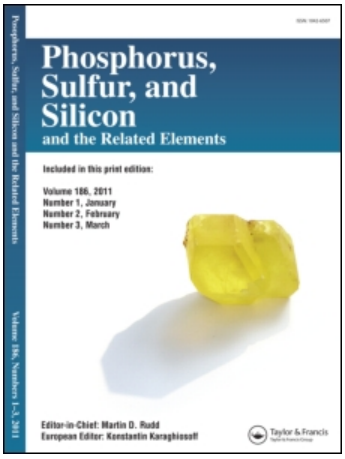

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SYNTHESIS OF 5-(7-HYDROXYHEPTYL)-1,2-DITHIOLAN-3-ONE 1-OXIDE, A CORE FUNCTIONALITY OF ANTIBIOTIC LEINAMYCIN

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5-(7-Hydroxyheptyl)-1,2-dithiolan-3-one 1-oxide was designed and synthesized in our laboratories that contain the heterocycle of 1,2-dithiolan-3-one 1-oxide, a reactive core of antibiotic leinamycin. In addition, the activated ester of 5-(7-hydroxyheptyl)-1,2-dithiolan-3-one 1-oxide was prepared, which presumably is useful for coupling this DNA-cleaving functionality to certain DNA-binding agents.

Keywords: Antibiotic; antitumor agents; heterocycle; leinamycin

Since the discovery of structural elucidation[1] and total synthesis[2] of the antibiotic leinamycin in 1990s, it has been demonstrated that this antibiotic exhibited potent activity against murine experimental tumor leukemia P388 and saccoma 180 as well as against Gram-positive bacteria.[3] Subsequent examination indicated that the latent DNA-cleaving activity of leinamycin is accountable for its cytotoxic properties.[4,5] Unlike any previously discovered natural products in molecular structure, on the other hand, leinamycin possesses the unique 1,2-dithiolan-3-one 1-oxide heterocycle as its reactive core.[6] In addition, certain mechanistic investigations revealed that the heterocycle of 1,2-dithiolan-3-one 1-oxide plays a crucial role in the thiol-activated DNA-cleaving processes in which free radicals are involved.[4–6] With the intention of further exploring the chemical and

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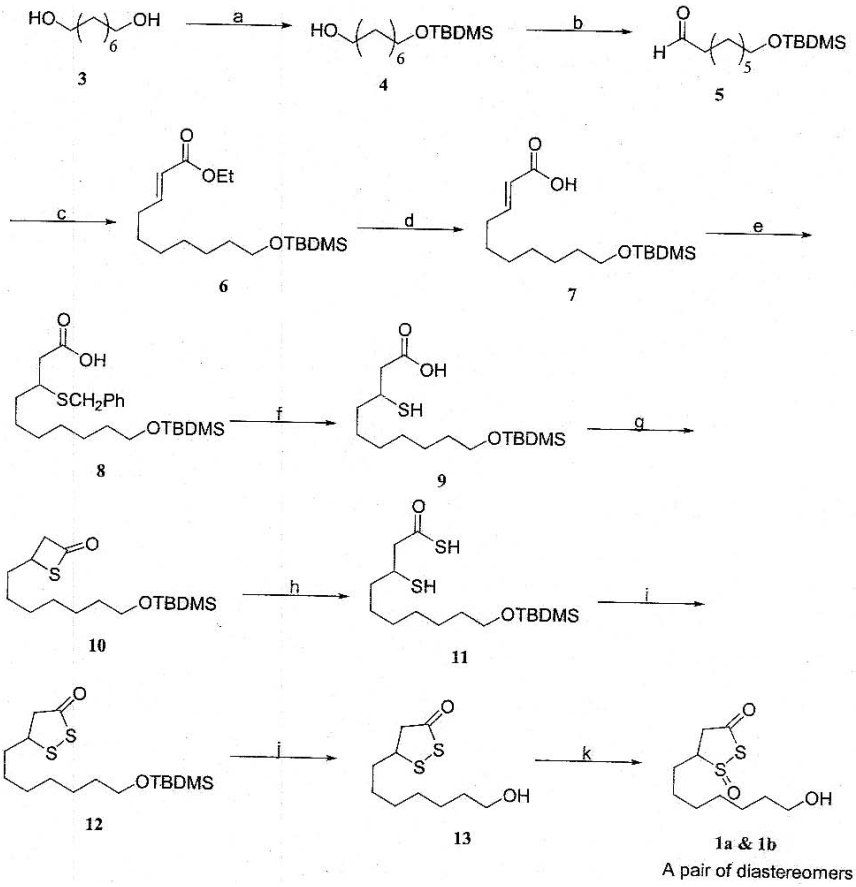
biological properties of leinamycin, we recently have designed and synthesized 5-(7-hydroxyheptyl)-1,2-dithiolan-3-one 1-oxide **1** in our laboratories that contains the heterocycle of 1,2-dithiolan-3-one 1-oxide in its structure, the reactive core of leinamycin.[6] In addition, the activated ester of 5-(7-hydroxyheptyl)-1,2-dithiolan-3-one 1-oxide **2** was prepared which presumably is useful for coupling this DNA-cleaving functionality to certain DNA-binding agents.[7,8] The synthesis of 5-(7-hydroxyheptyl)-1,2-dithiolan-3-one 1-oxide **1** as well as **2** is discussed in this article.

