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Synthesis of the Bis-spiroacetal $C_{25}-C_{40}$ Moiety of the Antimitotic Agent Spirastrellolide B using a Bis-dithiane Deprotection / Spiroacetalisation Sequence

Jack Li-Yang Chen and Margaret A. Brimble*

Department of Chemistry, University of Auckland, 23 Symonds Street, Auckland, New Zealand. E-mail: m.brimble@auckland.ac.nz

General Experimental Details

Thin-layer chromatography (TLC) was carried out using E. Merck silica gel plates using UV light as the visualising agent and/or developed using an ethanolic solution of vanillin or ammonium molybdate and cerium sulfate in aqueous sulfuric acid. Optical rotations were measured with a Perkin Elmer 341 polarimeter, using the sodium-D line (589 nm), with the concentration of the solution measured in grams per 100 mL. Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum 1000 FT-IR spectrometer with the absorption peaks expressed in wavenumbers (cm⁻¹) and recorded using a range of 450 to 4000 cm⁻¹. NMR spectra were recorded in CDCl₃ or C₆D₆ on either a Bruker BRX300 spectrometer operating at 300 MHz for ¹H nuclei and 75 MHz for ¹³C nuclei or a Bruker DRX400 spectrometer operating at 400 MHz for ¹H nuclei and 100 MHz for ¹³C nuclei. Chemical shifts are reported as parts per million (ppm) from tetramethylsilane ($\delta = 0$) and were measured relative to the solvent in which the sample was analysed (CDCl₃: δ 7.26 for ¹H NMR, δ 77.0 for ¹³C NMR and C_6D_6 : $\delta 7.15$ for ¹H NMR, $\delta 128.8$ for ¹³C NMR) and coupling constants (*J*) are reported in hertz (Hz) to the nearest 0.1 ppm. ¹H NMR data is reported as chemical shift in ppm, followed by relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad) and coupling constants where applicable. High resolution mass spectra were recorded using a VG70-SE spectrometer or on a micrOTOF-Q mass spectrometer.

Characterisation Data

(S)-2-(4-(tert-Butyldimethylsilyloxy)butan-2-yl)-1,3-dithiane (10)

R_f (hexanes/EtOAc 3:1) = 0.56; [α]_D¹⁸ –1.7 (c 1.57 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2954, 2929, 2895, 2856, 1471, 1462, 1255, 1095, 835, 774; ¹**H NMR** (300 MHz, CDCl₃): δ_{H} 4.15 (1H, d, J = 4.0 Hz), 3.70–3.56 (2H, m, 4-H), 2.93–2.77 (4H, m), 2.14–2.00 (2H, m), 1.90–1.73 (2H, m), 1.49 (1H, ddt, J = 13.7, 8.4, 5.7 Hz), 1.06 (3H, d, J = 7.0 Hz), 0.86 (9H, s), 0.05 (3H, s), 0.05 (3H, s); ¹³**C NMR** (75 MHz, CDCl₃): δ_{C} 61.0, 55.6, 36.8, 35.1, 31.1, 30.8, 26.4, 25.9, 18.3, 16.9, –5.3; **HRMS** Found (EI): M⁺ 306.1505, C₁₄H₃₀OS₂Si requires 306.1507.

(2S,3S)-1,2-Epoxy-3-(ethoxymethoxy)-5-(4-methoxybenzyloxy)pentane (8)

R_f (hexanes/EtOAc 3:1) = 0.24; [α]_D¹⁹ –37.3 (c 0.64 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2975, 2929, 2869, 1612, 1513, 1246, 1173, 1094, 1028, 846, 816; ¹**H NMR** (300 MHz, CDCl₃): δ_{H} 7.24 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 8.6 Hz), 4.86 (1H, d, J = 6.8 Hz), 4.72 (1H, d, J = 6.8 Hz), 4.64 (1H, d, J = 11.6 Hz), 4.40 (1H, d, J = 11.6 Hz), 3.80 (3H, s), 3.66–3.54 (4H, m), 3.49 (1H, q, J = 6.7 Hz), 3.00 (1H, ddd, J = 6.7, 4.3, 2.8 Hz), 2.73 (1H, dd, J = 4.8, 4.3 Hz), 2.52 (1H, dd, J = 4.8, 2.8 Hz), 1.91–1.84 (2H, m), 1.20 (3H, t, J = 7.1 Hz); ¹³**C NMR** (75 MHz, CDCl₃): δ_{C} 159.2, 130.3, 129.2, 113.7, 94.3, 75.3, 72.7, 65.9, 63.5, 55.2, 54.6, 43.7, 32.5, 15.0; **HRMS** Found (ESI): (M + Na)⁺, 319.1524, C₁₆H₂₄NaO₅ requires 319.1516.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-(2-((2'*S*,3'*S*)-3'-(ethoxymethoxy)-2'-hydroxy-5'-(4-methoxybenzyloxy)-pentan-1'-yl)-1,3-dithian-2-yl)butane (11)

