Synthesis and Anticancer Activity of Epipolythiodiketopiperazine Alkaloids

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General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks. The flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of argon. Cannulae or gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Where necessary (so noted), solutions were deoxygenated by sparging with argon for a minimum of 10 min. Flash column chromatography was performed as described by Still et al. using granular silica gel (60-Å pore size, 40–63 μm, 4–6% H₂O content, Zeochem). Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to short wave ultraviolet light (254 nm), reversibly stained with iodine (I₂ absorbed on silica) vapor, and irreversibly stained by treatment with an aqueous solution of ceric ammonium molybdate (CAM) followed by heating (~1 min) on a hot plate (~250 °C). Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of ~2 torr. The benzenesulfonyl photodeprotection was accomplished by irradiation in a Rayonet RMR-200 photochemical reactor (Southern New England Ultraviolet Company, Branford, CT, USA) equipped with 16 lamps (RPR-3500, 24 W, λmax = 350 nm, bandwidth ~ 20 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, acetonitrile, tetrahydrofuran, methanol, pyridine, toluene, and triethylamine were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure. Nitromethane and nitroethane (from Sigma–Aldrich) were purified by fractional distillation over calcium hydride and were stored over Linde 3 Å molecular sieves in Schlenk flasks sealed with septa and Teflon tape under argon atmosphere. Hünig’s base and benzene were dried by distillation from calcium hydride under an inert argon atmosphere and used directly. 1,4-Dimethoxynaphthalene, hafnium (IV) trifluoromethanesulfonate hydrate, and iodomethane were purchased from Alfa Aesar; 1-(triisopropylsilyl)-1H-pyrrole was purchased from Combi-Block; triphenylmethanesulfenyl chloride was purchased from TCI America, Inc; 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was purchased from OChem Incorporation. All other solvents and chemicals were purchased from Sigma–Aldrich. Silver tetrafluoroborate (≥99.99% trace metals basis) and hydrogen sulfide (≥99.5%) were purchased from Sigma–Aldrich. 1,4-Dimethoxynaphthalene was purified by crystallization from absolute ethanol.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded with a Bruker AVANCE-600 NMR spectrometer (with a Magnex Scientific superconducting actively-shielded magnet) or a Varian inverse probe 500 INOVA spectrometer, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent (CDCl₃: δ 7.26 (CHCl₃), acetone-d₆: δ 2.05 (acetone-d₃), acetonitrile-d₃: δ 2.13 (acetonitrile-d₃), DMSO-d₆: δ 2.50 (DMSO-d₆), methanol-d₄: δ 3.31 (methanol-d₄)). Data are reported as follows: chemical shift [multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, sp = septet, m = multiplet), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded with a Bruker AVANCE-600 NMR spectrometer (with a Magnex Scientific superconducting actively-shielded magnet), a Bruker AVANCE-400 NMR spectrometer (with a Magnex Scientific superconducting magnet), or a Varian 500 INOVA spectrometer, are reported in parts per million on the δ scale, and are referenced from the carbon resonances of the solvent (CDCl₃;
\[ \delta 77.23, \text{acetone-}d_6; \delta 29.84, \text{acetonitrile-}d_3; \delta 118.26, \text{DMSO-}d_6; \delta 39.52 \]. Data are reported as follows: chemical shift (multiplicity,\(^5\) coupling constant in Hertz,\(^5\) assignment). Fluorine-19 nuclear magnetic resonance (\(^{19}\text{F}\) NMR) spectra were recorded with a Varian Mercury 300 spectrometer, are reported in parts per million on the \(\delta\) scale, and are referenced from the fluorine resonance of neat trichlorofluoromethane (CFCl\(_3\); \(\delta 0\)). Data are reported as follows: chemical shift. Infrared data (IR) were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: frequency of absorption (cm\(^{-1}\)), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Optical Rotations were recorded on a Jasco P-1010 Polarimeter (chloroform, Aldrich, Chromasolv Plus 99.9%; acetone, Aldrich, Chromasolv Plus 99.9%) and specific rotations are reported as follows: [wavelength of light (\(\text{cm}^{-1}\)), specific rotation, concentration in grams/100 mL of solution, solvent]. Preparative HPLC was performed on a Waters system with the 1525 Binary HPLC Pump, 2489 UV/Vis Detector, 3100 Mass Detector, System Fluidics Organizer, and 2767 Sample Manager components. We are grateful to Dr. Li Li and Deborah Bass for obtaining the mass spectrometric data at the Department of Chemistry’s Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS using an electrospray (ESI) ionization source.

**Positional Numbering System.** At least three numbering systems for dimeric diketopiperazine alkaloids exist in the literature.\(^6\) In assigning the \(^1\text{H}\) and \(^{13}\text{C}\) NMR data of all intermediates en route to our different naturally occurring ETPs and their synthetic analogues, we wished to employ a uniform numbering scheme. For ease of direct comparison, particularly between early intermediates, non-thiolated diketopiperazines, and advanced compounds, the numbering system used by Barrow for (+)-WIN-64821 (using positional numbers 1–21) is optimal and used throughout this report. In key instances, the products are accompanied by the numbering system as shown below.

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\(^5\) Given if applicable.

Figure S1. List of dimeric epipolythiodiketopiperazines and diketopiperazines.7,8

Figure S2. List of C3-substituted epipolythiodiketopiperazines and diketopiperazines.9

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7 For the experimental procedure and characterization data, see: Kim, J.; Ashenhurst, J. A.; Movassaghi, M. Science 2009, 324, 238.
8 For the experimental procedure and characterization data, see: Kim, J.; Movassaghi, M. J. Am. Chem. Soc. 2010, 132, 14376.
Scheme S1. Synthesis of (+)-12,12'-dideoxyverticillin A (3) and other dimeric derivatives (14, 18, 21–23).

Reagents and conditions: (a) CoCl(PPh₃)₃, acetone, 46%; (b) Pyr₂AgMnO₄, CH₂Cl₂, 63%; (c) TBSCl, PPY (5 mol%), Et₃N, DMF, 55%; (d) 5% Na(Hg), NaH₂PO₄, MeOH, 87%; (e) K₂CS₃, TFA, CH₂Cl₂, 38% (18) and 56% (S2); (f) ethanolamine, acetone; KI₃, Pyr, 38% (14) and 62% (3).

Scheme S2. Synthesis of (+)-chaetocins A (4) and C (5), (+)-12,12'-dideoxychetracin A (6) and other dimeric derivatives (15–17, 20).

Reagents and conditions: (a) Pyr₂AgMnO₄, CH₂Cl₂, 55%; (b) H₂S, TFA, MeNO₂; iPrCOCl, CH₂Cl₂, 53% (2-steps); (c) hv (350 nm), l-ascorbic acid, 1,4-dimethoxybenzene, H₂O, MeCN, 51%; (d)
N$_2$H$_4$, THF, 0 °C; NaH, Ph$_3$SCl, 90%; (e) BF$_3$•OEt$_2$, DTBMP, Et$_3$SiH, CH$_2$Cl$_2$, 82%; (f) Otera’s cat., MeOH, PhMe, 85 °C, 92%; (g) N$_2$H$_4$, THF, 0 °C; TrSSCl, NEt$_3$, 86%; (h) N$_2$H$_4$, THF, 0 °C, 93%; (i) TrSSSCI, NEt$_3$, 80%; (j) TFAA, DTBMP, MeCN; BF$_3$•OEt$_2$, 91%; (k) HCO$_2$Ac; MeCN, BF$_3$•OEt$_2$, 60%; (l) Otera’s cat., MeOH, PhMe, 90 °C; N$_2$H$_4$, 95%; (m) Ac$_2$O, CH$_2$Cl$_2$, 70%; (n) HCl, MeOH, 52%.

**General Reagents and Methods for Biological Assays.** For biological assays, propidium iodide and phenazine methosulfate were purchased from Sigma–Aldrich. The 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium salt was obtained from Promega. Human erythrocytes were purchased from Bioreclamation and used within three days of receipt. Optical densities were recorded on a Spectramax Plus 384 (Molecular Devices, Sunnyvale, CA). Flow cytometry was performed on a BD Biosciences LSR II (San Jose, CA) and the data was analyzed as described using FACSDiva software (San Jose, CA).

**Cell Culture Information.** Cells were grown in media supplemented with fetal bovine serum (FBS) and antibiotics (100 μg/mL penicillin and 100 U/mL streptomycin). Specifically, experiments were performed using the following cell lines and media compositions: U-937, HeLa, H460, and 786-O (RPMI-1640 + 10% FBS), and MCF7 (EMEM + 10% FBS). Cells were incubated at 37 °C in a 5% CO$_2$, 95% humidity atmosphere.

**IC$_{50}$ Value Determination for Adherent Cells using Sulforhodamine B (SRB).** Adherent cells (HeLa, H460, 786-O, and MCF7) were added into 96-well plates (5,000 cells/well for HeLa cell line; 2,000 cells/well for H460, 786-O, and MCF7 cell lines) in 100 μL media and were allowed to adhere for 2-3 hours. Compounds were solubilized in DMSO as 100x stocks, added directly to the cells (100 μL final volume), and tested over a range of concentrations in triplicate (1% DMSO final) on a half-log scale. Concentrations tested ranged from 1 pM to 10 μM, depending on the potency of the compound. DMSO and cell-free wells served as the live and dead control, respectively. After 72 hours of continuous exposure, the plates were evaluated using the SRB colorimetric assay as described previously. Briefly, media was removed from the plate, and cells were fixed by the addition of 100 μL cold 10% trichloroacetic acid in water. After incubating at 4 °C for an hour, the plates were washed in water and allowed to dry. Sulforhodamine B was added as a 0.057% solution in 1% acetic acid (100 μL), and the plates were incubated at room temperature for 30 minutes, washed in 1% acetic acid, and allowed to dry. The dye was solubilized by adding 10 mM Tris base solution (pH 10.5, 200 μL) and incubating at room temperature for 30 minutes. Plates were read at λ = 510 nm. IC$_{50}$ values were determined from three or more independent experiments using TableCurve (San Jose, CA).

**IC$_{50}$ Value Determination for Non-Adherent Cells using MTS.** In a 96-well plate, compounds were pre-added as DMSO stocks in triplicate to achieve a final concentration of 1%. DMSO and cell-free wells served as the live and dead control, respectively. U-937 (5,000 cells/well) cells were distributed in 100 μL media to the compound-containing plate. After 72 hours, cell viability was assessed by adding 20 μL of a PMS/MTS solution to each well, allowing the dye to develop at 37 °C until the live

control had processed MTS, and reading the absorbance at $\lambda = 490$ nm. IC<sub>50</sub> values were determined from three or more independent experiments using TableCurve (San Jose, CA).

**Hemolysis Assay using Human Erythrocytes.** To prepare the erythrocytes, 0.1 mL of human blood was centrifuged (10,000 g, 2 min). The pellet was washed three times with saline (0.9% NaCl) via gentle resuspension and centrifugation (10,000 g, 2 min). Following the final wash, the erythrocytes were resuspended in 0.8 mL red blood cell (RBC) buffer (10 mM Na<sub>2</sub>HPO<sub>4</sub>, 150 mM NaCl, 1 mM MgCl<sub>2</sub>, pH 7.4).

DMSO stocks of compounds were added to 0.5 mL tubes in singlicate (1 µL, 3.3% DMSO final). The stocks were diluted with 19 µL RBC buffer. Positive control tubes contained DMSO in water, and negative control tubes contained DMSO in RBC buffer. A suspension of washed erythrocytes (10 µL) was added to each tube, and samples were incubated at 37 °C for 2 hours. Samples were centrifuged (10,000 g, 2 min), and the supernatant was transferred to a clear, sterile 384-well plate. The absorbance of the supernatants was measured at $\lambda = 540$ nm, and percent hemolysis was calculated relative to the average absorbance values measured for the controls.

![Figure S3](image)

**Figure S3.** Percent hemolysis following treatment with ETPs from Table 2. Error bars represent standard error of the mean, n ≥ 3.

**Apoptosis in U-937 Cells with Annexin V-FITC and Propidium Iodide (AnnV/PI).** DMSO stocks of compounds were added to a 24-well plate in singlicate (0.2% DMSO final). After compound addition, 0.5 mL of a U-937 cell suspension (250,000 cells/mL) was added and allowed to incubate for 24 hours. Following treatment, the cell suspensions were transferred to flow cytometry tubes and pelleted (500 g, 3 min). The media was removed by aspiration, and cells were resuspended in 200 µL AnnV binding buffer (10 mM HEPES, pH 7.4, 140 mM NaCl, 2.5 mM CaCl<sub>2</sub>) with 5 µg/mL PI and 1:90 dilution of AnnV. Samples were analyzed using flow cytometry.

**Apoptosis in U-937 Cells by Western Blot Analysis.** In a 24-well plate, compounds were added as DMSO stocks (0.2% DMSO final) in singlicate. After compound addition, 1.5 mL of a U-937 cell suspension (250,000 cells/mL) was added and allowed to incubate for 24 hours. The cell suspensions were transferred to 1.5 mL tubes and pelleted (600 g, 3 min). The media was removed via aspiration, and the cells were lysed by adding 40 µL of RIPA buffer (50 mM Tris, pH 8.0, 150 mM NaCl, 1% TX-100, 0.5% sodium deoxycholate, 0.1% SDS) with 1% Protease Inhibitor Cocktail Set III. Each sample
was then vigorously vortexed twice for 15 seconds, with a 15-minute incubation on ice following each agitation. The cellular debris was pelleted (16,100 g, 5 min), and then 33 μL of the protein suspension was transferred to fresh 0.5 mL tubes. The protein levels were quantified using a standard BCA (Thermo Scientific), after which the samples were diluted with deionized water to achieve equal protein concentrations for all samples.

Prior to analyzing the samples, 6x Laemmli sample buffer (350 mM Tris, pH 6.8, 12% SDS, 0.012% bromophenol blue, 47% glycerol) with 5% β-mercaptoethanol was added to each sample to achieve a final 1x concentration, after which the samples were incubated at 95 °C for 5 minutes to denature the protein samples. 20–30 μg of protein was added to a 15-well 4–20% Tris-HCl gel and run for 1 hour at 120 V. The gel was equilibrated PBS (pH 7.4) for 5 minutes, and then transferred to a PVDF membrane for 2 hours at 45 V.

Generally, blots were probed as follows. The blot was blocked overnight at 4 °C with a blocking agent in 0.05% Tris-Buffered Saline Tween-20 (TBST) and then probed for the primary antibody at a 1:1000 dilution with a blocking agent in TBST overnight at 4 °C. The blot was washed with TBST, and then probed with a secondary rabbit HRP antibody (1:10,000, Cell Signaling) in TBST for 1 hour at room temperature. The blot was washed with TBST and PBS, and then visualized with Pico luminescent substrate kit (Thermo Scientific). Caspase 3 and PARP were blocked in 5% milk, and actin was blocked in 5% BSA.
**C3-(5-Bromo-1-TIPS-indol-3'-yl)-pyrrolidinoindoline (+)-S12:**

A round-bottom flask was charged with *endo*-tetracyclic bromide (+)-54 (5.00 g, 10.5 mmol, 1 equiv), 2,6-di-tert-butyl-4-methylpyridine (DTBMP, 2.59 g, 12.6 mmol, 1.20 equiv), and 5-bromo-1-triisopropylsilyl-1H-indole12 (S11, 14.8 g, 42.0 mmol, 4.00 equiv), and the mixture was dried azeotropically (concentration of a benzene solution, 2 × 30 mL) under reduced pressure and placed under an argon atmosphere. Anhydrous nitroethane (120 mL) was introduced via syringe, and the mixture was cooled to 0 °C in an ice-water bath. A solution of silver(I) tetrafluoroborate (6.30 g, 32.4 mmol, 3.09 equiv) in anhydrous nitroethane (40 mL) at 0 °C was introduced via cannula to the solution containing the tetracyclic bromide (+)-54 over 20 min. After 5 min, a white precipitate was observed in the clear yellow reaction solution. The reaction flask was covered in aluminum foil, and the suspension was maintained at 0 °C. After 1 h, saturated aqueous sodium chloride solution (25 mL) was introduced, and the resulting biphasic mixture was vigorously stirred for 30 min at 0 °C. The reaction mixture was diluted with ethyl acetate (150 mL), was filtered through a Celite pad, and the solid was washed with ethyl acetate (3 × 50 mL). The combined filtrates were washed with 5% aqueous citric acid solution (2 × 100 mL), water (3 × 100 mL), and saturated aqueous sodium chloride solution (75 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting orange residue was purified by flash column chromatography (eluent: gradient, 2 → 10% acetone in dichloromethane) to afford the indole adduct (+)-S12 (6.56 g, 83.6%) as a white foam. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

1H NMR (600 MHz, CDCl3, 20 ºC):

δ 8.04 (app-d, J = 7.4, 2H, SO2Ph-o-H), 7.77 (d, J = 8.3, 1H, C9-H), 7.56 (app-t, J = 7.5, 1H, SO2Ph-p-H), 7.42 (app-dd, J = 7.8, 8.0, 2H, SO2Ph-m-H), 7.30 (d, J = 8.9, 1H, C8-H), 7.29 (app-dt, J = 1.1, 7.9, 1H, C11-H), 7.15 (app-dd, J = 1.8, 8.8, 1H, C12-H), 6.98 (app-t, J = 7.5, 1H, C13-H), 6.94 (s, 1H, C12-H), 6.84 (d, J = 7.4, 1H, C1-H), 6.55 (d, J = 1.3, 1H, C15-H), 6.28 (s, 1H, C15-H), 4.47 (dd, J = 8.0, 9.5, 1H, C14-H), 4.07 (d, J = 17.8, 1H, C15H3a), 3.94 (d, J = 17.8, 1H, C15H3b), 3.03 (dd, J = 7.6, 13.8, 1H, C15H4a), 3.00 (s, 3H, C17H3), 2.86 (dd, J = 10.0, 13.9, 1H, C12H3), 1.59 (app-sp, J = 7.5, 3H, C10H3), 1.08 (app-d, J = 8.5, 18H, C11-H).

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$^{13}$C NMR (100 MHz, CDCl$_3$, 20 ºC):

δ 167.7 (C$_{13}$), 166.8 (C$_{16}$), 141.3 (C$_{9}$), 139.7 (C$_{9}$), 137.1 (SO$_2$Ph-ips-C), 134.2 (SO$_2$Ph-p-C), 134.0 (C$_{4}$), 130.9 (C$_{2}$), 130.3 (C$_{4}$), 129.6 (C$_{7}$), 129.3 (SO$_2$Ph-m-C), 127.9 (SO$_2$Ph-o-C), 125.4 (C$_{7}$), 124.6 (C$_{6}$), 124.0 (C$_{9}$), 121.9 (C$_{9}$), 116.0 (C$_{8}$), 115.7 (C$_{8}$), 115.1 (C$_{3}$), 113.5 (C$_{6}$), 82.7 (C$_{2}$), 59.5 (C$_{11}$), 55.4 (C$_{5}$), 54.6 (C$_{12}$), 37.6 (C$_{12}$), 33.8 (C$_{17}$), 18.2 (C$_{11}$), 12.9 (C$_{10}$).

FTIR (thin film) cm$^{-1}$: 2949 (m), 2869 (m), 1681 (s), 1447 (m), 1396 (m), 1366 (m), 1178 (s), 1092 (w), 987 (w), 732 (m), 690 (w).

HRMS (ESI) (m/z):

calc’d for C$_{37}$H$_{44}$BrN$_4$O$_4$SSi [M+H]$^+$: 747.2030, found: 747.2025.

$[\alpha]_D^{24}$:

+93.6 ($c = 0.26$, CHCl$_3$).

TLC (10% acetone in dichloromethane), RF:

0.67 (UV, CAM).
**C3-(indol-3’-yl)-pyrrolidinoindoline (+)-59:**

A mixture of anhydrous methanol and ethyl acetate (3:2 v/v, 160 mL) was introduced into a round-bottom flask charged with the indole adduct (+)-S12 (6.56 g, 8.77 mmol, 1 equiv) and palladium on activated charcoal (10% w/w, 0.50 g, 0.47 mmol, 0.05 equiv). The flask was purged by three cycles of vacuum and dihydrogen and sealed under an atmosphere of hydrogen gas (15 psi). Triethylamine (1.50 mL, 10.7 mmol, 1.22 equiv) was introduced to the flask via syringe, and the resulting suspension was vigorously stirred at 23 °C. Upon completion of the reaction (ca 8 h) as monitored by TLC, the flask was purged by three cycles of vacuum and argon and sealed under argon atmosphere. Neat triethylamine trihydrofluoride13 (3.00 mL, 18.4 mmol, 2.15 equiv) was introduced to the flask via syringe and the resulting suspension was stirred at 23 °C. After 13 h, the reaction mixture was filtered through a pad of Celite. The solids were washed with ethyl acetate (3 × 50 mL). The combined filtrates were concentrated under reduced pressure. The resulting pale yellow solid was diluted in ethyl acetate (400 mL) and washed sequentially with an aqueous hydrochloric acid solution (1 N, 2 × 100 mL), water (2 × 100 mL), and saturated aqueous sodium chloride solution (50 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (eluent: 15% acetone in dichloromethane) to afford the indole adduct (+)-59 (4.59 g, 99.9%) as a white solid. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

1H NMR (600 MHz, CDCl3, 20 ºC):

δ 8.03 (br-s, 1H, N1'H), 7.75 (d, J = 8.2, 1H, C8'H), 7.50 (d, J = 7.6, 2H, SO2Ph-o-H), 7.38 (t, J = 7.5, 1H, SO2Ph-p-H), 7.35 (d, J = 8.2, 1H, C8'H), 7.30 (app-dt, J = 1.1, 7.8, 1H, C7'H), 7.19 (app-t, J = 7.6, 1H, C1'H), 7.10 (app-t, J = 7.9, 2H, SO2Ph-m-H), 7.09–7.06 (m, 1H, C4'H), 7.06 (app-t, J = 7.4, 1H, C4'H), 6.93 (app-t, J = 7.4, 1H, C6'H), 6.89 (d, J = 7.9, 1H, C3'H), 6.37 (s, 1H, C2'H), 6.16 (d, J = 2.3, 1H, C2'H), 4.56 (app-t, J = 8.1, 1H, C13'H), 4.13 (d, J = 17.5, 1H, C13'H), 3.85 (d, J = 17.5, 1H, C15'H), 3.09 (dd, J = 8.9, 14.1, 1H, C12'H), 3.03 (dd, J = 7.2, 14.1, 1H, C15'H), 2.90 (s, 3H, C17).

13C NMR (150 MHz, CDCl3, 20 ºC):

δ 167.5 (C11), 165.9 (C16), 139.6 (C9), 137.6 (SO2Ph-ipso-C), 137.4 (C7), 135.9 (C4), 133.1 (SO2Ph-p-C), 129.3 (C6), 128.6 (SO2Ph-m-C), 127.6 (SO2Ph-o-C), 125.2 (C8), 124.8 (C9), 124.6 (C5), 123.6 (C2), 122.9 (C7), 120.3 (C6), 119.0 (C5), 117.1 (C8), 115.0 (C3), 112.0 (C8'), 83.8 (C2), 58.8 (C11), 55.4 (C3), 54.6 (C15), 36.1 (C12), 33.8 (C17).

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FTIR (thin film) cm$^{-1}$: 3384 (br-m), 3013 (w), 2925 (w), 1681 (s), 1457 (m), 1399 (m), 1355 (m), 1169 (m), 1091 (w), 751 (m).


$[\alpha]_D^{23}$: +70.0 ($c = 0.15$, CHCl$_3$).

