Highly Enantioselective Oxidations of Ketene Dithioacetals Leading to *Trans* Bis-sulfoxides.

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General Experimental

Solvents and reagents: Commercial grade solvents were dried and purified by standard procedures, as specified in *Purification of Laboratory Chemicals*, 3rd ed. (Perrin, D. D.; Armarego, W. L. F. Pergamon Press: New York, 1988). *Chromatography:* Flash chromatography was performed on silica gel (400-630 mesh). TLC was performed on

aluminium-backed silica plates precoated with silica (0.2 mm), which were developed using standard visualising agents: UV fluorescence (254 & 366 nm), Δ , molybdic acid / Δ , anisaldehyde. *Optical rotations*: These were recorded at 589 nm (Na D-line) with a path length of 1 dm. Concentrations (c) are quoted in g / 100 mL. *Infra red spectra*: Only selected absorbances ($\nu_{\max}$) are reported. *^1H NMR spectra*: These were recorded at either 250, 270 or 400 MHz. Chemical shifts (δ_{H}) are quoted in parts per million (ppm), referenced to the appropriate solvent peak. *^{13}C NMR spectra*: These were recorded at either 68, 75.7 or 100 MHz. Chemical shifts (δ) are quoted in ppm referenced to the appropriate solvent peak. *Mass spectra*: Only the molecular ions (M^+) and major peaks are reported with intensities quoted as percentages of the base peak. Enantiomeric excesses were determined by HPLC using a chiracel chiral OD or OJ column.

General Procedure for the Synthesis of Ketene Dithioacetals 3a – 3e. 2-Cyclohexylidene-1,3-dithiane 3c.

2-Trimethylsilyl-1,3-dithiane (3.00 g, 15.63 mmol) was dissolved in THF (30 mL) under nitrogen with stirring. The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and $n\text{-BuLi}$ (1.6 M solution in hexanes: 11.70 mL, 18.73 mmol) was added. The solution was allowed to warm to $0\text{ }^{\circ}\text{C}$ over 5 hours. The solution was re-cooled to $-78\text{ }^{\circ}\text{C}$ and cyclohexanone (2.06 mL, 19.88 mmol) was added. The solution was allowed to warm to room temperature over 47 hours. The reaction solution was poured onto H_2O (50 mL) and extracted with CH_2Cl_2 (5 x 50 mL), dried (MgSO_4) and the solvent removed under reduced pressure. Purification by column chromatography, on SiO_2 , (hexane / Et_2O , 1:0 – 0.9:0.1) afforded **3c** as a colourless solid (1.922 g, 61 %); mp (EtOH) $94\text{--}94.5\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 1.55 (m, 6H), 2.13 (dtd, $J = 6.0\text{ Hz}$, $J = 4.0\text{ Hz}$, $J = 2.0\text{ Hz}$, 2H), 2.46 (m, 4H), 2.86 (ddd, $J = 6.0\text{ Hz}$, $J = 4.0\text{ Hz}$, $J = 2.0\text{ Hz}$, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.4, 26.8, 27.6, 30.5, 32.2, 114.0, 145.3; MS (EI) m/z 200 (M^+), 125, 84. The physical data for this material matched that reported in literature.¹

2-Pentylidene-1,3-dithiane 3a.

The reaction mixture was allowed to warm to room temperature and stirred for 20 hours. Purification by column chromatography, on SiO_2 , (hexane / Et_2O , 1:0 – 0.9:0.1) afforded

3a as a pale yellow oil (1.876 g, 96 %); $R_f = 0.64$ (50 % Et₂O / hexane); ¹H NMR (400 MHz, CDCl₃) δ 0.90 (t, $J = 7.0$ Hz, 3H), 1.27-1.41 (m, 4H), 2.16 (ddd, $J = 6.0$ Hz, $J = 4.0$ Hz, $J = 2.0$ Hz, 2H), 2.22 (q, $J = 7.0$ Hz, 2H), 2.85 (td, $J = 4.0$ Hz, $J = 2.0$ Hz, 4H), 5.96 (t, $J = 7.0$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 22.3, 15.4, 29.2, 29.7, 30.5, 31.2, 125.0, 135.0; MS (CI) m/z 189 (MH⁺), 145, 99. No spectral data was reported in the literature for this known compound.²

2-Cyclohexylmethylidene-1,3-dithiane 3b.

