

Supplementary Material

A bis(disulfide)-linked offset cryptophane

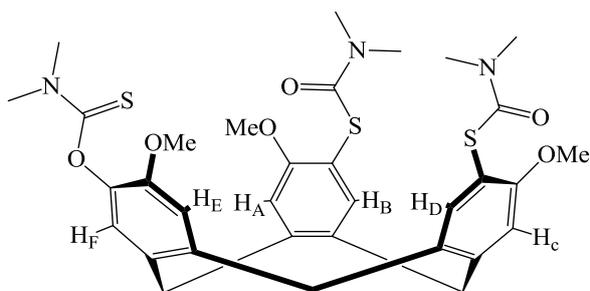
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Synthesis

Dimethyl-thiocarbamic acid *O*-(7,13-bis-dimethylthiocarbamoyloxy-3,8,12-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononen-2-yl) ester **3a** was synthesised by previously reported procedure. All other chemicals were obtained from Sigma-Aldrich Chemical Company or Lancaster Synthesis Ltd and were used without further purification. ¹H Nuclear Magnetic Resonance spectra were recorded using a Bruker Avance 500 instrument. ¹³C Nuclear Magnetic Resonance spectra were recorded using a Bruker DPX 300 instrument. ¹H spectra are referenced to tetramethylsilane and chemical shifts given in parts per million downfield from TMS. Microanalyses were obtained on a Carlo Erba Elemental Analyser MOD 1106 instrument, found composition is reported to the nearest 0.05 %. Infrared spectra were recorded on a Perkin-Elmer FTIR spectrometer and samples analysed as solids.

Dimethyl-thiocarbamic acid *O*-(7,12-bis-dimethylcarbamoylsulfanyl-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononen-2-yl) ester, **3b**

Dimethyl-thiocarbamic acid *O*-(7,13-bis-dimethylthiocarbamoyloxy-3,8,12-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononen-2-yl) ester (1.016 g, 1.52 mmol) in diphenyl ether (70 mL) was

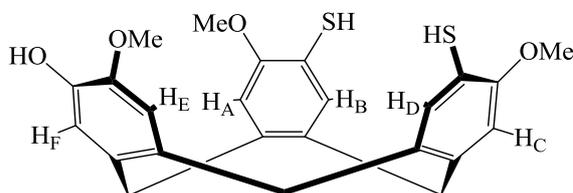


heated under vacuum to 100°C and then at 265°C under argon for 4 hours. After cooling to R.T. the solution was poured onto hexane (200 mL), and the light yellow precipitate was collected by filtration and washed with hot hexane (50mL). The yellow precipitate was triturated in MeOH:Et₂O (1:5, 20 mL), and the resulting white precipitate was collected by filtration. Gradient flash column chromatography (silica gel, CH₂Cl₂:EtOAc, 1:0 → 2:1) afforded **3b** as a white solid. Yield: 0.324 g; 32%, melting point: 172.6-174.0°C.