RESULTS AND DISCUSSION

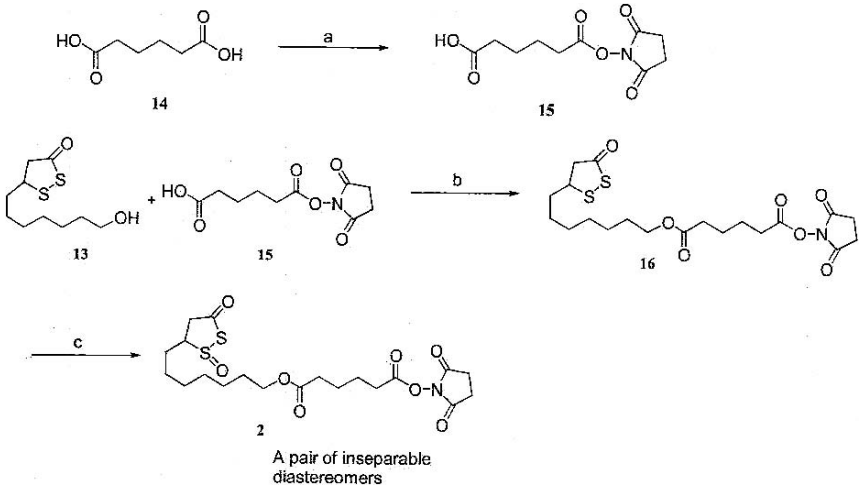
Scheme 1 depicts our synthetic route toward 5-(7-hydroxyheptyl)-1,2-dithiolan-3-one 1-oxide starting with a monosilylation reaction of octane-1,8-diol by using stoichiometric equivalent sodium hydride as base. The aldehyde **5** was obtained through an oxidation reaction of the alcohol **4** with PDC.[9] Olefination of **5** was carried out via an Horner-Emmons type reaction involving phosphonate anions.[10] Hydrolysis of **6** posed a challenge in our synthesis because this ester is exceptionally stable toward many commonly used hydrolytic reagents such as sodium hydroxide and potassium hydroxide/aqueous-ethanol. After several attempts, our hydrolysis of **6** was accomplished successfully by stirring this ester in KO*t*Bu/*t*BuOH. The yield of this reaction in our studies can even be optimized to 87% when LiOH/EtOH is used. Benzyl thioether **8** was obtained through a reaction of prop-2-enoic acid **7** with toluene-α-thiol in piperidine.[11] Since the mercapto acid **9** is too unstable to survive in many purification processes, Li/liquid ammonia[12] was employed to carry out this debenzylation reaction. Cyclization reaction of **9** in the solution of isobutyl chloroformate and triethylamine gave rise to the corresponding thiolactone **10**. The ring-opening reaction of thiolactone **10** afforded the corresponding mercapto thioic acid **11**, a process catalyzed by hydrogen sulfide.[11] Oxidative reaction of **11** with sodium iodate supported on neutral alumina in biphases circumstance and gave rise to the ring-closure product **12**.[13] Desilylation of **12** in hydrochloric acid/ethanol was used to produce the corresponding alcohol **13**. Finally, *m*CPBA was applied to accomplish the *S*-oxidation of 1,2-dithiolan-3-one moiety to afford the 1,2-dithiolan-3-one 1-oxide **1a** and **1b**, a pair of diastereomers separable through flash column chromatography.

In order to covalently linking the core functionality of leinamycin to certain DNA-binding agents for the future use, the activated ester **2** also was synthesized.[7,8] The linker **15** was prepared first through the



SCHEME 1 Synthesis of **1a** and **1b**: (a) TBDMSCl, NaH, THF, rt, 67%; (b) PDC, CH_2Cl_2, rt, 65%; (c) triethyl phosphonacetate, NaH, THF, −70°C to rt, 64%; (d) LiOH, EtOH, rt, 87%; (e) toluene-α-thiol, piperidine, reflux, overnight, 66%; (f) Li, NH_3(l), −78 to −60°C, then NH_4Cl(s) 98%; (g) isobutylchloroformate, Et_3N, CH_2Cl_2, −10 to 0°C, 56%; (h) H_2S(g), Et_3N, −40 to −30°C, then HCl (aq), rt; (i) $NaIO_3$-Al_2O_3, $CHCl_3$-hexane, rt, 40 min, 87%; (j) HCl (aq)-EtOH, rt, 30 min, 92%; (k) *m*CPBA, CH_2Cl_2, −50 to −40°C, 80%.