TLC (25% acetone in dichloromethane), Rf: 0.41 (UV, CAM).
C3-(Indol-3'-yl) hexacyclic diol (–)-56:

Freshly prepared tetra-n-butylammonium permanganate\textsuperscript{1+1,15,16} (767 mg, 2.12 mmol, 3.79 equiv) was added as a solid to a solution of the indole adduct (+)-59 (287 mg, 0.56 mmol, 1 equiv) in dichloromethane (20 mL) at 23 °C. After 30 min, the dark purple solution was diluted with saturated aqueous sodium sulfite solution (20 mL) and then with ethyl acetate (160 mL). The resulting mixture was washed sequentially with saturated aqueous sodium hydrogenocarbonate solution (50 mL), water (2 × 50 mL), and saturated aqueous sodium chloride solution (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and were concentrated under reduced pressure. The resulting yellow residue was purified by flash column chromatography (eluent: gradient, 10 → 25% acetone in dichloromethane) to afford the diol (–)-56 (127 mg, 41.6%) as a white solid.\textsuperscript{17} Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

\textsuperscript{1}H NMR (600 MHz, acetone-\textit{d}_6, 20 °C):

\(\delta\) 9.85 (br-s, 1H, N1'H), 8.01 (d, \(J = 8.2\), 1H, C5'H), 7.56 (d, \(J = 8.1\), 1H, C8'H), 7.49 (d, \(J = 8.1\), 1H, C8'H), 7.41 (d, \(J = 7.5\), 1H, C4'H), 7.35 (app-t, \(J = 7.5\), 1H, SO\textsubscript{2}Ph-p'H), 7.35 (app-t, \(J = 7.5\), 1H, C1'H), 7.24 (app-t, \(J = 7.6\), 1H, C7'H), 7.20 (app-t, \(J = 7.5\), 1H, C6'H), 7.17 (app-t, \(J = 7.5\), 1H, C6'H), 7.04 (d, \(J = 7.5\), 2H, SO\textsubscript{2}Ph-o'H), 6.98 (app-t, \(J = 7.8\), 2H, SO\textsubscript{2}Ph-m'H), 6.80 (d, \(J = 6.2\), 1H, C15OH), 6.66 (s, 1H, C2'H), 6.22 (s, 1H, C11OH), 5.65 (d, \(J = 2.5\), 1H, C2'H), 5.15 (d, \(J = 6.0\), 1H, C13'H), 3.64 (d, \(J = 15.1\), 1H, C12'H), 3.01 (d, \(J = 15.1\), 1H, C15H), 2.95 (s, 3H, C17H3).

\textsuperscript{13}C NMR (150 MHz, acetone-\textit{d}_6, 20 °C):

\(\delta\) 168.1 (C13), 165.7 (C16), 140.4 (C9), 139.3 (SO\textsubscript{2}Ph-ipso-C), 138.8 (C3), 138.6 (C9'), 133.7 (SO\textsubscript{2}Ph-p-C), 129.8 (C2), 128.9 (SO\textsubscript{2}Ph-m-C), 127.5 (SO\textsubscript{2}Ph-o-C), 126.3 (C3), 126.2 (C9), 125.7 (C13), 125.2 (C3), 122.9 (C7), 120.4 (C6), 119.6 (C5), 118.2 (C8), 115.7 (C3), 113.0 (C8), 88.6 (C11), 85.3 (C7), 83.9 (C15), 55.3 (C5), 45.1 (C12), 31.8 (C17).

FTIR (thin film) cm\textsuperscript{-1}:

3392 (br-m), 1700 (s), 1460 (w), 1400 (w), 1360 (m), 1169 (m), 1091 (w), 750 (w).


\textsuperscript{15} Tetra-n-butylammonium permanganate was prepared according to a literature procedure (Karaman, H.; Barton, R. J.; Robertson, B. E.; Lee, D. G. J. Org. Chem. 1984, 49, 4509) and dried under reduced pressure at room temperature.


\textsuperscript{17} Analytically pure samples of polar diol (–)-56 could be obtained by trituration with minimal amount of chloroform.

$[\alpha]_D^{24}$: $-71.4$ ($c = 0.114$, acetone).

m.p.: 212 °C.

TLC (20% acetone in dichloromethane), R$_f$: 0.24 (UV, CAM).
C3-(Indol-3’-yl) epidithiodiketopiperazine 26:

A slow stream of hydrogen sulfide gas was introduced into a solution of diol (–)-56 (254 mg, 466 μmol, 1 equiv) in anhydrous nitroethane (20 mL) at 0 °C, providing a saturated hydrogen sulfide solution. After 20 min, trifluoroacetic acid (TFA, 15 mL) was added slowly via syringe, and the slow introduction of hydrogen sulfide into the mixture was maintained for another 20 min. The reaction mixture was left under an atmosphere of hydrogen sulfide. The ice–water bath was removed, and the yellow solution was allowed to warm to 23 °C. After 2 h, a slow stream of argon gas was introduced into the solution. After 15 min, the reaction mixture was diluted with ethyl acetate (150 mL) and slowly poured into saturated aqueous sodium hydrogenocarbonate solution (70 mL) at 23 °C. The organic layer was sequentially washed with water (3 × 40 mL) and saturated aqueous sodium chloride solution (25 mL), was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure to afford the corresponding bisthiol S13 that was used in the next step without further purification.

The orange residue was dissolved in ethyl acetate (120 mL). A slow stream of dioxygen gas was introduced into the solution. After 4 h, the yellow solution was concentrated under reduced pressure. The orange residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 15% ethyl acetate in dichloromethane) to afford the epidithiodiketopiperazine 26 (205 mg, 76.7%) as a white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

$^1$H NMR (600 MHz, acetone-$d_6$, 20 ºC):

δ 10.05 (br-s, 1H, N1'H), 7.65 (d, $J = 8.1$, 1H, C8'H), 7.55 (d, $J = 7.5$, 1H, C5'H), 7.50 (d, $J = 8.0$, 1H, C5'H), 7.48 (d, $J = 8.8$, 1H, C6'H), 7.46 (app-dt, $J = 1.0$, 7.5, 1H, C7'H), 7.39 (t, $J = 7.4$, 1H, SO2Ph-p-H), 7.30 (app-t, $J = 0.8$, 7.5, 1H, C6'H), 7.22 (dd, $J = 7.2$, 8.0, 1H, C7'H), 7.12 (app-dd, $J = 1.0$, 8.4, 2H, SO2Ph-o-H), 7.10 (dd, $J = 7.3$, 7.9, 1H, C8'H), 7.00 (dd, $J = 7.5$, 8.2, 2H, SO2Ph-m-H), 6.63 (s, 1H, C2'H), 5.98 (d, $J = 2.6$, 1H, C2'H), 5.80 (s, 1H, C1'H), 3.95 (d, $J = 15.6$, 1H, C12'H a), 3.17 (s, 3H, C17'H3), 2.92 (d, $J = 15.7$, 1H, C12'H b).

$^{13}$C NMR (150 MHz, acetone-$d_6$, 20 ºC):

δ 165.9 (C13), 161.0 (C16), 141.5 (C9), 138.7 (SO2Ph-ipso-C), 138.5 (C9p), 138.1 (C3), 134.0 (SO2Ph-p-C), 130.1 (C7), 129.0 (SO2Ph-m-C), 127.7 (SO2Ph-o-C), 126.6 (C8), 125.9 (C6), 125.8 (C5), 125.0 (C2), 123.0 (C5), 120.6 (C3), 119.2 (C4), 119.1 (C5), 114.1 (C3), 113.1 (C8), 85.7 (C2), 75.5 (C11), 69.1 (C13), 56.4 (C3), 42.6 (C12), 31.8 (C17).
FTIR (thin film) cm\(^{-1}\): 3392 (w), 3060 (w), 2990 (w), 1693 (s), 1447 (w), 1358 (m), 1234 (w), 1169 (m), 1089 (w), 1052 (w), 964 (w), 736 (m), 587 (m).

HRMS (ESI) (m/z): calc’d for C\(_{28}\)H\(_{23}\)N\(_4\)O\(_4\)S\(_3\) [M+H]\(^+\): 575.0876, found 575.0885; calc’d for C\(_{28}\)H\(_{23}\)N\(_4\)NaO\(_4\)S\(_3\) [M+Na]\(^+\): 597.0695, found 597.0704.

TLC (20% ethyl acetate in dichloromethane), R\(_f\): 0.62 (UV, CAM).
General Procedure for the Friedel–Crafts Nucleophilic Substitution. A round-bottom flask was charged with endo-tetracyclic bromide (+)-54 (1 equiv), 2,6-di-tert-butyl-4-methylpyridine (DTBMP, 2.10 equiv), and the nucleophile (for 68: tetrafluoroborate as nucleophilic fluorine source, for 69: 1-(triisopropylsilyl)-1H-pyrrole, for 70: anisole), and the mixture was dried azotropically (concentration of an anhydrous benzene solution, 2 x 10 mL) under reduced pressure and placed under an argon atmosphere. Anhydrous nitroethane (4 mL) was introduced via syringe, and the mixture was cooled to 0 °C in an ice–water bath. A solution of silver(I) tetrafluoroborate (2.30 equiv) in anhydrous nitroethane (1 mL) at 0 °C was introduced via syringe to the solution containing the tetracyclic bromide (+)-54 over 1 min. The reaction flask was covered in aluminum foil. The ice–water bath was removed, and the reaction mixture was allowed to warm to 23 °C. After 1 h, saturated aqueous sodium chloride solution (10 mL) was introduced, and the resulting biphasic mixture was vigorously stirred for 30 min at 23 °C. The reaction mixture was diluted with ethyl acetate (50 mL), was filtered through a Celite pad, and the solids were washed with ethyl acetate (3 x 15 mL). The combined filtrates were washed with 5% aqueous citric acid solution (2 x 20 mL), water (3 x 20 mL), and saturated aqueous sodium chloride solution (15 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure.

General Procedure for the Regio- and Stereoselective Hydroxylation. Freshly prepared tetra-n-butylammonium permanganate (4.0 equiv) was added as a solid to a solution of the corresponding diketopiperazine (54, 68–70) (1 equiv) in dichloromethane (0.05 M) at 23 °C. After 2 h, the dark purple solution was diluted with saturated aqueous sodium sulfate solution (20 mL) and then with ethyl acetate (120 mL). The resulting mixture was washed sequentially with saturated aqueous sodium hydrogen carbonate solution (20 mL), water (4 x 20 mL), and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure.

18 C3-Fluoro Friedel–Crafts adduct 68: 1H NMR (600 MHz, CDCl3, 20 °C): δ 7.79 (app-dd, J = 0.9, 8.2, 2H, SO2Ph-α-H), 7.56 (d, J = 8.2, 1H, C4-H), 7.50 (t, J = 7.5, 1H, SO2Ph-β-H), 7.39–7.35 (m, 1H, C3-H), 7.38 (dd, J = 7.9, 8.3, 2H, SO2Ph-α-H), 7.34 (d, J = 7.7, 1H, C15-H), 7.15 (dd, J = 7.5, 7.6, 1H, C11-H), 6.07 (d, J = 14.5, 1H, C9-H), 4.53 (dd, J = 8.2, 8.4, 1H, C6i-H), 4.17 (d, J = 17.6, 1H, C6a-H), 3.86 (d, J = 17.6, 1H, C5-H), 3.06–2.97 (m, 1H, C4-H), 2.93–2.83 (m, 3H, C2-H, C3-H). 13F NMR (282.4 MHz, CDCl3, 20 °C): δ –133.3. MS (ESI) (m/z): [M+H]+: 416.22, [M+Na]+: 438.25, [2M+H]+: 833.73, [2M+Na]+: 853.59. TLC (20% acetone in dichloromethane), Rf: 0.46 (UV, CAM).

19 C3-(N-TIPS-Pyrrol-3'-yl) Friedel–Crafts adduct 69: 1H NMR (600 MHz, CDCl3, 20 °C): δ 8.03 (app-dd, J = 1.0, 7.3, 2H, SO2Ph-α-H), 7.63 (d, J = 7.7, 1H, C5-H), 7.54 (app-dd, J = 1.5, 7.5, 1H, SO2Ph-β-H), 7.43 (app-t, J = 7.6, 2H, SO2Ph-α-H), 7.16–7.11 (m, 1H, C3-H), 7.05–6.99 (m, 2H, C4-H + C4-H), 6.69–6.65 (m, 1H, C3-H), 6.53–5.49 (m, 1H, C1-H), 6.09 (s, 1H, C1-H), 5.83–5.79 (m, 1H, C5-H), 4.33 (dd, J = 8.2, 8.9, 1H, C6-H), 4.10 (d, J = 17.8, 1H, C4-H), 3.95 (app-dd, J = 2.0, 17.6, 1H, C6i-H), 2.99 (s, 3H, C2-H), 2.84 (dd, J = 7.4, 13.3, 1H, C6i-H), 2.73 (dd, J = 10.0, 13.3, 1H, C6i-H), 1.40 (app-dsp, J = 1.6, 7.5, 3H, SiCH(CH3)3), 1.08 (d, J = 7.6, 9H, SiCH(CH3)3). 13C NMR (150 MHz, CDCl3, 20 °C): δ 167.7 (C3), 166.8 (C4), 139.5 (C5), 137.6 (SO2Ph-ipso-C), 135.9 (C6), 133.4 (SO2Ph-β-C), 129.0 (SO2Ph-α-C), 128.3 (C7), 128.2 (SO2Ph-γ-C), 125.7 (C8a), 125.0 (C8b), 124.6 (C9a), 124.0 (C9b), 121.2 (C10), 115.6 (C11), 109.4 (C12), 84.8 (C13), 59.5 (C14), 55.3 (C15), 54.5 (C16), 39.6 (C17), 33.6 (C18), 17.9 (SiCH(CH3)3). MS (ESI) (m/z): [M+H]+: 619.49, [M+Na]+: 641.49, [2M+Na]+: 1261.37. TLC (20% acetone in dichloromethane), Rf: 0.48 (UV, CAM).

20 C3-(p-Methoxyphenyl) Friedel–Crafts adduct 70: 1H NMR (600 MHz, CDCl3, 20 °C): δ 7.60 (app-dd, J = 0.7, 8.1, 1H, C4-H), 7.46 (app-dd, J = 1.1, 8.4, 2H, SO2Ph-α-H), 7.34 (app-dd, J = 1.1, 17.5, 1H, SO2Ph-β-H), 7.30–7.26 (m, 1H, C3-H), 7.14–7.11 (m, 2H, C4-H + C4-H), 7.11 (app-t, J = 7.5, 2H, SO2Ph-α-H), 6.67 (d, J = 8.9, 2H, C4-H), 6.63 (d, J = 8.9, 1H, C2-H), 6.15 (s, 1H, C1-H), 4.42 (dd, J = 7.6, 8.2, 1H, C6-H), 4.12 (d, J = 17.5, 1H, C6i-H), 3.78 (s, 3H, C2-H), 3.10 (dd, J = 6.8, 14.2, 1H, C6a-H), 2.91–2.85 (m, 1H, C6a-H), 2.90 (s, 3H, C2-H). MS (ESI) (m/z): [M+H]+: 526.31, [2M+Na]+: 1029.94. TLC (20% acetone in dichloromethane), Rf: 0.37 (UV, CAM).
C3-Bromo epidithiodiketopiperazines 30 and 34:

This compound was prepared in two steps starting from bishemiaminal S14\(^{21}\) (13.5 mg, 26.6 µmol)\(^{22}\) using the methodology developed to access the corresponding C3-(indol-3'-yl) epidithiodiketopiperazine 26\(^{23}\). The orange residue was purified by flash column chromatography on silica gel (eluents: gradient, 15 → 40% ethyl acetate in dichloromethane) to afford the β-epimer of epidithiodiketopiperazine 30 (6.3 mg, 44%) as a colorless oil and its α-epimer 34 (2.1 mg, 15%) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

β-epimer 30:\(^{24}\)

\(\text{δ 7.82 (d, J = 8.0, 2H, SO}_2\text{Ph-}\text{o-H}), 7.60 (d, J = 8.2, 1H, C\text{1H}), 7.52 (\text{app-dd, J = 7.4, 7.6, 1H, SO}_2\text{Ph-p-H}), 7.42–7.38 (m, 1H, C\text{2H}), 7.40 (\text{app-t, J = 7.7, 2H, SO}_2\text{Ph-m-H}), 7.35 (d, J = 7.7, 1H, C\text{3H}), 7.25 (\text{app-t, J = 7.6, 1H, C}\text{4H}), 6.47 (s, 1H, C\text{2H}), 6.42 (m, 1H, C\text{1H}), 5.22 (s, 1H, C\text{15H}), 3.82 (d, J = 15.4, 1H, C\text{12H}), 3.19 (d, J = 15.4, 1H, C\text{13H}), 3.11 (s, 3H, C\text{17H}).\)

\(^{21}\) S14: \(^1\text{H NMR (600 MHz, MeOD-}\text{d}_4, 20 ^\circ\text{C})\): δ 7.89 (app-dd, J = 0.8, 8.2, 2H, SO\text{2Ph-}\text{o-H}), 7.56 (t, J = 7.5, 1H, SO\text{2Ph-p-H}), 7.47 (d, J = 8.3, 1H, C\text{1H}), 7.44 (dd, J = 7.5, 8.2 2H, SO\text{2Ph-m-H}), 7.38 (d, J = 7.7, 1H, C\text{2H}), 7.33 (app-ddt, J = 1.0, 7.7, 1H, C\text{3H}), 7.16 (app-dt, J = 0.6, 7.5, 1H, C\text{4H}), 6.55 (s, 1H, C\text{5H}), 4.99 (s, 1H, C\text{6H}), 3.71 (d, J = 15.4, 1H, C\text{15H}), 3.09 (d, J = 15.4, 1H, C\text{16H}), 2.86 (s, 3H, C\text{17H}). MS (ESI) (m/z): [2M+Na]+: 1039.24. TLC (20% acetone in dichloromethane), Rf: 0.40 (UV, CAM).

\(^{22}\) Please see pages S14 and S18 for experimental details.

\(^{23}\) Please see page S16 for experimental details.

\(^{24}\) The relative stereochemistry of the episulfide bridge of the β-epimer 30 has been confirmed by key NOESY cross-peaks on the corresponding bis(methylthioether).
FTIR (thin film) cm⁻¹: 2926 (m), 2857 (w), 1771 (m), 1697 (s), 1551 (w), 1449 (m), 1368 (s), 1170 (s), 1090 (w), 1055 (w), 756 (s).

HRMS (ESI) (m/z):
calc’d for C₂₀H₁₆BrN₃NaO₄S₃ [M+Na]^+: 559.9379, found 559.9392.

TLC (20% ethyl acetate in dichloromethane), Rf: 0.47 (UV, I₂, CAM).

α-epimer 34:

¹H NMR (600 MHz, CDCl₃, 20 ºC): δ 7.91 (d, J = 8.1, 2H, SO₂Ph-ο-H), 7.53–7.51 (m, 1H, SO₂Ph-p-H), 7.52 (d, J = 7.9, 1H, C₈H), 7.41 (app-t, J = 7.7, 2H, SO₂Ph-m-H), 7.38 (d, J = 7.9, 1H, C₃H), 7.32 (dd, J = 7.6, 8.0, 1H, C₇H), 7.17 (app-t, J = 7.6, 1H, C₈H), 6.61 (s, 1H, C₂H), 5.16 (s, 1H, C₁₅H), 4.25 (d, J = 15.0, 1H, C₁₂H₃a), 3.09 (d, J = 15.0, 1H, C₁₂H₃b), 2.95 (s, 3H, C₁₇H₃).

¹³C NMR (150 MHz, CDCl₃, 20 ºC): δ 164.1 (C₁₃), 160.9 (C₁₆), 138.8 (C₉), 138.2 (SO₂Ph-ipso-C), 134.1 (SO₂Ph-p-C), 133.6 (C₄), 131.5 (C₇), 129.2 (SO₂Ph-m-C), 128.4 (SO₂Ph-o-C), 126.8 (C₆), 125.2 (C₅), 117.7 (C₈), 87.7 (C₂), 73.8 (C₁₁), 68.9 (C₁₅), 58.2 (C₃), 45.0 (C₁₂), 31.9 (C₁₇).

FTIR (thin film) cm⁻¹: 3296 (w), 3008 (m), 2925 (s), 2855 (s), 1771 (m), 1699 (s), 1552 (m), 1463 (s), 1447 (s), 1368 (s), 1171 (s), 1091 (s), 1057 (m), 757 (s).

HRMS (ESI) (m/z):
calc’d for C₃₀H₁₈BrN₃NaO₄S₁ [M+Na]^+: 559.9379, found 559.9396.

TLC (20% ethyl acetate in dichloromethane), Rf: 0.56 (UV, I₂, CAM).
C3-Fluoro epidithiodiketopiperazines 31 and 35:

This compound was prepared in two steps starting from bishemiaminal **S16** (15.1 mg, 33.7 μmol) using the methodology developed to access the corresponding C3-(indol-3’-yl) epidithiodiketopiperazine **26**. The orange residue was purified by flash column chromatography on silica gel (eluent: gradient, 15 → 40% ethyl acetate in dichloromethane) to afford the β-epimer of epidithiodiketopiperazine **31** (5.4 mg, 34%) as a colorless oil and its α-epimer **35** (2.1 mg, 13%) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

**β-epimer 31.**

**1H NMR (600 MHz, CDCl3, 20 °C):**

δ 7.68 (app-dd, J = 1.1, 7.4, 2H, SO2Ph-o-H), 7.64 (d, J = 8.2, 1H, C8-H), 7.51 (t, J = 7.5, 1H, SO2Ph-p-H), 7.50 (app-dt, J = 1.1, 6.7, 1H, C1-H), 7.38 (dd, J = 7.6, 8.1, 2H, SO2Ph-m-H), 7.40–7.36 (m, 1H, C6-H), 7.28 (d, J = 7.6, 1H, Cβ-H), 6.31 (d, J = 11.8, 1H, C15-H), 5.23 (s, 1H, C21-H), 3.65 (app-t, J = 15.2, 4H, C15O-CH2-CH2).  

**13C NMR (150 MHz, CDCl3, 20 °C):**

δ 166.7 (SO2Ph), 159.5 (C13, C14), 136.8 (SO2Ph-p-C), 132.2 (d, J = 3.2, C12), 130.6 (d, J = 23.5, C16), 129.2 (SO2Ph-m-C), 128.0 (SO2Ph-o-C), 126.8 (C11), 125.5 (C11S), 118.5 (C15), 101.7 (J = 202.3, C8), 88.5 (d, J = 4.1, C15), 83.1 (d, J = 33.0, C2), 83.0 (C12), 42.9 (d, J = 29.7, C13), 32.6 (C11S). **19F NMR (282.4 MHz, CDCl3, 20 °C):** δ -133.2. FTIR (thin film) cm⁻¹: 3365 (br-m), 1695 (br-s), 1447 (m), 1402 (m), 1365 (m), 1342 (m), 1173 (m), 1087 (w), 1023 (w), 912 (w), 729 (m), 600 (m). HRMS (ESI) (m/z): calc'd for C20H19FN3O6S [M+H]+: 448.0973, found 448.0963; calc'd for C20H19FN3O6S [M+Na]+: 470.0793, found 470.0780. TLC (20% acetone in dichloromethane), Rf: 0.29 (UV, CAM).

The relative stereochemistry of the episulfide bridge of the β-epimer **31** has been confirmed by key NOESY cross-peaks on the corresponding bis(methylthioether). Our assignment is supported by key NOESY signals (1H,1H) in ppm: (1.93,3.11), (3.11,7.41), (2.94,6.45). This derivatized compound was prepared in one step using the methodology developed to access (+)-glicadin B (see reference 9). **1H NMR (600 MHz, CDCl3, 20 °C):** δ 7.94 (d, J = 8.0, 2H, SO2Ph-o-H), 7.72 (d, J = 8.3, 1H, C1-H), 7.56 (app-dd, J = 7.4, 7.5, 1H, SO2Ph-p-H), 7.49–7.45 (m, 1H, C8-H), 7.47 (app-t, J = 7.7, 2H, SO2Ph-m-H), 7.41 (d, J = 7.7, 1H, C1-H), 7.20 (app-t, J = 7.5, 1H, C1-H), 6.45 (d, J = 17.5, 1H, C15-H), 4.58 (s, 1H, C21-H), 3.06 (s, 3H, C15OCH2CH2), 2.94 (dd, J = 14.3, 20.1, 1H, Cβ-H), 2.30 (s, 3H, C15OCH2), 1.93 (s, 3H, C15OCH2). **13C NMR (150 MHz, CDCl3, 20 °C):** δ 164.3 (C16), 160.2 (C15), 144.1 (d, J = 5.1, C11S), 138.3 (SO2Ph-p-C), 133.6 (SO2Ph-C), 132.4 (d, J = 3.2, C12), 129.3 (SO2Ph-m-C), 128.8 (d, J = 23.9, C16), 127.5 (SO2Ph-o-C), 125.3 (d, J = 2.7, C8), 124.2 (C11S), 117.1 (d, J = 1.8, C15), 102.8 (d, J = 200.8, C12), 82.0 (d, J = 32.5, C15), 70.6 (d, J = 6.5, C21), 67.1 (C15), 45.5 (d, J = 31.8, C15), 32.8 (C17), 16.9 (C11), 15.2 (C15OCH2). **19F NMR (282.4 MHz, CDCl3, 20 °C):** δ -135.0. MS (ESI) (m/z): [M+H]+: 530.52, [2M+H]+: 1038.00.
1H, C_{12}H_{9}, 3.13 (s, 3H, C_{17}H_{3}), 2.89 (app-d, J = 15.1, 1H, C_{12}H_{9}).