^1H NMR (CDCl_3 , 500 MHz): δ (ppm.) 2.99 (broad s, 6H, $\text{S}=\text{CNCH}_3$), 3.10 (broad s, 6H, $\text{S}=\text{CNCH}_3$), 3.29 (s, 3H, $\text{O}=\text{CNCH}_3$), 3.44 (s, 3H, $\text{O}=\text{CNCH}_3$), 3.66-3.71 (m, 3H, 3 x CH_{exo}), 3.80 (s, 1H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.71-4.79 (m, 3H, 3 x CH_{endo}), 6.87 (s, 1H, H_E), 6.91 (s, 1H, H_A or H_C), 6.92 (s, 1H, H_A or H_C), 7.03 (1H, H_F), 7.44 (1H, H_B or H_D), 7.46 (s, 1H, H_B or H_D). ^{13}C NMR (CDCl_3 , 75 MHz): δ (ppm.) 36.25 (CH_2), 36.53 (CH_2), 36.75 (CH_2), 36.91 (4 x NCH_3), 38.68 (NCH_3), 43.28 (NCH_3), 56.25 (OCH_3), 56.31 (OCH_3), 56.41 (OCH_3), 113.05, 113.72, 114.37, 114.88, 115.01, 125.18, 130.72, 130.93, 131.31, 131.76, 138.10, 139.40, 141.45, 142.91, 143.01, 150.12, 158.64, 158.69, 166.25 ($\text{C}=\text{O}$), 166.32 ($\text{C}=\text{O}$), 187.88 ($\text{C}=\text{O}$). IR (solid state): ν (cm^{-1}) 2932 (m), 1723 (w), 1664 (s), 1595 (m), 1513 (s), 1491 (s), 1382 (s), 1260 (s), 1204 (m), 1139 (s), 1095 (s), 1055 (s), 907 (w), 843 (w), 730 (w), 687 (w), 655 (w). High resolution mass spec: (ES+): 708.1685 (calc. for $[\text{C}_{33}\text{H}_{39}\text{N}_3\text{O}_6\text{S}_3\cdot\text{K}]^+$: 708.1633). Elemental analysis for $\text{C}_{33}\text{H}_{39}\text{N}_3\text{O}_6\text{S}_3\cdot\text{H}_2\text{O}$ after product was dried *in vacuo*, found, (calculated) (%): C 58.85 (59.17), H 5.85 (5.87), N 6.20 (6.27) S 14.00 (14.36).

Synthesis of 7,12-dimercapto-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a,d,g*]cyclononen-2-ol, **3c**

3b (0.233 g, 0.35 mmol) was added to argon degassed MeOH (30 mL). KOH pellets (6.758 g) were added at the reaction was heated under reflux for 5 hours. The reaction was allowed to



cool to R.T. and the reaction was then acidified with 2M HCl (aq.). The resulting white precipitate was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with H_2O (2 x 30 mL) and brine (30 mL), dried (MgSO_4) and solvent removed under reduced pressure. The white precipitate was recrystallized from CH_2Cl_2 after the addition of hexane, to afford **3a** as a white crystalline solid. Yield 0.115 g: 78%, melting point: 224.7-225.5°C

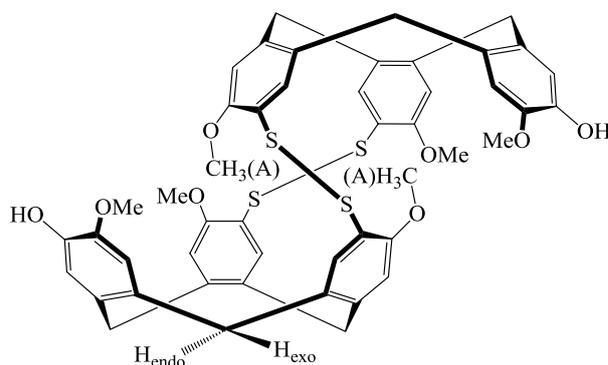
^1H NMR (CDCl_3 , 300 MHz): δ (ppm.) 3.46-3.55 (m, 3H, 3 x CH_{exo}), 3.71 (s, 1H, SH), 3.72 (s, 1H, SH), 3.86 (s, 6H, 2 x OCH_3), 3.87 (s, 3H, OCH_3), 4.60-4.70 (m, 3H, 3 x CH_{endo}), 5.42 (s, 1H, OH), 6.76 (s, 1H, H_A or H_C), 6.77 (s, 1H, H_A or H_C), 6.79 (s, 1H, H_E), 6.89 (s, 1H, H_F), 7.20 (s, 1H, H_B or H_D), 7.21 (s, 1H, H_B or H_D). ^{13}C NMR (CDCl_3 , 75MHz): δ (ppm.) 35.89 (CH_2), 36.25 (CH_2), 36.57 (CH_2), 56.03 (OCH_3), 56.08 (OCH_3), 56.13 (OCH_3), 112.09, 112.16, 115.45, 118.17, 118.37, 130.64, 130.67, 131.03, 131.74, 131.84, 132.42, 137.76, 138.00, 144.18, 144.27, 145.40, 153.71, 153.81. IR (solid state): ν (cm^{-1}) 3444 (m) (O-H),

