

SULFANYLATION OF 1,3-DITHIANE ANIONS BY 5-(ALKYLSULFANYL)-1-PHENYLTETRAZOLES

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Dedicated to Dr. Alfred Bader on the occasion of his 85th birthday.

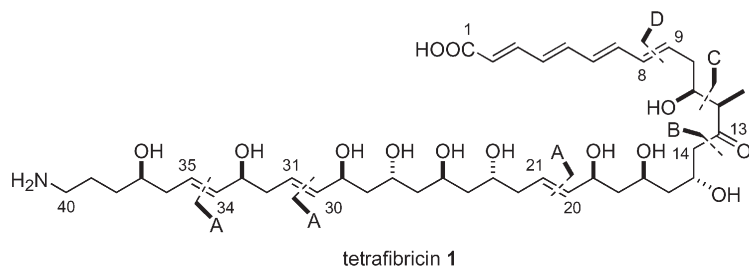
An unusual reaction between 1,3-dithiane anions and by 5-(alkylsulfanyl)-1-phenyltetrazoles has been discovered in which the dithiane anion formally displaces the 1-phenyltetrazole ring from sulfur to provide a sulfanylated dithiane.

Keywords: Tetrafibricin; Total synthesis; 1,3-Dithianes; 5-(Alkylsulfanyl)-1-phenyltetrazoles; Nucleophilic additions; Sulfanylations; Sulfur chemistry.

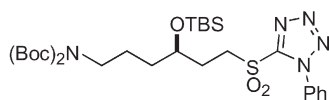
The natural product tetrafibricin **1** was isolated in 1993 by Kamayama and coworkers, and they assigned its two-dimensional constitution by a battery of spectroscopic methods¹. The compound has a linear carbon backbone featuring 11 stereocenters (10 with hydroxy groups and one with a methyl group), is a tetraene, with three isolated trans double bonds, and assorted other functional groups. In 2003, Kishi and coworkers assigned the three-dimensional structure (configuration) of **1** without resorting to derivatization or degradation by comparing NMR spectra of the natural product in both chiral and achiral solvents to an NMR database of fragment spectra². Roush³ and Cossy⁴ have described syntheses of fragments of **1**.

We have advanced a retrosynthetic strategy in Fig. 1 of the disassembled tetrafibricin **1** into six main fragments **2–7**. Though the synthesis has not yet been completed, all of the fragments have been made, and assorted couplings have been established⁵. Along the way to making the C21–C30 fragment **4**, we encountered an unusual reaction between a dithiane anion⁶ and a 5-(alkylsulfanyl)-1-phenyltetrazoles. Herein we describe this reaction, which, in the context of the tetrafibricin synthesis, proved to be a tempo-

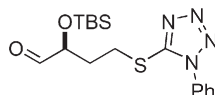
rary roadblock. We also describe a straightforward detour around this roadblock to complete the synthesis of a modified C21-C30 fragment.



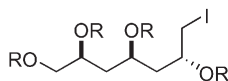
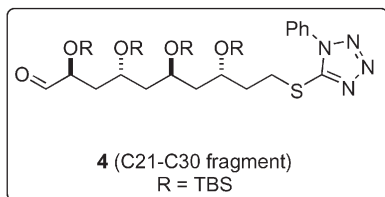
A = Kocienski-Julia olefination; **B** = Dithiane alkylation; **C** = Asymmetric aldol; **D** = HWE olefination



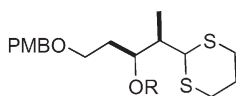
2 (C35-C40 fragment)



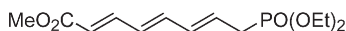
3 (C31-C34 fragment)



5 (C14-C20 fragment)
R = TBS



6 (C9-C13 fragment)



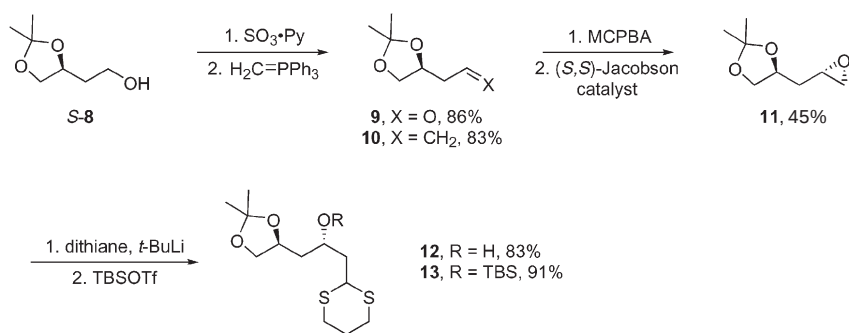
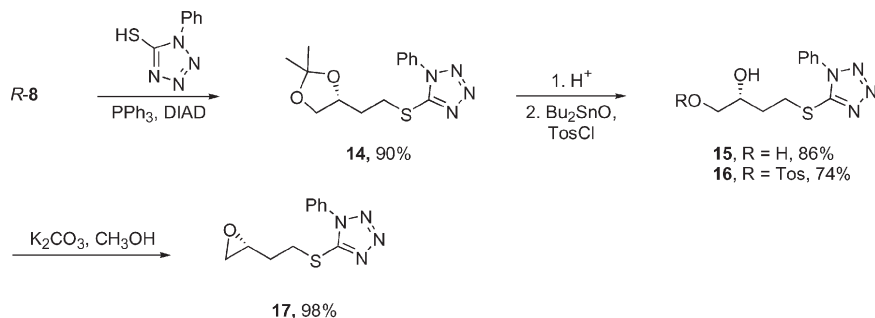
7 (C1-C8 fragment)

PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl

FIG. 1
Structure of tetrafibricin **1** and high level retrosynthetic analysis

RESULTS AND DISCUSSION

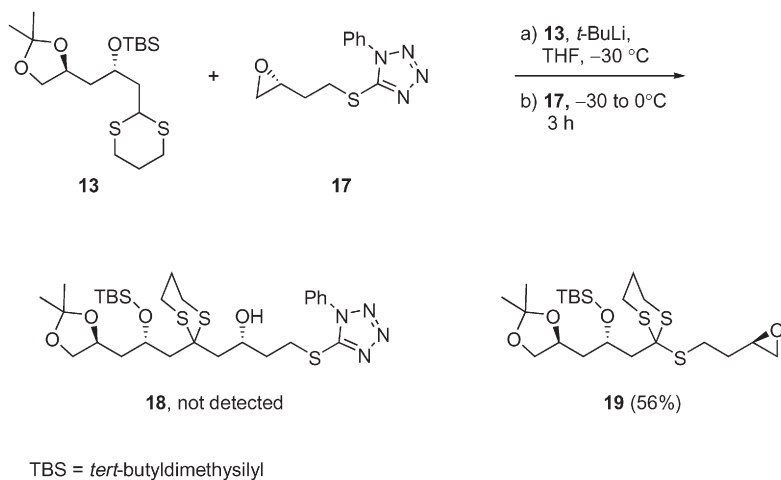
The two fragments **13** and **17** needed to make **4** were synthesized as shown in Scheme 1. Oxidation⁷ of commercially available dioxolane alcohol (*S*)-**8** to aldehyde **9** was followed by the Wittig reaction and non-selective epoxidation of the resulting alkene **10** to give a mixture of epoxide isomers. Hydrolytic kinetic resolution with the (*S,S*)-Jacobsen catalyst then gave **11** in 45% yield⁸. Dithiane opening of the epoxide **11** gave alcohol **12**, which was protected with *tert*-butyldimethylsilyltriflate (TBSOTf) to give **13**. Synthesis of **17** started from the enantiomer (*R*)-**8**. The alcohol was converted to a phenylthiotetrazole **14**, then the acetal was cleaved to give diol **15**. Standard mono-tosylation and base treatments of **16** provided epoxide **17**.

Synthesis of dithiane **13**Synthesis of epoxide **17**

TBS = *tert*-butyldimethylsilyl

SCHEME 1
Synthesis of the precursors **13** and **17** for dithiane alkylation

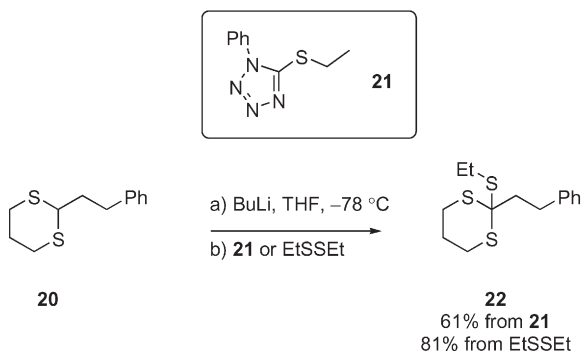
Treatment of dithiane **13** with *t*-BuLi in THF at -30 to -20 °C to generate the anion was followed by addition of epoxide **17** (Scheme 2). After warming to 0 °C and stirring for 3 h, TLC analysis showed that the starting materials were mostly consumed and a single new spot was evident. After standard workup and flash chromatography, the new product was isolated in 56% yield. It was clear from the initial NMR spectrum that the two fragments were united. However, it was also clear that the target product **18** was not formed because the resonances for the epoxide protons remained. A complete characterization by 1D and 2D NMR spectroscopy⁵ and mass spectrometry showed that the product was **19**, resulting from formal sulfanylation of the dithiane anion by **17**. The epoxide survives **17**, but the 1-phenyltetrazole is apparently displaced!



SCHEME 2
Sulfanylation of dithiane **13** by S-alkyl-N-phenylthioalkyltetrazole **17**

Central to the structure assignment was the high resolution MS spectrum of **19**, which showed the presence of three sulfur atoms (HRMS EI, 479.1780 corresponding to $[M^+ - \text{Me}]$ for $\text{C}_{21}\text{H}_{39}\text{O}_4\text{S}_3\text{Si}$). The connection of the sulfur of the starting phenylthiotetrazole to the carbon of the 1,3-dithiane was indicated by the MS fragmentation pattern as well as by features in the NMR spectra including the absence of a dithiane proton in the ^1H NMR spectrum and the absence of cross-peaks in HMBC spectrum between right and left sides of the molecule (due to insulation by the chain sulfur atom).