13C NMR (150 MHz, CDCl$_3$, 20 ºC):
\[\delta 164.5 (C_3), 160.0 (C_6), 143.2 (d, J = 4.8, C_5), 137.3 (SO_2Ph-ipso-C), 133.8 (SO_2Ph-p-C), 130.1 (SO_2Ph-m-C), 127.9 (SO_2Ph-o-C), 126.8 (d, J = 2.8, C_9), 124.8 (C_7), 119.4 (d, J = 2.2, C_8), 102.3 (d, J = 205.5, C_9), 82.7 (d, J = 31.8, C_2), 74.4 (d, J = 6.2, C_{11}), 68.4 (C_{15}), 39.2 (d, J = 2.3, C_{12}), 32.3 (C_{17}).

19F NMR (282 MHz, CDCl$_3$, 20 ºC):
\[\delta -137.7.

FTIR (thin film) cm$^{-1}$:
2999 (w), 2920 (w), 1693 (s), 1447 (w), 1368 (m), 1173 (w), 1088 (w), 914 (w), 719 (w).

HRMS (ESI) (m/z):
calc’d for C$_{20}$H$_{17}$FN$_3$O$_4$S$_3$ [M+H]$^+$: 478.0360, found 478.0375; calc’d for C$_{20}$H$_{16}$FN$_3$NaO$_4$S$_3$ [M+Na]$^+$: 500.0179, found 500.0198.

TLC (20% ethyl acetate in dichloromethane), $R_f$: 0.27 (UV, I$_2$, CAM).

$\alpha$-epimer 35:

$^1$H NMR (600 MHz, CDCl$_3$, 20 ºC):
\[\delta 7.74 (d, J = 8.5, 2H, SO_2Ph-o-H), 7.59 (d, J = 8.2, 1H, C_3H), 7.51 (app-dt, J = 1.1, 7.6, 1H, SO_2Ph-p-H), 7.43 (dd, J = 7.5, 7.6, 1H, C_7H), 7.40 (d, J = 7.5, 1H, C_8H), 7.39 (app-t, J = 7.6, 2H, SO_2Ph-m-H), 7.20 (dd, J = 7.5, 7.6, 1H, C_4H), 6.43 (d, J = 11.5, 1H, C_6H), 5.21 (s, 1H, C_{15}H), 3.89 (dd, J = 5.2, 15.2, 1H, C_{17}H_{9}), 3.01 (s, 3H, C_{17}H_{3}), 2.85 (app-ddd, J = 0.5, 15.9, 16.6, 1H, C_{17}H_{9}).

13C NMR (150 MHz, CDCl$_3$, 20 ºC):
\[\delta 164.2 (C_{13}), 161.6 (C_{16}), 141.9 (d, J = 3.7, C_3), 137.0 (SO_2Ph-ipso-C), 134.0 (SO_2Ph-p-C), 130.2 (d, J = 2.8, C_7), 129.2 (SO_2Ph-m-C), 128.6 (d, J = 19.5, C_4), 128.0 (SO_2Ph-o-C), 126.8 (C_9), 125.4 (C_8), 118.5 (C_6), 101.8 (d, J = 170.3, C_3), 83.1 (d, J = 26.9, C_9), 74.0 (d, J = 4.0, C_{11}), 68.6 (C_{13}), 39.2 (d, J = 26.4, C_{12}), 31.9 (C_{17}).

19F NMR (282 MHz, CDCl$_3$, 20 ºC):
\[\delta -134.1.

FTIR (thin film) cm$^{-1}$:
3069 (w), 2991 (w), 1699 (s), 1448 (w), 1367 (m), 1335 (m), 1173 (m), 1089 (w), 908 (w), 730 (m), 720 (m).

HRMS (ESI) (m/z):
calc’d for C$_{20}$H$_{17}$FN$_3$O$_4$S$_3$ [M+H]$^+$: 478.0360, found 478.0372; calc’d for C$_{20}$H$_{16}$FN$_3$NaO$_4$S$_3$ [M+Na]$^+$: 500.0179, found 500.0199.

TLC (20% ethyl acetate in dichloromethane), $R_f$: 0.16 (UV, I$_2$, CAM).
C3-(Pyrrol-3'-yl) epidisulfidodiketopiperazine 32:

This compound was prepared in two steps starting from bishemiaminal S18 (308 mg, 473 μmol) using the methodology developed to access the corresponding C3-(indol-3'-yl) epidisulfidodiketopiperazine 26. The orange residue was purified by flash column chromatography on silica gel (eluent: gradient, 10 → 40% ethyl acetate in dichloromethane) to afford the epidisulfidodiketopiperazine 32 (128 mg, 51.5%) as a pale yellow solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

¹H NMR (600 MHz, CDCl₃, 20 °C):
δ 7.86 (br-s, 1H, N₁H), 7.57 (d, J = 8.1, 1H, C₃H), 7.49 (d, J = 8.4, 2H, SO₂Ph₂-OH), 7.36 (app-dt, J = 1.1, 7.6, 1H, SO₂Ph₂-p-H), 7.35 (app-t, J = 8.2, 1H, C₃H), 7.23 (d, J = 7.5, 1H, C₁H), 7.19 (dd, J = 7.4, 7.5, 1H, C₃H), 7.15 (app-dt, J = 0.9, 7.4, 2H, SO₂Ph₂-m-H), 6.72–6.69 (m, 1H, C₃H), 6.28 (s, 1H, C₇H), 6.03–5.99 (m, 1H, C₁H), 5.58–5.54 (m, 1H, C₃H), 5.22 (s, 1H, C₁₅H), 3.60 (d, J = 15.5, 1H, C₁₂H₅), 3.13 (s, 3H, C₁₇H₃), 2.82 (d, J = 15.5, 1H, C₁₂H₅).

¹³C NMR (150 MHz, CDCl₃, 20 °C):
δ 165.4 (C₁₃), 160.3 (C₁₆), 140.9 (C₉), 138.6 (SO₂Ph₂-ipso-C), 137.2 (C₁₂), 133.2 (SO₂Ph₂-p-C), 129.5 (C₇), 128.5 (SO₂Ph₂-m-C), 127.6 (SO₂Ph₂-o-C), 126.0 (C₈), 124.5 (C₉), 123.5 (C₅), 119.6 (C₅), 118.5 (C₃), 117.1 (C₂), 106.4 (C₁), 87.1 (C₂), 74.4 (C₁₁), 68.4 (C₁₃), 55.4 (C₃), 44.2 (C₁₂), 32.2 (C₁₇).

FTIR (thin film) cm⁻¹:
3391 (w), 2925 (w), 1699 (s), 1458 (m), 1360 (m), 1169 (m), 1090 (w), 749 (m).

S18: ¹H NMR (600 MHz, acetone-d₆, 20 °C): δ 7.75 (app-dd, J = 0.8, 7.5, 2H, SO₂Ph₂-oH), 7.54 (app-dd, J = 0.9, 7.5, 1H, SO₂Ph₂-p-H), 7.37 (app-dd, J = 0.7, 7.6, 2H, SO₂Ph₂-m-H), 7.30 (d, J = 7.6, 1H, C₁H), 7.26 (app-dd, J = 0.4, 7.7, 1H, C₇H), 7.22 (app-dd, J = 1.1, 7.6, 1H, C₁H), 7.12 (app-dd, J = 1.1, 7.4, 1H, C₃H), 6.72–6.69 (m, 1H, C₁H), 6.66–6.63 (m, 1H, C₃H), 6.39 (s, 1H, C₇H), 6.25 (br-s, 1H, C₁₅H), 6.09 (br-s, 1H, C₁₅H), 5.71–5.68 (m, 1H, C₁H), 5.05 (s, 1H, C₃H), 3.35 (d, J = 14.7, 1H, C₁H), 2.92 (s, 3H, C₁₇H₃), 2.85 (d, J = 14.7, 1H, C₁₅H), 1.46 (sp, J = 7.5, 3H, SiCH(CH₃)₂), 1.08 (d, J = 7.5, 18H, SiCH(CH₃)₂). MS (ESI) (m/z): [M+Na]+: 547.0539. TLC (20% acetone in dichloromethane), Rf 0.44 (UV, I₃, CAM).

The relative stereochemistry of the episulfide bridge 32 has been confirmed by key NOESY cross-peaks on the corresponding bis(methylthioether). Our assignment is supported by key NOESY signals (¹H,¹H) in ppm: (1.89,3.06), (2.91,6.07–6.04), (2.91,6.47). This derivatized compound was prepared in one step using the methodology developed to access (+)-gliclacidin B (see reference 9). ¹H NMR (600 MHz, CDCl₃, 20 °C): δ 8.07 (br-s, 1H, N₁H), 7.84 (d, J = 7.5, 2H, SO₂Ph₂-oH), 7.50 (d, J = 8.2, 1H, C₁H), 7.37 (t, J = 7.5, 1H, SO₂Ph₂-p-H), 7.35 (app-t, J = 7.9, 2H, SO₂Ph₂-m-H), 7.28 (app-dd, J = 1.1, 7.8, 1H, C₇H), 7.19 (d, J = 7.4, 1H, C₁H), 7.09 (dd, J = 7.4, 7.5, 1H, C₃H), 6.65–6.62 (m, 1H, C₃H), 6.47 (s, 1H, C₇H), 6.07–6.04 (m, 1H, C₃H), 5.86–5.82 (m, 1H, C₇H), 4.50 (s, 1H, C₁H), 3.06 (d, J = 14.4, 1H, C₁₅H), 3.06 (s, 3H, C₁₇H₃), 2.91 (d, J = 14.4, 1H, C₁₅H), 2.23 (s, 3H, C₃SCH₃), 1.89 (s, 3H, C₁₇SCH₃). ¹³C NMR (150 MHz, CDCl₃, 20 °C): δ 165.3 (C₁₃), 162.6 (C₁₆), 142.1 (C₉), 140.0 (SO₂Ph₂-ipso-C), 137.5 (C₇), 132.8 (SO₂Ph₂-p-C), 128.9 (SO₂Ph₂-m-C), 128.8 (C₁₃), 127.1 (SO₂Ph₂-o-C), 125.7 (C₅), 124.9 (C₉), 123.5 (C₅), 119.3 (C₅), 117.0 (C₃), 115.6 (C₁₇), 106.3 (C₉), 86.0 (C₁₂), 69.7 (C₁₁), 67.7 (C₁₃), 53.1 (C₅), 45.7 (C₁₅), 32.5 (C₁₂), 17.3 (C₁₅SCH₃), 15.5 (C₁₇SCH₃).
HRMS (ESI) (m/z): calc’d for C_{24}H_{20}N_{4}NaO_{4}S_{3} [M+Na]^+: 547.0539, found 547.0560.

TLC (20% ethyl acetate in dichloromethane), Rf: 0.33 (UV, I_{2}, CAM).
C3-(p-Methoxyphenyl) epidithiodiketopiperazine 33:

This compound was prepared in two steps starting from bishemiaminal S2029 (380 mg, 709 µmol)22 using the methodology developed to access the corresponding C3-(indol-3'-yl) epidithiodiketopiperazine 26.23 The orange residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 25% ethyl acetate in dichloromethane) to afford the epidithiodiketopiperazine 33 (321 mg, 80.0%) as a pale yellow solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.30

$^1$H NMR (600 MHz, CDCl$_3$, 20 ºC):

δ 7.64 (d, J = 8.0, 1H, C$_2$H), 7.40 (app-dt, J = 1.4, 7.0, 1H, C$_1$H), 7.33 (d, J = 8.0, 2H, SO$_2$Ph-ο-H), 7.29 (t, J = 7.5, 1H, SO$_2$Ph-p-H), 7.28–7.23 (m, 2H, C$_2$H + C$_4$H), 7.02 (dd, J = 7.6, 7.8, 2H, SO$_2$Ph-m-H), 6.76 (d, J = 8.7, 2H, C$_2$H), 6.62 (d, J = 8.7, 1H, C$_3$H), 6.39 (s, 1H, C$_4$H), 5.28 (s, 1H, C$_{15}$H), 3.78 (s, 3H, C$_3$H$_3$), 3.63 (d, J = 15.6, 1H, C$_{12}$H$_3$), 3.13 (s, 3H, C$_{17}$H$_3$), 2.87 (d, J = 15.6, 1H, C$_{12}$H$_3$).

$^{13}$C NMR (150 MHz, CDCl$_3$, 20 ºC):

δ 165.2 (C$_{13}$), 160.2 (C$_{15}$), 158.9 (C$_{4}$), 141.3 (C$_{9}$), 138.3 (SO$_2$Ph-ipo-C), 135.8 (C$_{8}$), 133.1 (SO$_2$Ph-p-C), 131.2 (C$_{8}$), 129.9 (C$_{8}$), 128.6 (SO$_2$Ph-m-C), 128.0 (C$_{7}$), 127.3 (SO$_4$Ph-o-C), 126.2 (C$_{7}$), 125.8 (C$_{7}$), 119.1 (C$_{9}$), 114.5 (C$_{8}$), 87.8 (C$_{2}$), 74.6 (C$_{11}$), 68.4 (C$_{15}$), 59.5 (C$_{3}$), 55.5 (C$_{5}$), 45.6 (C$_{12}$), 32.2 (C$_{17}$).

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29 S20: $^1$H NMR (600 MHz, DMSO-d$_6$, 20 ºC): δ 7.44 (t, J = 7.5, 1H, SO$_2$Ph-p-H), 7.38 (d, J = 7.8, 1H, C$_4$H), 7.34 (app-t, J = 8.8, 1H, C$_4$H), 7.26 (d, J = 7.4, 2H, SO$_2$Ph-ο-H), 7.21 (app-dt, J = 0.6, 7.3, 1H, C$_1$H), 7.14 (dd, J = 7.6, 8.1, 2H, SO$_2$Ph-m-H), 7.01 (d, J = 7.5, 1H, C$_4$H), 6.76 (d, J = 8.8, 2H, C$_2$H), 6.66 (d, J = 8.8, 1H, C$_1$H), 6.22 (s, 1H, C$_3$H), 5.00 (d, J = 7.4, 1H, C$_{15}$H), 3.74 (s, 3H, C$_3$H$_3$), 3.19 (d, J = 15.0, 1H, C$_4$H), 2.77 (s, 3H, C$_4$H$_3$), 2.67 (d, J = 15.0, 1H, C$_{12}$H$_3$). $^{13}$C NMR (100 MHz, DMSO-d$_6$, 20 ºC): δ 166.6 (C$_{11}$), 165.8 (C$_{15}$), 158.0 (C$_8$), 139.4 (C$_9$), 134.0 (SO$_2$Ph-ipo-C), 137.8 (C$_9$), 133.4 (C$_8$), 133.2 (SO$_2$Ph-p-C), 128.9 (C$_7$), 128.7 (SO$_2$Ph-m-C), 128.0 (C$_9$), 126.7 (SO$_4$Ph-o-C), 126.7 (C$_7$), 125.7 (C$_8$), 117.0 (C$_9$), 114.0 (C$_8$), 87.3 (C$_2$), 86.0 (C$_{11}$), 80.9 (C$_{15}$), 57.4 (C$_3$), 55.1 (C$_{15}$), 49.7 (C$_{12}$), 30.5 (C$_{17}$). MS (ESI) (m/z): [M+H]$^+$: 537.39, [M+Na]$^+$: 558.43, [2M+Na]$^+$: 1094.13. TLC (20% acetone in dichloromethane), Rf: 0.50 (UV, CAM).

30 The relative stereochemistry of the episulfide bridge 33 has been confirmed by key NOESY cross-peaks on the corresponding bis(methylthioether). Our assignment is supported by key NOESY signals ($^1$H,$^1$H) in ppm: (1.89,3.13), (3.13,7.13–7.07), (2.98,6.47). This derivatized compound was prepared in one step using the methodology developed to access (+)-gliocladin B (see reference 9). ($^1$H NMR (600 MHz, CDCl$_3$, 20 ºC): δ 7.85 (app-dd, J = 0.7, 7.7, 2H, SO$_2$Ph-ο-H), 7.54 (d, J = 8.1, 1H, C$_4$H), 7.48 (t, J = 7.3, 1H, SO$_2$Ph-p-H), 7.35 (app-t, J = 7.8, 2H, SO$_2$Ph-m-H), 7.30 (app-dt, J = 1.4, 7.5, 1H, C$_1$H), 7.13–7.07 (m, 2H, C$_1$H + C$_4$H), 6.89 (d, J = 8.8, 2H, C$_1$H), 6.70 (d, J = 8.8, 2H, C$_1$H), 6.64 (s, 1H, C$_3$H), 4.48 (s, 1H, C$_{15}$H), 3.75 (s, 3H, C$_{11}$H), 3.13 (d, J = 14.3, 1H, C$_{12}$H$_3$), 3.06 (s, 3H, C$_{12}$H$_3$), 2.98 (d, J = 14.4, 1H, C$_{15}$H), 1.89 (s, 3H, C$_{15}$H), 1.85 (s, 3H, C$_{15}$H). $^{13}$C NMR (150 MHz, CDCl$_3$, 20 ºC): δ 165.1 (C$_{13}$), 162.3 (C$_{15}$), 158.8 (C$_{8}$), 142.3 (C$_{8}$), 140.1 (SO$_2$Ph-ipo-C), 136.7 (C$_{9}$), 134.2 (C$_{8}$), 132.9 (SO$_2$Ph-p-C), 129.1 (SO$_2$Ph-m-C), 127.1 (C$_{7}$), 127.1 (C$_{7}$), 127.0 (SO$_2$Ph-o-C), 124.9 (C$_{7}$), 123.8 (C$_{7}$), 117.1 (C$_{9}$), 114.4 (C$_{8}$), 85.8 (C$_2$), 69.8 (C$_{11}$), 67.6 (C$_{13}$), 57.0 (C$_3$), 55.5 (C$_{5}$), 45.7 (C$_{12}$), 32.5 (C$_{15}$), 17.2 (C$_{17}$SO$_2$H), 15.5 (C$_{15}$SO$_2$H).}
FTIR (thin film) cm$^{-1}$: 3065 (w), 3006 (w), 2931 (w), 2839 (w), 1698 (s), 1512 (m), 1459 (m), 1363 (m), 1255 (m), 1170 (m), 1035 (w), 755 (m).

HRMS (ESI) (m/z): calc’d for C$_{27}$H$_{23}$N$_3$NaO$_5$S$_3$ [M+Na]$^+$: 588.0692, found 588.0694.

TLC (20% ethyl acetate in dichloromethane), R$_f$: 0.42 (UV, I$_2$, CAM).
**Hexacyclic triphenylmethanedisulfide (+)-71:**

Anhydrous hydrazine (150 μL, 4.77 mmol, 11.1 equiv) was added via syringe to a solution of aminothioisobutyrate (+)-51 (240 mg, 428 μmol, 1 equiv) in anhydrous tetrahydrofuran (50 mL) at 0 °C. After 1 h, the reaction mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL) and ethyl acetate (120 mL). The organic layer was sequentially washed with saturated aqueous ammonium chloride solution (50 mL), water (2 × 50 mL), and saturated aqueous sodium chloride solution (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the hexacyclic aminothiol that was used in the next step without further purification.

Triethylamine (600 μL, 4.27 mmol, 10.0 equiv) and solid triphenylmethanesulfenyl chloride (665 mg, 2.14 mmol, 5.00 equiv) were sequentially added to a solution of hexacyclic aminothiol in anhydrous tetrahydrofuran (60 mL) at 0 °C under an argon atmosphere. After 90 min, the solution was partitioned between saturated aqueous ammonium chloride (50 mL) and ethyl acetate (130 mL). The anhydrous tetrahydrofuran (60 mL) at 0 ºC. After 1 h, the reaction mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL) and ethyl acetate (130 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL), and the combined organic layers were washed sequentially with water (2 × 50 mL) and saturated aqueous sodium chloride solution (30 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford triphenylmethanedisulfide (+)-71 (242 mg, 81.4%) as a white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

**1H NMR (600 MHz, acetonitrile-d₃, 20 °C):**

δ 9.16 (br-s, 1H, N₃H), 7.37 (d, J = 7.4, 1H, C₁H), 7.36 (d, J = 7.6, 1H, C₅H), 7.34–7.30 (m, 6H, C(Ph-OH)₃), 7.30–7.26 (m, 3H, C(Ph-p-H)₃), 7.18–7.15 (m, 6H, C(Ph-m-H)₃), 7.15–7.11 (m, 1H, C₇H), 7.10

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31 This hexacyclic aminothiol can be purified by flash column chromatography on silica gel (eluent: gradient, 10 → 30% ethyl acetate in dichloromethane) to afford triphenylmethanedisulfide (+)-71 (242 mg, 81.4%) as a white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

32 This sequence can also be combined as a sequential single-flask two-step process to afford (+)-71 in 74% yield.

33 Triphenylmethanedisulfide (+)-71 has also been characterized by NMR in CDCl₃: ¹H NMR (600 MHz, CDCl₃, 20 °C): δ 8.00 (br-s, 1H, N₁H), 7.31 (d, J = 7.8, 1H, C₁H), 7.30 (d, J = 7.8, 1H, C₅H), 7.29–7.26 (m, 6H, C(Ph-OH)₃), 7.29–7.26 (m, 3H, C(Ph-p-H)₃), 7.20–7.17 (m, 6H, C(Ph-m-H)₃), 7.16 (d, J = 7.7, 1H, C₁H), 7.15 (d, J = 8.1, 1H, C₅H), 7.02 (d, J = 7.5, 1H, C₇H), 6.83 (d, J = 2.5, 1H, C₁H), 6.74–6.68 (m, 1H, C₅H), 6.74–6.68 (m, 1H, C₇H), 6.74–6.68 (m, 1H, C₁H), 5.82 (s, 1H, C₇H), 5.24 (d, J = 3.6, 1H, C₅H), 4.99 (br-s, 1H, N₂H), 4.07 (d, J = 3.6, 1H, C₇H), 3.43 (d, J = 14.7, 1H, C₇H), 3.00 (s, 3H, C₇H), 2.57 (d, J = 14.7, 1H, C₇H).

¹³C NMR (150 MHz, CDCl₃, 20 °C): δ 167.6 (C₁), 161.3 (C₃), 147.6 (C₅), 142.9 (C₇), 137.0 (C₈), 131.8 (C₉), 129.4 (C₁₀), 125.0 (C₁₁), 122.7 (C₁₂), 122.2 (C₁₃), 120.4 (C₁₄), 120.2 (C₁₅), 119.7 (C₁₆), 117.3 (C₁₇), 111.8 (C₁₈), 110.4 (C₁₉), 82.5 (C₂₀), 77.2 (C₂₁), 69.0 (C₂₂), 54.2 (C₂₃), 50.9 (C₂₄), 29.3 (C₂₅), 29.3 (C₂₆), TLC (5% methanol in dichloromethane), Rf: 0.27 (UV, CAM).
(app-dt, J = 0.8, 7.6, 1H, C7H), 6.97 (d, J = 2.7, 1H, C2H), 6.96 (app-t, J = 8.0, 1H, C8H), 6.68 (d, J = 7.9, 1H, C3H), 6.64–6.60 (m, 1H, C9H), 5.75 (d, J = 1.0, 1H, C2H), 5.60 (br-s, 1H, N1H), 5.11 (s, 1H, C15H), 4.59 (br-s, 1H, C15OH), 3.32 (d, J = 14.5, 1H, C12Hα), 2.89 (s, 3H, C17H3), 2.70 (d, J = 14.5, 1H, C12Hβ).

13C NMR (150 MHz, acetonitrile-d3, 20 ºC):
δ 166.9 (C13), 164.1 (C16), 149.2 (C9), 145.0 (C(Ph-ipsoc)), 138.1 (C9), 133.3 (Cq), 131.2 (C(Ph-m-C)), 129.4 (Cγ), 128.8 (C(Ph-o-C)), 128.4 (C(Ph-p-C)), 125.8 (C4), 125.4 (C3), 122.8 (C7), 122.7 (C2), 120.3 (C9), 120.3 (C8), 120.1 (C6), 118.6 (C5), 112.7 (C5), 110.6 (C8), 83.1 (C2), 78.4 (CPh3), 78.4 (C13), 73.1 (C11), 54.3 (C3), 49.4 (C12), 29.1 (C18).

FTIR (thin film) cm⁻¹:
3345 (br-m), 3056 (w), 2926 (w), 1674 (s), 1483 (m), 1459 (m), 1442 (m), 1388 (m), 745 (s), 700 (s).

HRMS (ESI) (m/z):
calc’d for C41H35N4O3S2 [M+H]+: 695.2145, found: 695.2147.

[α]D24:
+165.2 (c = 0.12, CHCl3).