R_f (hexanes/EtOAc 3:1) = 0.19; [α]_D¹⁸ –22.5 (c 0.40 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2961, 2927, 2900, 2864, 1611, 1513, 1463, 1383, 1247, 1087, 1030, 905, 832, 774, 619; ¹**H NMR** (300 MHz, CDCl₃): δ_{H} 7.26 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 8.6 Hz), 4.73 (1H, d, J = 7.0 Hz), 4.70 (1H, d, J = 7.0 Hz), 4.44 (2H, s), 4.17–4.11 (1H, m), 3.80 (3H, s), 3.76–3.51 (7H, m), 3.32 (1H, d, J = 3.9 Hz), 2.94–2.71 (4H, m), 2.40 (1H, dqd, J = 10.4, 6.7, 2.0 Hz), 2.29–2.18 (1H, m), 2.17–1.99 (3H, m), 1.97–1.88 (2H, m), 1.81 (1H, dddd, J = 14.1, 7.9, 5.7, 5.7 Hz), 1.33–1.24 (1H, m), 1.20 (3H, t, J = 7.1 Hz), 1.15 (3H, d, J = 6.8 Hz), 0.90 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ¹³C NMR (75 MHz, CDCl₃): δ_{C} 159.1, 130.4, 129.3, 113.7, 94.9, 78.6, 72.6, 69.2, 66.7, 63.7, 61.6, 58.3, 55.2, 37.6, 35.0, 34.6, 30.7, 25.9, 25.7, 24.8, 18.3, 15.0, 14.6, –5.4; **HRMS** Found (ESI): MH⁺, 603.3193, C₃₀H₅₅O₆S₂Si requires 603.3204.

(S)-3-(2-((2'S,3'S)-2'-(Benzyloxy)-3'-(ethoxymethoxy)-5'-(4-methoxybenzyloxy)-pentan-1'-yl)-1,3-dithian-2-yl)butanal (13)

R_f (hexanes/EtOAc 2:1) = 0.53; [α]_D¹⁸ –58.8 (c 0.85 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2931, 2889, 2860, 1720, 1612, 1513, 1455, 1372, 1245, 1179, 1093, 1030, 819, 737, 699; ¹**H NMR** (400 MHz, CDCl₃): δ_{H} 9.73 (1H, d, J = 2.0 Hz), 7.34–7.22 (7H, m), 6.87 (2H, d, J = 8.6 Hz), 4.75 (1H, d, J = 7.0 Hz), 4.66 (1H, d, J = 7.0 Hz), 4.62 (1H, d, J = 10.8 Hz), 4.58 (1H, d, J = 10.8 Hz), 4.43 (2H, s), 4.07–3.98 (2H, m), 3.80 (3H, s), 3.66–3.53 (4H, m), 3.24 (1H, dd, J = 17.6, 3.3 Hz), 2.87–2.67 (5H, m), 2.40 (1H, ddd, J = 17.6, 8.8, 2.0 Hz), 2.31 (1H, br d, J = 15.3 Hz), 2.12-1.83 (4H, m), 1.68 (1H, ddt, J = 14.5, 9.0, 5.5 Hz), 1.22 (3H, t, J = 7.0 Hz), 1.11 (3H, d, J = 6.7 Hz); ¹³**C NMR** (100 MHz, CDCl₃): δ_{C} 201.5, 159.1, 138.3, 130.6, 129.2, 128.2, 128.2, 127.5, 113.7, 94.4, 76.9, 72.6, 72.5, 71.7, 67.0, 63.6, 58.1, 55.3, 47.7, 34.5, 34.0, 29.6, 25.8, 25.5, 25.0, 15.7, 15.1; **HRMS** Found (ESI): MH⁺, 577.2643, C₃₁H₄₅O₆S₂ requires 577.2652.