2989 (m), 2923 (m), 2840 (m), 2551 (m) (S-H), 1621 (m), 1593 (m), 1513 (s), 1494 (s), 1473 (s), 1462 (s), 1441 (s), 1382 (m), 1361 (m), 1270 (s), 1254 (s), 1254 (s), 1202 (m), 1175 (m), 1138 (m), 1123 (m), 1082 (m), 1061 (s), 1016 (m), 983 (w), 942 (m), 920 (w), 880 (m), 850 (m), 850 (m), 839 (m), 771 (w), 743 (m), 728 (m), 637 (w), 626 (w), 602 (w), 509 (w). High resolution mass spec: (ES-): 439.1062 (calc. for $[C_{24}H_{23}O_4S_2]^-$: 439.1043). Elemental analysis for $C_{24}H_{24}O_4S_2$ after product was dried *in vacuo*, found, (calculated) (%): C 65.45 (65.43), H 5.55 (5.49), S 14.25 (14.56).

Synthesis of bis(disulfide)-linked offset cryptophane, **3**

7,12-Dimercapto-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononen-2-ol

3c (0.277 g, 0.63 mmol) was added to argon degassed MeOH (500 mL). Anhydrous Et_3N (0.53 mL, 3.78 mmol) was added and whilst stirring KI (0.042 g, 0.25 mmol) was added followed by drop-wise addition of iodine



dissolved in argon degassed MeOH (80 mL) over 4 hours, during which time the reaction turned purple. The reaction was stirred for a further 12 hours at R.T. Conc. HCl (aq.) was added drop-wise to acidify the reaction and the solvent was removed under reduced pressure. The product was taken up in CH_2Cl_2 (3 x 50 mL) and the organic extract was washed with $Na_2S_2O_3$ (2 x 50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and solvent removed under reduced pressure. The precipitate was purified by flash column chromatography (silica gel, CH_2Cl_2 : EtOAc 9:1 \rightarrow 3:2) to afford the clean title compound as a light yellow precipitate. Yield 0.089 g; 32%; melting point: 325.7-327.1°C with slight decomposition.

1H NMR (d_6 -DMSO, 300 MHz): δ (ppm.) 0.95 (s, 6H, H_A), 3.48-3.57 (m, 6H, CH_{exo}), 3.80 (s, 6H, CH_3), 3.88 (s, 6H, CH_3), 4.5-4.74 (m, 6H, C_{endo}), 6.02 (s, 2H, CH aryl), 6.95 (s, 2H, CH aryl), 7.02 (s, 2H, CH aryl), 7.09 (s, 2H, CH aryl), 7.25 (s, 2H, CH aryl), 7.77 (s, 2H, CH aryl), 8.57 (s, 2H, OH). ^{13}C NMR (d_6 -DMSO, 75 MHz): δ (ppm.) 34.21 (CH_2), 35.14 (CH_2), 35.35 (CH_2), 52.18 (CH_3), 55.97 (CH_3), 56.36 (CH_3), 110.83, 112.56, 114.13, 116.35, 120.21, 120.65, 123.53, 130.77, 131.16, 131.96, 132.62, 139.36, 140.15, 141.93, 144.84, 146.51, 154.02, 158.16. IR (solid state): ν (cm^{-1}) 3491 (w) (O-H), 2922 (w), 1591 (s), 1511 (s), 1476 (s), 1380 (s), 1360 (m), 1318 (m), 1251 (s), 1198 (s), 1174 (s), 1136 (s), 1115 (m), 1098 (w), 1076 (m), 1048 (s), 977 (w), 938 (w), 921 (w), 893 (m), 879 (m), 844 (m), 816 (w), 763 (w),

744 (w), 727 (w), 671 (w), 630 (w), 596 (w), 512 (w), 471 (w). High resolution mass spec: (ES+): 899.1794 (calc. for $[C_{48}H_{44}O_8S_4.Na]^+$: 899.1811). Elemental analysis for $C_{48}H_{44}O_8S_4.2H_2O$ after product was dried *in vacuo*, found, (calculated) (%): C 62.95 (63.13), H 5.05 (5.30), S 14.15 (14.05).