TLC (5% methanol in dichloromethane), Rf:
0.44 (UV, CAM).
(+)-12-Deoxybionectin A (10): 9,34

Hafnium(IV) trifluoromethanesulfonate hydrate (800 mg) was added as a solid to a colorless solution of hexacyclic triphenylmethanedisulfide (+)-71 (100 mg, 144 μmol, 1 equiv) in anhydrous acetonitrile (40 mL) at 23 °C. A bright yellow coloration was observed immediately after the addition. The suspension was stirred at 23 °C under an argon atmosphere. After 15 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate (60 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed sequentially with water (3 × 50 mL) and saturated aqueous sodium chloride solution (30 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 1 → 6% acetone in dichloromethane) to afford (+)-12-deoxybionectin A (10) (50.2 mg, 80.3 %) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.35

1H NMR (600 MHz, CDCl3, 20 ºC):
δ 8.07 (br-s, 1H, N 1'H), 7.48 (d, J = 8.0, 1H, C 5'H), 7.37 (d, J = 8.2, 1H, C 8'H), 7.25 (d, J = 8.3, 1H, C5'H), 7.20 (app- dt, J = 0.7, 7.7, 1H, C 7'H), 7.20 (app-dt, J = 0.7, 7.7, 1H, C 7'H), 7.09 (app-t, J = 7.6, 1H, C6'H), 6.95 (d, J = 2.5, 1H, C2'H), 6.88 (app-t, J = 7.4, 1H, C6'H), 6.76 (d, J = 7.9, 1H, C1'H), 5.95 (s, 1H, C2'H), 5.30 (br-s, 1H, N 1'H), 5.21 (s, 1H, C15'H), 4.10 (d, J = 15.4, 1H, C12'Ha), 3.15 (s, 3H, C17'H3), 2.95 (d, J = 15.4, 1H, C12'Hb).

13C NMR (150 MHz, CDCl3, 20 ºC):
δ 165.8 (C13), 162.2 (C16), 148.2 (C9), 137.5 (C8), 132.0 (C11), 129.4 (C2), 125.1 (C4), 124.3 (C3), 122.9 (C7), 122.9 (C7), 120.4 (C6), 120.1 (C6), 119.6 (C5), 116.7 (C3), 111.9 (C8), 110.4 (C8), 83.0 (C2), 74.8 (C11), 68.4 (C15), 56.1 (C1), 43.6 (C12), 32.2 (C17).

FTIR (thin film) cm⁻¹:
3358 (br-w), 3006 (w), 2926 (w), 1684 (s), 1609 (w), 1460 (w), 1383 (w), 1232 (m), 748 (m).

HRMS (ESI) (m/z):

[α]D 24:
+387.3 (c = 0.10, CHCl3).

TLC (10% acetone in dichloromethane), Rf:
0.54 (UV, CAM).

35 The relative stereochemistry of the epidisulfide bridge 10 has been confirmed by key NOESY signals (1H,1H) in ppm: (1.99,3.31), (3.31,7.16), (3.20,6.06) on the corresponding bis(methylthioether) – i.e., (+)-gliocladin B (7, see reference 9).
C3-(Indol-3'-yl) epispirithiodiketopiperazine 29:

This compound was prepared in two steps starting from aminothioisobutyrate (+)-51 (26.5 mg, 47.3 μmol) using the methodology developed to access the corresponding C3-(indol-3'-yl) epidithiodiketopiperazine (+)-12-deoxybionectin A (10) (Please see pages S27 and S29 for details). The residue was purified by flash column chromatography on silica gel (eluent: gradient, 2 → 10% acetone in dichloromethane) to afford epispirithiodiketopiperazine 29 (10.3 mg, 46.7%) as a colorless oil.

Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.36

1H NMR (600 MHz, CDCl₃, 20 ºC):

Major conformer: δ 8.10 (br-s, 1H, N₁'H), 7.46 (d, J = 8.1, 1H, C₅'H), 7.35 (d, J = 8.0, 1H, Cₓ'H), 7.21 (app-dt, J = 0.7, 6.9, 1H, C₅'H), 7.18 (app-t, J = 7.6, 1H, C₆'H), 7.14 (d, J = 7.3, 1H, C₅'H), 7.06 (app-t, J = 7.5, 1H, C₆'H), 6.92 (d, J = 2.4, 1H, C₂'H), 6.81 (d, J = 8.3, 1H, C₂'H), 6.80 (app-t, J = 7.5, 1H, C₈'H), 5.85 (s, 1H, C₂'H), 4.87 (s, 1H, C¹₅'H), 3.80 (d, J = 14.6, 1H, C₁₂'H), 3.20 (s, 3H, C₁₇'H₂), 3.16 (d, J = 14.6, 1H, C₁₂'H₁o).37

Minor conformer: δ 8.11 (br-s, 1H, N₁'H), 7.54 (d, J = 8.1, 1H, C₅'H), 7.36 (d, J = 7.9, 1H, C₅'H), 7.22–7.18 (m, 1H, C₅'H), 7.12 (d, J = 7.4, 1H, C₅'H), 7.11 (dd, J = 7.6, 7.7, 1H, C₅'H), 7.09 (app-t, J = 7.6, 1H, C₆'H), 6.94 (d, J = 2.4, 1H, C₂'H), 6.78 (app-t, J = 7.5, 1H, C₈'H), 6.71 (d, J = 7.7, 1H, C₂'H), 6.19 (s, 1H, C₁₂'H₂), 5.21 (s, 1H, C₁₅'H), 3.70 (d, J = 14.7, 1H, C₁₂'H₁o), 3.09 (d, J = 14.7, 1H, C₁₂'H₁o), 3.02 (s, 3H, C₁₇'H₂).37

13C NMR (150 MHz, CDCl₃, 20 ºC):

Major conformer: δ 168.9 (C₁₃), 164.5 (C₁₀), 149.6 (C₅), 137.3 (C₂), 130.8 (C₆), 129.9 (C₇), 125.0 (C₈), 124.8 (C₂), 122.8 (C₇), 122.5 (C₂), 120.3 (C₈), 120.0 (C₆), 119.7 (C₅), 116.5 (C₃), 111.8 (C₈), 110.6 (C₆), 82.1 (C₂), 79.3 (C₁₁), 67.2 (C₁₅), 54.2 (C₃), 49.2 (C₁₂), 31.2 (C₁₇).

Minor conformer: δ 167.4 (C₁₃), 163.2 (C₁₁), 148.2 (C₂), 137.4 (C₂), 131.4 (C₆), 129.2 (C₇), 125.1 (C₈), 124.3 (C₂), 122.8 (C₇), 122.5 (C₂), 120.3 (C₆),

36 Upon concentration or in concentrated solution, the epispirithiodiketopiperazine 29 tends to degrade, thus rendering its isolation and characterization particularly arduous.

37 The resonance for N₁'H was not observed.
120.2 (C₆), 119.7 (C₅), 116.7 (C₃), 111.9 (C₈), 109.8 (C₇), 83.7 (C₂), 74.8 (C₁₁), 71.2 (C₁₃), 54.3 (C₃), 46.8 (C₁₂), 32.5 (C₁₇).

FTIR (thin film) cm⁻¹:
3397 (br-m), 3061 (w), 2922 (w), 2852 (w), 1693 (s), 1458 (m), 1382 (m), 1265 (w), 1170 (m), 1092 (w), 1026 (w), 737 (m).

HRMS (ESI) (m/z):
calc’d for CₙH₁₉N₄O₂S₃ [M+H]⁺: 467.0665, found: 467.0669.

TLC (10% acetone in dichloromethane), Rf: 0.61 (UV, I₂, CAM).
A slow stream of hydrogen sulfide gas was introduced into a solution of diol (–)-56 (185 mg, 340 mmol, 1 equiv) in anhydrous dichloromethane (30 mL) at 0 °C, providing a saturated hydrogen sulfide solution. After 20 min, trifluoroacetic acid (6 mL) was added via syringe over 10 min, and the slow introduction of hydrogen sulfide into the mixture was maintained for another 10 min. The reaction mixture was left under an atmosphere of hydrogen sulfide for an additional 2 h at 0 °C. A slow stream of argon gas was introduced into the solution. After 15 min, the reaction mixture was diluted with ethyl acetate (150 mL) and slowly poured into saturated aqueous sodium hydrogenocarbonate solution (50 mL). The organic layer was sequentially washed with water (3 × 40 mL) and saturated aqueous sodium chloride solution (40 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 25% acetone in dichloromethane) to afford thiohemiaminal 48 (171 mg, 89.8 %) as an orange solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

$^{1}$H NMR (600 MHz, CDCl$_3$, 20 ºC):

δ 7.89 (br-s, 1H, N 1'H), 7.87 (d, J = 8.2, 1H, C$_8$H), 7.45 (d, J = 7.7, 2H, SO$_2$Ph-o-H), 7.44–7.39 (m, 1H, C$_9$H), 7.34 (t, J = 7.4, 1H, SO$_2$Ph-p-H), 7.31 (d, J = 8.2, 1H, C$_8$H), 7.21–7.18 (m, 2H, C$_5$H + C$_6$H), 7.17 (dd, J = 7.4, 7.8, 1H, C$_9$H), 7.03 (app-t, J = 7.8, 2H, SO$_2$Ph-m-H), 6.92 (dd, J = 7.5, 7.6, 1H, C$_{5}'$H), 6.73 (d, J = 8.0, 1H, C$_7$H), 6.61 (s, 1H, C$_{2}'$H), 5.42 (s, 1H, C$_{15}$H), 4.53 (br-s, 1H, C$_{15}$OH), 3.82 (d, J = 14.9, 1H, C$_{12}$H$_a$), 3.11 (s, 3H, C$_{17}$H$_3$), 2.99 (d, J = 14.9, 1H, C$_{12}$H$_b$), 2.61 (s, 1H, C$_{11}$SH).

$^{13}$C NMR (150 MHz, CDCl$_3$, 20 ºC):

δ 166.2 (C$_{13}$), 165.8 (C$_{10}$), 140.9 (C$_9$), 137.3 (SO$_2$Ph-ipso-C), 136.8 (C$_9$), 135.9 (C$_4$), 133.3 (SO$_2$Ph-p-C), 129.4 (C$_3$), 128.6 (SO$_2$Ph-m-C), 127.5 (SO$_2$Ph-o-C), 126.0 (C$_6$), 125.0 (C$_5$), 124.1 (C$_4$), 123.9 (C$_7$), 122.9 (C$_6$), 120.5 (C$_2$), 118.7 (C$_5$), 118.4 (C$_8$), 114.2 (C$_7$), 111.9 (C$_8$), 84.5 (C$_2$), 77.3 (C$_{13}$), 69.5 (C$_{11}$), 53.8 (C$_3$), 51.8 (C$_{12}$), 29.3 (C$_{17}$).

FTIR (thin film) cm$^{-1}$: 3394 (br-w), 2926 (w), 2547 (w), 1700 (s), 1662 (s), 1457 (m), 1359 (m), 1168 (s), 1090 (m), 1024 (w), 734 (m).

HRMS (ESI) (m/z): calc’d for C$_{28}$H$_{24}$N$_4$NaO$_5$S$_2$ [M+Na]$^+$: 583.1080, found: 583.1095.

TLC (20% ethyl acetate in dichloromethane), Rf: 0.09 (UV, CAM).
C3-(Indol-3’-yl) epitrithiodiketopiperazine 27:

This compound was prepared in two steps starting from thiohemiaminal 48 (25.0 mg, 44.6 μmol) using the methodology developed to access the corresponding C3-(indol-3’-yl) epidithiodiketopiperazine (+)-12-deoxybionectin A (10) (Please see pages S27 and S29 for details). The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 30% ethyl acetate in dichloromethane) to afford epitrithiodiketopiperazine 27 (11.3 mg, 41.8 %) as a white solid. Structural assignments were made with additional information from gCOSY, H SQC, and gHMBC data. Based on 1H NMR analysis at 20 °C in CDCl₃, the product exists as a 3:7 mixture of minor:major conformers.38

1H NMR (600 MHz, CDCl₃, 20 ºC):

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<th>Proton</th>
<th>δ (ppm)</th>
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<td>N₁' H</td>
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<td>C₉ H</td>
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<td>7.19 (dd, J = 6.9, 7.9)</td>
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<td>C₅+ C₆ H</td>
<td>7.16-7.12 (m)</td>
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<tr>
<td>C₇ H</td>
<td>7.09 (dd, J = 7.8)</td>
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<td>C₅+ C₆ Ph-p-H</td>
<td>6.96 (dd, J = 7.4, 7.7)</td>
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<td>C₈' H</td>
<td>6.89 (d, J = 8.0)</td>
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<td>C₇' H</td>
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<td>C₁₃ H</td>
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<th>Proton</th>
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13C NMR (150 MHz, CDCl₃, 20 ºC):

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<td>127.5 (SO₂Ph-o-C)</td>
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<td>C₉</td>
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</table>

38 Upon concentration or in concentrated solution, the epitrithiodiketopiperazine 27 tends to degrade, thus rendering its isolation and characterization particularly arduous. One of the by-products has been identified as the corresponding epidithiodiketopiperazine 26.
Minor conformer: δ 169.9 (C₁₃), 161.5 (C₁₈), 141.2 (C₉), 138.1 (SO₂Ph-ips-C), 137.1 (C₉'), 136.6 (C₄), 132.9 (SO₂Ph-p-C), 129.7 (C₇), 128.2 (SO₂Ph-m-C), 127.4 (SO₂Ph-o-C), 126.5 (C₉), 124.7 (C₃), 124.2 (C₂), 123.9 (C₄), 123.2 (C₇), 120.8 (C₆'), 119.4 (C₈), 118.7 (C₅), 114.2 (C₃), 112.0 (C₈'), 85.4 (C₂), 75.0 (C₁₁), 71.4 (C₁₉), 54.1 (C₃), 46.3 (C₁₂), 33.2 (C₁₇).

FTIR (thin film) cm⁻¹: 3394 (br-m), 3017 (w), 2922 (w), 2852 (w), 1699 (s), 1460 (m), 1364 (m), 1236 (w), 1169 (m), 1082 (m), 1049 (w), 750 (m).


TLC (10% ethyl acetate in dichloromethane), Rf: 0.46 (UV, CAM).
C3-(Indol-3'-yl) epitetrathiodiketopiperazine 28:

This compound was prepared in two steps starting from thiohemiaminal 48 (49.3 mg, 88.0 μmol) using the methodology developed to access the corresponding C3-(indol-3'-yl) epidithiodiketopiperazine (+)-12-deoxybionectin A (10) (Please see pages S27 and S29 for details). The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 30% acetate in dichloromethane) to afford epitetrathiodiketopiperazine 28 (25.0 mg, 44.4 %) as a white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

$^1$H NMR (600 MHz, CDCl₃, 20 ºC):

δ 7.92 (br-s, 1H, N₁'H), 7.69 (d, $J = 7.8$, 2H, SO₂Ph-o-H), 7.58 (d, $J = 8.1$, 1H, C₀'H), 7.40 (t, $J = 7.4$, 1H, SO₂Ph-p-H), 7.34 (d, $J = 8.2$, 1H, C₈'H), 7.31 (app-t, $J = 7.8$, 1H, C₇'H), 7.22–7.16 (m, 4H, C₅'H + C₇'H + SO₂Ph-m-H), 7.11 (app-t, $J = 7.4$, 1H, C₀'H), 7.04 (d, $J = 7.8$, 1H, C₈'H), 7.01 (dd, $J = 7.1$, 7.7, 1H, C₆'H), 6.95 (s, 1H, C₅'H), 6.45 (d, $J = 2.2$, 1H, C₂'H), 5.23 (s, 1H, C₁₁'H), 3.47 (d, $J = 14.8$, 1H, C₁₂'Ha), 3.06 (s, 3H, C₁₇'H₃), 3.03 (d, $J = 14.8$, 1H, C₁₂'Hb).

$^{13}$C NMR (150 MHz, CDCl₃, 20 ºC):

δ 168.2 (C₁₃), 162.8 (C₁₆), 141.8 (C₀), 138.5 (SO₂Ph-ips-o-C), 137.3 (C₀), 136.4 (C₄), 133.2 (SO₂Ph-p-C), 129.7 (C₁), 128.8 (SO₂Ph-m-C), 127.7 (SO₂Ph-o-C), 125.7 (C₀), 124.6 (C₃), 124.3 (C₄), 123.0 (C₂), 123.0 (C₇), 120.7 (C₀), 118.8 (C₃), 117.3 (C₄), 115.8 (C₃), 112.0 (C₃), 85.2 (C₂), 76.0 (C₁₁), 68.3 (C₁₅), 53.6 (C₃), 49.1 (C₁₂), 32.5 (C₁₇).

FTIR (thin film) cm⁻¹:

3395 (br-w), 3061 (w), 2924 (w), 2853 (w), 1690 (s), 1458 (w), 1382 (m), 1240 (w), 1170 (m), 1023 (w), 734 (m), 591 (m).

HRMS (ESI) (m/z):

calc’d for C₂₈H₂₂N₄NaO₄S₅ [M+Na]⁺: 661.0137, found 661.0120.

TLC (10% ethyl acetate in dichloromethane), Rf: 0.30 (UV, I₂, CAM).

39 The isolation and purification of epitetrathiodiketopiperazine 28 were complicated by its instability in solution.
C3-(N-Boc-indol-3'-yl) bis(benzylthioether) 43:

Trifluoroacetic acid (4 mL) was slowly added via syringe to a stirred solution of diol (−)-56 (70.0 mg, 128.6 μmol, 1 equiv) and benzyl mercaptan (BnSH, 600 μL, 5.12 mmol, 39.7 equiv) in anhydrous nitroethane (5 mL) at 23 °C. After 3 h, the reaction mixture was diluted with ethyl acetate (100 mL) and slowly poured into saturated aqueous sodium hydrogenocarbonate solution (40 mL) at 23 °C. The organic layer was sequentially washed with water (3 × 40 mL) and saturated aqueous sodium chloride solution (25 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 40% ethyl acetate in hexanes) to afford the bis(benzylthioether) 43 (77.8 mg, 79.9%) as a pale yellow oil. [A minor diastereomer was also isolated from this reaction (13.0 mg, 13.3%)].

4-Dimethylaminopyridine (DMAP, 8.0 mg, 65.5 μmol, 0.26 equiv) was added. After 1 h, the reaction mixture was diluted with ethyl acetate (60 mL). The resulting mixture was sequentially washed with aqueous 5% citric acid solution (30 mL), water (2 × 20 mL), and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (eluent: gradient, 10 → 40% ethyl acetate in hexanes) to afford the N-Boc-indole adduct 43 (47.0 mg, 69.2%) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

1H NMR (600 MHz, CDCl3, 20 °C):

δ 8.03 (br-s, 1H, C8H), 7.79 (d, J = 8.2, 1H, C2H), 7.47 (d, J = 7.4, 2H, C2H), 7.45–7.39 (m, 3H, C2H + SO2Ph-O-H), 7.37 (dd, J = 7.5, 7.6, 2H, C2H), 7.32–7.28 (m, 2H, C3H + C1H), 7.24 (dd, J = 7.4, 7.5, 1H, C2H), 7.22–7.17 (m, 3H, C3H + SO2Ph-p-H), 7.17 (app-t, J = 7.5, 1H, C6H), 7.11 (app-t, J = 7.6, 1H, C6H), 7.01 (d, J = 7.5, 1H, C2H), 7.00–6.92 (m, 5H, C3H + C3H + SO2Ph-m-H), 6.68 (s, 1H, C2H), 6.51 (br-s, 1H, C2H), 4.47 (s, 1H, C15H), 3.96 (d, J = 14.0, 1H, C19H), 3.85 (d, J = 14.0, 1H, C19H).

40 S22: 1H NMR (600 MHz, CDCl3, 20 °C): δ 7.85 (d, J = 8.0, 1H, C2H), 7.75 (d, J = 7.4, 1H, C2H), 7.41 (t, J = 7.5, 1H, SO2Ph-p-H), 7.38–7.27 (m, 7H), 7.27–7.23 (m, 1H), 7.22–7.15 (m, 4H), 7.18 (app-t, J = 7.5, 2H, SO2Ph-m-H), 7.14–7.10 (m, 2H, C2H + C2H), 7.10–7.05 (m, 2H), 6.80–6.76 (m, 2H), 6.71 (s, 1H, C2H), 6.41 (d, J = 2.5, 1H, C2H), 4.48 (s, 1H, C1H), 4.06 (d, J = 12.9, 1H, C3H), 3.81 (d, J = 13.6, 1H, C2H), 3.79 (d, J = 12.8, 1H, C3H), 3.76 (d, J = 13.7, 1H, C19H), 3.39 (d, J = 14.4, 1H, C19H), 2.83 (d, J = 14.4, 1H, C19H), 2.53 (s, 3H, C19H). MS (ESI) (m/z): [M+H]+: 757.56, [M+Na]+: 779.60, [M+K]+: 795.55. TLC (50% ethyl acetate in hexanes), Rf: 0.40 (UV, CAM).
$^{13}$C NMR (150 MHz, CDCl$_3$, 20 ºC):

$$\delta \ 165.2 \ (C_{13}), \ 163.4 \ (C_{16}), \ 140.9 \ (C_{carbamate}), \ 142.1 \ (C_9), \ 138.3 \ (C_6), \ 137.3 \ (SO_2Ph-ipso-C), \ 136.0 \ (C_4), \ 136.0 \ (C_{25}), \ 135.7 \ (C_{20}), \ 132.7 \ (SO_2Ph-p-C), \ 129.9 \ (C_{21}), \ 129.7 \ (C_{26}), \ 129.7 \ (SO_2Ph-m-C), \ 129.5 \ (C_7), \ 128.9 \ (C_{22}), \ 128.5 \ (SO_2Ph-o-C), \ 128.4 \ (C_{27}), \ 127.8 \ (C_{23}), \ 127.4 \ (C_4), \ 127.2 \ (C_{29}), \ 126.0 \ (C_6), \ 125.1 \ (C_7), \ 124.7 \ (C_2), \ 124.1 \ (C_3), \ 123.3 \ (C_6), \ 120.0 \ (C_3), \ 119.2 \ (C_5), \ 119.1 \ (C_8), \ 115.9 \ (C_8), \ 84.4 \ (OC(CH$_3$)$_3$), \ 83.6 \ (C_2), \ 70.6 \ (C_{11}), \ 63.4 \ (C_{13}), \ 53.2 \ (C_4), \ 45.5 \ (C_{12}), \ 37.5 \ (C_{19}), \ 37.0 \ (C_{24}), \ 31.5 \ (C_{17}), \ 28.4 \ (OC(CH$_3$)$_3$).$$

FTIR (thin film) cm$^{-1}$:

$$3214 \ (br-w), \ 3062 \ (w), \ 3027 \ (w), \ 2979 \ (w), \ 2930 \ (w), \ 2856 \ (w), \ 1734 \ (s), \ 1696 \ (s), \ 1668 \ (s), \ 1476 \ (m), \ 1454 \ (s), \ 1373 \ (s), \ 1270 \ (s), \ 1235 \ (s), \ 1171 \ (s), \ 1158 \ (s), \ 1097 \ (m), \ 1026 \ (m), \ 754 \ (s), \ 703 \ (m).$$

HRMS (ESI) ($m/z$):

calc’$d$ for $C_{47}H_{44}N_4NaO_6S_3$ [M+Na]$^+$: 879.2315, found 879.2303.

TLC (30% ethyl acetate in hexanes), Rf:

$$0.33 \ (UV, \ CAM).$$
C3-(N-Boc-indol-3′-yl) epidithiodiketopiperazine 24:
A solution of DMAP in anhydrous dichloromethane (0.17 M, 25 μL, 2.5 mol%) was added via syringe to a solution of epidithiodiketopiperazine 26 (98.3 mg, 171 μmol, 1 equiv) and di-tert-butyl dicarbonate (77.6 mg, 355 μmol, 2.08 equiv) in anhydrous dichloromethane (20 mL) at 23 °C. After 2 h, another portion of DMAP solution (25 μL, 2.5 mol%) was added. After 5 h, the reaction mixture was diluted with ethyl acetate (100 mL). The resulting mixture was sequentially washed with aqueous 5% citric acid solution (50 mL), water (2 × 50 mL), and saturated aqueous sodium chloride solution (30 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (eluent: gradient, 30 → 60% ethyl acetate in hexanes) to afford the N-Boc-epidithiodiketopiperazine 24 (93.3 mg, 80.9%) as a pale yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

$^1$H NMR (600 MHz, CDCl₃, 20 ºC):
δ 8.05 (br-s, 1H, C₈(H)), 7.85 (d, $J$ = 8.1, 1H, C₈(H)), 7.48 (app-dt, $J$ = 4.5, 8.1, 1H, C₇(H)), 7.38 (app-dt, $J$ = 1.3, 7.7, 1H, SO₂Ph-p-H), 7.55 (d, $J$ = 7.1, 1H, C₉(H)), 7.34–7.30 (m, 2H, C₅(H) + C₆(H)), 7.28 (dd, $J$ = 7.1, 7.3, 1H, C₇(H)), 7.17 (app-t, $J$ = 7.4, 1H, C₈(H)), 7.13 (d, $J$ = 7.6, 2H, SO₂Ph-o-H), 6.82 (dd, $J$ = 7.6, 8.1, 2H, SO₂Ph-m-H), 6.55 (s, 1H, C₁₂(H)), 6.18 (br-s, 1H, C₁(H)), 5.29 (s, 1H, C₁₅(H)), 3.88 (d, $J$ = 15.6, 1H, C₁₂(H)a), 3.17 (s, 3H, C₁₇(H)₃), 2.67 (d, $J$ = 15.6, 1H, C₁₂(H)b), 1.66 (s, 9H, OC(C(CH₃)₃)).

