

Supporting information

[2+2] Photocycloadditions of Thiomaleimides

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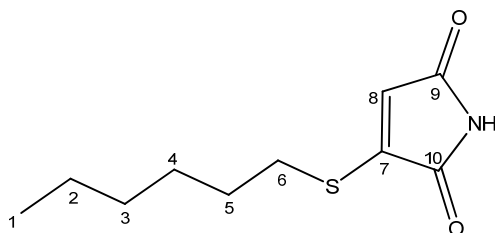
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General

All reactions were carried out at atmospheric pressure with stirring unless otherwise stated. Solvents and reagents were purchased from suppliers and used without any further purification. Normal phase silica gel (BDH) and sand (VWR) were used for flash chromatography. All reactions were monitored by thin layer chromatography (TLC) unless otherwise stated. TLC plates pre-coated with silica gel 60 F₂₅₄ on aluminium (Merck KGaA) were used, detection was by UV (254 or 365 nm) or chemical stain (KMnO₄ or vanillin). High and low resolution mass spectrometry was performed using a VG70 SE operating in modes ES, EI, FAB or CI (+ or -) depending on the sample. ¹H Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz, 500 MHz and 600 MHz and ¹³C NMR at 100MHz, 125 MHz and 150 MHz on Bruker AVANCE III 400, AVANCE 500 and AVANCE III 600 spectrometers at ambient temperature. Chemical shifts were measured in parts per million (ppm) and are quoted as δ . Coupling constants, *J*, are quoted in Hertz (Hz) to 1 decimal place. The multiplicity of the signal is indicated as s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, defined as all multipeak signals where overlap produces complex line shapes. All peaks should be taken as sharp unless otherwise described. Where necessary, assignments were made with the aid of DEPT, COSY, HMQC, HSQC, HMBC or NOESY correlation experiments. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. UV-Vis spectroscopy was carried out on a UV-2400PC Series. Elemental analyses were carried out by Gillian Maxwell at University College London. The term 'degassed' refers to the process of removing O₂ from a solution by bubbling argon through the solution. Irradiations were carried out using a medium pressure 125W mercury lamp (Photochemical Reactors Ltd.) and a pyrex immersion well (Photochemical Reactors Ltd.) cooled *via* running water.

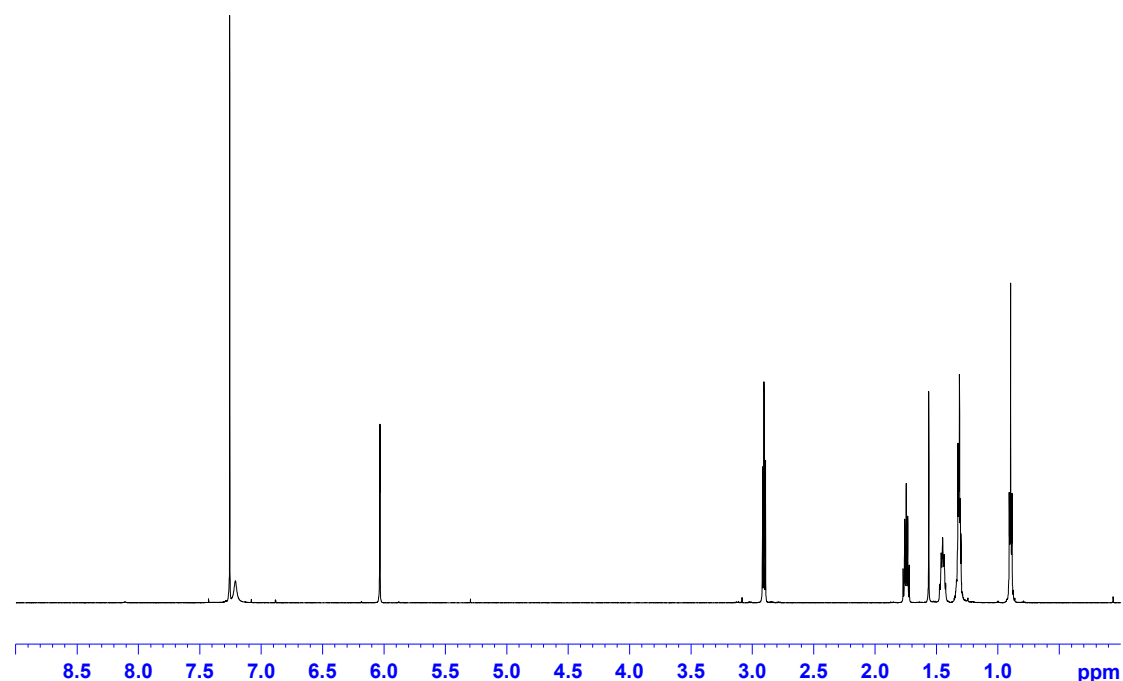
Synthesis, analytical data and NMR spectra of novel compounds