(2S,4S)-1-(*tert*-Butyldiphenylsilyloxy)-5-(1,3-dithian-2-yl)-2-(ethoxymethoxy)-4-methoxypentane (6)

R_f (hexanes/EtOAc 3:1) = 0.45; $[α]_D^{19}$ = -19.3 (*c* 1.28 in CHCl₃); **IR** $ν_{max}$ (film)/cm⁻¹ 2930, 2890, 2857, 1471, 1427, 1389, 1076, 1028, 822, 790, 739, 700, 613, 523, 518; 1 **H NMR** (300 MHz, CDCl₃): $δ_H$ 7.70–7.66 (4H, m), 7.45–7.34 (6H, m), 4.81 (1H, d, J = 6.8 Hz), 4.72 (1H, d, J = 6.8 Hz), 4.13 (1H, dd, J = 7.8, 6.1 Hz), 3.88–3.80 (1H, m), 3.73–3.49 (5H, m), 3.37 (3H, s), 2.94–2.76 (4H, m), 2.15–2.06 (1H, m), 2.03–1.73 (4H, m), 1.64–1.55 (1H, m), 1.15 (3H, t, J = 7.1), 1.05 (9 H, s); 13 C **NMR** (75 MHz, CDCl₃): $δ_C$ 135.6, 133.4, 129.6, 127.6, 95.2, 75.5, 74.2, 66.7, 63.4, 56.5, 43.6, 40.2, 37.2, 30.4, 30.3, 26.8, 25.9, 19.2, 15.0; **HRMS** Found (EI): M^+ , 548.2455, $C_{29}H_{44}O_4S_2Si$ requires 548.2450.

(1S,3S)-3-(2-((2'S,3'S)-2'-(Benzyloxy)-3'-(ethoxymethoxy)-5'-(4-methoxybenzyloxy)-pentan-1'-yl)-1,3-dithian-2-yl)-1-<math>(2-((2''S,4''S)-5''-(tert-butyldiphenylsilyloxy)-4''-(ethoxymethoxy)-2''-methoxypentan-1''-yl)-1,3-dithian-2-yl)butan-1-ol (17a)

R_f (hexanes/EtOAc 3:1) = 0.26; [α]_D²⁰ –54.8 (*c* 0.67 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2930, 2900, 2856, 1612w, 1513, 1460, 1427, 1390, 1247, 1178, 1102, 1095, 1031, 823, 752, 701, 612; ¹**H NMR** (300 MHz, CDCl₃): δ_{H} 7.70–7.67 (4H, m), 7.44–7.21 (13H, m), 6.85 (2H, d, J = 8.6 Hz), 4.83 (1H, d, J = 6.9 Hz), 4.76 (1H, d, J = 7.0 Hz), 4.76 (1H, d, J = 7.0 Hz), 4.66 (1H, d, J = 7.0 Hz), 4.65 (1H, d, J = 10.9 Hz), 4.57 (1H, d, J = 10.9 Hz), 4.42 (2H, s), 4.06–3.93 (3H, m), 3.88–3.77 (5H, m), 3.74–3.52 (8H, m), 3.36 (3H, s), 2.98–2.45 (9H, m), 2.31–2.21 (2H, m), 2.14–1.99 (4H, m), 1.96–1.66 (8H, m), 1.20 (3H, t, J = 7.0 Hz), 1.17 (3H, t, J = 7.0 Hz), 1.15 (3H, d, J = 7.0 Hz), 1.05 (9H, s); ¹³**C NMR** (75 MHz, CDCl₃): δ_{C} 159.1, 138.8, 135.7, 133.5, 130.8, 129.6, 129.2, 128.1, 127.6, 127.3, 113.7, 95.2, 94.3, 77.2, 76.1, 75.1, 72.9, 72.4, 71.7, 70.8, 67.2, 66.8, 63.6, 63.4, 59.2, 58.4, 56.1, 55.3, 39.8, 39.1, 36.3, 34.6, 33.3, 29.7, 26.9, 26.0, 25.6, 25.5, 25.2, 24.4, 19.2, 15.1, 14.8; **HRMS** Found (ESI): (M + Na)⁺, 1147.4900, C₆₀H₈₈NaO₁₀S₄Si requires 1147.4922.