The unusual transformation of **13** and **17** to **19** presumably requires only a dithiane anion and a 5-(alkylsulfanyl)-1-phenyltetrazole. Accordingly, we generated the anion from 2-phenylethyldithiane **20** as usual and then added 5-(ethylsulfanyl)-1-phenyltetrazole (**21**) (Scheme 3). Standard work-up and purification provided the now expected product **22** in 61% yield. The same product **22** was also prepared by a standard sulfanylation of the anion of dithiane **20** with diethyldisulfide. These two samples of **22** were identical.



SCHEME 3
Simple model sulfanylations

The mechanism for this formal displacement of the phenyltetrazole ring by the dithiane anion is not clear; however, the economical $\text{S}_{\text{N}}2$ displacement mechanism at sulfur does not seem reasonable since tetrazole is not a leaving group and since the epoxide survives. We postulate that the transformation may be initiated by addition of the dithiane anion to the tetrazole ring. This could ultimately result in a role reversal with the thiolate anion emerging as a nucleophile and the dithiane attached to a leaving group. A highly speculative series of steps for this process is outlined in Fig. 2.

Though interesting, the observed reaction is a minor roadblock for the synthesis of the C21–C30 fragment of tetrafibricin. A detour was quickly put into place as shown in Scheme 4. Reaction of dithiane anion derived from **13** with 4-methoxybenzyl-protected epoxide **23** provided alkylated dithiane **24**. Cleavage of the dithiane, 1,3-anti-reduction of the resulting hydroxy ketone **25** and finally TBS protection of **26** provided protected pentaol **27** as a single isomer. The hydroxy groups of this pentaol are suit-

ably differentiated for further fragment coupling on either end of the molecule, and significant progress along these lines has been made⁵.

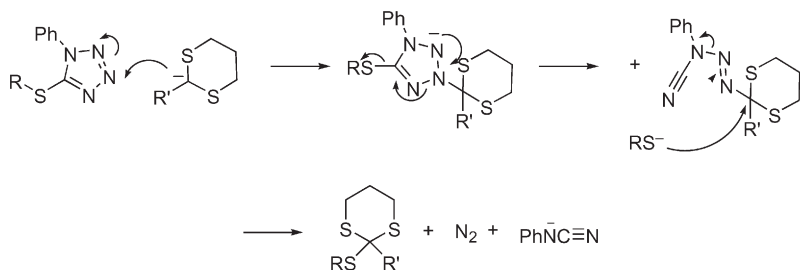
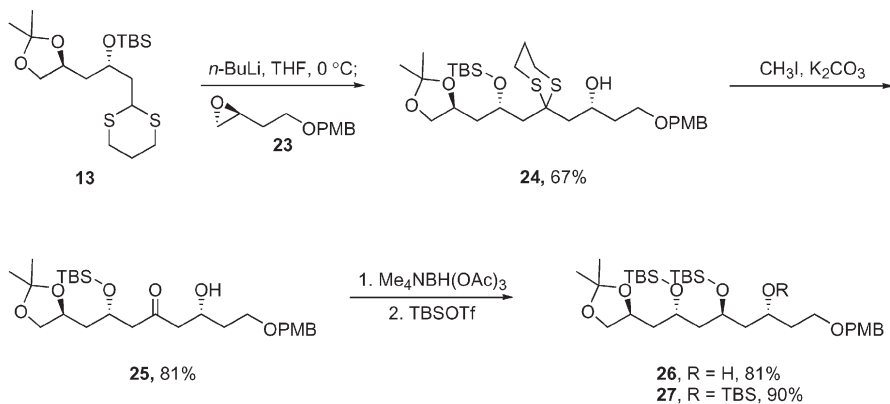


FIG. 2
A speculative mechanism for the sulfanylation



PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl

SCHEME 4
Synthesis of alternative C21-C30 fragment 27

CONCLUSIONS

An unusual reaction between dithiane anions and 5-(alkylsulfanyl)-1-phenyltetrazoles has been discovered. The dithiane anion formally displaces the tetrazole ring to provide a sulfanylated 1,3-dithiane. The mechanism of the process is not clear, though direct displacement at sulfur does not seem probable. Instead, addition of the dithiane anion to the tetrazole ring may initiate the transformation. While there are simpler ways to

sulfanylate 1,3-dithianes, the observed chemoselectivity of the new transformation (terminal epoxide survives unscathed) may render it interesting in some settings.

EXPERIMENTAL

General

Optical rotations were measured on a Perkin–Elmer 241 polarimeter at the Na D-line ($\lambda = 589$ nm) using a 1-dm cell at 20 °C. $[\alpha]_D$ values are given in $\text{deg cm}^2 \text{g}^{-1}$. IR spectra were recorded on a Mattson Genesis Series FTIR using thin film deposition on NaCl plates (wave-numbers in cm^{-1}). ^1H NMR spectra were measured on a Bruker Avance DPX 300 spectrometer (at 300 MHz) or on an Avance DRX 500 spectrometer (at 500 MHz) in CDCl_3 . ^{13}C NMR spectra were measured on a Bruker Avance DPX 300 spectrometer (at 75 MHz), or on an Avance DRX 500 spectrometer (at 125 MHz) in CDCl_3 . Chemical shifts are given in ppm (δ -scale) and were determined relative to the residual proton signal for CHCl_3 (7.27) and the carbon signal for CDCl_3 (77.09). Coupling constants (J) are given in Hz. High resolution mass spectra were obtained on a VG Autospec double focusing instrument and are reported in units of m/z . For column chromatography 230–400 mesh silica gel was used (Sorbent Technologies).