3. 3-Hexylsulfanyl-pyrrole-2,5-dione

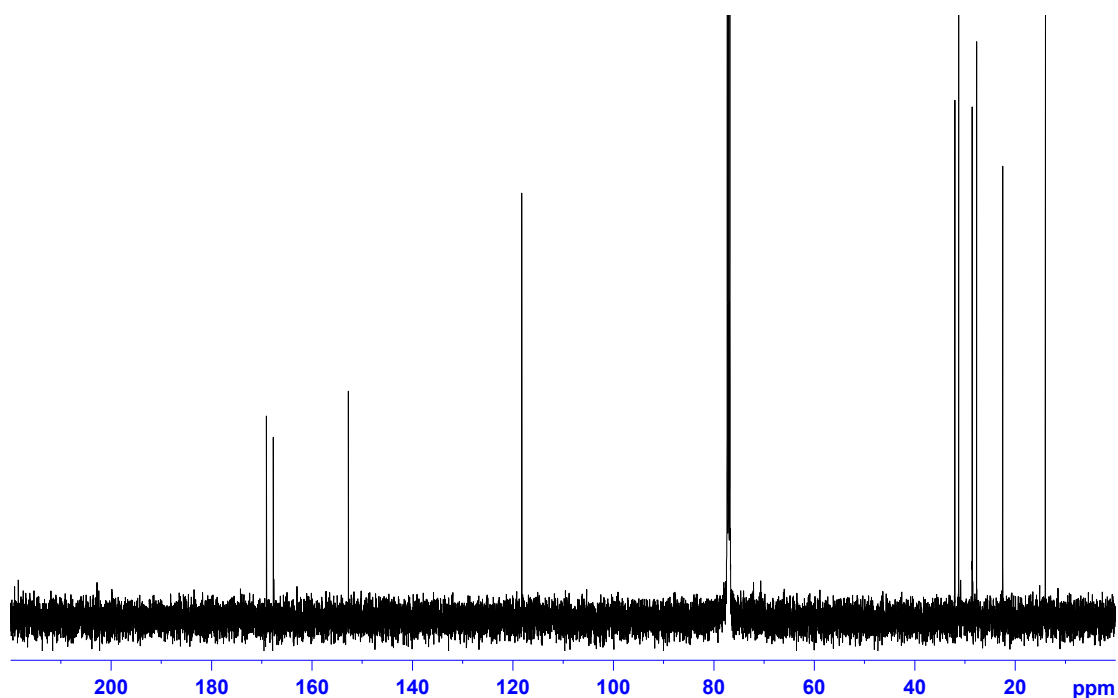


To bromomaleimide¹ (300 mg, 1.69 mmol) and sodium acetate (138 mg, 1.69 mmol) in methanol (100 mL) was added hexanethiol (237 μ L, 1.69 mmol). After 5 minutes the solvent was removed *in vacuo* and purification by flash chromatography (10% ethyl acetate in petroleum ether) afforded **3** as an off-white powder (362 mg, 1.69 mmol) in 100% yield. δ_{H} (500 MHz, CDCl_3) 7.35 (s, 1H, NH), 6.04 (s, 1H, H-8), 2.91 (t, 2H, $J = 7.4$, H₂-6), 1.78-1.72 (m, 2H, H₂-5), 1.48-1.42 (m, 2H, CH₂), 1.33-1.30 (m, 4H, 2 x CH₂), 0.90 (t, 3H, $J = 6.9$, H₃-1); δ_{C} (125 MHz, CDCl_3) 169.06 (C=O), 167.69 (C=O), 152.74 (C7), 118.24 (C8), 32.06 (C6), 31.26 (CH₂), 28.58 (CH₂), 27.70 (CH₂), 22.52 (CH₂), 14.03 (C1); IR (solid, cm^{-1}) 3200 (m), 2918 (m), 1703 (s); MS (ES-) m/z (relative intensity): 212 ([M-H], 100); Exact Mass Calcd for $[\text{C}_{10}\text{H}_{15}\text{NO}_2\text{S}]\text{-H}$ requires m/z 212.0745 Found 212.0753 (ES-); Elemental analysis: Calc for $\text{C}_{10}\text{H}_{15}\text{NO}_2\text{S}$: C: 56.31, H: 7.09, N: 6.57 Found: C: 55.96, H: 7.02, N: 6.56; m.p. 99-101 $^{\circ}\text{C}$; UV (Acetonitrile) $\epsilon_{247} = 12000$ and $\epsilon_{347} = 9500 \text{ cm}^{-1}\text{M}^{-1}$.