The reaction mixture was allowed to warm to room temperature and stirred for 37 hours. The crude product was purified by trituration with EtOH to afford **3b** as a colourless solid (347 mg, 62 %), mp (EtOH) 47-48 °C; $R_f = 0.66$ (50 % Et₂O / hexane); ¹H NMR (400 MHz, CDCl₃) δ 0.98-1.40 (m, 5H), 1.68 (m, 5H), 2.17 (tt, $J = 8.0$ Hz, $J = 4.0$ Hz, 2H), 2.52 (m, 1H), 2.85 (td, $J = 8.0$ Hz, $J = 4.0$ Hz, 4H), 5.82 (d, $J = 9.0$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 25.7, 26.0, 26.2, 30.1, 30.8, 32.7, 38.8, 123.9, 140.9; MS (EI) m/z 214 (M⁺), 171, 84. The ¹H NMR spectral data for this material matched that reported in literature.³

2-Phenylmethylidene-1,3-dithiane 3d.

The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. Purification by column chromatography, on SiO₂, (10 % Et₂O / hexane) afforded **3d** as a pale yellow oil (943 mg, 90 %); $R_f = 0.40$ (10 % Et₂O / hexane); ¹H NMR (270 MHz, CDCl₃) δ 2.15 – 2.26 (m, 2H), 2.92 – 3.04 (m, 4H), 6.85 (s, 1H), 7.17 – 7.46 (m, 5H); ¹³C NMR (68 MHz, CDCl₃) δ 24.4, 29.2, 126.8, 128.1, 129.0, 130.7, 136.2. The ¹H NMR spectral data for this material matched that reported in literature.⁴

2-(4-Methoxyphenylmethylidene)-1,3-dithiane 3e.

The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. Purification by column chromatography, on SiO₂, (10 % Et₂O / hexane) afforded **3e** as a pale yellow oil (1.17 g, 98 %); $R_f = 0.28$ (10 % Et₂O / hexane); ¹H NMR (400 MHz, CDCl₃) δ 2.17 – 2.23 (m, 2H), 2.92 – 3.00 (m, 4H), 3.80 (s, 3H), 6.84 (s, 1H), 6.89 (d, $J = 8.9$ Hz, 2H), 7.48 (d, $J = 8.9$ Hz, 2H); ¹³C NMR (67.9 MHz, CDCl₃) δ 24.5, 29.5, 30.2,

55.3, 113.6, 127.8, 129.0, 129.6, 130.4, 158.6. The ^1H NMR spectral data for this material matched that reported in literature.⁵

2-(1-Phenylethylidene)-1,3-dithiane 3f.

2-Diethylphosphoryl-1,3-dithiane (0.5 g, 1.95 mmol) was dissolved in THF (5 mL) under nitrogen with stirring. The solution was cooled to -78°C and *n*-BuLi (1.6 M solution in hexanes: 1.34 mL, 2.15 mmol) was added. The solution was stirred at -78°C for 1 hour. Acetophenone (0.25 mL, 2.15 mmol) was then added and the reaction mixture stirred at -78°C for 1 hour, then allowed to warm to room temperature over 20 hours. After removal of solvents under reduced pressure the residue was dissolved in chloroform (15 mL). The solution was washed with saturated aqueous NH_4Cl (15 mL) and H_2O (15 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude olefin was purified by flash column chromatography, on SiO_2 (EtOAc / petrol, 2:98) which afforded **3f** as a colourless oil (0.340 g, 78 %), $R_f = 0.3$ (5 % EtOAc / petrol); ^1H NMR (250 MHz, CDCl_3) δ 2.11 (dddd, $J = 7.3$ Hz, $J = 6.5$ Hz, $J = 6.2$ Hz, $J = 5.2$ Hz, 2H), 2.21 (s, 3H), 2.79 (ddd, $J = 6.5$ Hz, $J = 6.2$ Hz, $J = 0.2$ Hz, 2H), 3.00 (ddd, $J = 7.3$ Hz, $J = 5.2$ Hz, $J = 0.2$ Hz, 2H), 7.18-7.38 (m, 5H). The ^1H NMR spectral data for this material matched that reported in literature.⁶

General Procedure for the Synthesis of Ketene Dithioacetal Dioxides 4. (1*R*,3*R*)-2-Cyclohexylidene-1,3-dithiane-1,3-dioxide 4c.