$^{13}$C NMR (150 MHz, CDCl₃, 20 ºC):
δ 165.1 (C₁₃), 160.3 (C₁₈), 149.2 (C₉(carbamate)), 141.0 (C₉), 137.5 (SO₂Ph-ips-o-C), 137.5 (C₉′), 135.9 (C₄), 132.8 (SO₂Ph-p-C), 130.3 (C₇), 128.1 (SO₂Ph-m-C), 127.1 (SO₂Ph-o-C), 126.7 (C₆), 125.6 (C₄′), 125.4 (C₆′), 124.5 (C₂), 123.6 (C₇′), 123.6 (C₈′), 120.1 (C₈), 119.0 (C₉), 118.5 (C₇′), 116.0 (C₉′), 84.6 (OC(CH₃)₃), 84.1 (C₂), 74.4 (C₁₁), 68.5 (C₁₅), 55.2 (C₃), 42.2 (C₁₂), 32.3 (C₁₇), 28.4 (OC(CH₃)₃).

FTIR (thin film) cm⁻¹:
2978 (w), 2929 (w), 1733 (s), 1677 (m), 1454 (m), 1371 (s), 1256 (m), 1157 (s), 1092 (m), 751 (s).

HRMS (ESI) (m/z):
calc’d for C₁₃H₃₀N₄NaO₆S₃ [M+Na]⁺: 697.1220, found 697.1231.

TLC (50% ethyl acetate in hexanes), Rf:
0.39 (UV, I₂, CAM).
C3-(N-Boc-Indol-3'-yl) bis(S-MOM)ether 40:

Sodium borohydride (50.0 mg, 1.32 mmol, 6.06 equiv) was added as a solid to a solution of epidithiodiketopiperazine 24 (147 mg, 218 μmol, 1 equiv) in anhydrous tetrahydrofuran (15 mL) and anhydrous methanol (60.0 μL) at 23 °C. After 2 h, chloromethyl methyl ether (MOMCl, 500 μL, 1.42 mmol, 30.4 equiv) was added to the reaction mixture. After 1 h, triethylamine (200 μL, 1.42 mmol, 6.53 equiv) was added to the reaction mixture. After 4 h, the white reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 10–40% ethyl acetate in hexanes) to afford the bis(S-MOM) derivative 40 (4.3 mg, 7.8 μmol, 73.4%) as a colorless oil.41

Trifluoroacetic acid (2 mL) was added to a solution of the N-Boc-indole S23 (6.1 mg, 7.8 μmol, 1 equiv) in anhydrous dichloromethane (5 mL) at 0 °C. After 30 min, the ice–water bath was removed, and the solution was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with ethyl acetate (50 mL) and slowly poured into saturated aqueous sodium hydrogen carbonate solution (25 mL). The organic layer was sequentially washed with water (2 × 30 mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 30 → 70% ethyl acetate in hexanes) to afford the bis(S-MOM)ether 40 (4.3 mg, 81%) as a pale yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

1H NMR (600 MHz, CDCl3, 20 °C):

δ 7.87 (br-s, 1H, C12H), 7.79 (d, J = 8.2, 1H, C12H), 7.72 (d, J = 7.7, 2H, SO2Ph-o-H), 7.41 (app-dd, J = 7.4, 7.5, 1H, SO2Ph-p-H), 7.32 (app-dt, J = 0.9, 7.8, 1H, C10H), 7.29 (d, J = 8.1, 1H, C10H), 7.19 (dd, J = 7.7, 8.0, 2H, SO2Ph-m-H), 7.14 (app-t, J = 7.5, 1H, C12H), 7.14 (d, J = 7.4, 1H, C12H), 7.08 (dd, J = 7.4, 7.7, 1H, C10H), 6.83 (dd, J = 7.4, 7.8, 1H, C9H), 6.70 (d, J = 8.0, 1H, C10H), 6.68 (s, 1H, C12H), 6.51 (d, J = 2.5, 1H, C12H), 5.17 (d, J = 11.8, 1H, C21H), 5.11

41 S23: 1H NMR (600 MHz, CDCl3, 20 °C): δ 8.03 (br-s, 1H, C12H), 7.84 (app-dd, J = 0.5, 8.2, 1H, C12H), 7.53 (br-d, J = 7.4, 2H, SO2Ph-o-H), 7.38 (app-ddd, J = 1.5, 7.4, 8.2, 1H, C12H), 7.30 (app-t, J = 7.6, 1H, C10H), 7.27 (app-dt, J = 0.9, 8.3, 1H, C10H), 7.19 (app-dd, J = 0.8, 7.5, 1H, C10H), 7.15 (app-dd, J = 0.9, 7.4, 1H, C10H), 7.05 (dd, J = 7.7, 7.8, 2H, SO2Ph-m-H), 7.00 (dd, J = 7.4, 7.6, 2H, SO2Ph-p-H), 6.73 (d, J = 7.8, 1H, C10H), 6.72 (s, 1H, C12H), 6.65 (s, 1H, C12H), 5.21 (d, J = 11.8, 1H, C12H), 5.08 (app-d, J = 12.7, 1H, C12H), 4.95 (s, 1H, C12H), 4.46 (d, J = 11.8, 1H, C12H), 4.30 (d, J = 12.7, 1H, C12H), 3.46 (s, 3H, C3H), 3.39 (d, J = 14.7, 1H, C12H), 3.23 (d, J = 14.7, 1H, C12H), 3.08 (s, 3H, C12H), 2.92 (s, 3H, C12H), 1.66 (s, 9H, OC(CH3)3). TLC (50% ethyl acetate in hexanes). RF: 0.49 (UV, CAM).
(d, J = 12.7, 1H, C_{19}H_a), 4.91 (s, 1H, C_{13}H), 4.44 (d, J = 11.8, 1H, C_{21}H_b), 4.35 (d, J = 12.7, 1H, C_{19}H_b), 3.51 (d, J = 14.7, 1H, C_{12}H_a), 3.45 (s, 3H, C_{22}H_3), 3.29 (d, J = 14.7, 1H, C_{12}H_b), 3.07 (s, 3H, C_{17}H_3), 2.93 (s, 3H, C_{20}H_3).

$^{13}$C NMR (150 MHz, CDCl$_3$, 20 ºC):

δ 165.7 ($^{C}_{13}$), 163.2 ($^{C}_{16}$), 141.6 ($^{C}_{9}$), 138.4 (SO$_2$Ph-ipso-C), 137.3 ($^{C}_{9}'$), 136.4 ($^{C}_{4}$), 133.0 (SO$_2$Ph-p-C), 129.0 ($^{C}_{7}$), 128.8 (SO$_2$Ph-m-C), 127.5 (SO$_2$Ph-o-C), 125.2 ($^{C}_{9}$), 125.0 ($^{C}_{5}$), 124.5 ($^{C}_{4}$), 122.9 ($^{C}_{2}$), 122.7 ($^{C}_{7}$), 120.4 ($^{C}_{6}$), 119.1 ($^{C}_{5}$), 117.0 ($^{C}_{8}$), 116.5 ($^{C}_{9}$), 111.7 ($^{C}_{8}'$), 84.6 ($^{C}_{2}$), 76.5 ($^{C}_{21}$), 75.5 ($^{C}_{19}$), 70.5 ($^{C}_{11}$), 64.9 ($^{C}_{15}$), 56.8 ($^{C}_{20}$), 56.6 ($^{C}_{22}$), 53.7 ($^{C}_{3}$), 49.2 ($^{C}_{12}$), 32.3 ($^{C}_{17}$).

FTIR (thin film) cm$^{-1}$:

3390 (w), 3004 (w), 2927 (w), 2823 (w), 1693 (s), 1666 (s), 1461 (m), 1392 (s), 1364 (s), 1312 (m), 1265 (w), 1235 (w), 1181 (s), 1084 (s), 751 (s).

HRMS (ESI) ($m/z$):

calc’d for C$_{32}$H$_{32}$N$_4$NaO$_6$S$_3$ [M+Na]$^+$: 687.1376, found: 687.1378.

TLC (50% ethyl acetate in hexanes), Rf:

0.38 (UV, CAM).
C3-(Indol-3'-yl) bis(S-MOM)ether 41:

A 20 × 150 mm Pyrex tube was sequentially charged with bis(S-MOM)ether S23 (92.2 mg, 121 μmol, 1 equiv), L-ascorbic acid (310 mg, 1.76 mmol, 14.6 equiv), sodium L-ascorbate (380 mg, 1.92 mmol, 15.9 equiv), and 1,4-dimethoxynaphthalene (1.25 g, 6.64 mmol, 55.1 equiv), and the mixture was placed under an argon atmosphere. A solution of water in acetonitrile (20% v/v, 24 mL) that was purged with argon for 15 min at 23 °C was transferred to the flask via cannula. The system was vigorously stirred under an argon atmosphere and irradiated with a Rayonet photoreactor equipped with 16 lamps emitting at 350 nm at 25 °C. After 2.5 h, the lamps were turned off, and the reaction mixture was diluted with ethyl acetate (100 mL) and diethyl ether (50 mL). The resulting solution was filtered, and the solution was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with ethyl acetate (100 mL) and diethyl ether (50 mL). The resulting solution was sequentially washed with saturated aqueous sodium hydrogenocarbonate solution (50 mL), water (2 × 40 mL), and saturated aqueous sodium chloride solution (40 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 20 → 60% ethyl acetate in hexanes) to afford aniline S24 (61.7 mg, 81.9%) as a pale yellow oil.

Trifluoroacetic acid (2 mL) was added to a solution of the N-Boc-indole S24 (6.0 mg, 9.6 μmol, 1 equiv) in anhydrous dichloromethane (5 mL) at 0 °C. After 30 min, the ice–water bath was removed, and the solution was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with ethyl acetate (50 mL) and slowly poured into saturated aqueous sodium hydrogenocarbonate solution (25 mL) at 23 °C. The organic layer was sequentially washed with water (3 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 20 → 60% ethyl acetate in hexanes) to afford the bis(S-MOM)ether 41 (4.6 mg, 91%) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

\[ 1^H \text{NMR (600 MHz, CDCl}_3, 20 ^\circ \text{C):} \]

- δ 7.98 (br-s, 1H, N1H), 7.38 (d, J = 8.0, 1H, C10H), 7.32 (d, J = 8.2, 1H, C11H), 7.16 (app-t, J = 7.2, 1H, C12H), 7.14 (d, J = 6.9, 1H, C13H), 7.10 (app-dt, J = 1.0, 7.8, 1H, C14H), 7.02 (app-t, J = 7.2, 1H, C15H), 7.01 (d, J = 2.7, 1H, C16H), 6.73 (dd, J = 7.3, 7.5, 1H, C17H), 6.71 (d, J = 7.8, 1H, C18H), 6.05 (s, 1H, C19H), 5.22 (d, J = 11.7, 1H, C21H), 5.13 (d, J = 8.2, 1H, C20H).

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42 S24: \[ 1^H \text{NMR (600 MHz, CDCl}_3, 20 ^\circ \text{C):} \] δ 8.11 (br-s, 1H, N1H), 7.46 (br-s, 1H, C1H), 7.37 (d, J = 7.9, 1H, C1H), 7.26 (app-t, J = 7.6, 1H, C1H), 7.10 (d, J = 7.2, 1H, C1H), 7.13–7.08 (m, 3H, C1H + C1H + C1H), 6.74–6.67 (m, 2H, C1H + C1H), 6.04 (s, 1H, C1H), 5.19 (d, J = 11.7, 1H, C1H), 5.16 (d, J = 12.6, 1H, C1H), 4.90 (s, 1H, C1H), 4.52 (d, J = 11.7, 1H, C1H), 4.31 (d, J = 12.6, 1H, C1H), 3.55 (d, J = 14.1, 1H, C1H), 3.45 (d, J = 14.1, 1H, C1H), 3.47 (s, 3H, C1H), 3.06 (s, 3H, C1H), 2.91 (s, 3H, C1H), 1.65 (s, 9H, OC(CH3)3). HRMS (ESI) (m/z): calc’d for C31H36N4NaO6S2 [M+Na]$: 647.1968, found: 647.1976. TLC (50% ethyl acetate in hexanes), Rf: 0.74 (UV, CAM).
Synthesis and Anticancer Activity of Epipolythiodiketopiperazine Alkaloids
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12.6, 1H, C19H1), 4.93 (s, 1H, C15H), 4.53 (d, J = 11.7, 1H, C20H1b), 4.34 (d, J = 12.6, 1H, C19H1b), 3.48 (s, 2H, C12H), 3.48 (s, 3H, C22H3), 3.07 (s, 3H, C17H3), 2.95 (s, 3H, C20H3).

13C NMR (150 MHz, CDCl3, 20 ºC):

δ 166.1 (C13), 165.4 (C16), 148.5 (C9), 137.4 (C9'), 132.8 (C4), 128.6 (C7), 125.3 (C4'), 124.9 (C8), 122.6 (C7'), 121.6 (C5), 120.2 (C6'), 119.9 (C5'), 119.6 (C6), 119.4 (C3'), 111.6 (C8'), 109.3 (C8), 82.6 (C2), 77.0 (C31), 75.7 (C19), 69.3 (C11), 65.1 (C15), 57.0 (C20), 56.5 (C22), 54.3 (C3), 48.0 (C12), 32.0 (C17).

FTIR (thin film) cm⁻¹:

3394 (br-w), 3013 (w), 2928 (w), 2823 (w), 1693 (s), 1669 (s), 1461 (m), 1393 (m), 1363 (m), 1265 (w), 1180 (s), 752 (s).

HRMS (ESI) (m/z):
calc’d for C26H28N4NaO4S2 [M+Na]+: 547.1444, found: 547.1434.

TLC (50% ethyl acetate in hexanes), Rf:

0.43 (UV, CAM).
C3-(N-Boc-Indol-3'-yl) bis(S-MEM)ether 42 and C3-(N-Boc-indol-3'-yl) S15-MEM ether 47:

Sodium borohydride (9.8 mg, 250 μmol, 3.6 equiv) was added as a solid to a solution of epidithiodiketopiperazine 24 (47.0 mg, 69.6 μmol, 1 equiv) in anhydrous tetrahydrofuran (8 mL) and anhydrous methanol (50 μL) at 23 ºC. After 80 min, 2-methoxyethoxymethyl chloride (MEMCl, 300 μL, 2.63 mmol, 37.7 equiv) followed by triethylamine (400 μL, 2.85 mmol, 40.9 equiv) were added to the reaction mixture. After 12 h, the yellow reaction mixture was partitioned between aqueous 5% citric acid solution (30 mL) and ethyl acetate (80 mL). The isolated organic layer was washed sequentially with water (2 × 30 mL) and saturated aqueous sodium chloride solution (20 mL), was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 10 → 25% ethyl acetate in dichloromethane) to afford the bis(S-MEM)ether adduct 42 (57.6 mg, 80.2%) and the S15-MEM-adduct 47 (10.0 mg, 18.8%) as colorless oils. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

C3-(N-Boc-indol-3'-yl) bis(S-MEM)ether 42:

\[ \delta 8.02 \text{ (br-s, 1H, C_8'H)}, 7.83 \text{ (d, J = 8.2, 1H, C_9'H)}, 7.56 \text{ (br-d, J = 6.2, 2H, SO_2Ph-o-H)}, 7.36 \text{ (dd, J = 7.7, 8.0, 1H, C_8'H)}, 7.32 \text{ (t, J = 7.3, 1H, SO_2Ph-p-H)}, 7.24 \text{ (d, J = 7.8, 1H, C_5'H)}, 7.16 \text{ (d, J = 7.4, 1H, C_3'H)}, 7.10 \text{ (app-t, J = 7.6, 1H, C_6'H)}, 7.08 \text{ (app-t, J = 7.5, 2H, SO_2Ph-m-H)}, 6.96 \text{ (app-t, J = 7.5, 1H, C_6'H)}, 6.79 \text{ (s, 1H, C_2'H)}, 6.67–6.61 \text{ (m, 1H, C_5'H)}, 6.62 \text{ (s, 1H, C_3'H)}, 5.21 \text{ (d, J = 12.0, 1H, C_23'H_a)}, 5.13 \text{ (d, J = 12.8, 1H, C_19'H_a)}, 5.00 \text{ (s, 1H, C_13'H_a)}, 4.63 \text{ (d, J = 12.0, 1H, C_23'H_a)}, 4.47 \text{ (d, J = 12.8, 1H, C_19'H_a)}, 4.00–3.94 \text{ (m, 1H, C_24'H_b)}, 3.67–3.64 \text{ (m, 2H, C_24'H_b + C_25'H_a)}, 3.61–3.56 \text{ (m, 1H, C_25'H_a)}, 3.41 \text{ (d, J = 14.9, 1H, C_12'H)}, 3.39 \text{ (s, 3H, C_26'H_3)}, 3.38–3.33 \text{ (m, 2H, C_13'H)}, 3.31 \text{ (s, 3H, C_25'H_a)}, 3.28–3.23 \text{ (m, 1H, C_20'H_a)}, 3.23 \text{ (d, J = 14.9, 1H, C_12'H)}, 3.20–3.14 \text{ (m, 1H, C_25'H_a)}, 3.09 \text{ (s, 3H, C_17'H)}, 1.69 \text{ (s, 9H, (OC(CH_3)_3)}.

\[ \delta 165.3 \text{ (C_{13})}, 163.1 \text{ (C_{18})}, 149.3 \text{ (C_{carbamate})}, 141.7 \text{ (C_{9})}, 137.9 \text{ (SO_2Ph-ipso-C)}, 136.3 \text{ (C_7)}, 135.7 \text{ (C_4)}, 133.0 \text{ (SO_2Ph-p-C)}, 129.3 \text{ (C_7)}, 128.6 \text{ (SO_2Ph-m-C)}, \]
127.4 (SO₂Ph-ο-C), 127.2 (C₆), 125.5 (C₈), 125.0 (C₇), 124.9 (C₉), 124.5 (C₇'), 123.2 (C₆'), 120.3 (C₅), 119.1 (C₂), 117.9 (C₈), 115.7 (C₈'), 84.4 (OC(CH₃)₃), 83.8 (C₂), 75.2 (C₂₃), 74.0 (C₁₉), 71.6 (C₂₅), 71.6 (C₂₁), 70.3 (C₁₁), 68.2 (C₂₀), 68.1 (C₃₄), 64.9 (C₁₅), 59.3 (C₂₂), 59.2 (C₂₆), 53.3 (C₃), 48.6 (C₁₁), 32.2 (C₁₇), 28.4 (OC(CH₃)₃).

FTIR (thin film) cm⁻¹:
2920 (m), 2851 (m), 1734 (s), 1699 (s), 1668 (s), 1454 (s), 1373 (s), 1310 (m), 1272 (m), 1158 (s), 1088 (s), 1025 (m), 752 (s).

HRMS (ESI) (m/z):

TLC (20% ethyl acetate in dichloromethane), Rf: 0.44 (UV, I₂, CAM).

C₃-(N-Boc-indol-3'-yl) S15-MEM ether 47:

1H NMR (600 MHz, CDCl₃, 20 ºC):
δ 8.04 (br-s, 1H, C₈H), 7.85 (d, J = 8.1, 1H, C₇H), 7.45 (app-dt, J = 1.0, 8.0, 1H, C₇H), 7.38 (br-d, J = 6.2, 2H, SO₂Ph-ο-H), 7.31 (app-t, J = 7.8, 1H, C₉H), 7.29–7.21 (m, 3H, C₅H + C₆H + SO₂Ph-ipso-H), 7.12 (dd, J = 7.4, 7.6, 1H, C₈H), 6.95 (app-t, J = 7.7, 2H, SO₂Ph-m-H), 6.91 (d, J = 7.8, 1H, C₃H), 6.67 (s, 1H, C₂H), 6.53 (s, 1H, C₃H), 5.25 (d, J = 11.9, 1H, C₂₃Hₐ), 5.09 (s, 1H, C₁₅H), 4.71 (d, J = 11.9, 1H, C₂₃H₉), 4.00–3.96 (m, 1H, C₂₄Hₐ), 3.70–3.62 (m, 2H, C₂₄H₉ + C₂₅Hₐ), 3.62–3.58 (m, 1H, C₂₅H₉), 3.43 (d, J = 14.6, 1H, C₁₂H₉), 3.40 (s, 3H, C₂₆H₉), 3.13 (s, 3H, C₁₇H₃), 2.87 (d, J = 14.6, 1H, C₁₂H₉), 1.66 (s, 9H, (OC(CH₃)₃).

13C NMR (150 MHz, CDCl₃, 20 ºC):
δ 167.5 (C₁₃), 162.2 (C₁₆), 149.2 (C_carbamate), 142.2 (Cₖ), 137.8 (SO₂Ph-ipso-C), 135.6 (C₇), 135.6 (C₈), 132.8 (SO₂Ph-p-C), 129.9 (C₇), 128.3 (SO₂Ph-m-C), 127.3 (SO₂Ph-o-C), 126.9 (C₉), 126.3 (C₈), 125.2 (C₇), 124.9 (C₉), 124.8 (C₇), 123.4 (C₆), 119.6 (C₅), 119.3 (C₈), 119.0 (C₅'), 115.9 (C₈'), 84.5 (OC(CH₃)₃), 83.8 (C₂), 74.0 (C₂₃), 71.6 (C₂₅), 68.4 (C₉), 68.1 (C₁₁), 64.3 (C₁₅), 59.3 (C₂₆), 53.4 (C₃), 51.2 (C₁₂), 32.7 (C₁₇), 28.4 (OC(CH₃)₃).

FTIR (thin film) cm⁻¹:
2978 (w), 2922 (w), 1734 (m), 1697 (m), 1454 (m), 1372 (s), 1272 (w), 1235 (w), 1157 (m), 1091 (m), 752 (s).

HRMS (ESI) (m/z):

TLC (20% ethyl acetate in dichloromethane), Rf: 0.24 (UV, I₂, CAM).
C3-(Indol-3'-yl) dithiepanethione 36:
Sodium borohydride (4.9 mg, 0.13 mmol, 3.4 equiv) was added as a solid to a solution of epidithiodiketopiperazine 26 (22.0 mg, 38.3 \( \mu \)mol, 1 equiv) in anhydrous tetrahydrofuran (5 mL) and anhydrous methanol (50 \( \mu \)L) at 23 °C. After 45 min, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 \( \times \) 20 mL) and the combined organic layers were washed sequentially with water (2 \( \times \) 20 mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the hexacyclic bisthiol S25 that was used in the next step without further purification.