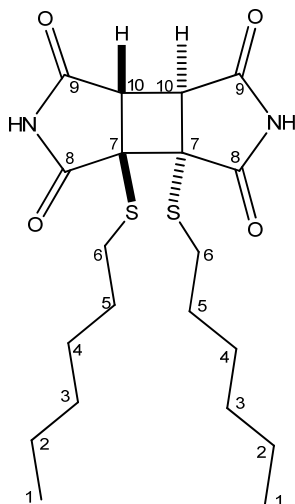
¹H NMR



¹³C NMR



4. (4RS, 5RS, 9SR, 10SR) - 4, 5-Dihexylsulfanyl-2,7-diaza-bicyclo [3.5.0.0^{5,9}]decantetra-1,3,6,8-one. Stereochemistry and regiochemistry defined with analogy to dimer model, see page S10.



Method 1: **3** (25 mg, 0.116 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* to afford **4** as an off-white solid (25 mg, 0.116 mmol) in 100% yield. δ_{H} (500 MHz, CDCl₃) 3.14-3.09 (m, 4H, 2 x H-10 and 2 x HH-6), 2.84 (dt, 2H, $J = 11.0$ and 7.6 , 2 x HH-6), 1.56-1.50 (m, 4H, 2 x H₂-5), 1.38-1.33 (m, 4H, 2 x H₂-4), 1.31-1.25 (m, 8H, 2 x H₂-3 and 2 x H₂-2), 0.87

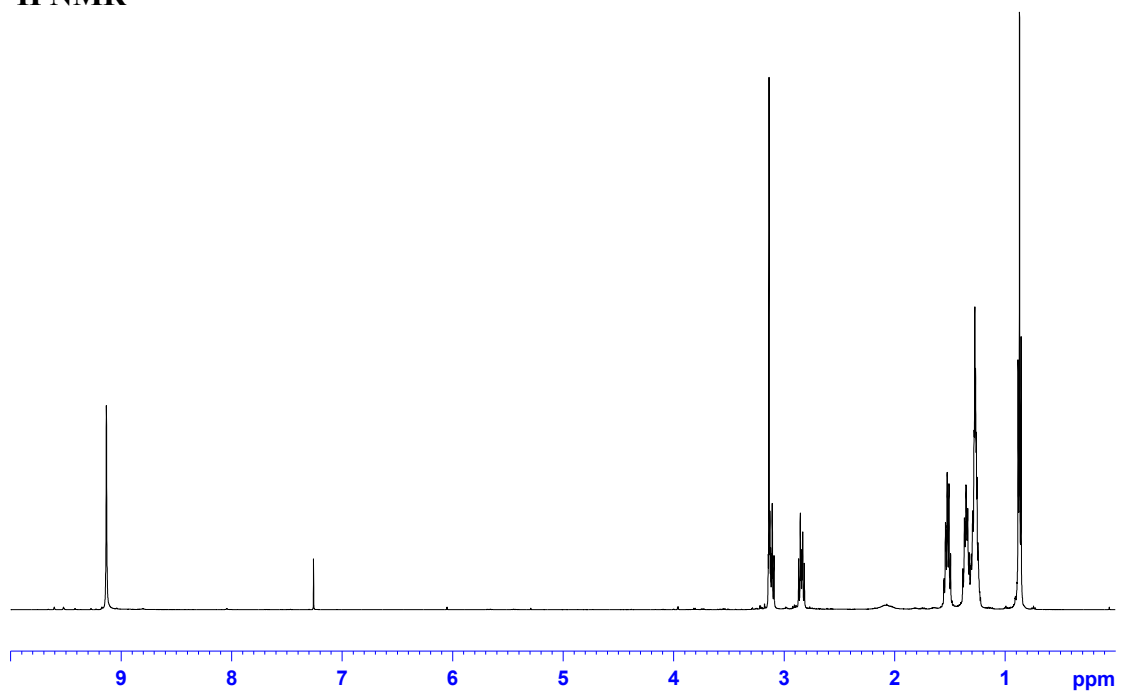
(t, 6H, $J = 7.0$, 2 x H₃-1); δ_{C} (125 MHz, CDCl₃) 173.37 (2 x C=O), 172.82 (2 x C=O), 56.26 (2 x C7), 45.66 (2 x C10), 31.36 (2 x CH₂), 31.16 (2 x H₂-6), 28.64 (2 x CH₂), 28.53 (2 x CH₂), 22.51 (2 x CH₂), 14.07 (2 x C1); IR (solid, cm⁻¹) 3194 (m), 2933 (m), 1719 (s); MS (ES-) m/z (relative intensity): 425 ([M-H], 35), 212 (100); Exact Mass Calcd for [C₂₀H₃₀N₂O₄S₂]-H requires m/z 425.1584 Found 425.1584 (ES-); m.p. 116-118 °C.