(+)-Diethyl tartrate (0.34 mL, 2.01 mmol) and titanium (IV) isopropoxide (0.15 mL, 0.50 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature, under nitrogen and stirred for 20 minutes. 2-Cyclohexylidene-1,3-dithiane was dissolved in CH_2Cl_2 (1.0 mL) and added to the reaction mixture, which was then cooled to -40°C and stirred for 1 hour. Cumene hydroperoxide (80 %; 0.76 mL, 4.01 mmol) was added, the mixture stirred at -40°C for 10 minutes, then allowed to stand at -20°C for 22 hours. Distilled water (0.36 mL) was added and the reaction mixture allowed to warm to room temperature with stirring for 1 hour. The reaction mixture was filtered through a pad of celite, washed well

with CH₂Cl₂ and the solvent removed under reduced pressure. Purification by column chromatography on SiO₂ (hexane: Et₂O / EtOH, 1:1:0 – 0:1:0 – 0:1:1) afforded **4c** as a colourless solid (173 mg, 75 %): mp (EtOH / hexane) 159.5-161 °C; [α]_D²² –21.5 (*c* 1.0, CHCl₃); IR (neat) 2919, 1042 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.69 (m, 2H), 1.75-1.88 (m, 4H), 2.53 (tt, *J* = 9.0 Hz, *J* = 5.0 Hz, 2H), 2.84 (m, 4H), 3.39 (dt, *J* = 14.5 Hz, *J* = 5.0 Hz, 2H), 3.53 (dt, *J* = 14.5 Hz, *J* = 9.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 7.5, 25.9, 28.2, 32.7, 40.3, 135.5, 168.9; MS (EI) *m/z* 232 (M⁺), 215, 184; HRMS (EI) found *m/z* 232.0594 (M⁺), C₁₀H₁₆S₂O₂ requires 232.0591.

(1*R*,3*R*)-2-Pentylidene-1,3-dithiane-1,3-dioxide **4a.**

Purification by column chromatography, on SiO₂, (hexane: Et₂O: EtOH, 1:1:0 – 0:1:0 – 0:1:1) afforded **4a** as a pale yellow oil, which crystallised on standing (380 mg, 65 %), mp 45-47 °C; R_f = 0.09 (20 % EtOH / Et₂O); [α]_D²⁰ –15.1 (*c* 1.0, CHCl₃); IR (neat) 2957, 1041 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 0.93 (t, *J* = 7.0 Hz, 3H), 1.37 (sextet, *J* = 7.0 Hz, 2H), 1.51 (m, 2H), 2.36 (dm, *J* = 16.0 Hz, 1H), 2.46 (dt, *J* = 14.0 Hz, *J* = 7.0 Hz, 1H), 2.62 (m, 2H), 2.78 (ddd, *J* = 13.5 Hz, *J* = 9.0 Hz, *J* = 3.0 Hz, 1H), 3.08 (dddd, *J* = 16.0 Hz, *J* = 9.0 Hz, *J* = 5.5 Hz, *J* = 3.0 Hz, 1H), 3.23 (dtd, *J* = 13.5 Hz, *J* = 5.5 Hz, *J* = 3.0 Hz, 1H), 3.63 (dm, *J* = 12.0 Hz, 1H), 6.69 (t, *J* = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.7, 14.9, 22.2, 28.2, 30.9, 49.0, 55.5, 141.1, 144.5; MS (CI) *m/z* 221 (MH⁺), 205, 187; HRMS (CI) found *m/z* 221.0667 (MH⁺), C₉H₁₆S₂O₂ requires 221.0669.