(1S,3S)-3-(2-((2'S,3'S)-2'-(Benzyloxy)-3'-hydroxy-5'-(4-methoxybenzyloxy)-pentan-1'-yl)-1,3-dithian-2-yl)-1-<math>(2-((2''S,4''S)-5''-(tert-butyldiphenylsilyloxy)-4''-hydroxy-2''-methoxypentan-1''-yl)-1,3-dithian-2-yl)-butan-1-ol

R_f (hexanes/EtOAc 2:1) = 0.15; [α]_D²² –4.8 (c 0.38 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2961, 2926, 2857, 1735w, 1612w, 1513, 1455, 1427, 1378, 1248, 1076br, 1037, 908, 822, 737, 701, 670, 608; ¹**H NMR** (300 MHz, CDCl₃): $δ_{\text{H}}$ 7.69–7.66 (4H, m), 7.46–7.26 (13H, m), 6.86 (2H, d, J = 8.6 Hz), 4.76 (1H, d, J = 10.9 Hz), 4.54 (1H, d, J = 11.4 Hz), 4.43 (2H, s), 4.03–3.87 (5H, m), 3.80 (3H, s), 3.73–3.52 (4H, m), 3.36 (3H, s), 3.24 (1H, br s), 3.03 (1H, br s), 2.93–2.61 (8H, m), 2.56–2.45 (1H, m), 2.35 (1H, br d, J = 15.2 Hz), 2.27–2.14 (3H, m), 2.06–1.64 (9H, m), 1.24 (3H, d, J = 6.7 Hz), 1.07 (9 H, s); ¹³**C NMR** (75 MHz, CDCl₃): $δ_{\text{C}}$ 159.2, 138.9, 135.6, 133.3, 130.2, 129.7, 129.3, 128.2, 127.9, 127.7, 127.4, 113.8, 78.9, 77.2, 72.9, 72.3, 71.8, 71.7, 69.6, 69.1, 68.2, 58.6, 58.2, 56.6, 55.2, 40.7, 38.5, 36.1, 35.3, 33.0, 31.5, 26.9, 26.1, 25.8, 25.6, 25.5, 25.1, 24.5, 19.3, 15.1; **HRMS** Found (ESI): (M + Na)⁺, 1031.4070, C₅₄H₇₆NaO₈S₄Si requires 1031.4084.

 $(2S,\!3S,\!5R,\!7S,\!9S,\!11S,\!13S,\!15S) - 3 - (Benzyloxy) - 9 - ((\textit{tert}-butyldiphenylsilyloxy) methyl) - 2 - (1'-(4-methoxybenzyloxy)) - (1'-($

R_f (hexanes/EtOAc 4:1) = 0.19; [α]_D²⁰ –5.8 (*c* 0.27 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2954, 2932, 2854, 1732, 1613, 1514, 1428, 1362, 1301, 1249, 1194, 1071, 1005, 822, 738, 701, 619; ¹**H NMR** (300 MHz, CDCl₃): δ_{H} 7.70–7.66 (4H, m), 7.43–7.26 (13H, m), 6.87 (2H, d, J = 8.8 Hz), 4.54 (1H, d, J = 12.1 Hz), 4.49 (1H, d, J = 11.4 Hz), 4.37 (1H, d, J = 11.4 Hz), 4.34 (1H, d, J = 12.1 Hz), 4.35–4.30 (1H, m), 4.09–3.98 (3H, m), 3.79 (3H, s), 3.77–3.49 (5H, m), 3.33 (3H, s), 2.37–2.30 (2H, m), 2.17–1.91 (7H, m), 1.35–1.17 (2H, m), 1.04–1.03 (12H, m); ¹³**C NMR** (75 MHz, CDCl₃): δ_{C} 159.1, 138.2, 135.7, 135.6, 133.9, 130.7, 129.5, 129.4, 128.3, 127.6, 127.3, 114.8, 113.8, 96.7, 83.3, 78.8, 77.8, 73.6, 72.8, 71.1, 70.2, 67.1, 66.8, 55.3, 41.1, 41.0, 39.4, 34.1, 31.7, 29.1, 26.8, 19.3, 12.3; **HRMS** Found (ESI): (M + Na)⁺, 833.4038, C₄₈H₆₂NaO₉Si requires 833.4055.