Method 2: **3** (5 mg, 0.023 mmol) was dissolved in acetonitrile (300 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* to afford **4** as an off-white solid (5 mg, 0.023 mmol) in 100% yield. Spectra matched that obtained above.

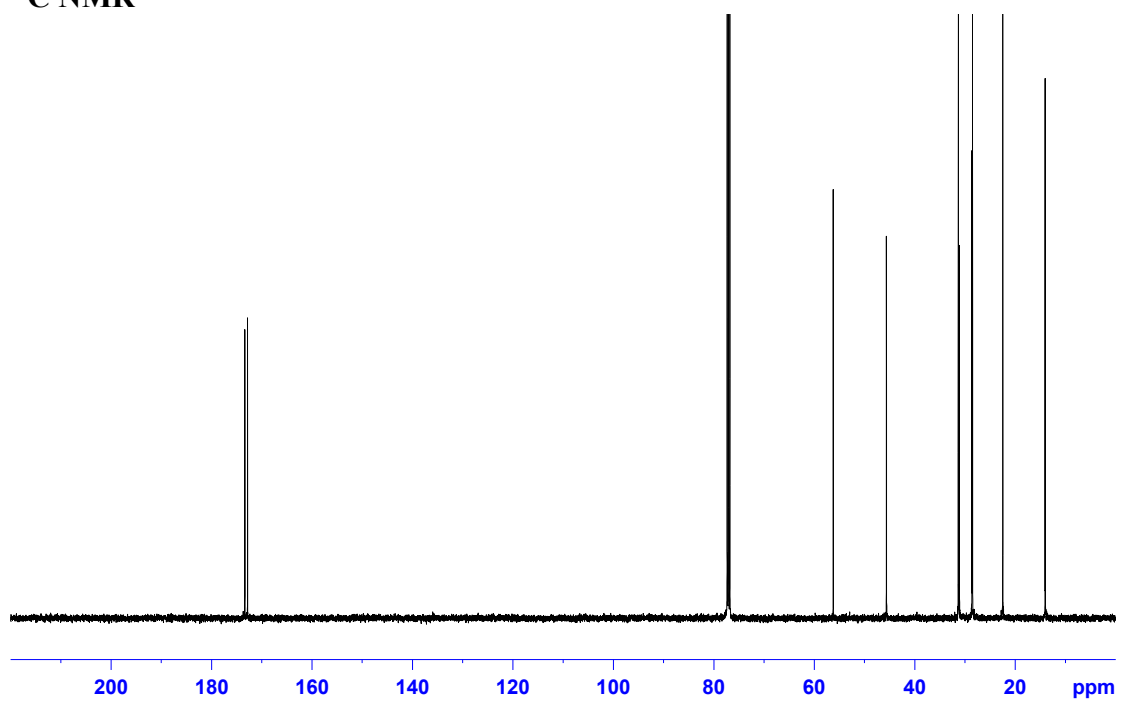
Method 3: **3** (25 mg, 0.116 mmol) was dissolved in water:acetonitrile (23.75 mL:1.25 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* to afford **4** as an off-white solid (25 mg, 0.116 mmol) in 100% yield. Spectra matched that obtained above.