(1*R*,3*R*)-2-Cyclohexylmethylidene-1,3-dithiane-1,3-dioxide **4b.**

The reaction mixture was left for 6 hours after the addition of cumene hydroperoxide. Purification by column chromatography afforded **4b** as a white solid (357 mg, 62 %), mp (EtOH / hexane) 198.0-199.5 °C; R_f = 0.23 (20 % EtOH / Et₂O); [α]_D²⁰ –21.6 (*c* 1.0, CHCl₃); IR (neat) 2921, 1042 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.15-1.40 (m, 5H), 1.48 (m, 1H), 1.77 (m, 4H), 2.36 (dm, *J* = 16.0 Hz, 1H), 2.61 (td, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 2.76 (td, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 2.83 (m, 1H), 3.09, (dddd, *J* = 16.0 Hz, *J* = 13.0 Hz, *J* = 13.0 Hz, *J* = 3.0 Hz, *J* = 3.0 Hz, 1H), 3.22 (ddd, *J* = 13.0 Hz, *J* = 6.0 Hz, *J* = 3.0 Hz, 1H), 3.64 (dm, *J* = 13.0 Hz, 1H), 6.55 (d, *J* = 10.0 Hz, 1H); ¹³C NMR (100 MHz,

CDCl₃) δ 14.9, 25.1, 25.3, 25.4, 32.4, 32.9, 38.4, 49.4, 55.5, 142.8, 145.6; MS (EI) m/z 246 (M⁺), 229, 198, 181. The physical and spectral data and optical rotation values agreed with those previously reported in literature.^{5,7}

(1*R*,3*R*)-2-Phenylmethylidene-1,3-dithiane-1,3-dioxide 4d.

The reaction mixture was left for 24 hours after addition of cumene hydroperoxide. Purification by column chromatography afforded **4d** as a colourless solid (94 mg, 73 %), mp (CH₂Cl₂ / hexane) 174-175 °C; [α]_D²² +102.5 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 2.37 - 2.42 (dm, *J* = 18.5 Hz, 1H), 2.81 (ddd, *J* = 15.8 Hz, *J* = 12.9 Hz, *J* = 2.3 Hz, 1H), 2.90 (ddd, *J* = 12.2 Hz, *J* = 11.9 Hz, *J* = 2.6 Hz, 1H), 3.09 – 3.23 (m, 1H), 3.25 – 3.34 (dm, *J* = 15.8 Hz, 1H), 3.70 3.78 (dm, *J* = 11.8 Hz, 1H), 7.44 (s, 5H), 7.52 (s, 1H). The physical and spectral data and optical rotation values agreed with those previously reported in literature.⁵

(1*R*,3*R*)-2-(4-methoxyphenylmethylidene)-1,3-dithiane-1,3-dioxide 4e.

The reaction mixture was left for 21 hours after addition of cumene hydroperoxide. Purification by column chromatography afforded **4e** as a colourless solid (100 mg, 71 %), mp (CH₂Cl₂ / hexane) 150-152 °C; [α]_D²² +106.3 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 2.41 (dm, *J* = 17.0 Hz, 1H), 2.79 – 2.92 (m, 2H), 3.11 – 3.23 (m, 1H), 3.25 – 3.32 (dm, *J* = 11.7 Hz, 1H), 3.71 (dddd, *J* = 11.7 Hz, *J* = 5.1 Hz, *J* = 2.1 Hz, *J* = 1.3 Hz, 1H), 3.86 (s, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.40 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H). The physical and spectral data and optical rotation values agreed with those previously reported in literature.⁵

(1*R*,3*R*)-2-(1-phenylethylidene)-1,3-dithiane-1,3-dioxide 4f.

The reaction mixture was left for 18 hours after the addition of cumene hydroperoxide. Purification by column chromatography afforded **4f** as a colourless solid (82 mg, 60 %); mp (EtOAc) 110-113 °C; *R*_f = 0.2 (10 % EtOH / EtOAc); [α]_D²³ –183.0 (*c* 0.98, CHCl₃); IR (KBr) 2962, 2923, 1641, 1561, 1035 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 2.47-2.60 (m, 2H), 2.67 (s, 3H), 3.22-3.51 (m, 3H), 3.69-3.85 (m, 1H), 7.32-7.52 (m, 5H); ¹³C NMR

(75.5 MHz, CDCl₃) δ 7.5, 22.6, 40.5, 40.9, 127.7, 128.7, 129.9, 138.3, 139.3, 163.3; MS (EI) m/z 254 (M⁺), 206, 115. Anal. Calcd for C₁₂H₁₄O₂S₂ (254.36): C, 56.66; H, 5.55; Found: C, 56.51; H, 5.51.