X-Ray Crystallography

A single crystal of $3 \cdot (DMF)(Et_2O)$ was mounted on a MiTeGen loop fibre under oil and flash frozen to 150(1) K using a stream of cold N_2 . Data was collected on a Rigaku Saturn diffractometer using synchrotron radiation ($\lambda = 0.6889 \text{ \AA}$) at station I19 at the Diamond Light Source in the UK. Data were corrected for Lorentzian and polarization effects and absorption corrections were applied using multi-scan methods. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix on F^2 using SHELXL-97. All non-hydrogen atoms were refined as anisotropic, and hydrogen positions were included at geometrically estimated positions. The ether solvent molecule was refined with restraints on its O-C and C-C bond distances, and the DMF was disordered with the carbonyl groups refined across two positions.

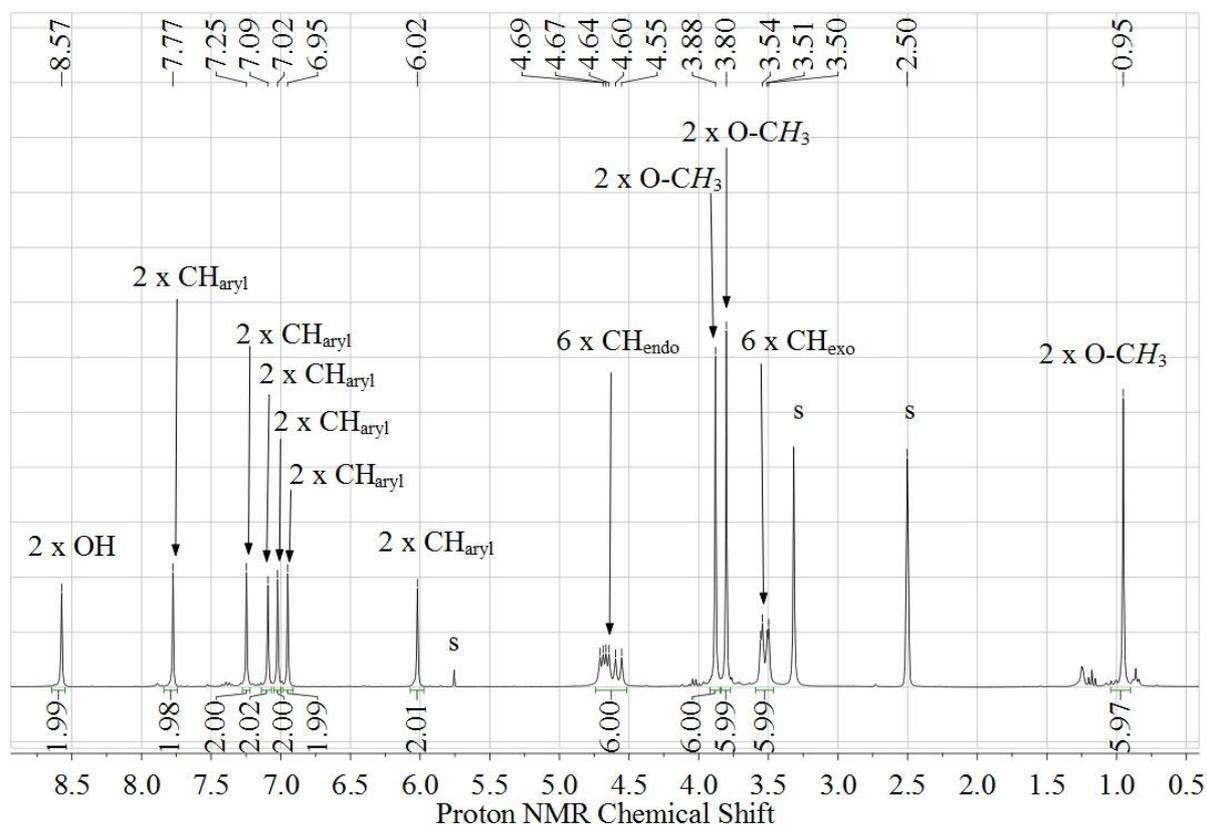


Figure S1: 300 MHz 1H NMR Spectra for compound **3** in d_6 -DMSO.

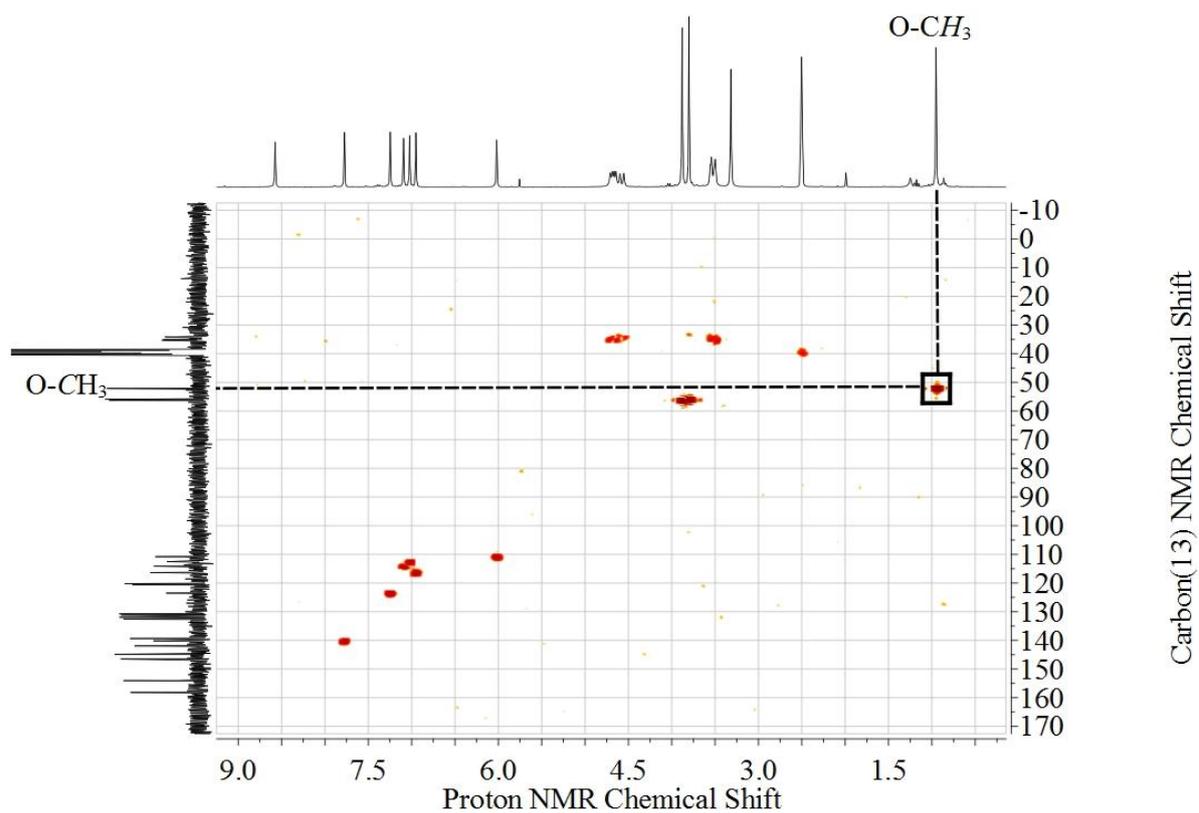


Figure S2: Heteronuclear single-quantum correlation spectra for compound **3**, highlighting correlation between shielded methoxy ¹H signal and methoxy ¹³C signal in *d*₆-DMSO.