2-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]acetaldehyde (**9**)

Aldehyde **9** was obtained by oxidation of the commercially available 2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]ethan-1-ol ((S)-**8**) using the Parikh–Doering protocol^{7a} (pyr-SO_3 , DMSO) in 86% yield.

(4S)-4-Allyl-2,2-dimethyl-1,3-dioxolane (**10**)

To a solution of $\text{CH}_3\text{PPh}_3\text{Br}$ (15.8 g, 44.2 mmol) in THF (500 ml) at 0 °C, *n*-BuLi (1.6 M in hexane, 27.6 ml, 44.2 mmol) was added. The reaction mixture was stirred for 20 min followed by cooling to -78 °C. A solution of aldehyde **9** (4.9 g, 34 mmol) in THF (5 ml) was slowly added. After 30 min, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into saturated aqueous NH_4Cl (300 ml) and the aqueous layer was extracted with Et_2O (2×300 ml). The combined organic layers were dried over anhydrous MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (silica gel, 20% ethyl acetate in hexanes) afforded **10** (4.0 g, 83%) as a volatile oil. ^1H NMR (300 MHz, CDCl_3): 1.37 (s, 3 H), 1.43 (s, 3 H), 2.25–2.34 (m, 1 H), 2.37–2.48 (m, 1 H), 3.59 (dd, $J = 8.2, 7.1$, 1 H), 4.03 (dd, $J = 8.2, 6.0$, 1 H), 4.13–4.21 (m, 1 H), 5.07–5.17 (m, 2 H), 5.81 (ddt, $J = 17.0, 10.4, 7.1$, 1 H). ^{13}C NMR (75 MHz, CDCl_3): 25.7, 26.9, 38.1, 69.0, 75.2, 109.0, 117.7, 133.7.

(4S)-2,2-Dimethyl-[(2S)-epoxyprop-1-yl]-1,3-dioxolane (**11**)

MCPBA (5.82 g, 33.74 mmol) was added to a solution of the alkene **10** (4.0 g, 28.12 mmol) in dichloromethane (200 ml). The resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched by addition of saturated aqueous NaHCO_3 solution. The

layers were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous MgSO_4 , filtered, and concentrated under vacuum. Purification by column chromatography (30% EtOAc in hexanes) gave 4.35 g (98%) of epoxide as a ~1:1 mixture of epimers. This mixture was used directly in the next step.

Acetic acid (62 μl , 1.09 mmol) and (S,S)-Jacobson catalyst (164.7 mg, 0.27 mmol) were added to a solution of the above epoxide (4.30 g, 27.18 mmol) in THF (0.26 ml). The reaction mixture was cooled to 0 °C and water (0.27 ml, 14.95 mmol) was added in one portion. The mixture was warmed up to room temperature and stirred for 16 h. The volatile components were removed by vacuum transfer into a cooled (–78 °C) receiving flask. The recovered epoxide was further purified by flash column chromatography (30% EtOAc in hexanes) to obtain 1.95 g (45%) of the pure epoxide **11** as a colorless oil. ^1H NMR (500 MHz, CDCl_3): 1.31 (s, 3 H), 1.36 (s, 3 H), 1.49 (ddd, J = 13.8, 7.3, 5.5, 1 H), 1.91 (ddd, J = 14.2, 7.8, 4.1, 1 H), 2.45 (dd, J = 4.6, 2.3, 1 H), 2.75 (t, J = 4.6, 1 H), 2.97–3.00 (m, 1 H), 3.53 (t, J = 7.3, 1 H), 4.05 (dd, J = 7.8, 5.6, 1 H), 4.22–4.27 (m, 1 H). ^{13}C NMR (126 MHz, CDCl_3): 25.6, 26.9, 37.1, 47.1, 49.3, 69.3, 73.6, 108.9. IR (neat): 2987, 2942, 2872, 1454, 1371, 1060. HRMS for $\text{C}_7\text{H}_{11}\text{O}_3$ ($\text{M} - \text{CH}_3$) $^+$: calculated 143.0708, found 143.0706.

(2S)-1-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(1,3-dithian-2-yl)propan-2-ol (**12**)

t-BuLi (1.7 M in pentane, 5.3 ml, 9.0 mmol) was added to a solution of 1,3-dithiane (1.10 g, 9.04 mmol) in THF/HMPA (5 ml/0.3 ml) at –78 °C. After 30 min, a solution of **11** (1.3 g, 8.2 mmol) in THF (3 ml) and HMPA (1 ml) was added to the above reaction mixture. After 1 h at –78 °C, the reaction mixture was allowed to warm to 0 °C, followed by addition of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over MgSO_4 and concentrated. The crude product was purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to yield **12** (1.9 g, 83%) as an oil, $[\alpha]_D^{25} +6.75$ (c 0.80 CHCl_3). ^1H NMR (500 MHz, CDCl_3): 1.36 (s, 3 H), 1.42 (s, 3 H), 1.69–1.79 (m, 2 H), 1.84–1.99 (m, 3 H), 2.10–2.16 (m, 1 H), 2.67 (d, J = 5.0, 1 H), 2.82–2.95 (m, 4 H), 3.59 (t, J = 7.8, 1 H), 4.09 (dd, J = 8.2, 6.0, 1 H), 4.14–4.20 (m, 1 H), 4.27 (dd, J = 8.9, 5.3, 1 H), 4.31–4.36 (m, 1 H). ^{13}C NMR (126 MHz, CDCl_3): 25.6, 25.9, 26.9, 30.1, 30.3, 39.8, 42.8, 44.2, 66.1, 69.4, 73.4, 108.9. IR (neat): 3435, 2983, 2935, 2899, 1456, 1423, 1370. EIMS: (M^+) 278. HRMS for $\text{C}_{12}\text{H}_{22}\text{O}_3\text{S}_2$ (M^+): calculated 278.1010, found 278.1006.