reaction of adipic acid and *N*-hydroxysuccinimide catalyzed by DMAP followed by the condensation[14] between 1,2-dithiolan-3-ones **13** and **15**. Subsequent oxidation of **16** by *m*CPBA afforded the desired product 1,2-dithiolan-3-one 1-oxides **2** comprising two inseparable diastereomers in 1:1 ratio (deduced from ^{1}H NMR and ^{1}H-^{1}H COSY NMR) with the chiral centers at 1′ and 3 positions (see Figure 1).



SCHEME 2 Synthesis of **2**: (a) NHS, DCC, cat. DMAP, THF, 0°C, 49%; (b) DCC, cat. DMAP, CH_2Cl_2, 0°C, 44%; (c) *m*CPBA, CH_2Cl_2, −50 to 40°C, 45%.

EXPERIMENTAL

All ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Advance DPX 400 FT-NMR Spectrometer or Varian Unity INOVA 500 FT-NMR Spectrometer. Low resolution mass spectra were obtained on Fisons VG Platform Mass Spectrometer, or Hewelett Packard G1800C GCD Series II GCMS. High resolution mass spectra (HRMS) were measured by Finnigan MAT95 Mass Spectrometer. All reactions were monitored by thin layer chromatography (TLC) performed on Merck precoated silica gel 60 F_{254} plates. Flash column chromatography was carried out on columns of NA or Merck Keisel silica gel 60 (230–400 mesh).

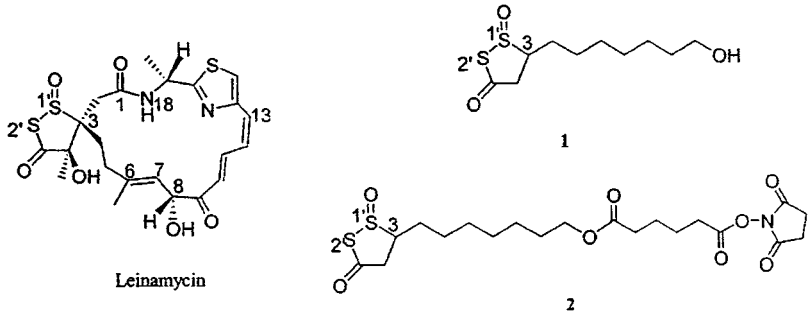


FIGURE 1 Structures of leinamycin and the newly designed core functionalities of the antibiotic.

THF and dichloromethane were distilled from Na/benzophenone and CaH_2, respectively, prior to use. Unless otherwise noted, materials and solvents were obtained from commercial suppliers and used without further purification.

8-*tert*-Butyldimethylsiloxy-*n*-octan-1-ol (4)

60% w/w sodium hydride (9.0 g, 0.226 mmol) was suspended in distilled THF (400 mL) followed by the addition of octane-1,8-diol **3** (29.70 g, 0.204 mmol) in THF (150 mL). The mixture was stirred at room temperature for 2 h at which time a large amount of opaque white precipitates were formed. After the addition of *tert*-butyldimethylsilyl chloride (34.0 g, 0.226 mmol) in THF (50 mL), the mixture was stirred vigorously at room temperature overnight. The reaction was quenched by the addition of ca 300 mL of saturated aqueous K_2CO_3 and extracted with diethyl ether (2 × 250 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, and concentrated in vacuo to afford **4** (35.60 g, 67%) as colorless syrup: ^{1}H NMR δ ($CDCl_3$) 0.04 (s, 6H), 0.89 (s, 9H), 1.34 (m, 6H), 1.54 (m, 6H), 3.59 (t, 2H, $J = 6.5$ Hz), 3.64 (t, 2H, $J = 6.5$ Hz); ^{13}C NMR δ ($CDCl_3$) −5.27, 18.37, 25.63, 25.66, 25.72, 25.97, 29.38, 32.76, 32.83, 63.06, 63.29; ESIMS m/z (%) 261 [$(M + 1)^+$, 8], 257 (12), 169 (6), 147 (100).