(1R)-2-Cyclohexylidene-1,4-dithiane-1-monoxide 6c.

mp (EtOAc / hexane) 127 – 129 °C; R_f = 0.59 (50 % Et₂O / hexane); [α]_D²² –167.9 (c 1.0, CHCl₃); IR (neat) 2922, 1575, 1053 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.53 – 1.74 (m, 6H), 1.86 (m, 1H), 2.52-2.76 (m, 6H), 2.85-2.95 (m, 2H), 3.12 (dtd, J = 14.3 Hz, J = 4.0 Hz, J = 2.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 15.8, 26.4, 27.9, 28.3, 30.9, 31.9, 33.7, 48.7, 143.0, 157.0; MS (CI) m/z 217 (MH⁺), 201, 167. HRMS (CI) found m/z 217.0715 (MH⁺), C₁₀H₁₆S₂O requires 217.0720.

¹H NMR spectrum of 4a.

^1H NMR spectrum of 4c.

^1H NMR spectrum of 6c.

(1*R*,3*R*)-2-Pentylidene-1,3-dithiane-1,3-dioxide 4a.

Chiracel OD column; 20 °C; 1.0 mL/min; 50 % isopropanol: hexane; Major (*R,R*)-enantiomer retention time 10.4 min; Minor (*S,S*)- enantiomer retention 6.5 min.

Racemic:

Enantiopure:

(1*R*)-2-Pentylidene-1⁴-dithiane-1-monoxide 6a.

Chiracel OD column; 20 °C; 1.0 mL/min; 10 % isopropanol: hexane; Major geometric (*R*)-enantiomer retention time 9.8 min; Major geometric (*S*)-enantiomer retention 14.9 min; Minor geometric (*R*)-enantiomer retention time 12.4 min; Minor geometric (*S*)-enantiomer retention time 11.4 min.

Racemic:

Enantiopure:

(1*R*,3*R*)-2-Cyclohexylmethyldiene-1,3-dithiane-1,3-dioxide 4b.

Chiracel OD column; 20 °C; 1.0 mL/min; 50 % isopropanol: hexane; Major (*R,R*)-enantiomer retention time 7.6 min; Minor (*S,S*)- enantiomer retention 5.4 min.

Racemic:

Enantiopure:

(1*R*,3*R*)-2-Cyclohexylidene-1,3-dithiane-1,3-dioxide 4c.

Chiracel OD column; 20 °C; 1.0 mL/min; 10 % isopropanol: hexane; Major (*R,R*)-enantiomer retention time 22.0 min; Minor (*S,S*)- enantiomer retention time 19.7 min.

Racemic:

Enantiopure:

(1*R*)-2-Cyclohexylidene-1,4-dithiane-1-monoxide 6c.

Chiracel OJ column; 20 °C; 1.0 mL/min; 2 % isopropanol: hexane; Major (*R*)-enantiomer retention time 46.2 min; Minor (*S*)- enantiomer retention 59.4 min.

Racemic:

Enantiopure:

(1*R*,3*R*)-2-Phenylmethyldiene-1,3-dithiane-1,3-dioxide 4d.

Chiracel OD column; 20 °C; 1.0 mL/min; 50 % isopropanol: hexane; Major (*R,R*)-enantiomer retention time 15.0 min; Minor (*S,S*)- enantiomer retention 11.5 min.

Racemic:

Enantiopure:

(1*R*,3*R*)-2-(4-methoxyphenylmethylidene)-1,3-dithiane-1,3-dioxide 4e.

Chiracel OD column; 20 °C; 1.0 mL/min; 50 % isopropanol: hexane; Major (*R,R*)-enantiomer retention time 20.9 min; Minor (*S,S*)- enantiomer retention time 11.2 min.

Racemic:

Enantiopure:

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