                                     |
| $θ$ range                     | 3.225–23.256                               |
| observed refls.              | 5284                                       |
| $x$, $y$ (weighting scheme)   | 0.1620, 0.0                                |
| hydrogen refinement           | constr                                     |
| Flack parameter               | 0.0(10)                                    |
| refls in refinement           | 8128                                       |
| parameters                   | 532                                        |
| restraints                    | 7                                          |
| $R(F_{obs})$                  | 0.0931                                     |
| $R_w(F^2)$                    | 0.2635                                     |
| $S$                           | 1.035                                      |
| shift/error$\text{max}$       | 0.001                                      |
| max electron density/e Å$^{-3}$| 0.568                                      |
| min electron density/e Å$^{-3}$| −0.305                                     |
| Property                        | Value                                      |
|--------------------------------|--------------------------------------------|
| net formula                    | C_{22}H_{30}O_{4}                           |
| $M$/g mol$^{-1}$               | 358.46                                     |
| crystal size/mm                | 0.080 x 0.050 x 0.030                      |
| $T$/$K$                        | 100.(2)                                    |
| radiation                      | MoKα                                       |
| diffractometer                 | 'Bruker D8 Venture TXS'                    |
| crystal system                 | orthorhombic                               |
| space group                    | 'P 21 21 21'                               |
| $a$/Å                          | 6.77460(10)                                |
| $b$/Å                          | 11.7096(3)                                 |
| $c$/Å                          | 23.4581(6)                                 |
| $\alpha$/°                     | 90                                         |
| $\beta$/°                      | 90                                         |
| $\gamma$/°                     | 90                                         |
| $V$/Å³                         | 1860.88(7)                                 |
| $Z$                            | 4                                          |
| calc. density/g cm$^{-3}$      | 1.279                                      |
| $\mu$/mm$^{-1}$                | 0.086                                      |
| absorption correction         | Multi-Scan                                 |
| transmission factor range      | 0.8996–0.9705                              |
| refls. measured               | 11364                                      |
| $R_{int}$                      | 0.0360                                     |
| mean $\sigma$(I)/I            | 0.0502                                     |
| $\theta$ range                | 3.473–28.278                               |
| observed refls.               | 3970                                       |
| $x$, $y$ (weighting scheme)    | 0.0409, 0.3301                             |
| hydrogen refinement           | constr                                     |
| Flack parameter               | $-0.1(6)$                                  |
| refls in refinement           | 4554                                       |
| parameters                    | 240                                        |
| restraints                     | 0                                          |
| $R(F_{obr})$                   | 0.0424                                     |
| $R_w(F^2)$                     | 0.0956                                     |
| $S$                            | 1.038                                      |
| shift/error$^\text{max}$       | 0.001                                      |
| max electron density/e Å$^{-3}$| 0.269                                      |
| min electron density/e Å$^{-3}$| $-0.245$                                   |
Antibacterial assays

Supplementary Figure 67 Color-coding was used to indicate the decalin stereochemistry (blue = cis-decalin, green = trans-decalin) and to highlight the modified arene component. The effective concentrations (EC50 values) that inhibited the growth of two MRSA strains (DSM 11822/RKI 11-02670) are given in μM.
Supplementary Table 21 Antibacterial activities of meroterpenoids against Gram-positive pathogens\(^1\). EC\(_{50}\) and MIC values are given in µM.

| Cmpd no | MRSA DSM MIC | MRSA DSM EC\(_{50}\) | MRSA RKI MIC | MRSA RKI EC\(_{50}\) | E. faecium MIC | E. faecium EC\(_{50}\) |
|---------|---------------|----------------------|--------------|----------------------|----------------|----------------------|
| 1       | >100          | >100                 | >100         | >100                 | >100           | >100                 |
| 2       | 10            | 5                    | 5            | 5                    | 12             | 8                    |
| 3       | 76            | 22                   | 56           | 22                   | >100           | 14                   |
| 4       | 1.4           | 1                    | 2            | 1                    | >100           | >100                 |
| 5       | 13            | 6                    | 15           | 12                   | >100           | 20                   |
| 9       | 11            | 8                    | 10           | 6                    | 10             | 8                    |
| 38      | 13            | 6                    | 11           | 8                    | 100            | 15                   |
| 39      | 15            | 6                    | 12           | 8                    | 100            | 15                   |
| 40      | 0.8           | 0.2                  | 4            | 0.6                  | >100           | >100                 |
| 41      | >100          | >100                 | >100         | >100                 | >100           | >100                 |
| 42      | >100          | >100                 | >100         | >100                 | >100           | >100                 |
| 43      | 100           | 70                   | 12           | 9                    | >100           | >100                 |
| 44      | >100          | >100                 | >100         | >100                 | >100           | >100                 |
| 45      | 6             | 3                    | 6            | 6                    | 35             | 13                   |
| 46      | 47            | 33                   | 22           | 20                   | >100           | 80                   |
| 47      | 29            | 15                   | 22           | 15                   | 52             | 32                   |
| 48      | >100          | 83                   | 94           | 49                   | >100           | >100                 |
| 49      | >100          | 77                   | >100         | 75                   | >100           | 100                  |
| 50      | 77            | 53                   | 37           | 28                   | >100           | >100                 |
| 51      | 46            | 31                   | 68           | 49                   | >100           | 13                   |
| Linezolid | 1.3         | 0.6                  | 0.6          | 0.2                  | 20             | 7                    |
| Ciprofloxacin | 20         |                      |              |                      | 7              |                      |

\(^1\) All compounds were inactive (>100 µM) against *Acinetobacter baumannii* (DSM 30007), *Escherichia coli* (DSM 1116), *Klebsiella pneumoniae* (DSM 11678) and *Pseudomonas aeruginosa* PA7 (DSM 24068).
Antiproliferative assays

Supplementary Table 22 Antiproliferative activities of meroterpenoids against four mammalian cell lines. EC$_{50}$ values are given in µM.

| Cmpd no | L929 | KB-3-1 | MCF-4 | FS4-LTM |
|---------|------|--------|-------|---------|
| 1       | 51   | 51     | 32    | >100    |
| 2       | >100 | 16     | 14    | 25      |
| 3       | 30   | 25     | 15    | 61      |
| 4       | 49   | 12     | 12    | 25      |
| 5       | 14   | 12     | 27    | 26      |
| 9       | 14   | 11     | 23    | 33      |
| 38      | 19   | 25     | 15    | 25      |
| 39      | 34   | 29     | 23    | 26      |
| 40      | 7    | 7      | 9     | 14      |
| 41      | >100 | >100   | >100  | >100    |
| 42      | >100 | >100   | >100  | >100    |
| 43      | 40   | 20     | 13    | 21      |
| 44      | >100 | 75     | >100  | >100    |
| 45      | >100 | 40     | 27    | >100    |
| 46      | 9    | 24     | 13    | 32      |
| 47      | 3    | 13     | 13    | >100    |
| 48      | 45   | 87     | 43    | 69      |
| 49      | 10   | 21     | 8     | 16      |
| 50      | 54   | 24     | 28    | 46      |
| 51      | 27   | 56     | 25    | 45      |
| Auranofin | 1.2 | 1.2     | 1.1   | 1.7     |
| Staurosporine | 0.5 | 2.2     | 1.8   | 2.0     |

2
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