2-[(2S)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]propyl]-1,3-dithiane (**13**)

To a solution of alcohol **12** (320 mg, 1.15 mmol) and 2,6-lutidine in CH_2Cl_2 at –78 °C, TBSOTf was added. The reaction mixture was stirred for 1.5 h, then poured into water (25 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over anhydrous MgSO_4 and concentrated. The crude product was purified by flash column chromatography to yield **13** (410 mg, 91%) as an oil, $[\alpha]_D^{25} -1.65$ (c 4.79 CHCl_3). ^1H NMR (500 MHz, CDCl_3): 0.07 (s, 3 H), 0.09 (s, 3 H), 0.87 (s, 9 H), 1.30 (s, 3 H), 1.36 (s, 3 H), 1.59 (ddd, J = 13.7, 8.2, 5.0, 1 H), 1.77 (ddd, J = 13.7, 7.8, 4.6, 1 H), 1.79–1.88 (m, 3 H), 2.05–2.11 (m, 1 H), 2.75–2.87 (m, 4 H), 3.44 (t, J = 7.8, 1 H), 3.99–4.09 (m, 3 H), 4.11–4.16 (m, 1 H), 4.13 (dtd, J = 10.5, 7.8, 5.0, 1 H).

^{13}C NMR (126 MHz, CDCl_3): -4.6, -4.4, 25.8, 25.9, 27.1, 30.3, 30.5, 41.4, 43.6, 43.9, 66.6, 69.9, 72.8, 77.3, 108.5.

5-((2-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]ethyl)sufanyl)-1-phenyl-1H-tetrazole (**14**)

Diisopropyl azodicarboxylate (2.80 g, 14.0 mmol) was added to a solution of (*R*)-**8** (1.2 g, 8.2 mmol), 1-phenyl-1H-tetrazole-5-thiol (2.60 g, 14.8 mmol) and triphenylphosphine (3.00 g, 11.5 mmol) in THF (20 ml) at 0 °C. The mixture was stirred at room temperature for 3 h, water (20 ml) was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) provided **14** (2.23 g, 7.29 mmol, 89%) as an oil, $[\alpha]_{\text{D}} +12.3$ (c 1.19 CHCl_3). ^1H NMR (500 MHz, CDCl_3): 1.90–2.09 (m, 2 H), 2.55 (br s, 1 H), 3.42–3.55 (m, 1 H), 3.56–3.68 (m, 2 H), 3.68–3.81 (m, 1 H), 3.85–4.13 (m, 2 H), 7.58 (br s, 5 H). ^{13}C NMR (126 MHz, CDCl_3): 29.8, 33.7, 66.4, 69.5, 124.0, 129.9, 130.4, 133.5, 155.1. IR (neat): 3384, 2936, 1644, 1596, 1499, 1462, 1388, 1318, 1280. EIMS: $(\text{M} + \text{H})^+$ 267. HRMS for $\text{C}_{10}\text{H}_{11}\text{N}_4\text{O}_1\text{S}$ ($\text{M} - \text{CH}_3\text{O}$) $^+$: calculated 235.0653, found 235.0658.

(2R)-4-[(1-Phenyl-1H-tetrazol-5-yl)sufanyl]butane-1,2-diol (**15**)

To a solution of **14** (600 mg, 1.96 mmol) in methanol (10 ml), a drop of acetyl chloride (estimated amount, 20 mg) was added. After 30 min, the reaction mixture was concentrated and the crude product was purified by flash column chromatography (80% ethyl acetate in hexanes) to provide the title compound (510 mg, 86 %) as a viscous oil, $[\alpha]_{\text{D}} +11$ (c 0.78 CHCl_3). ^1H NMR (500 MHz, CDCl_3): 1.90–2.09 (m, 2 H), 2.55 (br s, 1 H), 3.42–3.55 (m, 1 H), 3.56–3.68 (m, 2 H), 3.68–3.81 (m, 1 H), 3.85–4.13 (m, 2 H), 7.58 (br s, 5 H). ^{13}C NMR (126 MHz, CDCl_3): 29.8, 33.7, 66.4, 69.5, 124.0, 129.9, 130.4, 133.5, 155.1. IR (neat): 3384, 2936, 1644, 1596, 1499, 1462, 1388, 1318, 1280. EIMS: $(\text{M} + \text{H})^+$ 267. HRMS for $\text{C}_{10}\text{H}_{11}\text{N}_4\text{O}_1\text{S}$ ($\text{M} - \text{CH}_3\text{O}$) $^+$: calculated 235.0653, found 235.0658.