8-*tert*-Butyldimethylsiloxy-*n*-octan-l-al (5)

To a slurry mixture of PDC (61.0 g, 0.161 mmol) and activated molecular sieves (type 5A powder, 20 g) in distilled CH_2Cl_2 (150 mL) was added a solution of **4** (28.5 g, 0.108 mmol) in distilled CH_2Cl_2 (100 mL). The mixture was stirred vigorously at room temperature for 4 h. After the addition of diethyl ether (100 mL), the ethereal mixture was suction-filtered, and the filter-cake was washed with diethyl ether and EtOAc. After evaporation under vacuum, the residue was purified by flash column chromatography with hexane:EtOAc (15:1, v/v) as eluent to afford **5** (18.16 g, 65%) as a colorless syrup: ^{1}H NMR δ ($CDCl_3$) 0.04 (s, 6H), 0.89 (s, 9H), 1.31 (bs, 6H), 1.50 (bt, 2H, $J = 6.5$ Hz), 1.63 (bt, 2H, $J = 7.0$ Hz), 2.42 (td, 2H, $J = 7.5$, 2.0 Hz), 3.59 (t, 2H, $J = 6.5$ Hz), 9.76 (t, 1H, $J = 2.0$ Hz); ^{13}C NMR δ ($CDCl_3$) −5.34, 18.29, 21.96, 25.56, 25.91, 29.09, 32.70, 43.82, 63.10, 202.68; ESIMS m/z (%) 259 [$(M + 1)^+$ 100], 257 (31); HRESIMS found 259.2225, calculated for $C_{14}H_{31}O_2Si$ 259.2257.

10-*tert*-Butyldimethylsiloxy-dec-2-enoic Acid Ethyl Ester (6)

Triethyl phosphonoacetate (13.0 mL, 65.8 mmol) was added dropwise to 60% w/w NaH (5.26 g, 65.8 mmol) in distilled THF (250 mL) at room

temperature. The mixture was stirred at room temperature for 2 h at which time certain heat evolutions were observable. After the addition of **5** (17.0 g, 65.8 mmol) in distilled THF (150 mL), the mixture was heated at reflux for 1.5 h. After cooling the mixture to room temperature, solvent was removed under reduced pressure to yield a yellow syrup. The residue was dissolved in CH_2Cl_2, washed with water (30 mL), brine (40 mL), and dried over Na_2SO_4. After evaporation under vacuum, the crude product was purified by flash column chromatography with hexane:EtOAc (30:1, v/v) as eluent to afford **6** (13.8 g, 64%) as a slightly yellow oil: ^{1}H NMR δ ($CDCl_3$) 0.04 (s, 6H), 0.89 (s, 9H), 1.28 (t, 3H, $J = 7.0$ Hz), 1.30 (bs, 4H), 1.47 (m, 6H), 2.18 (m, 2H), 3.58 (t, 2H, $J = 7.0$ Hz), 4.17 (q, 2H, $J = 7.5$ Hz), 5.80 (dt, 1H, $J = 15.5$, 1.5 Hz), 6.95 (m, 1H); ^{13}C NMR δ ($CDCl_3$) −5.25, 14.30, 18.39, 25.71, 26.00, 27.98, 29.14, 29.20, 32.19, 32.83, 60.14, 63.26, 121.25, 149.46, 166.82; ESIMS m/z (%) 329 [$(M + 1)^+$, 100]; HRESIMS found 329.2418, calculated for $C_{18}H_{37}O_3Si$ 329.2384.

10-*tert*-Butyldimethylsiloxy-dec-2-enoic Acid (7)

To a solution of **6** (12.67 g, 38.56 mmol) in ethanol (70 mL) and water (2 mL) was added 56% w/w LiOH (9.70 g, 231.0 mmol) at room temperature. The mixture was stirred vigorously at the same temperature for 20 h followed by filtration of the mixture through a filter paper. The filter-cake was washed with an appropriate volume of EtOAc. After evaporation under vacuum, the residue was dissolved in water (30 mL) which was acidified to pH 4-5 by adding 10% aqueous HCl. The aqueous mixture was extracted with CH_2Cl_2 (3 × 90 mL). The organic phase was washed with brine (30 mL) and dried over Na_2SO_4. After evaporation under vacuum, the crude product was purified by flash column chromatography using hexane: EtOAc (10:1 → 5:1, v/v) as eluent to afford **7** (10.08 g, 87%) as a colorless oil which was readily formed a white crystal at room temperature: ^{1}H NMR δ ($CDCl_3$) 0.05 (s, 6H), 0.89 (s, 9H), 1.31 (bs, 5H), 1.48 (m, 5H), 2.22 (q, 2H, $J = 7.0$ Hz), 3.60 (t, 2H, $J = 7.0$ Hz), 5.83 (d, 1H, $J = 15.5$ Hz), 7.08 (quintet, 1H, $J = 7.0$ Hz); ^{13}C NMR δ ($CDCl_3$) −5.28, 18.36, 25.66, 25.97, 27.81, 29.10, 29.14, 32.28, 32.77, 63.23, 120.55, 152.40, 171.81; ESIMS m/z (%) 301 [$(M + 1)^+$, 100], 275 (5), 187 (7), 169 (7); HRESIMS found 300.2122, calculated for $C_{16}H_{32}O_3Si$ 300.2124.