(2S, 3S, 5R, 7S, 9S, 11S, 13S, 15S) - 3 - (Benzyloxy) - 9 - ((tert-butyldiphenylsilyloxy) methyl) - 2 - (1'-(4-methoxybenzyloxy) ethan - 2'-yl) - 11 - methoxy - 15 - methyl - 1,6,8 - trioxadispiro [4.1.5.3] pentadecan - 13 - yl imidazole - 1 - carbothioate

R_f (hexanes/EtOAc 2:1) = 0.19; [α]_D²⁰ –26.5 (*c* 0.10 in CHCl₃); **IR** v_{max} (film)/cm⁻¹ 2961, 2929, 2857, 1710, 1615, 1514, 1463, 1386, 1284, 1247, 1096, 1027, 969, 824, 741, 702; ¹**H NMR** (300 MHz, CDCl₃): δ_{H} 8.34 (1H, br s), 7.63–7.55 (5H, m), 7.43–7.25 (11H, m), 7.20 (2H, d, J = 8.8 Hz), 7.04 (1H, br s), 6.82 (2H, d, J = 8.8 Hz), 5.89–5.82 (1H, m), 4.53 (1H, d, J = 12.1 Hz), 4.42–4.24 (5H, m), 4.11–4.06 (1H, m), 3.96 (1H, dd, J = 11.6, 3.5 Hz), 3.79 (1H, dd, J = 11.6, 4.7 Hz), 3.77 (3H, s), 3.74–3.65 (1H, m), 3.56–3.49 (2H, m), 3.22 (3H, s), 2.99 (1H, dd, J = 17.6, 4.8 Hz), 2.75 (1H, dd, J = 17.6, 7.3 Hz), 2.36–2.27 (2H, m), 2.18–2.04 (3H, m), 2.01–1.93 (1H, m), 1.88–1.69 (2H, m), 1.26–1.24 (1H, m), 1.03–1.00 (12 H, m); ¹³**C NMR** (75 MHz, CDCl₃): δ_{C} 211.9, 159.0, 137.8, 136.9, 135.5, 132.9, 129.8, 129.1, 128.3, 128.1, 127.8, 127.7, 127.5, 127.3, 115.4, 113.7, 82.5, 81.7, 78.8, 78.1, 73.2, 72.5, 71.1, 67.3, 64.4, 57.2, 55.3, 41.5, 40.9, 39.9, 36.1, 35.5, 29.7, 26.7, 19.2, 12.1; **HRMS** Found (ESI): MH⁺, 921.4171, C₅₂H₆₅N₂O₉SSi requires 921.4175.

(2S, 3S, 5R, 7S, 9S, 11S, 15S) - 3 - (Benzyloxy) - 9 - ((tert-butyldiphenylsilyloxy) methyl) - 2 - (1'-(4-methoxybenzyloxy) ethan - 2'-yl) - 11 - methoxy - 15 - methyl - 1,6,8 - trioxadispiro [4.1.5.3] pentadecane (3)

¹**H NMR** (400 MHz, CDCl₃): $δ_H$ 7.66–7.64 (4H, m), 7.42–7.20 (13H, m), 6.83 (2H, d, J = 8.6 Hz), 4.52 (1H, d, J = 12.1 Hz), 4.41 (1H, d, J = 11.4 Hz), 4.37–4.34 (2H, m), 4.31–4.21 (2H, m), 4.11–4.07 (1H, m), 3.77 (3H, s), 3.75–3.70 (1H, m), 3.65–3.62 (2H, m), 3.58–3.47 (2H, m) 3.26 (3H, s), 2.85 (1H, dd, J = 17.0, 7.1 Hz), 2.65 (1H, dd, J = 17.0, 5.3 Hz), 2.38–2.25 (3H, m), 2.14–1.95 (5H, m), 1.84–1.75 (1H, m), 1.04–1.01 (12H, m); **HRMS** Found (ESI): MH⁺, 817.4094, C₄₈H₆₂NaO₈Si requires 817.4106.