(2R)-2-Hydroxy-4-[(1-phenyl-1H-tetrazol-5-yl)sufanyl]butyl
4-Methylbenzene-1-sulfonate (**16**)

To a solution of **15** (290 mg, 1.28 mmol) in CH_2Cl_2 (10 ml), Bu_2SnO (64 mg, 0.26 mmol), tosyl chloride (244 mg, 1.28 mmol) and triethylamine (130 mg, 1.28 mmol) were added. The reaction mixture was stirred for 3 h followed by dilution with water (10 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over anhydrous MgSO_4 and concentrated. The crude product was purified by flash column chromatography (silica gel, ethyl acetate–hexanes 1:1) to yield the title compound (400 mg, 74%), $[\alpha]_{\text{D}} +10.0$ (c 0.74 CHCl_3). ^1H NMR (500 MHz, CDCl_3): 1.87–2.03 (m, 2 H), 2.39 (s, 3 H), 3.43–3.50 (m, 2 H), 3.92–4.03 (m, 4 H), 7.30 (d, $J = 8.2$, 2 H), 7.53 (s, 5 H), 7.75 (d, $J = 8.2$, 2 H). ^{13}C NMR (126 MHz, CDCl_3): 21.4, 29.2, 32.7, 66.9, 73.1, 123.6, 127.7, 129.7, 129.8, 130.1, 132.3, 133.3, 144.9, 154.4. IR (neat): 3400, 3060, 2946, 1597, 1499, 1387, 1357, 1243. HRMS for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_4\text{S}_2$: calculated 443.0824, found 443.0804.

5-((2-[(2R)-Oxiran-2-yl]ethyl)sulfanyl)-1-phenyl-1H-tetrazole (**17**)

To a solution of **16** (440 mg, 1.05 mmol) in CH₃OH–dichloromethane (9:1, 10 ml), K₂CO₃ (173 mg, 1.25 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, concentrated, then diluted with dichloromethane (10 ml) and water (10 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous MgSO₄ and concentrated to provide **17** (211 mg, 81%) as an oil, $[\alpha]_D^{+15.0}$ (c 1.13 CHCl₃). ¹H NMR (500 MHz, CDCl₃): 1.92 (td, *J* = 14.2, 6.9, 1 H), 2.21–2.29 (t, *J* = 4.6, 1 H), 2.52 (dd, *J* = 4.6, 2.7, 1 H), 2.74–2.78 (m, 1 H), 3.01–3.06 (m, 1 H), 3.45–3.54 (m, 2 H), 7.49–7.56 (m, 5 H). ¹³C NMR (126 MHz, CDCl₃): 29.8, 32.0, 46.8, 50.6, 123.7, 129.8, 130.1, 133.5, 153.9. IR (neat): 3056, 2991, 2924, 1596, 1500, 1461. HRMS (EI) for C₁₁H₁₂N₄O₁S: calculated 248.0732, found 248.0721.

2-[(2S)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]propyl]-2-((2-[(2R)-oxiran-2-yl]ethyl)sulfanyl)-1,3-dithiane (**19**)

t-BuLi (1.7 M in pentane, 0.14 ml, 0.24 mmol) was added to a solution of dithiane **13** in THF (0.8 ml) at –30 °C. After 30 min, epoxide **17** (58.9 mg, 0.284 mmol) in THF (0.2 ml) was added to the reaction mixture and stirred at –30 °C for additional 30 min. Then the mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched with saturated aqueous NH₄Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to yield **19** (66 mg, 56%) as a colorless oil, $[\alpha]_D^{+21.2}$ (c 1.72 CHCl₃). ¹H NMR (500 MHz, CDCl₃): 0.12 (s, 3 H), 0.16 (s, 3 H), 0.89 (s, 9 H), 1.33 (s, 3 H), 1.41 (s, 3 H), 1.61 (ddd, *J* = 13.7, 8.3, 4.6, 1 H), 1.81–1.87 (m, 3 H), 2.04–2.09 (m, 1 H), 2.23–2.29 (m, 3 H), 2.53 (dd, *J* = 5.0, 2.8, 1 H), 2.58–2.71 (m, 4 H), 2.78–2.80 (m, 1 H), 2.99–3.04 (m, 1 H), 3.14–3.35 (m, 2 H), 3.51–3.54 (m, 1 H), 4.06 (dd, *J* = 7.8, 5.5, 1 H), 4.17–4.23 (m, 1 H), 4.26–4.31 (m, 1 H). ¹³C NMR (126 MHz, CDCl₃): –4.2, –3.8, 18.1, 24.6, 25.9, 26.1, 27.1, 27.5, 27.8, 29.6, 31.9, 43.3, 47.2, 51.4, 52.0, 60.4, 67.2, 70.1, 73.2, 108.6. IR (neat): 2983, 2953, 2855, 1472, 1252. HRMS (EI) for C₂₁H₃₉O₄S₃Si (M – CH₃)⁺: calculated 479.1779, found 479.1780.