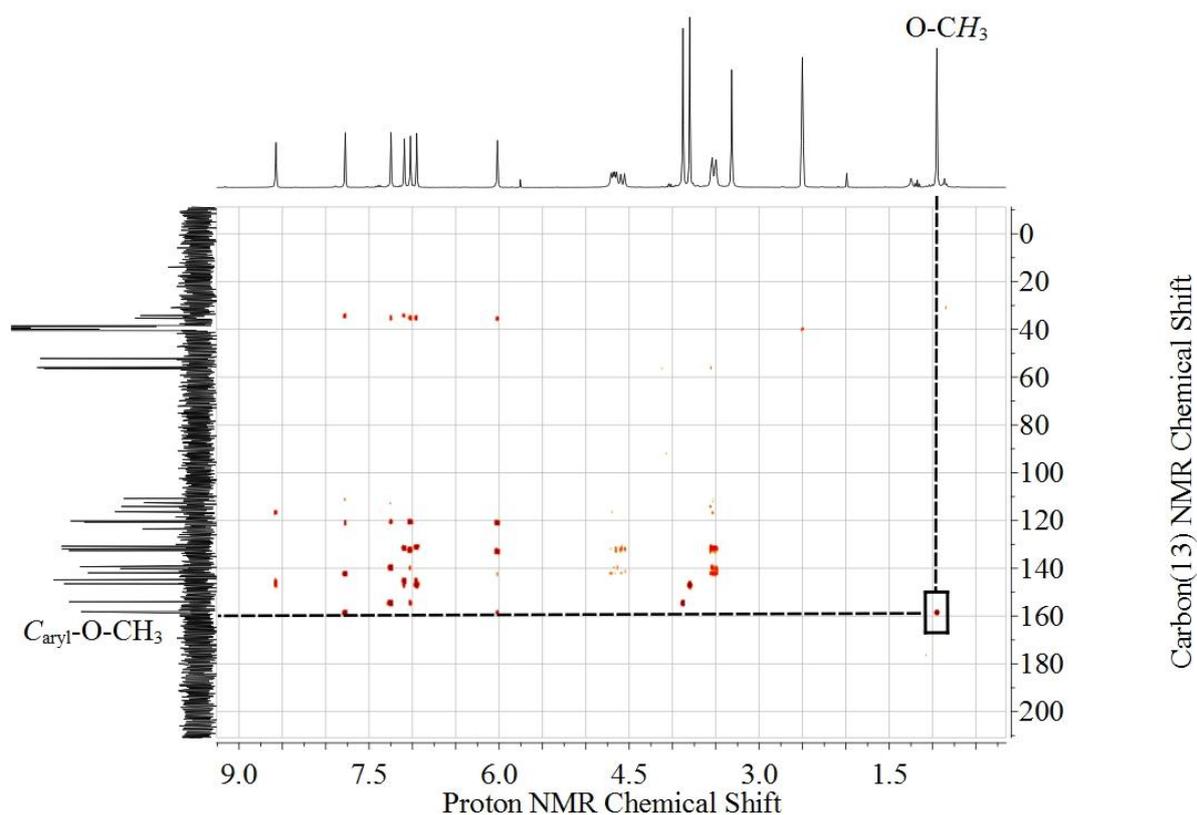


Figure S3: Heteronuclear multiple-bond correlation spectra for compound **3**, highlighting correlation between shielded methoxy ^1H signal and aromatic ^{13}C signal in d_6 -DMSO.