Method 4: **3** (5 mg, 0.023 mmol) was dissolved in water:acetonitrile (285 mL:15 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* to afford **4** as an off-white solid (5 mg, 0.023 mmol) in 100% yield. Spectra matched that obtained above.

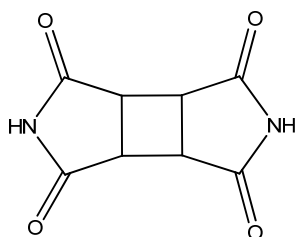
^1H NMR



^{13}C NMR

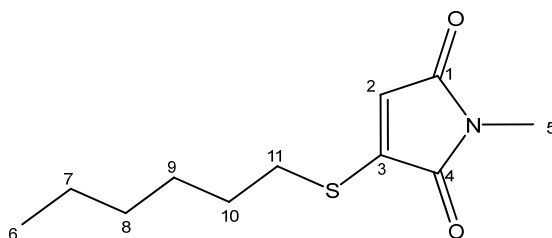


2,7-diaza-bicyclo [3.5.0.0^{5,9}]decanetra-1,3,6,8-one. Stereochemistry not defined.



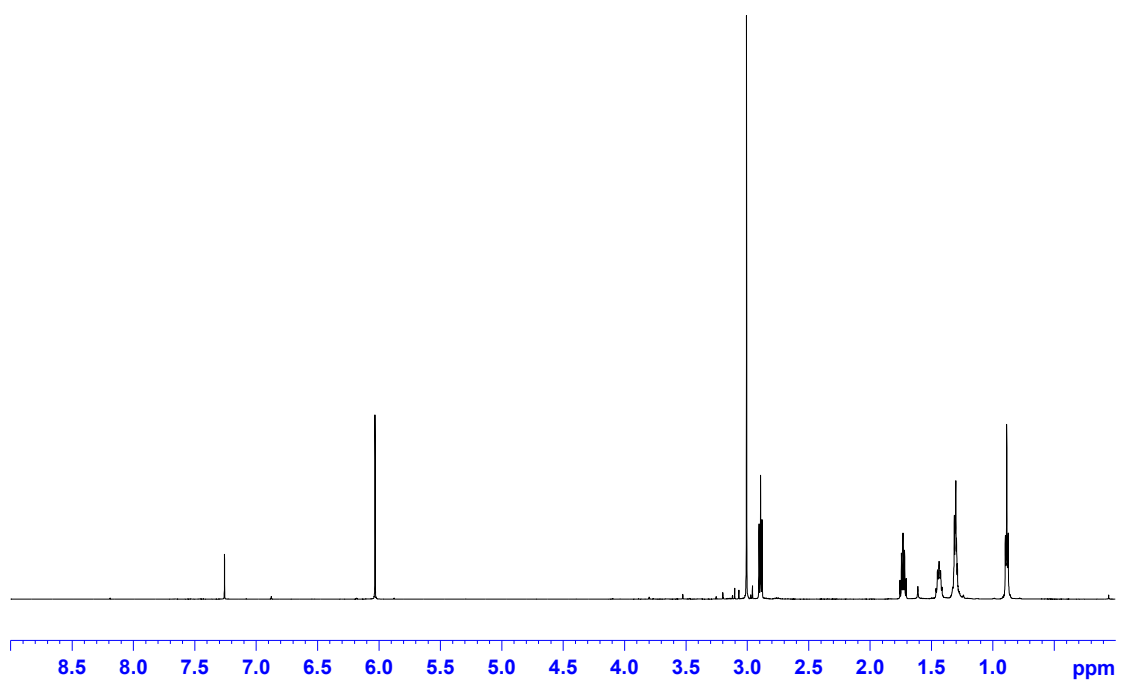
Maleimide (23 mg, 0.232 mmol) was dissolved in acetonitrile (50 mL). The resulting solution was degassed for 30 minutes and irradiated to complete consumption of starting material in pyrex glassware (1 hour) with stirring. The solvent was removed *in vacuo* to afford the title compound as an off-white solid (23 mg, 0.232 mmol) in 100% yield. δ_{H} (600 MHz, MeOD) 4.74 (br s, 2H, 2 x NH), 3.76 (s, 4H, 4 x CH); δ_{C} (150 MHz, MeOD) 178.22 (4 x C=O), 42.08 (4 x CH); Data is in accordance with P. Boule and J. Lemaire, *J. Chim. Phys. Phys.-Chim. Biol.*, 1980, **77**, 161-165.