1,1'-Thiocarbonyldiimidazole (TCDI, 108 mg, 606 \( \mu \)mol, 15.8 equiv) was added as a solid to the solution of bisthiol S25 in anhydrous dichloromethane (6 mL) at 23 °C. After 22 h, the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 \( \rightarrow \) 25\% ethyl acetate in dichloromethane) to afford the dithiepanethione 36 (8.4 mg, 34\%) as a pale yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.43

\[ \begin{align*}
\text{1H NMR (600 MHz, CDCl}_3, 20 ^\circ \text{C):} & \quad \delta \ 7.86 \ (\text{br-s, 1H, N'-H}), \ 7.75 \ (d, J = 8.2, 1H, C_9H), \\
& \quad 7.49 \ (\text{app-dd, } J = 1.0, 8.3, 2H, S02Ph-o-H), \ 7.43-7.36 \ (m, 2H, C_7H + S02Ph-p-H), \ 7.35 \ (d, J = 8.1, 2H, C_8H), \ 7.23-7.17 \ (m, 3H, C_5H + C_6H + C_7'H), \\
& \quad 7.10 \ (dd, J = 7.6, 8.1, 2H, S02Ph-m-H), \ 6.98 \ (\text{app-dt, } J = 0.5, 7.5, 1H, C_6'H), \ 6.89 \ (d, J = 8.0, 1H, C_5H), \ 6.64 \ (s, 1H, C_2'H), \ 6.36 \ (d, J = 2.5, 1H, C_1'H), \\
& \quad 5.05 \ (s, 1H, C_15'H), \ 3.96 \ (d, J = 15.6, 1H, C_12H_a), \ 3.18 \ (s, 3H, C_3'), \ 2.80 \ (d, J = 15.6, 1H, C_12H_b). \\
\text{13C NMR (150 MHz, CDCl}_3, 20 ^\circ \text{C):} & \quad \delta \ 214.3 \ (C_{19}), \ 164.3 \ (C_{13}), \ 159.4 \ (C_{18}), \ 140.9 \ (C_9), \ 137.5 \ (S02Ph-ipso-C), \ 137.3 \ (C_9'), \ 135.1 \ (C_4), \ 133.2 \ (S02Ph-p-C), \ 130.2 \ (C_7), \ 128.7 \ (S02Ph-m-C), \ 127.4 \ (S02Ph-o-C), \ 126.2 \ (C_6), \ 124.6 \ (C_5), \ 122.4 \ (C_4), \\
& \quad 124.1 \ (C_2), \ 123.2 \ (C_7), \ 120.7 \ (C_6), \ 118.8 \ (C_3), \ 118.5 \ (C_8), \ 113.8 \ (C_3'), \ 112.0 \ (C_8'), \ 85.3 \ (C_2'), \ 75.3 \ (C_11), \ 69.5 \ (C_{15}), \ 54.6 \ (C_3), \ 45.8 \ (C_{12}), \ 32.7 \ (C_{17}). \\
\text{FTIR (thin film) cm}^{-1}: & \quad 3393 \ (\text{br-w}), \ 2921 \ (m), \ 2851 \ (w), \ 1703 \ (s), \ 1459 \ (m), \ 1361 \ (m), \ 1168 \ (m), \ 1089 \ (w), \ 1016 \ (w), \ 907 \ (w), \ 733 \ (m).
\end{align*} \]

43 Upon concentration or in concentrated solution, the dithiepanethione 36 tends to degrade, thus rendering its isolation and characterization particularly arduous.
HRMS (ESI) (m/z): calc’d for C_{29}H_{23}N_{4}O_{4}S_{4} [M+H]^+: 619.0597, found 619.0609; calc’d for C_{29}H_{22}N_{4}NaO_{4}S_{4} [M+Na]^+: 641.0416, found 641.0424.

TLC (20% ethyl acetate in dichloromethane), Rf: 0.68 (UV, I2, CAM).
C3-(Indol-3'-yl) dithiocarbonate 37:

Sodium borohydride (4.9 mg, 0.13 mmol, 3.3 equiv) was added as a solid to a solution of epidithiodiketopiperazine 26 (22.6 mg, 39.3 μmol, 1 equiv) in anhydrous tetrahydrofuran (5 mL) and anhydrous methanol (50 μL) at 23 °C. After 45 min, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were washed sequentially with water (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the hexacyclic bisthiol S25 that was used in the next step without further purification.

1,1'-Carbonyldiimidazole (CDI, 80.0 mg, 493 μmol, 12.0 equiv) was added as a solid to the solution of bisthiol S25 in anhydrous dichloromethane (10 mL) at 23 °C. After 24 h, the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 20% ethyl acetate in dichloromethane) to afford the dithiocarbonate 37 along with epidithiodiketopiperazine 26. Both compounds were separated by preparative HPLC [Waters X-Bridge preparative HPLC column, C18, 5 μm, 19 × 250 mm; 20.0 mL/min; gradient, 20 → 90% acetonitrile in water, 20 min; tR(37) = 15.35 min, tR(26) = 14.50 min] to afford 37 (2.0 mg, 8%) as a pale yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

1H NMR (600 MHz, CDCl3, 20 °C):

δ 7.84 (br-s, 1H, N1H), 7.78 (d, J = 8.2, 1H, C8H), 7.45 (d, J = 8.4, 2H, SO2Ph-o-H), 7.41 (app-dd, J = 1.6, 7.3, 7.7, 1H, C7H), 7.37 (app-dt, J = 1.0, 6.4, 1H, SO2Ph-p-H), 7.35 (d, J = 8.2, 1H, C8'H), 7.21 (app-dd, J = 0.8, 7.2, 7.6, 1H, C7'H), 7.19 (app-dt, J = 0.9, 7.3, 1H, C6'H), 7.16 (app-dd, J = 1.1, 7.6, 1H, C6'H), 7.06 (dd, J = 7.6, 8.3, 2H, SO2Ph-m-H), 6.99 (app-dt, J = 0.7, 7.5, 1H, C6'H), 6.90 (d, J = 7.9, 1H, C6'H), 6.64 (s, 1H, C2H), 6.26 (d, J = 2.6, 1H, C2'H), 5.17 (s, 1H, C15H), 3.92 (d, J = 15.5, 1H, C12'H), 3.20 (s, 3H, C3'), 2.78 (d, J = 15.5, 1H, C17H).

13C NMR (150 MHz, CDCl3, 20 °C):

δ 185.4 (C19), 165.0 (C13), 160.0 (C16), 141.0 (C9), 137.3 (SO2Ph-ipso-C), 137.3 (C9'), 135.2 (C8), 133.2 (SO2Ph-p-C), 130.2 (C2), 128.7 (SO2Ph-m-C), 127.5 (SO2Ph-o-C), 126.2 (C6), 124.6 (C3), 124.1 (C2), 123.2 (C7), 120.7 (C8), 118.7 (C5), 118.7 (C6), 113.8 (C3), 112.0 (C4), 85.3 (C2), 72.6 (C11), 66.6 (C15), 54.5 (C3), 46.5 (C12), 32.6 (C17).

44 Epidithiodiketopiperazine 26 was also recovered (2.9 mg, 12%).
FTIR (thin film) cm$^{-1}$: 3396 (br-m), 2924 (m), 2853 (w), 1696 (m), 1460 (m), 1383 (m), 1169 (m), 1091 (w), 1051 (w), 735 (m).

HRMS (ESI) (m/z): calc’d for C$_{29}$H$_{22}$N$_4$NaO$_5$S$_3$ [M+Na]$^+$: 625.0645, found 625.0652.

TLC (20% ethyl acetate in dichloromethane), $R_f$: 0.57 (UV, I$_2$, CAM).
C3-(Indol-3'-yl) dithioacetal 38:

Sodium borohydride (15.0 mg, 0.400 mmol, 9.88 equiv) was added as a solid to a solution of epidithiodiketopiperazine 26 (23.1 mg, 40.2 μmol, 1 equiv) in anhydrous THF (5 mL) and diiodomethane (0.2 mL) at 0 °C under an argon atmosphere.45 After 5 min, anhydrous methanol (50 μL) was added. After 50 min, the reaction mixture was partitioned between aqueous hydrochloric acid solution (1 N, 25 mL) and ethyl acetate (80 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed sequentially with water (2 × 30 mL) and saturated aqueous sodium chloride solution (30 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 20% ethyl acetate in dichloromethane) to afford dithioacetal 38 (10.8 mg, 45.6%) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data. Based on 1H NMR analysis at 20 °C in CDCl3, the product exists as a 1:4 mixture of minor:major conformers.

1H NMR (600 MHz, CDCl3, 20 ºC):

Major conformer: δ 7.89 (br-s, 1H, N1'H), 7.87 (d, J = 8.2, 1H, C8'H), 7.65 (d, J = 7.7, 2H, SO2Ph-o-H), 7.43 (app-dd, J = 7.4, 7.5, 1H, SO2Ph-p-H), 7.37 (app-ddd, J = 1.3, 7.4, 8.2, 1H, C1'H), 7.31 (d, J = 8.2, 1H, C6'H), 7.15 (dd, J = 7.7, 7.9, 2H, SO2Ph-m-H), 7.14 (app-t, J = 7.3, 1H, C7'H), 7.10 (app-t, J = 7.5, 1H, C2'H), 7.02 (app-dd, J = 0.4, 7.4, 1H, C3'H), 6.81 (app-dd, J = 7.4, 7.7, 1H, C5'H), 6.57 (s, 1H, C2'H), 6.51 (d, J = 8.0, 1H, C3'H), 6.43 (d, J = 2.4, 1H, C2'H), 4.86 (s, 1H, C19'Ha), 4.55 (d, J = 14.8, 1H, C19'Hb), 3.86 (d, J = 14.9, 1H, C12'Ha), 3.71 (d, J = 14.8, 1H, C19'Hb), 3.08 (s, 3H, C17'H3), 3.16 (s, 3H, C17'H3), 2.70 (d, J = 14.9, 1H, C12'Hb).

Minor conformer: δ 7.78 (d, J = 8.3, 1H, C8'H), 7.78 (br-s, 1H, N1'H), 7.44–7.40 (m, 1H, C1'H), 7.35 (d, J = 7.7, 2H, SO2Ph-o-H), 7.32–7.29 (m, 1H, C1'H), 7.28 (d, J = 8.3, 1H, C8'H), 7.27–7.21 (m, C8'H SO2Ph-p-H), 7.20 (d, J = 8.0, 1H, C1'H), 7.12–7.07 (m, 2H, C6'H + C2'H), 6.93 (dd, J = 7.7, 8.0, 2H, SO2Ph-m-H), 6.57 (s, 1H, C2'H), 5.97 (d, J = 2.5, 1H, C2'H), 5.26 (s, 1H, C19'H), 4.01 (d, J = 15.6, 1H, C19'Hb), 3.56 (d, J = 14.9, 1H, C19'Hb), 3.16 (s, 3H, C17'H3), 3.11 (d, J = 15.8, 1H, C12'Hb), 2.72 (d, J = 15.8, 1H, C12'Hb).

**13C NMR (150 MHz, CDCl₃, 20 ºC):**

**Major conformer:** δ 167.5 (C₁₃), 161.7 (C₁₆), 140.5 (C₉), 137.3 (C₇ᵣ), 136.6 (SO₂Ph-ipso-C), 136.1 (C₄ᵣ), 133.4 (SO₂Ph-p-C), 129.5 (C₇), 128.8 (SO₂Ph-m-C), 128.0 (SO₂Ph-o-C), 125.7 (C₆ᵣ), 124.6 (C₃), 124.4 (C₄ᵣ), 124.1 (C₂), 122.9 (C₇), 120.4 (C₆), 119.0 (C₅), 117.8 (C₉), 113.9 (C₃ᵣ), 111.8 (C₈), 85.4 (C₂), 70.6 (C₁₁), 65.2 (C₁₅), 54.4 (C₃), 48.1 (C₁₂), 32.7 (C₁₇), 31.7 (C₁₉).

**Minor conformer:** δ 165.3 (C₁₃), 160.5 (C₁₆), 140.8 (C₉), 137.6 (C₇ᵣ), 137.2 (SO₂Ph-ipso-C), 136.6 (C₄ᵣ), 133.0 (SO₂Ph-p-C), 129.9 (C₇), 128.4 (SO₂Ph-m-C), 127.3 (SO₂Ph-o-C), 126.1 (C₆ᵣ), 124.8 (C₃), 124.4 (C₄ᵣ), 124.2 (C₂), 123.2 (C₇), 120.8 (C₆), 119.1 (C₅), 118.8 (C₉), 114.2 (C₃ᵣ), 111.9 (C₈), 84.8 (C₂), 74.5 (C₁₁), 68.5 (C₁₅), 55.7 (C₃), 42.6 (C₁₂), 32.7 (C₁₇), 32.3 (C₁₉).

**FTIR (thin film) cm⁻¹:**

3392 (br-m), 3059 (w), 2977 (w), 1690 (s), 1451 (w), 1361 (m), 1266 (w), 1170 (m), 1090 (w), 1022 (m), 736 (m).

**HRMS (ESI) (m/z):**

calc’d for C₂₉H₂₄N₄NaO₄S₃ [M+Na]⁺: 611.0852, found 611.0850.

**TLC (10% ethyl acetate in dichloromethane), Rf:** 0.40 (UV, I₂, CAM).
C3-(Indol-3'-yl) epimonothiodiketopiperazine 25: 

Triethylphosphite (10.0 μL, 58.4 μmol, 21.4 equiv) was added to the solution of epidithiodiketopiperazine 26 (8.6 mg, 15 μmol, 1 equiv) in anhydrous tetrahydrofuran (4 mL) at 23 °C. After 6 h, the reaction mixture was diluted sequentially with saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (60 mL). The organic layer was washed with water (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL), was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 2 → 8% ethyl acetate in dichloromethane) to afford the epimonothiodiketopiperazine 25 (5.1 mg, 63%) as a white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

1H NMR (600 MHz, acetone-d6, 20 ºC):

δ 9.95 (br-s, 1H, N 1'H), 7.64 (d, J = 8.1, 1H, C8'H), 7.59 (d, J = 7.8, 1H, C5'H), 7.52 (d, J = 7.3, 1H, C2'H), 7.48 (d, J = 8.0, 1H, C6'H), 7.44 (app- dt, J = 1.1, 7.8, 1H, C7'H), 7.32 (app-tt, J = 0.9, 7.4, 1H, SO2Ph-p-H), 7.28 (app-dt, J = 0.9, 7.6, 1H, C1'H), 7.26 (app-dt, J = 0.9, 7.6, 1H, C5'H), 7.20 (app-dt, J = 0.8, 7.5, 1H, C6'H), 6.98 (app-dd, J = 1.0, 8.3, 2H, SO2Ph-o-H), 6.90 (app-t, J = 7.5, 2H, SO2Ph-m-H), 6.19 (s, 1H, C2'H), 5.67 (d, J = 2.6, 1H, C2'H), 5.17 (s, 1H, C1'H), 3.70 (d, J = 15.4, 1H, C12'Ha), 3.11 (s, 3H, C17'H3), 2.84 (d, J = 15.4, 1H, C12'Hb).

13C NMR (150 MHz, acetone-d6, 20 ºC):

δ 173.9 (C13), 171.6 (C16), 141.4 (C3), 138.7 (SO2Ph-ipso-C), 138.7 (C9), 137.9 (C4), 133.9 (SO2Ph-p-C), 130.2 (C7), 129.0 (SO2Ph-m-C), 127.2 (SO2Ph-o-C), 126.4 (C8), 125.7 (C5), 125.3 (C2), 124.9 (C3), 123.0 (C7), 120.6 (C6), 119.0 (C5), 118.6 (C8), 115.3 (C3), 113.1 (C8), 83.3 (C2), 81.9 (C1), 73.0 (C15), 59.4 (C3), 35.3 (C12), 31.4 (C17).

FTIR (thin film) cm⁻¹:

3357 (br-w), 3059 (w), 2919 (w), 2851 (w), 1740 (s), 1713 (s), 1457 (m), 1358 (m), 1261 (w), 1169 (m), 1086 (w), 971 (w), 737 (s), 685 (m).

HRMS (ESI) (m/z):


TLC (10% ethyl acetate in dichloromethane), Rf: 0.76 (UV, I2, CAM).


47 Limited solubility of epimonothiodiketopiperazine 25 was observed in CH2Cl2, CHCl3, EtOAc, MeOH, DMSO; this low solubility resulted in difficulty to acquire high quality spectroscopic data.
C3-(Indol-3'-yl) bisthioacetate 44:

Sodium borohydride (4.9 mg, 0.13 mmol, 3.3 equiv) was added as a solid to a solution of epidithiodiketopiperazine 26 (22.6 mg, 39.3 µmol, 1 equiv) in anhydrous tetrahydrofuran (5 mL) and anhydrous methanol (50 µL) at 23 °C. After 45 min, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed sequentially with water (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the hexacyclic bisthiol S25 that was used in the next step without further purification.

Acetyl chloride (200 µL, 2.80 mmol, 71.3 equiv) was added to the solution of bisthiol S25 in anhydrous dichloromethane (6 mL) and anhydrous pyridine (300 µL, 3.72 mmol, 94.7 equiv) at 23 °C. After 4 h, the reaction mixture was diluted with ethyl acetate (60 mL) and washed with aqueous 5% citric acid solution (2 × 20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford bisthioacetate 44 (17.0 mg, 62.7%) as a pale yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

\[ \delta 8.01 \text{ (br-s, 1H, } N_1 H) \], \[ 7.78 \text{ (d, } J = 8.1, 1H, C_1 H) \], \[ 7.75 \text{ (d, } J = 8.2, 2H, SO_2 Ph-o-H) \], \[ 7.42 \text{ (app-dt, } J = 1.0, 7.5, 1H, SO_2 Ph-p-H) \], \[ 7.37-7.33 \text{ (m, 1H, C_5 H)} \], \[ 7.29 \text{ (d, } J = 8.2, 1H, C_8 H) \], \[ 7.21 \text{ (dd, } J = 7.6, 8.3, 2H, SO_2 Ph-m-H) \], \[ 7.12 \text{ (dd, } J = 7.4, 8.0, 1H, C_3 H) \], \[ 7.08-7.03 \text{ (m, 2H, C_2 H + C_6 H)} \], \[ 6.81 \text{ (dd, } J = 7.2, 7.9, 1H, C_6 H) \], \[ 6.72 \text{ (s, 1H, C_3 H)} \], \[ 6.58 \text{ (d, } J = 8.0, 1H, C_3 H) \], \[ 6.55 \text{ (d, } J = 2.5, 1H, C_2 H) \], \[ 6.09 \text{ (s, 1H, C_15 H)} \], \[ 3.44 \text{ (d, } J = 14.7, 1H, C_12 H_2) \], \[ 3.26 \text{ (d, } J = 14.7, 1H, C_12 H_2) \], \[ 2.98 \text{ (s, 3H, C_17 H_3)} \], \[ 2.48 \text{ (s, 3H, C_22 H_3)} \], \[ 2.06 \text{ (s, 3H, C_20 H)} \].

\[ \delta 194.0 \text{ (C_{21})} \], \[ 193.9 \text{ (C_{19})} \], \[ 165.1 \text{ (C_{13})} \], \[ 161.9 \text{ (C_{16})} \], \[ 142.0 \text{ (C_9)} \], \[ 137.7 \text{ (SO_2 Ph-ipso-C)} \], \[ 137.3 \text{ (C_9)} \], \[ 135.2 \text{ (C_4)} \], \[ 133.3 \text{ (SO_2 Ph-p-C)} \], \[ 129.6 \text{ (C_7)} \], \[ 129.0 \text{ (SO_2 Ph-m-C)} \], \[ 127.5 \text{ (SO_2 Ph-o-C)} \], \[ 125.1 \text{ (C_6)} \], \[ 124.9 \text{ (C_3)} \], \[ 124.4 \text{ (C_4)} \], \[ 122.9 \text{ (C_2)} \], \[ 122.8 \text{ (C_7)} \], \[ 120.4 \text{ (C_8)} \], \[ 118.7 \text{ (C_9)} \], \[ 116.6 \text{ (C_3)} \], \[ 115.7 \text{ (C_7)} \], \[ 111.9 \text{ (C_5)} \], \[ 84.8 \text{ (C_2)} \], \[ 73.3 \text{ (C_{11})} \], \[ 63.5 \text{ (C_{15})} \], \[ 53.6 \text{ (C_3)} \], \[ 49.3 \text{ (C_{12})} \], \[ 32.3 \text{ (C_{17})} \], \[ 30.6 \text{ (C_{20})} \], \[ 30.5 \text{ (C_{22})} \].
FTIR (thin film) cm⁻¹:

3395 (br-m), 3063 (w), 2923 (m), 2852 (w), 1699 (br-s), 1459 (m), 1368 (m), 1311 (w), 1172 (m), 1121 (m), 1093 (m), 1025 (w), 954 (w), 734 (m).

HRMS (ESI) (m/z):

calc’d for C_{32}H_{28}N_{4}NaO_{6}S_{3} [M+Na]⁺: 683.1063, found 683.1047.

TLC (20% ethyl acetate in dichloromethane), Rf: 0.52 (UV, I₂, CAM).
Sodium borohydride (3.7 mg, 0.10 mmol, 5.2 equiv) was added as a solid to a solution of epidithiodiketopiperazine \( \text{26} \) (10.8 mg, 18.8 \( \mu \text{mol} \), 1 equiv) in anhydrous tetrahydrofuran (5 mL) and anhydrous methanol (50 \( \mu \text{L} \)) at 23 °C. After 45 min, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 \( \times \) 20 mL), and the combined organic layers were washed sequentially with water (2 \( \times \) 20 mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the hexacyclic bisthiol \( \text{S25} \) that was used in the next step without further purification.

A solution of methanesulfinyl chloride \( \text{49} \) in dichloromethane (1.6 M, 250 \( \mu \text{L} \), 402 \( \mu \text{mol} \), 21.4 equiv) was added to the solution of bisthiol \( \text{S25} \) in anhydrous dichloromethane (5 mL) and anhydrous pyridine (100 \( \mu \text{L} \), 1.24 mmol, 66.0 equiv) at 0 °C. After 10 min, the ice–water bath was removed, and the yellow solution was allowed to warm to 23 °C. After 2 h, the reaction mixture was diluted sequentially with saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (60 mL). The organic layer was sequentially washed with saturated aqueous ammonium chloride solution (20 mL), water (2 \( \times \) 15 mL), and saturated aqueous sodium chloride solution (15 mL). The aqueous layer was extracted with ethyl acetate (2 \( \times \) 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 30% ethyl acetate in hexanes) to afford the \( \text{N-thiomethyl bis(methyldisulfane)} \text{45} \) (6.5 mg, 49%) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

**\( \text{C3-(Indol-3'-yl) N-(thiomethyl) bis(methyldisulfane)} \text{45}\)**

**1H NMR (600 MHz, CDCl\(_3\), 20 °C):**

\[ \delta \ 7.74 \ (d, J = 8.1, 1H, C_8H), \ 7.57 \ (d, J = 8.2, 1H, C_8H), \ 7.42–7.37 \ (m, 1H, C_7H), \ 7.39 \ (d, J = 8.2, 2H, SO_2Ph-\sigma-H), \ 7.35 \ (app-dt, J = 1.0, 7.4, 1H, SO_2Ph-p-H), \ 7.31 \ (app-dt, J = 0.8, 7.7, 1H, C_{15}H), \ 7.27 \ (app-dt, J = 1.0, 7.6, 1H, C_8H), \ 7.21 \ (app-dt, J = 0.8, 7.5, 1H, C_8H), \ 7.09 \ (app-dt, J = 0.7, 7.5, 1H, C_8H), \ 7.01 \ (d, J = 7.9, 1H, C_8H), \ 6.97 \ (dd, J = 7.6, 8.2, 2H, SO_2Ph-m-H), \ 6.71 \ (s, 1H, C_2H), \ 6.08 \ (s, 1H, C_2H), \ 5.02 \ (s, 1H, C_{12}H_3), \ 3.29 \ (d, J = 15.0, 1H, C_{12}H_3), \ 3.25 \ (d, J = 15.0, 1H, C_{12}H_3), \ 3.17 \ (s, 3H, C_{17}H_3), \ 2.67 \ (3H, C_{20}H_3), \ 2.50 \ (s, 3H, C_{13}H_3), \ 2.29 \ (s, 3H, C_{19}H_3). \]

**13C NMR (150 MHz, CDCl\(_3\), 20 °C):**

\[ \delta \ 165.3 \ (C_{13}), \ 162.5 \ (C_{16}), \ 142.0 \ (C_9), \ 141.2 \ (C_9), \ 137.8 \ (SO_2Ph-ipso-C), \ 136.0 \ (C_4), \ 133.0 \ (C_2), \ 132.9 \]


(SO₂Ph-\(p\)-C), 129.7 (C₇), 128.4 (SO₂Ph-\(m\)-C), 127.3 (SO₂Ph-\(o\)-C), 125.9 (C₆), 125.8 (C₄), 124.6 (C₅), 123.7 (C₃), 121.6 (C₉), 119.1 (C₈), 118.8 (C₆), 117.6 (C₇), 111.7 (C₈), 84.8 (C₅), 79.2 (C₁₅), 73.9 (C₁₁), 53.5 (C₃), 46.0 (C₁₂), 32.7 (C₁₇), 24.4 (C₂₀), 24.0 (C₂₁), 23.3 (C₁₉).

FTIR (thin film) cm⁻¹:

2925 (w), 1699 (s), 1458 (m), 1359 (m), 1231 (w), 1168 (m), 1091 (w), 749 (m).