2-(Ethylsulfanyl)-2-phenethyl-1,3-dithiane (**22**)

BuLi (0.5 ml, 0.8 mmol) was added dropwise to a solution of dithiane⁹ **20** (179.2 mg, 0.8 mmol) in THF (10 ml) at –30 °C. The reaction mixture was stirred at this temperature for 1 h followed by addition of a solution of tetrazole¹⁰ **21** (164.8 mg, 0.8 mmol) in THF (2 ml). The reaction mixture was further stirred at –30 °C for 3 h and then quenched by the addition of saturated NH₄Cl solution. The mixture was diluted with ether and water, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under vacuum. Purification by flash column chromatography (silica gel, 5% EtOAc in hexanes) gave 205.4 mg of **22**. ¹H NMR (300 MHz, CDCl₃): 7.32–7.27 (m, 2 H), 7.23–7.18 (m, 3 H), 3.41–3.31 (m, 2 H), 3.00 (dd, *J* = 4.86, 12.48, 1 H), 3.00 (dd, *J* = 8.49, 8.59, 1 H), 2.70 (dd, *J* = 3.19, 4.49, 1 H), 2.66 (d, *J* = 3.70, 4.49, 1 H), 2.59 (q, *J* = 7.49, 2 H), 2.30 (dd, *J* = 4.62, 12.50, 1 H), 2.30 (dd, *J* = 8.38, 8.60, 1 H), 2.20–2.10 (m, 1 H), 1.95–1.80 (m, 1 H), 1.28 (t, *J* = 7.49, 3 H). ¹³C NMR (75 MHz, CDCl₃): 141.4, 128.5, 128.4, 126.0, 62.1, 44.7, 30.6, 27.4, 26.8, 25.0,

13.9. IR (neat): 2952, 2926, 1729, 1601, 1495, 1452, 1421, 1276. EIMS: $(M - SC_2H_5)^+$ 223. HRMS for $C_{12}H_{15}S_2$ ($M - SC_2H_5$)⁺ calculated 223.0615, found 223.0552.

Preparation of an Authentic Sample of **22**

BuLi (0.55 ml, 0.89 mmol) was added dropwise to a solution of dithiane **20** (200 mg, 0.89) in THF (5 ml) at -30°C . The resulting mixture was stirred at this temperature for 1 h followed by the addition of diethyl disulfide (0.20 ml, 0.89 mmol). The reaction mixture was stirred at -30°C for 3 h and then quenched by the addition of saturated NH_4Cl solution. The reaction mixture was diluted with ether, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by column chromatography (5% EtOAc in hexanes) to afford 205.4 mg (81%) of pure **22**. The spectroscopic data of this sample were identical to those of the product obtained by the reaction of dithiane **20** with tetrazole **21**.

(2R)-1-(2-[(2S)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-propyl]-1,3-dithian-2-yl)-4-[(4-methoxybenzyl)oxy]butan-2-ol (**24**)

To a solution of dithiane **13** (0.33 g, 0.84 mmol) in THF (1.2 ml) at 0°C , *n*-BuLi (1.6 M in hexane, 0.6 ml) was added. The reaction mixture was stirred at 0°C for 20 min, followed by cooling to -20°C . Then a solution of epoxide **23**¹¹ (0.18 g, 0.88 mmol) in THF (0.5 ml) was added. After 3 h at -10°C , the reaction was quenched with saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to yield **24** (340 mg, 67%) as a clear oil. 1H NMR (300 MHz, $CDCl_3$): 0.06 (s, 3 H), 0.12 (s, 3 H), 0.88 (s, 9 H), 1.34 (s, 3 H), 1.41 (s, 3 H), 1.52–1.80 (m, 3 H), 1.88–2.19 (m, 5 H), 2.20–2.39 (m, 2 H), 2.75–2.99 (m, 4 H), 3.51 (t, $J = 7.9$, 1 H), 3.57–3.63 (m, 3 H), 3.80 (s, 3 H), 4.06 (dd, $J = 13.5$, 7.7, 1 H), 4.12–4.23 (m, 3 H), 4.45 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): -4.2 , -3.7 , 14.3, 18.0, 24.7, 25.9, 26.0, 26.2, 26.7, 27.1, 37.7, 43.0, 46.7, 48.2, 51.2, 55.3, 60.4, 67.0, 67.5, 68.0, 70.1, 72.9, 73.3, 108.6, 113.8, 129.4, 130.4, 159.2. IR (neat): 3497, 2974, 2932, 2856, 1613, 1514, 1249, 1093. HRMS (EI) for $C_{30}H_{52}O_6S_2Si$ (M)⁺: calculated 600.2975, found 600.2955.

[(2S,6R)-2-(*tert*-Butyldimethylsilyl)oxy]-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-hydroxy-8-[(4-methoxybenzyl)oxy]octan-4-one (**25**)