5. 3-Hexylsulfanyl-1-methyl-pyrrole-2,5-dione

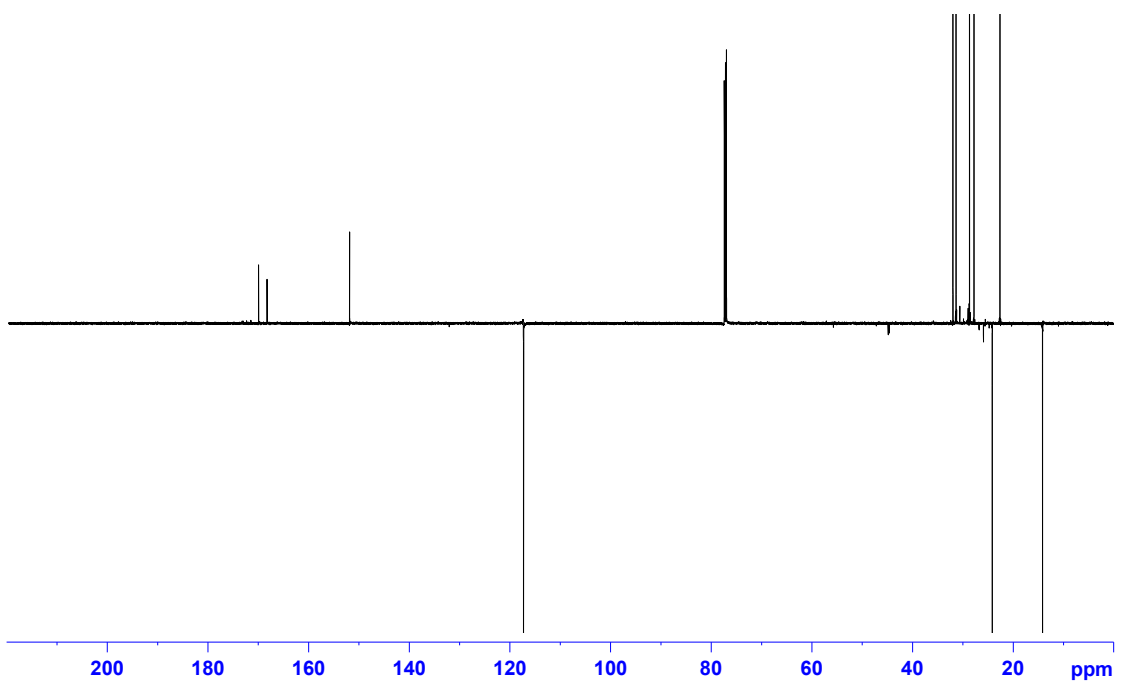


To N-methyl bromomaleimide¹ (100 mg, 0.53 mmol) and sodium acetate trihydrate (70 mg, 0.53 mmol) in methanol (15 mL) was added hexanethiol (74 μL , 0.58 mmol) in methanol (100 mL) dropwise over 1 hour with vigorous stirring. After 5 minutes the solvent was removed *in vacuo*. Purification by flash chromatography (gradient elution in 10% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **5** as a bright yellow solid (99 mg, 0.44 mmol) in 83% yield. δ_{H} (600 MHz, CDCl_3) 6.03 (s, 1H, H-2), 3.01 (s, 3H, H₃-5), 2.89 (t, 2H, $J = 7.6$, 2H, H₂-11), 1.76-1.71 (m, 2H, H₂-10), 1.46-1.41 (m, 2H, H₂-9), 1.33-1.27 (m, 4H, H₂-7 and H₂-8), 0.89 (t, 3H, $J = 6.5$, H₃-6); δ_{C} (125 MHz, CDCl_3) 171.47 (C=O), 169.94 (C=O), 151.84 (C3), 117.27 (C2), 31.92 (C11), 31.31 (CH₂), 28.64 (CH₂), 27.75 (CH₂), 24.10 (C5), 24.10 (C7), 14.09 (C6); IR (oil, cm^{-1}) 2727 (w), 1708 (s); MS (FAB+) m/z (relative intensity): 250 ([M+Na], 40), 228 (35), 199 (30), 176 (100); Exact Mass Calcd for $[\text{C}_{11}\text{H}_{17}\text{NO}_2\text{S}]+\text{Na}$ requires m/z 250.0878 Found 250.0880 (FAB+); m.p. 62-65 °C; UV (Acetonitrile) $\epsilon_{264} = 8010$ and $\epsilon_{360} = 3200 \text{ cm}^{-1}\text{M}^{-1}$.

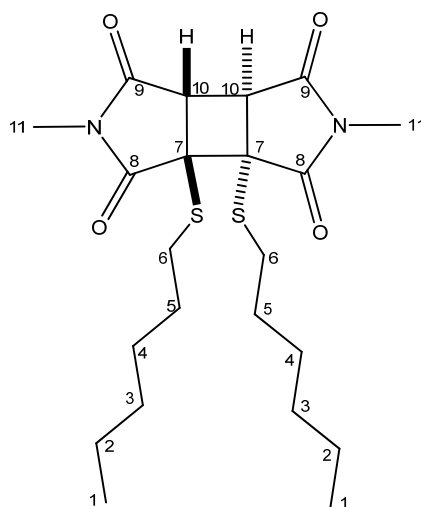
^1H NMR



^{13}C DEPTQ NMR

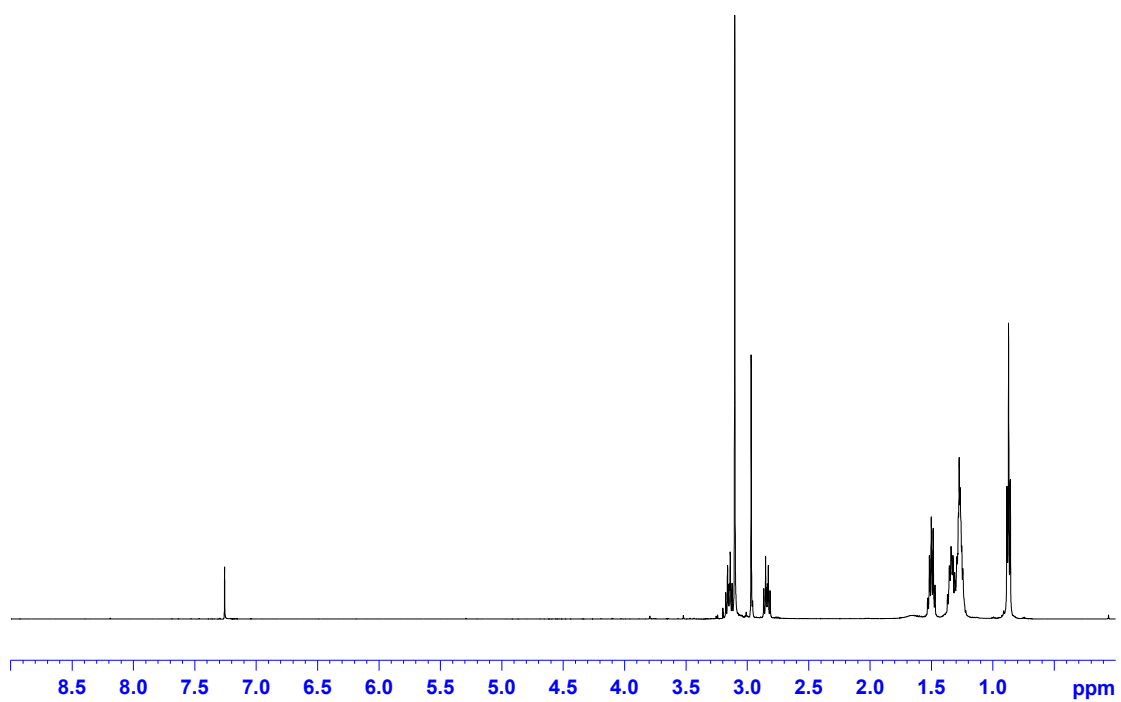


6. (4RS, 5RS, 9SR, 10SR) - 4, 5-Dihexylsulfanyl-2,7-dimethyl-2,7-diaza-bicyclo [3.5.0.0^{5,9}]decantetra-1,3,6,8-one. Stereochemistry and regiochemistry defined with analogy to dimer model, see page S10.