HRMS (ESI) (m/z):


TLC (50% ethyl acetate in hexanes), Rf:

0.60 (UV, I₂, CAM).
C3-(Indol-3′-yl) bis(methylidisulfane) 46:

Sodium borohydride (4.8 mg, 0.13 mmol, 3.7 equiv) was added as a solid to a solution of epidithiodiketopiperazine 26 (19.5 mg, 33.9 μmol, 1 equiv) in anhydrous tetrahydrofuran (5 mL) and anhydrous methanol (50 μL) at 23 °C. After 45 min, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed sequentially with water (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the hexacyclic bisthiol S25 that was used in the next step without further purification.

Dimethylidisulfide50 (200 μL, 2.23 mmol, 65.7 equiv) was added to the solution of bisthiol S25 in anhydrous tetrahydrofuran (6 mL) at 23 °C. After 19 h, the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 → 10% ethyl acetate in dichloromethane) to afford the bis(methylidisulfane) 46 (9.3 mg, 41%) as a colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

1H NMR (600 MHz, CDCl3, 20 ºC):

\[ \delta 7.85 \text{ (br-s, 1H, N1' H)}, 7.70 \text{ (d, J = 8.1, 1H, C8' H)}, 7.52 \text{ (d, J = 7.4, 2H, SO2Ph-o-H)}, 7.36 \text{ (app-dt, J = 1.3, 7.8, 1H, C7 H)}, 7.33 \text{ (t, J = 7.5, 1H, SO2Ph-p-H)}, 7.32 \text{ (d, J = 8.2, 1H, C8 H)}, 7.24 \text{ (app-dd, J = 0.8, 7.5, 1H, C1 H)}, 7.19 \text{ (app-ddd, J = 2.4, 5.8, 8.2, 1H, C3 H)}, 7.16 \text{ (app-dt, J = 0.8, 7.5, 1H, C5 H)}, 7.07 \text{ (app-dt, J = 0.5, 7.9, 2H, SO2Ph-m-H)}, 7.01–6.96 \text{ (m, 2H, C6 H + C7 H)}, 6.76 \text{ (s, 1H, C15 H)}, 6.28 \text{ (d, J = 2.6, 1H, C6 H)}, 5.00 \text{ (s, 1H, C15 H)}, 3.38 \text{ (d, J = 15.0, 1H, C12Ha)}, 3.26 \text{ (d, J = 15.0, 1H, C12Hb)}, 3.17 \text{ (s, 3H, C17 H3)}, 2.64 \text{ (s, 3H, C20 H3)}, 2.29 \text{ (s, 3H, C19 H3)}. \]

13C NMR (150 MHz, CDCl3, 20 ºC):

\[ \delta 165.4 \text{ (C13)}, 162.6 \text{ (C16)}, 141.8 \text{ (C9)}, 138.2 \text{ (SO2Ph-ipso-C)}, 137.3 \text{ (C9)}, 136.4 \text{ (C5)}, 133.0 \text{ (SO2Ph-p-C)}, 129.5 \text{ (C7)}, 128.6 \text{ (SO2Ph-m-C)}, 127.4 \text{ (SO2Ph-o-C)}, 125.7 \text{ (C6)}, 124.6 \text{ (C3)}, 124.2 \text{ (C4)}, 123.3 \text{ (C2)}, 122.9 \text{ (C7)}, 120.5 \text{ (C9)}, 118.9 \text{ (C5)}, 118.3 \text{ (C8)}, 115.7 \text{ (C3)}, 111.9 \text{ (C8)}, 85.2 \text{ (C2)}, 79.2 \text{ (C13)}, 74.0 \text{ (C11)}, 55.3 \text{ (C3)}, 46.4 \text{ (C12)}, 32.7 \text{ (C17)}, 24.4 \text{ (C20)}, 23.4 \text{ (C19)}. \]

FTIR (thin film) cm\(^{-1}\):

3392 (br-m), 3060 (w), 2921 (w), 1685 (s), 1459 (m), 1391 (m), 1266 (w), 1169 (m), 1092 (w), 1022 (w), 736 (m).

HRMS (ESI) (m/z): calc’d for C_{30}H_{28}N_{4}NaO_{4}S_{5} [M+Na]^+: 691.0606, found 691.0613.

TLC (20% ethyl acetate in dichloromethane), Rf: 0.67 (UV, I$_2$, CAM).
C3-(Indol-3'-yl)-pyrrolidinoindoline 74:

This compound was prepared in two steps starting from endo-tetracyclic bromide7 (+)-73 (512.5 mg, 10.5 mmol, 1 equiv) using the methodology developed to access the corresponding C3-(5-bromo-N-TIPS-indol-3'-yl)-pyrrolidinoindoline (+)-S12 (Please see page S10 for details) with DTBMP (339 mg, 1.65 mmol, 1.58 equiv), 5-bromo-1-triisopropylsilyl-1H-indole12 S11 (1.92 g, 5.45 mmol, 5.20 equiv), and silver(I) tetrafluoroborate (600 mg, 3.08 mmol, 2.95 equiv) in anhydrous nitroethane (12 mL). After 1 h, saturated aqueous sodium chloride solution (20 mL) was introduced, and the resulting biphasic mixture was vigorously stirred for 30 min at 0 °C. The reaction mixture was diluted with ethyl acetate (50 mL), was filtered through a Celite pad, and the solid was washed with ethyl acetate (3 × 15 mL). The combined filtrates were washed with 5% aqueous citric acid solution (2 × 25 mL), water (3 × 25 mL), and saturated aqueous sodium chloride solution (25 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (eluent: gradient, 1 → 10% acetone in dichloromethane) to afford the C3-(5-bromo-N-TIPS-indol-3'-yl)-pyrrolidinoindoline S26 (537 mg, 67.4%) as a white foam.51

The free indole was accessed in a one-pot two-step procedure using the methodology developed to access the corresponding C3-(indol-3'-yl)-pyrrolidinoindoline (+)-59 (Please see page S12 for details). The reaction mixture was filtered through a pad of Celite. The solids were washed with ethyl acetate (3 × 50 mL). The combined filtrates were concentrated under reduced pressure. The resulting pale yellow solid was diluted in ethyl acetate (150 mL) and washed sequentially with an aqueous hydrochloric acid solution (1 N, 2 × 50 mL), water (2 × 50 mL), and saturated aqueous sodium chloride solution (40 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure to afford the C3-(indol-3'-yl)-pyrrolidinoindoline 7452 (370 mg, 99.7%) as a white solid that was used in the next step without further purification.

51 S26: 1H NMR (600 MHz, CDCl3, 20 °C): δ 8.03 (d, J = 7.8, 2H, SO2Ph-o-H), 7.78 (d, J = 8.4, 1H, C5H), 7.54 (app-dd, J = 7.2, 7.8, 1H, SO2Ph-p-H), 7.40 (app-t, J = 7.8, 2H, SO2Ph-m-H), 7.30 (d, J = 8.9, 1H, C16H), 7.28 (app-dt, J = 1.0, 7.9, 1H, C7H), 7.15 (app-dd, J = 1.7, 8.8, 1H, C15H), 6.97 (dd, J = 7.5, 7.6, 1H, C17H), 6.95 (s, 1H, C14H), 6.82 (d, J = 7.3, 1H, C13H), 6.50 (br-s, 1H, C13H), 6.30 (s, 1H, C15H), 4.44 (dd, J = 7.8, 9.4, 1H, C7'H), 3.97 (q, J = 7.1, 1H, C17'H), 3.03 (dd, J = 7.5, 13.8, 1H, C16'H), 2.99 (s, 3H, C18H), 2.88 (dd, J = 9.8, 13.8, 1H, C3'H), 1.66 (dd, J = 7.1, 3H, C2'H), 1.59 (app-sp, J = 7.5, 3H, C12'H), 1.07 (app-d, J = 5.5, 18H, C13'H).

13C NMR (150 MHz, CDCl3, 20 °C): δ 169.2 (C16), 161.0 (C17), 141.3 (C10), 143.7 (CO), 137.1 (SO2Ph-ixpo-C), 134.2 (SO2Ph-p-C), 133.9 (C8), 130.9 (C1), 130.3 (C2), 129.5 (C13), 129.2 (SO2Ph-m-C), 127.0 (SO2Ph-n-C), 125.7 (C12), 124.5 (C12), 123.9 (C1), 121.9 (C10), 116.0 (C6), 115.1 (C14), 115.6 (C16), 113.6 (C14), 83.0 (C15), 59.5 (C15), 57.5 (C15), 55.3 (C15), 37.8 (C12), 29.6 (C18), 18.2 (C14), 14.8 (C11), 12.9 (C12).

TLC (20% acetone in dichloromethane), Rf: 0.76 (UV, CAM).

52 74: 1H NMR (600 MHz, CDCl3, 20 °C): δ 8.94 (br-s, 1H, N1H), 7.74 (d, J = 8.2, 1H, C1H), 7.46 (d, J = 8.2, 2H, SO2Ph-o-H), 7.35 (app-dt, J = 0.9, 7.5, 1H, SO2Ph-p-H), 7.34 (d, J = 8.3, 1H, C1H), 7.29 (dd, J = 7.5, 8.1, 1H, C1H), 7.19 (app-dt, J = 4.1, 8.2, 1H, C1H), 7.12 (d, J = 7.5, 1H, C7H), 7.09-7.04 (m, 3H, SO2Ph-m-C + C16H), 6.95 (app-d, J = 4.0, 2H, C1H + C1H), 6.40 (s, 1H, C1H), 6.09 (d, J = 2.0, 1H, C1H), 4.52 (app-t, J = 7.8, 1H, C1H), 4.07 (q, J = 7.0, 1H, C1H), 3.10 (app-d, J = 7.8, 2H, C1H), 2.90 (s, 3H, C14H), 1.61 (d, J = 7.1, 3H, C18H). MS (ESI) (m/z): [M+H]+: 527.25; [M+Na]+: 549.21. TLC (20% acetone in dichloromethane), Rf: 0.27 (UV, CAM).
C3-(Indol-3'-yl) dithiepanethiones 64 and 66:

Freshly prepared bis(pyridine)silver(I) permanganate $^{53}$ (800 mg, 2.08 mmol, 5.45 equiv) was added as a solid to a solution of indole adduct 74 (201 mg, 382 μmol, 1 equiv) in anhydrous pyridine (5 mL) at 23 °C. After 2 h, a second portion of bis(pyridine)silver(I) permanganate (600 mg, 1.56 mmol, 4.08 equiv) was added. After 2 h, the resulting thick brown suspension was diluted with saturated aqueous sodium sulfite solution (50 mL) and then with ethyl acetate (160 mL). The resulting mixture was washed sequentially with water (2 × 50 mL), aqueous 5% copper sulfate solution (3 × 50 mL), and saturated aqueous sodium chloride solution (30 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow residue was purified by flash column chromatography (eluent: gradient, 2 → 20% isopropanol in dichloromethane and hexanes (50%)) to afford the corresponding diols $^{54}$ (78.0 mg, 36.5%) as a yellow oil.

To a yellow solution of potassium trithiocarbonate $^{55}$ (250 mg, 1.34 mmol, 9.63 equiv) in anhydrous dichloromethane (6 mL) and trifluoroacetic acid (4 mL) at 23 °C was added a solution of the diol (78.0 mg, 139 μmol, 1 equiv) in dichloromethane (1 mL). After 2.5 h, the reaction mixture was diluted with ethyl acetate (60 mL) and washed with saturated aqueous sodium bicarbonate (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow residue was purified by flash column chromatography on silica gel (eluent: gradient, 2 → 8% ethyl acetate in dichloromethane) to afford an inseparable mixture of isomeric monomeric dithiepanethiones 64 and 66 (55.7 mg, 63.3%, 64:66, 5:1) as a pale yellow solid.

Isomers 64 and 66 were separated for the purpose of full and independent characterization by preparative HPLC [Waters X-Bridge preparative HPLC column, C18, 5 μm, 19 × 250 mm; 20.0 mL/min; gradient, 30 → 100% acetonitrile in water, 35 min; $t_R(64) = 21.3$ min, $t_R(66) = 23.4$ min]. Structural assignments were made using additional information from gCOSY, HSQC, and HMBC experiments.

**β-epimer 64:**

$^1$H NMR (600 MHz, CDCl$_3$, 20 °C):

δ 7.81 (br-s, 1H, N$_1$H), 7.74 (d, J = 8.2, 1H, C$_3$H), 7.44–7.39 (m, 1H, C$_3$H), 7.37 (app-dd, J = 0.7, 7.5, 2H, SO$_2$Ph-o-H), 7.35 (d, J = 8.1, 1H, C$_8$H), 7.34 (t, J = 7.5, 1H, SO$_2$Ph-p-H), 7.26–7.21 (m, 3H, C$_5$H + C$_6$H + C$_7$H), 7.08–7.04 (m, 2H, C$_2$H + C$_6$H), 7.02 (app-t, J = 7.7, 2H, SO$_2$Ph-m-H), 6.74 (s, 1H, C$_3$H), 6.20 (d, J = 2.5, 1H, C$_2$H), 3.91 (d, J = 15.6, 1H, 53. Firouzabadi, H.; Vessal, B.; Naderi, M. *Tetrahedron Lett.* 1982, 23, 1847.
54 The product was isolated as a mixture of isomers.
$^{13}$C NMR (100 MHz, CDCl$_3$, 20 ºC):
\[ \delta \ 215.9 (\text{C}_{19}), \ 165.0 (\text{C}_{13}), \ 161.0 (\text{C}_{18}), \ 141.1 (\text{C}_9), \ 137.8 (\text{SO}_2\text{Ph-}ipso-C), \ 137.3 (\text{C}_o), \ 135.4 (\text{C}_4), \ 133.1 (\text{SO}_2\text{Ph-}p-C), \ 130.2 (\text{C}_3), \ 128.5 (\text{SO}_2\text{Ph-}m-C), \ 127.3 (\text{SO}_2\text{Ph-}o-C), \ 126.3 (\text{C}_a), \ 124.7 (\text{C}_3), \ 124.1 (\text{C}_4), \ 124.0 (\text{C}_2), \ 123.2 (\text{C}_7), \ 120.8 (\text{C}_6), \ 119.0 (\text{C}_8), \ 118.8 (\text{C}_3), \ 114.1 (\text{C}_3'), \ 112.0 (\text{C}_8), \ 85.6 (\text{C}_2), \ 75.1 (\text{C}_15), \ 54.1 (\text{C}_3), \ 46.4 (\text{C}_12), \ 28.7 (\text{C}_{19}), \ 20.2 (\text{C}_{17}). \]

FTIR (thin film) cm$^{-1}$:
3397 (br-m), 3061 (w), 1688 (s), 1459 (w), 1361 (s), 1241 (w), 1170 (s), 1108 (w), 1001 (m), 908 (w), 734 (m).

HRMS (ESI) ($m/z$):
\[ \text{calc'd for C}_{30}\text{H}_{25}\text{N}_4\text{O}_4\text{S}_4 \ [\text{M+H}]^+: 633.0753, \text{ found 633.0744.} \]

TLC (50% ethyl acetate in hexanes), $R_f$:
0.33 (UV, CAM).

$\alpha$-epimer 66:

$^1$H NMR (600 MHz, CDCl$_3$, 20 ºC):
\[ \delta \ 7.80 \ (\text{app-dd}, \ J = 1.6, 6.8, 1\text{H}, \text{C}_8\text{H}), \ 7.72 \ (d, \ J = 8.0, 1\text{H}, \text{C}_8\text{H}), \ 7.54 \ (\text{br-s}, \ 1\text{H}, \text{N}_1\text{H}), \ 7.40-7.34 \ (m, 3\text{H}, \text{C}_5\text{H} + \text{C}_7\text{H} + \text{C}_8\text{H}), \ 7.22 \ (\text{app-t}, \ J = 7.5, 1\text{H}, \text{C}_4\text{H}), \ 7.20 \ (t, \ J = 7.4, 1\text{H}, \text{SO}_2\text{Ph-}p\text{-H}), \ 7.06 \ (\text{app-dd}, \ J = 0.9, 8.3, 2\text{H}, \text{SO}_2\text{Ph-}o\text{-H}), \ 6.81 \ (\text{dd}, \ J = 7.6, 8.1, 2\text{H}, \text{SO}_2\text{Ph-}m\text{-H}), \ 6.79 \ (s, \ 1\text{H}, \text{C}_3\text{H}), \ 5.55 \ (d, \ J = 2.5, 1\text{H}, \text{C}_2\text{H}), \ 4.04 \ (d, \ J = 15.6, 1\text{H}, \text{C}_{12}\text{H}_a), \ 3.11 \ (d, \ J = 15.6, 1\text{H}, \text{C}_{12}\text{H}_b), \ 2.98 \ (s, \ 3\text{H}, \text{C}_{18}\text{H}_3), \ 2.00 \ (s, \ 3\text{H}, \text{C}_{17}\text{H}_3). \]

$^{13}$C NMR (100 MHz, CDCl$_3$, 20 ºC):
\[ \delta \ 209.5 (\text{C}_{19}), \ 164.5 (\text{C}_{13}), \ 161.1 (\text{C}_{18}), \ 139.3 (\text{C}_9), \ 138.3 (\text{SO}_2\text{Ph-}ipso-C), \ 137.3 (\text{C}_o), \ 135.8 (\text{C}_4), \ 132.7 (\text{SO}_2\text{Ph-}p-C), \ 130.0 (\text{C}_3), \ 128.1 (\text{SO}_2\text{Ph-}m-C), \ 127.0 (\text{SO}_2\text{Ph-}o-C), \ 125.9 (\text{C}_a), \ 125.4 (\text{C}_3), \ 124.9 (\text{C}_2), \ 123.7 (\text{C}_4), \ 123.5 (\text{C}_7), \ 121.3 (\text{C}_6), \ 119.1 (\text{C}_5), \ 118.2 (\text{C}_8), \ 114.4 (\text{C}_3'), \ 112.0 (\text{C}_8'), \ 85.4 (\text{C}_2), \ 74.9 (\text{C}_15), \ 54.9 (\text{C}_3), \ 42.0 (\text{C}_{12}), \ 28.8 (\text{C}_{19}), \ 21.3 (\text{C}_{17}). \]

FTIR (thin film) cm$^{-1}$:
3396 (br-m), 2924 (w), 1698 (s), 1458 (m), 1364 (m), 1334 (m), 1251 (w), 1169 (m), 1091 (m), 1013 (m), 912 (w), 734 (m).

HRMS (ESI) ($m/z$):
\[ \text{calc'd for C}_{30}\text{H}_{25}\text{N}_4\text{O}_4\text{S}_4 \ [\text{M+H}]^+: 633.0753, \text{ found 633.0767.} \]

TLC (50% ethyl acetate in hexanes), $R_f$:
0.33 (UV, CAM).
Ethanolamine (4 mL) was added via syringe to a solution of the bisdithiepanethiones 64 and 66 (33.0 mg, 52.1 μmol, 1 equiv, 64:66, 5:1) in acetone (6 mL) at 23 °C. After 45 min, the reaction mixture was partitioned between ethyl acetate (100 mL) and aqueous hydrochloric acid solution (1 N, 30 mL). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). A solution of potassium triiodide in pyridine (2.5% w/v) was added dropwise to the combined organic layers until a persistent yellow color was observed. The resulting mixture was washed with aqueous hydrochloric acid (1 N, 20 mL), and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 20 → 50% ethyl acetate in hexanes) to afford an inseparable mixture of isomeric monomeric epidithiodiketopiperazines 60 and 62 (14.8 mg, 48.2%, 60:62, 5:1) as a pale yellow solid.

Isomers 60 and 62 were separated for the purpose of full and independent characterization by preparative HPLC [Waters X-Bridge preparative HPLC column, C18, 5 μm, 19 × 250 mm; 20.0 mL/min; gradient, 30 → 100% acetonitrile in water, 35 min; t<sub>R</sub>(60) = 18.0 min, t<sub>R</sub>(62) = 19.7 min]. Structural assignments were made using additional information from gCOSY, HSQC, and HMBC experiments.

**β-epimer 60:**

δ 8.01 (d, J = 7.3, 1H, C<sub>5'</sub>H), 7.73 (d, J = 8.0, 1H, C<sub>8'H</sub>), 7.60 (br- s, 1H, N 1'H), 7.41 (d, J = 6.6, 1H, C<sub>5'H</sub>), 7.39 (d, J = 7.8, 1H, C<sub>8</sub>H), 7.43–7.38 (m, 1H, C<sub>7'H</sub>), 7.38–7.31 (m, 2H, C<sub>6'H</sub> + C<sub>7</sub>H), 7.26–7.21 (m, 2H, C<sub>6</sub>H + SO<sub>2</sub>Ph-<sub>p</sub>-H), 7.11 (app- dd, J = 0.9, 8.3, 2H, SO<sub>2</sub>Ph-<sub>o</sub>-H), 6.85 (dd, J = 7.6, 8.1, 2H, SO<sub>2</sub>Ph-<sub>m</sub>-H), 6.84 (s, 1H, C<sub>2</sub>H), 5.58 (d, J = 2.5, 1H, C<sub>2'</sub>H), 4.00 (d, J = 15.1, 1H, C<sub>12</sub>H<sub>b</sub>), 3.19 (d, J = 15.1, 1H, C<sub>12</sub>H<sub>b</sub>), 2.97 (s, 3H, C<sub>18</sub>H<sub>3</sub>), 2.04 (s, 3H, C<sub>17</sub>H<sub>3</sub>).

**13C NMR (100 MHz, CDCl<sub>3</sub>, 20 °C):**

δ 166.0 (C<sub>13</sub>), 161.9 (C<sub>16</sub>), 140.9 (C<sub>9</sub>), 137.6 (SO<sub>2</sub>Ph-<i>ipso</i>-C), 137.2 (C<sub>9</sub>), 136.9 (C<sub>4</sub>), 133.0 (SO<sub>2</sub>Ph-<i>p</i>-C), 129.8 (C<sub>3</sub>), 128.3 (SO<sub>2</sub>Ph-<i>m</i>-C), 127.2 (SO<sub>2</sub>Ph-<i>o</i>-C), 126.1 (C<sub>6</sub>), 124.5 (C<sub>3</sub>), 124.3 (C<sub>4</sub>), 124.0 (C<sub>2</sub>), 123.1 (C<sub>7</sub>), 120.7 (C<sub>6</sub>), 119.3 (C<sub>8</sub>),...
118.7 (C5), 114.1 (C3), 112.1 (C8), 85.1 (C2), 73.9 (C13), 73.5 (C11), 55.3 (C3), 43.0 (C12), 27.8 (C18), 18.4 (C17).

FTIR (thin film) cm\(^{-1}\): 3396 (br-m), 3061 (w), 2924 (w), 2851 (w), 1704 (s), 1447 (w), 1360 (m), 1332 (s), 1244 (w), 1169 (s), 1109 (m), 1090 (m), 910 (w), 735 (s).

HRMS (ESI) (m/z): calc’d for C\(_{29}H_{25}N_4O_4S_3\) [M+H]+: 589.1032, found 589.1043.

TLC (50\% ethyl acetate in hexanes), R\(_f\): 0.27 (UV, CAM).

\(\alpha\)-epimer 62:

\(^1\)H NMR (600 MHz, CDCl\(_3\), 20 °C):
\(\delta\) 7.99 (d, \(J = 7.4\), 1H, C\(_5\)H), 7.70 (d, \(J = 8.0\), 1H, C\(_8\)H), 7.57 (br-s, 1H, N\(_1\)H), 7.40–7.34 (m, 3H, C\(_5\)H + C\(_8\)H + C\(_3\)H), 7.34–7.28 (m, 2H, C\(_8\)H + C\(_3\)H), 7.21 (app-dt, \(J = 1.7\), 7.6, 2H, C\(_8\)H + SO\(_2\)Ph-p-H), 7.08 (app-dd, \(J = 0.9\), 8.3, 2H, SO\(_2\)Ph-o-H), 6.82 (dd, \(J = 7.6\), 8.1, 2H, SO\(_2\)Ph-m-H), 6.82 (s, 1H, C\(_6\)H), 5.55 (d, \(J = 2.5\), 1H, C\(_2\)H), 3.97 (d, \(J = 15.1\), 1H, C\(_{12}\)H\(_a\)), 3.16 (d, \(J = 15.1\), 1H, C\(_{12}\)H\(_b\)), 2.94 (s, 3H, C\(_{18}\)H\(_3\)), 2.01 (s, 3H, C\(_{17}\)H\(_3\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\), 20 °C):
\(\delta\) 165.9 (C\(_{13}\)), 162.6 (C\(_{16}\)), 139.5 (C\(_9\)), 138.3 (SO\(_2\)Ph-ipso-C), 137.3 (C\(_9\)), 135.6 (C\(_4\)), 132.6 (SO\(_2\)Ph-p-C), 129.8 (C\(_3\)), 128.1 (SO\(_2\)Ph-m-C), 127.1 (SO\(_2\)Ph-o-C), 125.9 (C\(_6\)), 125.4 (C\(_3\)), 124.6 (C\(_2\)), 123.9 (C\(_4\)), 123.4 (C\(_7\)), 121.0 (C\(_6\)), 119.2 (C\(_5\)), 118.4 (C\(_8\)), 115.2 (C\(_9\)), 111.9 (C\(_8\)), 85.0 (C\(_2\)), 74.4 (C\(_11\)), 73.8 (C\(_{15}\)), 55.9 (C\(_3\)), 41.2 (C\(_{12}\)), 27.6 (C\(_{18}\)), 18.7 (C\(_{17}\)).