3-Benzylsulfanyl-10-(*tert*-butyldimethysiloxy)decanoic Acid (8)

A mixture of **7** (8.15 g, 27.1 mmol), toluene-α-thiol (3.20 mL, 27.3 mmol) and piperidine (15 mL) was heated at reflux overnight. After cooling

the mixture in ice bath, 10% aqueous HCl was added to allow the pH of the solution to reach 2-3. The resultant white suspension was extracted with diethyl ether (3 × 100 mL) and the combined extracts were washed with brine (3 × 40 mL) and dried over Na_2SO_4. After evaporation under vacuum, the crude product was purified by flash column chromatography with hexane: EtOAc (10:1 → 3:1, v/v) as eluent to afford pure **8** (7.57 g, 66%) as a colorless oil: ^{1}H NMR δ ($CDCl_3$) 0.05 (s, 6H), 0.90 (s, 9H), 1.26 (m, 7H), 1.38 (m, 1H), 1.51 (m, 4H), 2.60 (m, 2H), 2.96 (quintet, 1H, $J = 6.0$ Hz), 3.59 (t, 2H $J = 6.5$ Hz), 3.76 (s, 2H), 7.23 (dt, 1H, $J = 7.0$ Hz), 7.32 (m, 4H); ^{13}C NMR δ ($CDCl_3$) −5.26, 18.37, 25.28, 25.61, 25.69, 25.97, 26.53, 29.03, 29.22, 29.24, 29.68, 32.54, 32.79, 34.62, 34.79, 35.54, 40.61, 41.13, 63.31, 127.01, 128.46,128.90, 138.21, 176.91; ESIMS m/z (%) 424 [$(M + 1)^+$, 31], 394 (16), 379 (11), 378 (68), 327 (28), 311 (28), 256 (12), 228 (19), 227 (100); HRESIMS found 424.2430, calculated for $C_{23}H_{40}O_3SSi$ 424.2457.

10-(*tert*-Butyldimethysiloxy)-3-mercaptodecanoic Acid (9)

A flask was equipped with a stirrer, calcium chloride drying tube, nitrogen inlet, dry ice condenser, and ammonia inlet. After the flask was flushed thoroughly with a stream of nitrogen, the ammonia was passed through and condensed into the flask followed by the addition of **8** (6.80 g, 16.0 mmol) in distilled THF (50 mL) at −78°C. Finely divided metal lithium was added to allow the deep blue color of the solution to persist. The mixture was stirred at −60 to −78°C for 1.5 h followed by the addition of adequate amount of solid NH_4Cl to quench the reaction. After passing N_2 through the white slurry mixture to remove the remaining ammonia at room temperature, the solid residue was dissolved in water (50 mL) which was acidified with 15% v/v aqueous HCl to allow its pH to reach 2-3. The aqueous mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics was washed with water (30 mL), brine (3 × 25 mL), and dried over Na_2SO_4. Evaporation of solvent under vacuum afforded **9** (5.26 g, 98%) as a white turbid syrup with foul smell. This compound was subjected to the next step reaction without purification (this mercaptan is readily oxidized by oxygen in air): ^{1}H NMR δ ($CDCl_3$) 0.05 (s, 6H), 0.89 (s, 9H), 1.31 (bs, 6H), 1.51 (m, 5H), 1.66 (m, 1H), 1.72 (d, 1H, $J = 7.5$ Hz), 2.57 (dd, 1H, $J = 16.0, 8.5$ Hz), 2.74 (dd, 1H, $J = 16.0, 5.0$ Hz), 3.19 (m, 1H), 3.60 (t, 2H, $J = 6.5$ Hz); ^{13}C NMR δ ($CDCl_3$); −5.27, 18.37, 25.60, 25.69, 25.97, 26.96, 29.01, 29.10, 29.23, 32.76, 36.13, 38.09, 44.05, 63.28, 176.82; ESIMS m/z (%) 333 (M^+, 19), 327 (18), 311 (21), 275 (22), 256 (61), 228 (49), 227 (32), 211 (31), 183 (52), 143 (63), 136 (100).

4-(7-*tert*-Butyldimethysiloxyheptyl)thietan-2-one (10)