X-Ray Crystallography

A single crystal of **3**·(DMF)(Et₂O) was mounted on a MiTeGen loop fibre under oil and flash frozen to 150(1) K using a stream of cold N₂. Data was collected on a Rigaku Saturn diffractometer using synchrotron radiation ($\lambda = 0.6889 \text{ \AA}$) at station I19 at the Diamond Light Source in the UK. Data were corrected for Lorentzian and polarization effects and absorption corrections were applied using multi-scan methods. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix on F^2 using SHELXL-97.² All non-hydrogen atoms were refined as anisotropic, and hydrogen positions were included at geometrically estimated positions. The ether solvent molecule was refined with restraints on its O-C and C-C bond distances, and the DMF was disordered with the carbonyl groups refined across two positions. C₅₅H₆₁NO₁₀S₄, $M_r = 1024.29$, triclinic, $a = 11.768(7)$, $b = 15.158(8)$, $c = 15.531(8) \text{ \AA}$, $\alpha = 90.075(5)$, $\beta = 104.370(5)$, $\gamma = 103.99(1)^\circ$, $V = 2598(2) \text{ \AA}^3$, space group $P-1$, $Z = 2$, $\theta_{\text{max}} = 26.64^\circ$, 651 parameters, $R_1 = 0.0644$ (for 11134 data $I > 2\sigma(I)$), $wR_2 = 0.1839$ (all data), $S = 1.056$. CCDC 913995.

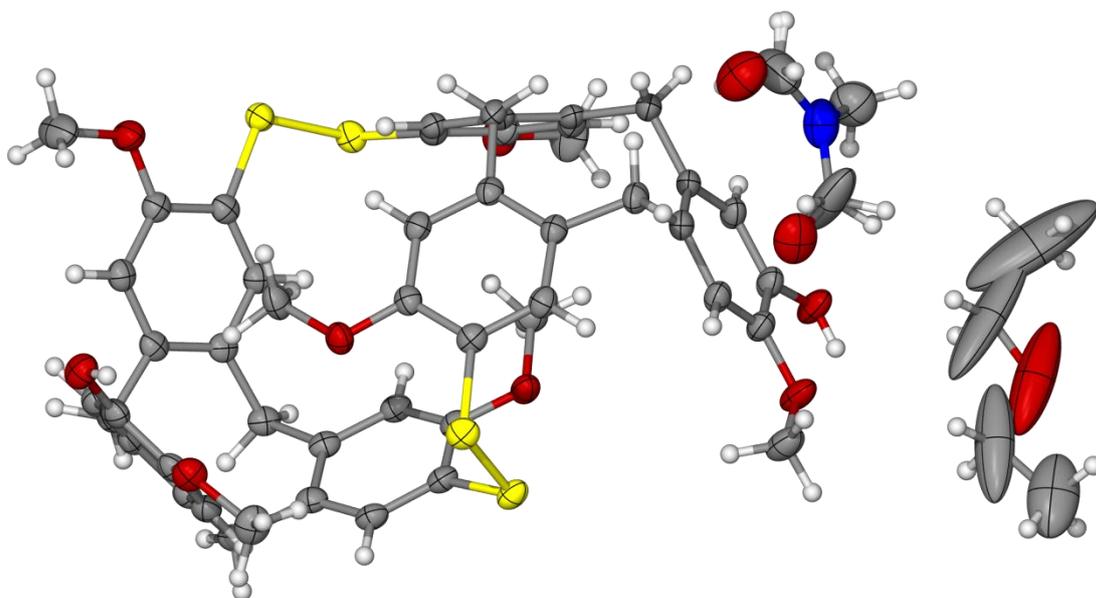


Figure S4: Asymmetric unit of the crystal structure of **3**·(DMF)(Et₂O). Ellipsoids are shown at 50% probability levels.

1. M. A. Little, J. Donkin, J. Fisher, M. A. Halcrow, J. Loder and M. J. Hardie, *Angew. Chem. Int. Ed.*, 2012, **51**, 764.
2. G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112.