FTIR (thin film) cm\(^{-1}\): 3395 (br-m), 2923 (w), 1701 (s), 1460 (w), 1359 (m), 1332 (m), 1247 (w), 1168 (m), 1090 (w), 912 (w), 734 (m).

HRMS (ESI) (m/z): calc’d for C\(_{29}H_{25}N_4O_4S_3\) [M+H]+: 589.1032, found 589.1037.

TLC (50\% ethyl acetate in hexanes), R\(_f\): 0.27 (UV, CAM).
Dimeric bisdithiepanethione 18:
Dimeric tetraol 22 (200 mg, 226 \( \mu \)mol, 1 equiv) was added as a solid to a yellow solution of potassium trithiocarbonate (632 mg, 3.39 mmol, 15.0 equiv) in anhydrous dichloromethane (5.1 mL) and trifluoroacetic acid (1.7 mL) at 23 °C. After 25 min, the reaction mixture was diluted with dichloromethane (60 mL) and washed with saturated aqueous sodium bicarbonate (125 mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford a yellow powder. This powder was purified by flash column chromatography on silica gel (eluent: 5% acetone in dichloromethane) to afford dimeric bisdithiepanethione 18 (88.8 mg, 38.0%) as an orange-yellow solid.

\[ \text{Dimeric tetraol 22 (200 mg, 226 } \mu \text{mol, 1 equiv) was added as a solid to a yellow solution of potassium trithiocarbonate (632 mg, 3.39 mmol, 15.0 equiv) in anhydrous dichloromethane (5.1 mL) and trifluoroacetic acid (1.7 mL) at 23 °C. After 25 min, the reaction mixture was diluted with dichloromethane (60 mL) and washed with saturated aqueous sodium bicarbonate (125 mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford a yellow powder. This powder was purified by flash column chromatography on silica gel (eluent: 5% acetone in dichloromethane) to afford dimeric bisdithiepanethione 18 (88.8 mg, 38.0%) as an orange-yellow solid.} \]

\[ \text{1H NMR (500 MHz, CDCl}_3, 20 °C):} \delta 7.75–7.65 (m, 2H, C\text{8H}), 7.75–7.65 (m, 4H, SO\text{2Ph- o-H}), 7.53 (app-t, J = 7.4, 2H, SO\text{2Ph-p-H}), 7.41 (app-t, J = 8.0, 4H, SO\text{2Ph-m-H}), 7.30–7.14 (m, 6H, C\text{6H, C\text{7H, C\text{5H}}}), 6.86 (s, 2H, C\text{2H}), 3.26 (d, J = 14.9, 2H, C\text{12H}_a), 3.09 (d, J = 14.9, 2H, C\text{12H}_b), 3.01 (s, 6H, C\text{18H}), 1.68 (s, 6H, C\text{17H}). \]

\[ \text{13C NMR (125.8 MHz, CDCl}_3, 20 °C):} \delta 215.1 (C=S), 164.1 (C\text{13}), 159.7 (C\text{16}), 142.7 (C\text{9}), 141.9 (SO\text{2Ph- ipso-C}), 133.1 (SO\text{2Ph-p-C}), 131.3 (C\text{12}), 129.2 (SO\text{2Ph-m-C}), 129.2 (C\text{8}), 125.5 (SO\text{2Ph- o-C}), 125.2 (C\text{7}), 124.5 (C\text{8}), 116.1 (C\text{3}), 81.6 (C\text{2}), 73.9 (C\text{11}), 73.6 (C\text{15}), 59.1 (C\text{3}), 44.7 (C\text{12}), 28.6 (C\text{18}), 19.3 (C\text{17}). \]

\[ \text{FTIR (thin film) cm}^{-1}: 1715 (s), 1691 (s), 1479 (m), 1462 (m), 1447 (m), 1359 (s), 1169 (s), 729 (m). \]

\[ \text{HRMS (ESI) (m/z):} \text{calc’d for C}_{44}\text{H}_{36}\text{N}_{6}\text{NaO}_{8}\text{S}_{8} [\text{M+Na}^+]: 1055.0252, \text{found 1055.0255.} \]

\[ \text{[\alpha]D}^{24}: + 230 (c 0.19, CHCl}_3). \]

\[ \text{TLC (5% acetone in dichloromethane), Rf: 0.27 (UV, CAM).} \]
Ethanolamine (500 μL) was added via syringe to a solution of dimeric bisdithiepanethione 18 (11.2 mg, 10.8 μmol, 1 equiv) in acetone (500 μL) at 23 °C. After 15 min, the reaction mixture was diluted with dichloromethane (30 mL) and aqueous hydrochloric acid solution (1 N, 30 mL). The organic layer was collected, and the aqueous layer was extracted with dichloromethane (2 × 5 mL). A solution of potassium triiodide in pyridine (2.5% w/v) was added dropwise to the combined organic layers until a persistent yellow color was observed. The resulting mixture was washed with aqueous hydrochloric acid (1 N, 30 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 5% acetone in dichloromethane) to afford dimeric epidithiodiketopiperazine 14 (3.9 mg, 38%) as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$, 20 ºC):

\[ \delta 7.85 \text{ (dd, } J = 1.4, 7.3, 4H, \text{SO}_2\text{Ph-o-H}), 7.68 \text{ (d, } J = 7.5, 2H, \text{C}_6\text{H}), 7.54 \text{ (tt, } J = 1.2, 7.5, 2H, \text{SO}_2\text{Ph-p-H}), 7.46 \text{ (app-t, } J = 8.0, 4H, \text{SO}_2\text{Ph-m-H}), 7.20 \text{ (app-dt, } J = 1.3, 7.5, 2H, \text{C}_8\text{H}), 7.16 \text{ (app-dt, } J = 1.2, 7.5, 2H, \text{C}_7\text{H}), 7.04 \text{ (dd, } J = 1.0, 7.6, 2H, \text{C}_5\text{H}), 6.83 \text{ (s, } 2H, \text{C}_2\text{H}), 3.55 \text{ (d, } J = 15.2, 2H, \text{C}_{12}\text{H}_a), 2.97 \text{ (s, } 6H, \text{C}_{18}\text{H}), 2.95 \text{ (d, } J = 15.2, 2H, \text{C}_{12}\text{H}_b), 1.62 \text{ (s, } 6H, \text{C}_{17}\text{H}).

$^{13}$C NMR (125.8 MHz, CDCl$_3$, 20 ºC):

\[ \delta 164.9 \text{ (C}_{13}), 160.8 \text{ (C}_{16}), 142.5 \text{ (C}_9), 142.4 \text{ (SO}_2\text{Ph-ipso-C}), 132.6 \text{ (SO}_2\text{Ph-p-C}), 130.9 \text{ (C}_4), 130.6 \text{ (C}_6), 129.0 \text{ (SO}_2\text{Ph-m-C}), 125.7 \text{ (SO}_2\text{Ph-o-C}), 125.2 \text{ (C}_7), 124.7 \text{ (C}_8), 116.3 \text{ (C}_3), 81.9 \text{ (C}_2), 73.8 \text{ (C}_{15}), 73.4 \text{ (C}_{11}), 60.5 \text{ (C}_5), 41.9 \text{ (C}_{12}), 27.8 \text{ (C}_{19}), 17.9 \text{ (C}_{17}).

FTIR (thin film) cm$^{-1}$:

1716 (s), 1688 (s), 1480 (m), 1462 (m), 1447 (w), 1348 (s), 1168 (m).

HRMS (ESI) (m/z):

calc’d for C$_{42}$H$_{37}$N$_6$O$_8$S$_6$ [M+H]$^+$: 945.0992, found 945.0968.

TLC (5% acetone in dichloromethane), Rf:

0.21 (UV, CAM).
C3-Propyl dithiepanethiones 65 and 67:

A solution of the tetracyclic diol S27 (228 mg, 470 μmol, 1 equiv) in dichloromethane (3.5 mL) was added to a yellow solution of potassium trithiocarbonate (438 mg, 2.35 mmol, 5.00 equiv) in anhydrous dichloromethane (7 mL) and trifluoroacetic acid (3 mL) at 23 °C. An additional portion of trifluoroacetic acid (1.5 mL) was added to the reaction mixture via syringe. After 25 min, the reaction mixture was diluted with dichloromethane (60 mL) and washed with saturated aqueous sodium bicarbonate (125 mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to yield a yellow powder. This powder was purified by flash column chromatography on silica gel (eluent: 20% acetone in dichloromethane) to afford diastereomeric dithiepanethiones 65 (137 mg, 52.0%) and 67 (38.7 mg, 14.7%) as yellow films.

β-epimer 65:

\[
\text{1H NMR (500 MHz, CDCl}_3, 20 ^\circ\text{C):}\]
\[
\delta 7.72 \ (d, J = 7.5, 2H, \text{SO}_2\text{Ph-o-H}), 7.52 \ (t, J = 7.5, 1H, \text{SO}_2\text{Ph-p-H}), 7.40 \ (\text{app-t}, J = 7.9, 2H, \text{SO}_2\text{Ph-m-H}), 7.35 \ (d, J = 7.1, 1H, C_6H), 7.29 \ (\text{app-dt}, J = 1.7, 8.2, 1H, C_5H), 7.19 \ (\text{app-dt}, J = 0.9, 7.7, 1H, C_4H), 7.16 \ (\text{dd}, J = 1.4, 7.6, 1H, C_3H), 6.29 \ (s, 1H, C_2H), 3.00 \ (s, 3H, C_18H), 2.98 \ (d, J = 15.1, 1H, C_12H_a), 2.75 \ (d, J = 15.1, 1H, C_12H_b), 1.79 \ (s, 3H, C_17H), 1.47–1.31 \ (m, 2H, C_2CH_2CH_3), 1.19–1.06 \ (m, 1H, CH_2CH_2H_5CH_3), 0.78 \ (\text{app-t}, J = 7.0, 3H, CH_2CH_2CH_3).
\]

\[
\text{13C NMR (125.8 MHz, CDCl}_3, 20 ^\circ\text{C):}\]
\[
\delta 215.9 \ (\text{C}=\text{S}), 164.7 \ (C_13H), 160.5 \ (C_16H), 141.6 \ (C_9H), 140.4 \ (\text{SO}_2\text{Ph-ipso-C}), 135.4 \ (C_3H), 133.3 \ (\text{SO}_2\text{Ph-p-C}), 129.7 \ (C_7H), 129.2 \ (\text{SO}_2\text{Ph-m-C}), 126.5 \ (\text{SO}_2\text{Ph-o-C}), 125.9 \ (C_6H), 123.6 \ (C_5H), 117.6 \ (C_4H), 83.7 \ (C_3H), 74.6 \ (C_11H), 73.5 \ (C_15H), 54.5 \ (C_2H), 46.1 \ (C_12H), 40.5 \ (CH_2CH_2CH_3), 28.5 \ (C_18H), 19.7 \ (C_17H), 18.0 \ (CH_2CH_2CH_3), 14.3 \ (CH_2CH_2CH_3).
\]

FTIR (thin film) cm⁻¹:

1711 (s), 1686 (s), 1477 (m), 1461 (m), 1447 (m), 1365 (s), 1167 (s), 732 (m).

HRMS (ESI) (m/z):

calc'd for C_{25}H_{25}N_3NaO_4S_4 [M+Na]^+: 582.0620, found 582.0646.

TLC (40% ethyl acetate in hexanes), Rf:

0.18 (UV, CAM).
α-epimer 67:

$^1$H NMR (500 MHz, CDCl$_3$, 20 ºC):

$\delta$ 7.79 (dd, $J = 1.0, 7.3$, 2H, SO$_2$Ph-o-H), 7.57 (d, $J = 8.0$, 1H, C$_2$H$_a$), 7.53 (t, $J = 7.5$, 1H, SO$_2$Ph-p-H), 7.40 (app-t, $J = 7.8$, 2H, SO$_2$Ph-m-H), 7.27 (app-Dt, $J = 1.4, 7.8$, 1H, C$_2$H$_b$), 7.12 (app-Dt, $J = 0.9, 7.6$, 1H, C$_2$H$_a$), 7.06 (dd, $J = 0.8, 7.5$, 1H, C$_2$H$_b$), 6.06 (s, 1H, C$_2$H$_c$), 3.42 (d, $J = 15.7$, 1H, C$_{12}$H$_a$), 2.97 (s, 3H, C$_3$H$_a$), 2.44 (d, $J = 15.7$, 1H, C$_{12}$H$_b$), 1.95 (s, 3H, C$_{17}$H$_b$), 1.37–1.26 (m, 1H, CH$_2$C$_{H_a}$H$_{C_b}$CH$_3$), 1.26–1.14 (m, 1H, CH$_2$CH$_2$H$_3$CH$_3$), 0.97–0.83 (m, 2H, CH$_2$CH$_2$CH$_3$), 0.69 (app-t, $J = 6.8$, 3H, CH$_2$CH$_2$CH$_3$).

$^{13}$C NMR (125.8 MHz, CDCl$_3$, 20 ºC):

$\delta$ 216.8 (C=S), 164.3 (C$_{13}$), 161.4 (C$_{15}$), 139.3 (C$_9$), 138.9 (SO$_2$Ph-ipso-C), 138.3 (C$_4$), 133.8 (SO$_2$Ph-p-C), 129.3 (SO$_2$Ph-m-C), 129.3 (C$_7$), 127.7 (SO$_2$Ph-o-C), 126.3 (C$_8$), 124.4 (C$_3$), 118.3 (C$_5$), 84.5 (C$_2$), 74.8 (C$_{11}$), 74.1 (C$_{15}$), 55.0 (C$_3$), 42.4 (C$_{12}$), 40.0 (CH$_2$CH$_2$CH$_3$), 28.6 (C$_{19}$), 21.0 (C$_{17}$), 18.3 (CH$_2$CH$_2$CH$_3$), 14.2 (CH$_2$CH$_2$CH$_3$).

FTIR (thin film) cm$^{-1}$:

1712 (s), 1691 (s), 1476 (m), 1461 (m), 1447 (m), 1368 (s), 1333 (s), 1172 (s), 727 (w).

HRMS (ESI) ($m/z$):

calc’d for C$_{25}$H$_{25}$N$_3$NaO$_4$S$_4$ [M+Na]$^+$: 582.0620, found 582.0636.

TLC (40% ethyl acetate in hexanes), $R_f$:

0.50 (UV, CAM).
β-C3-Propyl epidithiodiketopiperazine 61:
Ethanolamine (500 μL) was added via syringe to a solution of dithiepanethione 65 (13.3 mg, 23.8 μmol, 1 equiv) in acetone (500 μL) at 23 °C. After 15 min, the reaction mixture was diluted with dichloromethane (30 mL) and aqueous hydrochloric acid solution (2 N, 30 mL). The organic layer was collected, and the aqueous layer was extracted with dichloromethane (2 × 2 mL). A solution of potassium triiodide in pyridine (2.5% w/v) was added dropwise to the combined organic layers until a persistent yellow color was observed. The resulting mixture was washed with aqueous hydrochloric acid (2 N, 30 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 1% acetone in dichloromethane) to afford epidithiodiketopiperazine 61 (8.6 mg, 70%) as a clear film.

1H NMR (500 MHz, CDCl3, 20 ºC):
δ 7.80 (d, J = 7.0, 2H, SO2Ph-0-H), 7.53 (t, J = 7.0, 1H, SO2Ph-p-H), 7.46–7.37 (m, 1H, C8H), 7.46–7.37 (m, 2H, SO2Ph-m-H), 7.29 (app-dt, J = 1.1, 7.7, 1H, C7H), 7.16 (app-t, J = 7.6, 1H, C6H), 7.12 (d, J = 7.6, 1H, C5H), 6.09 (s, 1H, C2H), 3.19 (d, J = 15.2, 1H, CH2CH3), 2.98 (s, 3H, CH3), 2.57 (d, J = 15.2, 1H, CH2CH3), 1.87 (s, 3H, CH3), 1.43–1.30 (m, 1H, CH2CH3), 0.77–0.68 (m, 3H, CH2CH3).

13C NMR (125.8 MHz, CDCl3, 20 ºC):
δ 165.9 (C13), 161.6 (C16), 141.1 (C9), 139.8 (SO2Ph-ipso-C), 137.6 (C1), 133.4 (SO2Ph-p-C), 129.3 (C7), 129.2 (SO2Ph-m-C), 127.4 (SO2Ph-o-C), 125.9 (C8), 123.6 (C3), 118.4 (C8), 83.7 (C2), 73.7 (C11), 73.5 (C15), 55.9 (C1), 41.8 (C12), 40.0 (CH2CH2CH3), 27.7 (C18), 18.3 (CH2CH2CH3), 18.0 (C17), 14.3 (CH2CH2CH3).

FTIR (thin film) cm⁻¹:
1713 (s), 1688 (s), 1478 (m), 1460 (m), 1447 (m), 1341 (s), 1172 (s), 719 (w).

HRMS (ESI) (m/z):
calc’d for C20H25N3NaO4S3 [M+Na]+: 538.0899, found 538.0923.

TLC (1% acetone in dichloromethane), Rf: 0.21 (UV, CAM).
Synthesis and Anticancer Activity of Epipolythiodiketopiperazine Alkaloids
Nicolas Boyer, Karen C. Morrison, Justin Kim, Paul J. Hergenrother, and Mohammad Movassaghi*

α-C3-Propyl epidithiodiketopiperazine 63:
Ethanolamine (500 μL) was added via syringe to a solution of dithiepanethione 67 (13.3 mg, 23.8 μmol, 1 equiv) in acetone (500 μL) at 23 °C. After 15 min, the reaction mixture was diluted with dichloromethane (30 mL) and aqueous hydrochloric acid solution (2 N, 30 mL). The organic layer was collected, and the aqueous layer was extracted with dichloromethane (2 × 5 mL). A solution of potassium triiodide in pyridine (2.5% w/v) was added dropwise to the combined organic layers until a persistent yellow color was observed. The resulting mixture was washed with aqueous hydrochloric acid (2 N, 30 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 30% ethyl acetate in dichloromethane) to afford epidithiodiketopiperazine 63 (9.6 mg, 78%) as a clear film.

1H NMR (500 MHz, CDCl₃, 20 ºC):
δ 7.83 (dd, J = 0.8, 8.2, 2H, SO₂Ph-o-H), 7.53 (t, J = 7.4, 1H, SO₂Ph-p-H), 7.51 (d, J = 7.9, 1H, C₈H), 7.40 (app-t, J = 8.1, 2H, SO₂Ph-m-H), 7.28–7.19 (m, 1H, C₇H), 7.13–7.05 (m, 1H, C₆H), 6.14 (s, 1H, C₁₂H), 3.57 (d, J = 14.9, 1H, C₁₁H), 2.89 (s, 3H, C₁₈H), 2.37 (d, J = 14.9, 1H, C₁₂H), 1.93 (s, 3H, C₁₇H), 1.38–1.14 (m, 2H, CH₂C₂H₂CH₃), 1.00–0.85 (m, 2H, CH₃CH₂CH₃), 0.70 (app-t, J = 7.2, 3H, CH₃CH₂CH₃).

13C NMR (125.8 MHz, CDCl₃, 20 ºC):
δ 165.7 (C₁₃), 162.9 (C₁₆), 139.3 (C₉), 139.1 (SO₂Ph-ipso-C), 137.4 (C₄), 133.7 (SO₂Ph-p-C), 129.3 (SO₂Ph-m-C), 129.3 (C₇), 127.7 (SO₂Ph-o-C), 126.1 (C₆), 124.5 (C₅), 118.1 (C₈), 84.3 (C₂), 74.6 (C₁), 73.9 (C₁₃), 56.4 (C₁₄), 40.5 (C₁₂), 39.7 (CH₂C₂H₂CH₃), 27.5 (C₁₉), 18.7 (C₁₇), 18.1 (CH₃CH₂CH₃), 14.2 (CH₃CH₂CH₃).

FTIR (thin film) cm⁻¹:
1694 (s), 1447 (m), 1366 (s), 1331 (m), 1172 (s), 722 (w).

HRMS (ESI) (m/z):

TLC (30% ethyl acetate in hexanes), Rf:
0.21 (UV, CAM).
Dimeric bis(triphenylmethanetrisulfide) 19:

Anhydrous hydrazine (0.8 μL, 25 μmol, 5.00 equiv) was added via syringe to a solution of dianinodithioisobutyrate (+)-S5 (6.6 mg, 5.0 μmol, 1 equiv) in tetrahydrofuran (2 mL) at 0 °C. After 18 min, triethylamine (17.5 μL, 126 μmol, 25.0 equiv) and solid chloro(triphenylmethyl)disulfane (17.2 mg, 50.3 μmol, 10.0 equiv) were sequentially added to the reaction mixture under an inert atmosphere. After 13 min, saturated aqueous ammonium chloride (3 mL) was added to the reaction mixture. The solution was then poured into a separatory funnel containing saturated aqueous ammonium chloride (10 mL) and dichloromethane (15 mL). The aqueous layer was extracted with dichloromethane (2 × 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 35% ethyl acetate in hexanes) to afford dimeric bis(triphenylmethanetrisulfide) (+)-19 (7.4 mg, 82%) as a slightly off-white solid.

¹H NMR (500 MHz, CDCl₃, 20 °C):

δ 8.04 (d, J = 7.5, 4H, SO₂Ph-o-H), 7.64 (t, J = 7.9, 4H, SO₂Ph-p-H), 7.22–7.12 (m, 2H, C₆H₃), 7.22–7.12 (m, 18H, C(C₆H₅)₃), 6.99–6.90 (m, 12H, C(C₆H₅)₃), 6.80 (s, 2H, C₂H), 6.65 (br-s, 2H, C₅H), 6.57 (app-t, J = 8.1, 2H, C₇H), 6.08 (app-t, J = 7.0, 2H, C₆H), 4.43 (d, J = 11.9, 2H, C₁₇H₂a), 4.23 (d, J = 11.7, 2H, C₁₇H₂b), 3.31 (d, J = 14.5, 2H, C₁₃H₂a), 2.92 (d, J = 14.4, 2H, C₁₂H₂b), 2.71 (s, 6H, C₁₈H), 2.54 (app-sp, J = 7.1, 2H, CH₃isobutyrate), 1.79 (s, 6H, CH₃acetate), 1.11 (d, J = 7.0, 6H, CH₃isobutyrate), 1.08 (d, J = 7.1, 6H, CH₃isobutyrate).

¹³C NMR (125.8 MHz, CDCl₃, 20 °C):

δ 174.1 (C=Oisobutyrate), 170.1 (C=Oacetate), 164.1 (C₁₃), 161.2 (C₁₆), 143.3 (C(C₆H₅)₃), 142.8 (C₉), 140.5 (SO₂Ph-ipso-C), 133.4 (SO₂Ph-p-C), 130.7 (C₄), 130.5 (C(C₆H₅)₃), 129.6 (SO₂Ph-m-C), 129.4 (C₉), 128.0 (C(C₆H₅)₃), 127.3 (C(C₆H₅)₃), 127.3 (SO₂Ph-o-C), 124.0 (C₅), 123.8 (C₆), 112.8 (C₇), 86.2 (C₁₅), 80.9 (C₂), 75.2 (C₁₁), 73.3 (C(C₆H₅)₃), 64.7 (C₁₇), 60.7 (C₃), 42.8 (C₁₂), 33.6 (CH₃isobutyrate), 28.7 (C₁₈), 21.4 (CH₃acetate), 18.8 (CH₃isobutyrate).

FTIR (thin film) cm⁻¹:

1749 (s), 1708 (s), 1480 (m), 1462 (m), 1447 (m), 1380 (s), 1220 (m), 1173 (s), 729 (m), 699 (m).
HRMS (ESI) (m/z): calc’d for C_{92}H_{88}N_{7}O_{16}S_{8} [M+NH_{4}]^{+}: 1802.4048, found 1802.4073.

[α]_{D}^{24}: + 287 (c 0.35, CHCl_{3}).

TLC (35% ethyl acetate in hexanes), R_f: 0.23 (UV, CAM).
Copies of $^1$H, $^{13}$C and $^{19}$F NMR Spectra.

(+)-S12
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(+)-12-deoxybionectin A (10)
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[Diagram of molecular structure]

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