To a solution of **9** (5.26 g, 15.7 mmol) and freshly distilled Et_3N (2.20 mL, 20.4 mmol) in CH_2Cl_2 (40 mL) was added isobutyl chloroformate (2.30 mL, 17.3 mmol) at −10°C. The mixture was stirred for 30 min at which time its temperature was allowed to warm up to reach 0°C. It was diluted with CH_2Cl_2 (25 mL) and washed successively with cold 15% aqueous HCl (3 × 15 mL), diluted Na_2CO_3 aqueous solution (20 mL) and brine (20 mL). The combined organics were dried over Na_2SO_4. After evaporation under vacuum the residue was purified by flash column chromatography with hexane: EtOAc (20:1, v/v) as eluent to yield **10** (2.74 g, 56%) as a colorless syrup: ^{1}H NMR δ (C_6D_6) 0.07 (s, 6H), 0.98 (s, 9H), 1.03 (m, 2H), 1.05 (m, 2H), 1.12 (m, 2H), 1.28 (m, 4H), 1.49 (quintet, 2H, $J = 6.5$ Hz), 2.77 (m, 1H), 2.87 (dd, 1H, $J = 17.5, 3.5$ Hz), 3.31 (dd, 1H, $J = 17.0, 7.0$ Hz), 3.56 (t, 2H, $J = 6.0$ Hz); ^{13}C NMR δ (C_6D_6) −4.44, 19.20, 26.85, 29.49, 29.99, 30.19, 33.67, 33.88, 38.53, 61.61, 63.89, 189.58; ESIMS m/z (%) 318 [$(M + 1)^+$, 16], 317 (M^+, 100), 301 (8); HRESIMS found 316.1756, calculated for $C_{16}H_{32}O_2SSi$ 316.1742.

10-(*tert*-Butyldimethysiloxyheptyl)-3-mercaptodecanethioic Acid (11)

A solution of **10** (2.08 g, 6.58 mmol) in CCl_4 (12 mL) chilled at −30 to −40°C was saturated with hydrogen sulfide gas. The mixture was stirred at the same temperature for 20 min followed by the addition of freshly distilled Et_3N (1.07 mL, 9.87 mmol). The resultant solution was saturated with H_2S gas for 7 h followed by the introduction of N_2 to expel the remaining H_2S gas at 0°C. The mixture was diluted with $CHCl_3$ (20 mL) and washed with water (2 × 10 mL). The aqueous mixture was acidified with 10% aqueous HCl to allow its pH to reach 1-2. The organic phase was washed with brine (2 × 10 mL) and dried over Na_2SO_4. Evaporation of solvent under reduced pressure to afford **11** as a yellow oil with foul odor which was subjected to the oxidative coupling reaction in the next step without further purification (this thioic acid is not stable enough for further characterization): ^{1}H NMR δ ($CDCl_3$) 0.05 (s, 6H), 0.91 (s, 9H), 0.98 (bs, 2H), 1.40 (m, 4H), 1.43 (m, 6H), 2.67 (dd, 1H, $J = 16.0, 9.0$ Hz), 3.00 (dd, 1H, $J = 16.0, 5.5$ Hz), 3.60 (t, 2H, $J = 14.5$ Hz), 3.65 (m, 1H), 3.70 (m, 1H).

5-(7-*tert*-Butyldimethysiloxyheptyl)-1,2-dithiolan-3-one (12)

To a solution of **11** (2.33 g, 6.58 mmol) in the mixture of hexane: $CHCl_3$ (24 mL: 2 mL) was added $NaIO_3/Al_2O_3$-$NaIO_3$ (14.2 g). The mixture

was stirred at room temperature for 40 min followed by filtration. The filter-cake was washed with appropriate volume of CH_2Cl_2. The filtrate was concentrated in vacuo. The resultant residue was purified by flash column chromatography with hexane: EtOAc (15:1, v/v) as eluent to afford **12** (2.01 g, 87%) as a slightly yellow oil: ^{1}H NMR δ ($CDCl_3$) 0.04 (s, 6H), 0.89 (s, 9H), 1.32 (bs, 6H), 1.49 (m, 4H), 1.78 (m, 2H), 2.67 (dd, 1H, $J = 16.0$, 8.5 Hz), 3.00 (dd, 1H, $J = 16.5$, 5.5 Hz), 3.60 (t, 2H, $J = 7.0$ Hz), 3.70 (m, 1H); ^{13}C NMR δ ($CDCl_3$) −5.29, 18.34, 25.65, 25.95, 27.77, 29.12, 32.73, 32.86, 49.20, 49.25, 63.15, 206.47; ESIMS m/z (%) 349 [$(M + 1)^+$, 19], 317 (33), 301 (7), 256 (11), 236 (11), 235 (100), 217 (22); HRESIMS found 348.1588, calculated for $C_{16}H_{32}O_2S_2Si$ 348.1605.