To a solution of **24** (135 mg, 0.224 mmol) in acetonitrile and water (6:1, 3 ml), MeI (80 mg, 0.56 mmol) and K_2CO_3 (34 mg, 0.35 mmol) were added. The reaction mixture was stirred at 45°C for 6 h. The reaction mixture was diluted with Et_2O (5 ml), dried over anhydrous $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to yield **25** (93 mg, 81%) as an oil. 1H NMR (500 MHz, $CDCl_3$): 0.09 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.36 (s, 3 H), 1.42 (s, 3 H), 1.64 (ddd, $J = 13.8$, 8.3, 6.7, 1 H), 1.71–1.86 (m, 3 H), 2.60–2.68 (m, 4 H), 3.41 (d, $J = 3.2$, 1 H), 3.49 (t, $J = 7.8$, 1 H), 3.61–3.70 (m, 2 H), 3.83 (s, 3 H), 4.06 (dd, $J = 7.8$, 6.0, 1 H), 4.13–4.20 (m, 1 H), 4.25–4.31 (m, 1 H), 4.33–4.38 (m, 1 H), 4.47 (s, 2 H), 6.91 (d, $J = 8.7$, 2 H), 7.28 (d, $J = 8.7$, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): -4.7 , -4.5 , 18.0, 25.9, 27.1, 36.2, 41.6, 50.9, 52.0, 55.3, 66.2, 66.4, 67.6,

69.8, 72.7, 72.9, 108.8, 113.9, 129.3, 130.2, 159.3, 209.5. IR (neat): 3466, 2952, 2931, 1708, 1514, 1302, 1090, 777. HRMS (ES) for $C_{27}H_{46}NaO_7Si$ ($M + Na$)⁺: calculated 533.2911, found 533.2886.

(3*S*,5*S*,7*R*)-5,7-Bis[(*tert*-butyldimethylsilyl)oxy]-8-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[(4-methoxybenzyl)oxy]octan-3-ol (**26**)

To a solution of **25** (88 mg, 0.17 mmol) in acetonitrile (0.54 ml) at -25 °C, a solution of $(CH_3)_4NBH(OAc)_3$ (68 mg, 0.26 mmol) in acetic acid (0.1 ml) was added. The reaction mixture was stirred at that temperature for 48 h, quenched with aqueous sodium potassium tartarate (1.0 M, 0.8 ml), diluted with ethyl acetate and neutralized with sodium hydrogen carbonate. The aqueous layer was extracted with ethyl acetate; the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to yield the title compound (76 mg, 86%) as an oil. Crude **26** was taken to the next step without further purification. ¹H NMR (500 MHz, $CDCl_3$): 0.12 (s, 3 H), 0.14 (s, 3 H), 0.90 (s, 9 H), 1.34 (s, 3 H), 1.38 (s, 3 H), 1.50–1.62 (m, 3 H), 1.66–1.75 (m, 2 H), 1.78–1.92 (m, 3 H), 3.48 (t, $J = 8.0$, 1 H), 3.57 (brs, 1 H), 3.60–3.71 (m, 2 H), 3.80 (s, 3 H), 3.89 (brs, 1 H), 4.05 (dd, $J = 7.8$, 6.0, 1 H), 4.09–4.24 (m, 3 H), 4.26–4.34 (m, 1 H), 4.45 (s, 2 H), 6.87 (d, $J = 8.7$, 2 H), 7.24 (d, $J = 8.7$, 2 H). ¹³C NMR (76 MHz, $CDCl_3$): -4.8, -4.4, 18.0, 25.9, 27.1, 36.9, 40.4, 43.1, 43.9, 55.3, 66.0, 68.4, 68.8, 69.3, 69.9, 70.1, 72.8, 73.0, 108.9, 113.9, 129.3, 130.3, 159.4. IR (neat): 3449, 2984, 2934, 2857, 1613, 1514, 1249. HRMS (EI) for $C_{27}H_{48}NaO_7Si$ ($M + Na$)⁺: calculated 535.3067, found 535.3072.

(4*S*)-2,2-Dimethyl-4-[(2*S*,4*S*,6*R*)-2,4,6-tris[(*tert*-butyldimethylsilyl)oxy]-8-[(4-methoxybenzyl)oxy]octyl]-1,3-dioxolane (**27**)

To a solution of **26** (44.0 mg, 0.0858 mmol) in dichloromethane (5 ml) at 0 °C, TBSOTf (46.5 mg, 0.176 mmol) and 2,6-lutidine (54.3 mg, 0.506 mmol) were added. The reaction mixture was stirred at that temperature for 1 h followed by quenching with water. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude reaction mixture by flash column chromatography (silica gel, 10% ethyl acetate in hexanes) gave **27** (50 mg, 80%) as a clear oil. ¹H NMR (300 MHz, $CDCl_3$): 0.07 (s, 18 H), 0.88 (s, 18 H), 0.89 (s, 9 H), 1.33 (s, 3 H), 1.38 (s, 3 H), 1.48–1.87 (m, 8 H), 3.42–3.52 (m, 3 H), 3.75–3.84 (m, 4 H), 3.85–3.94 (m, 2 H), 4.00–4.04 (m, 1 H), 4.13–4.26 (m, 1 H), 4.41 (s, 2 H), 6.87 (d, $J = 8.8$, 2 H), 7.25 (d, $J = 7.7$, 2 H). ¹³C NMR (75 MHz, $CDCl_3$): -4.4, -4.2, -4.1, -3.7, -3.5, 18.1, 26.0, 27.2, 37.9, 41.3, 46.3, 47.3, 55.3, 66.7, 67.4, 67.5, 67.7, 70.0, 72.7, 108.6, 113.8, 129.3, 130.8, 159.1. IR (neat): 2953, 2857, 1511, 1250. HRMS (EI) for $C_{39}H_{76}NaO_7Si_3$ ($M + Na$)⁺: calculated 129.0552, found 129.0550.

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