5-(7-Hydroxyheptyl)-1,2-dithiolan-3-one (13)

To a solution of **12** (1.462 g, 4.201 mmol) in EtOH (20 mL) was added aqueous HCl (15%, 0.9 mL). The mixture was stirred at room temperature for 40 min followed by the addition of Et_3N (0.5 mL). The organic phase was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL), washed with water (20 mL), brine (20 mL), and dried over Na_2SO_4. After evaporation under vacuum, the crude product was purified by flash column chromatography with hexane: EtOAc (5:1, v/v) to yield **13** (0.906 g, 92%) as a yellow syrup: ^{1}H NMR δ (C_6D_6) 0.92 (m, 3H), 1.01 (m, 4H), 1.18 (m, 3H), 1.35 (quintet, 2H, $J = 7.5$ Hz), 1.97 (dd, 2H, $J = 16.5$, 8.5 Hz), 2.25 (dd, 1H, $J = 16.5$, 5.5 Hz), 2.83 (m, 1H), 3.35 (t, 2H, $J = 7.0$ Hz); ^{13}C NMR δ (C_6D_6) 25.98, 27.83, 29.29, 29.40, 32.72, 33.01, 48.80, 49.02, 62.56, 205.44; ESIMS m/z (%) 234. (M^+, 100), 217 (24); HRESIMS found 234.0747, calculated for $C_{10}H_{18}O_2S_2$ 234.0746.

5-(7-Hydroxyheptyl)-1,2-dithiolan-3-one 1-Oxide (1)

To a solution of **13** (0.521 g, 2.22 mmol) in distilled CH_2Cl_2 (15 mL) was added a solution of 70–75% *m*CPBA (1.410 g, 5.55 mmol) in distilled CH_2Cl_2 (10 mL). The mixture was stirred at −40 to −50°C for 30 min. After warming up the mixture to 0°C, saturated sodium sulfite solution was added followed by the extraction of the aqueous suspension with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated sodium sulfite aqueous solution (20 mL), water (20 mL), brine (20 mL), and dried over Na_2SO_4. After evaporation under vacuum, the crude product was purified by flash column chromatography with hexane: EtOAc (5:1 → 1:2, v/v) as eluent to afford two diastereomers **1a** and **1b, 1a** (0.220 g, 39%, a colorless oil): ^{1}H NMR δ (C_6D_6) 0.827 (m, 1H), 1.01 (m, 2H), 1.11 (m, 4H), 1.21 (quintet, 2H, $J = 7.0$ Hz), 1.43 (m, 3H), 2.18 (dd, 1H, $J = 20.0$, 5.0 Hz), 2.24 (m, 1H), 2.72 (dd, 1H, $J = 16.5$,

12.0 Hz), 3.40 (t, 2H, $J = 6.2$ Hz); ^{13}C NMR δ (C_6D_6) 25.89, 26.62, 28.03, 29.19, 29.37, 32.89, 41.82, 62.52, 64.37, 200.25; ESIMS m/z (%) 251 [$(M + 1)^+$, 100], 233 (38), 65 (35); HRESIMS found 251.0959, calculated for $C_{10}H_{19}O_3S_2$ 251.0944. **1b** (0.231 g, 41%, a colorless oil): ^{1}H NMR δ (C_6D_6) 0.64 (m, 1H), 0.77 (m, 4H), 0.98 (m, 3H), 1.17 (m, 2H), 1.39 (quintet, 2H, $J = 5.0$ Hz), 2.19 (dd, 1H, $J = 17.0$, 1.0 Hz), 2.69 (q, 1H, $J = 6.0$ Hz), 3.20 (dd, 1H, $J = 17.5$, 6.5 Hz), 3.40 (t, 2H, $J = 6.0$ Hz); ^{13}C NMR δ (C_6D_6) 25.90, 27.16, 28.81, 29.18, 32.87, 42.27, 62.50, 66.82, 201.44; ESIMS m/z (%) 251 [$(M + 1)^+$, 100], 233 (41), 65 (55);HRESIMS found 251.0986, calculated for $C_{10}H_{19}O_3S_2$ 251.0944.

Hexanedioic Acid Mono-(2,5-dioxo-pyrrolidin-1-yl)Ester (15)

To a solution of adipic acid **14** (5.02 g, 34.1 mmol) and *N*-hydroxysuccinimide (4.05 g, 40.9 mmol) in distilled THF (60 mL) was added *N*,*N*′-dicyclohexylcarbodiimide (7.22 g, 34.9 mmol) in distilled THF (20 mL) at 0°C. The mixture was stirred at the same temperature for 15 min followed by the addition of a catalytic amount of DMAP (~30 mg) in one portion. The mixture was stirred overnight at which time it was allowed to warm up to room temperature. After filtration of the resultant DHU, the filtrate was concentrated by rotavaporation. The residue was redissolved in CH_2Cl_2 (50 mL), washed with water (2 × 20 mL), brine (20 mL) and dried over Na_2SO_4. After evaporation under vacuum, the residue was purified by flash column chromatography with hexane: EtOAc: CH_2Cl_2 (10:10:1, v/v/v) as eluent to afford **15** (3.83 g, 49%) as a white crystal: ^{1}H NMR δ ($CDCl_3$) 1.79 (m, 4H), 2.42 (t, 2H, $J = 7.0$ Hz), 2.65 (t, 2H, $J = 7.0$ Hz), 2.84 (bd, 4H, $J = 4.5$ Hz), ^{13}C NMR δ ($CDCl_3$) 23.88, 24.09, 25.80, 30.81, 33.58, 168.50, 169.53, 179.23; ESIMS m/z (%) 244 [$(M + 1)^+$, 38], 226 (11), 225 (100), 111 (9), 91 (14); HRESIMS found 243.1318, calculated for $C_{10}H_{13}NO_6$ 243.1294.

Hexanedioic Acid 2,5-dioxo-pyrrolidin-1-yl Ester 7-heptyl-[5-(1,2-dithiolan-3-one)] Ester (16)

To a solution of **15** (0.301 g, 1.239 mmol) and **13** (0.264 g, 1.130 mmol) in distilled CH_2Cl_2 (6 mL) was added *N*,*N*′-dicyclohexylcarbodiimide (0.260 g, 1.241 mmol) in distilled CH_2Cl_2 (2 mL) at 0°C. The mixture was stirred at the same temperature for 10 min followed by the addition of a catalytic amount of DMAP (~15 mg). After 3 h at room temperature, the resultant DHU was filtered off. The filter-cake was washed with CH_2Cl_2. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography with hexane: EtOAc (5:1, v/v)

as eluent to afford **16** (0.223 g, 44%) as a white semi solid: ^{1}H NMR δ (C_6D_6) 0.91 (m, 3H), 1.03 (m, 2H), 1.13 (m, 2H), 1.24 (m, 1H), 1.43 (m, 6H), 1.56 (bs, 2H), 1.71 (bs, 2H), 2.00 (t, 2H, $J = 8.5$ Hz), 2.04 (dd, 1H, $J = 16.0$, 6.5 Hz), 2.08 (t, 2H, $J = 7.0$ Hz), 2.31 (dd, 1H, $J = 16.0$, 5.5 Hz), 2.89 (m, 1H), 4.00 (t, 2H, $J = 7.0$ Hz); ^{13}C NMR δ (C_6D_6) 24.01, 24.08, 25.16, 25.92, 27.69, 28.84, 29.05, 30.46, 32.59, 33.55, 48.68, 48.89, 64.11, 168.68, 169.78, 172.40, 205.21; ESIMS m/z (%) 460 [$(M + 1)^+$, 24], 449 (44), 349 (9), 345 (21), 225 (100); HRESIMS found 459.1861, calculated for $C_{20}H_{29}NO_7S_2$ 459.1857.

Hexanedioic Acid 2,5-dioxo-pyrrolidin-l-yl Ester 7-heptyl-[5-(1,2-dithiolan-3-one 1-oxo)] Ester (2)

To a solution of **16** (0.188 g, 0.409 mmol) in distilled CH_2Cl_2 (20 mL) was added 70 to 75% *m*CPBA (0.250 g, 1.024 mmol) in distilled CH_2Cl_2 (4 mL). The mixture was stirred at -40 to -50°C for 45 min. Upon raising temperature to 0°C, saturated sodium sulfite aqueous solution was added followed by the extraction of the aqueous suspension with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with saturated sodium, sulfite aqueous solution (3 × 10 mL), water (20 mL), brine (20 mL), and dried over Na_2SO_4. After evaporation under vacuum, the crude product was purified by flash column chromatography with hexane: EtOAc (5:1→1:1, v/v) as eluent to afford **2** (two inseparable diastereomers* in 1:1 ratio, 0.090 g, 45%) as a colorless oil: ^{1}H NMR δ (C_6D_6) 0.83 (m, 2H), 0.96 (m, 2H), 1.04 (m, 3H), 1.15 (m, 3H), 1.44 (m, 6H), 1.55 (bs, 2H), 1.69 (bs, 2H), 2.01 (t, 2H, $J = 7.0$), 2.07 (t, 2H, $J = 7.0$ Hz), 2.22 (dd, 1H, $J = 19.5$, 2.5 Hz), 2.31 (m, 0.5 H)*, 2.75 (dd, 1H, $J = 16.5$, 12.5 Hz), 3.20 (m, 0.5 H)*, 4.01 (t, 2H, $J = 7.0$ Hz); ^{13}C NMR δ (C_6D_6) 24.12, 24.20, 25.27, 25.99, 26.65, 27.16, 28.05, 28.81, 28.94, 28.99, 29.10, 29.29, 30.56, 33.68, 41.88, 42.31, 64.15, 64.33, 66.89, 168.79, 168.88, 172.50, 200.27; ESIMS m/z (%) 476 (M^+, 29), 450 (9), 449 (35), 361 (21), 226 (12), 225 (100), 65 (21); HRESIMS found 476.1444, calculated for $C_{20}H_{29}NO_8S_2$ 476.1475.

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