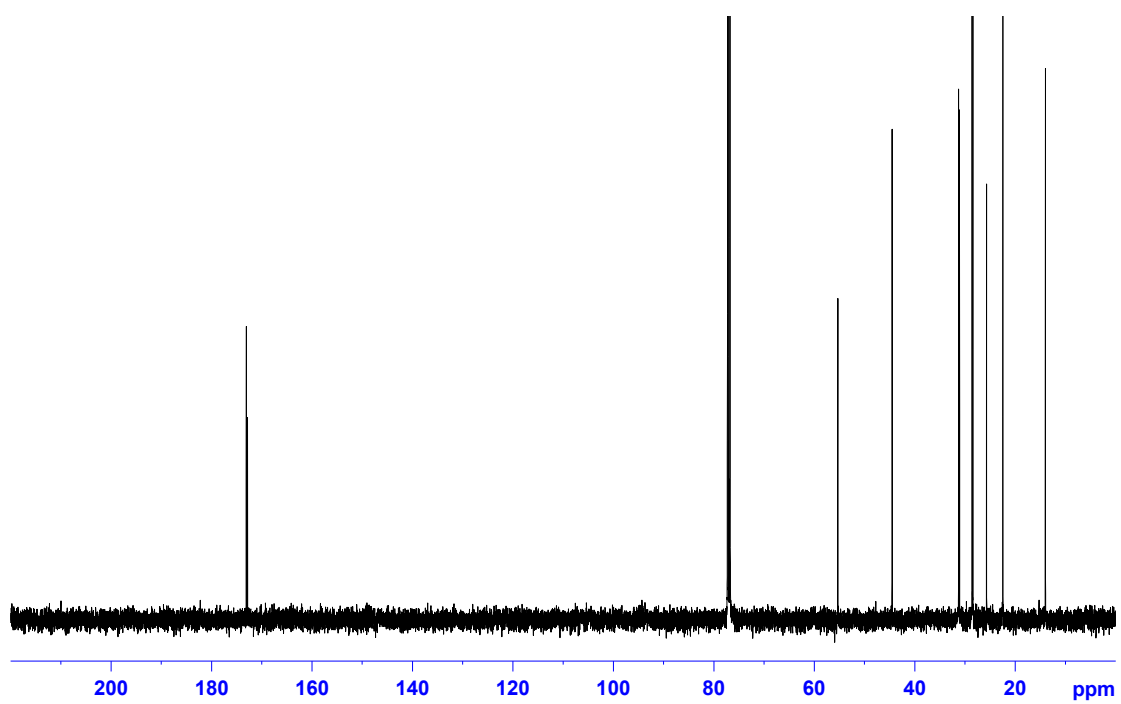


5 (25 mg, 0.11 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* to afford **6** as an off white solid (25 mg, 0.11 mmol) in 100% yield. δ_{H} (500 MHz, CDCl_3) 3.15 (dt, 2H, $J = 11.0$ and 7.3 , 2 x HH-6), 3.11 (s, 6H, 2 x H_3 -11), 2.97 (s, 2H, 2 x H-10), 2.84 (dt, 2H, $J = 11.0$ and 7.5 , 2 x HH-6), 1.53-1.47 (m, 4H, 2 x H_2 -5), 1.37-1.25 (m, 12H, 6 x CH_2), 0.87 (t, 6H, $J = 6.7$, 2 x H_3 -1); δ_{C} (125 MHz, CDCl_3) 173.11 (2 x C=O), 172.87 (2 x C=O), 55.39 (2 x C7), 44.56 (2 x C11), 31.34 (2 x CH_2), 31.16 (2 x CH_2), 28.66 (2 x CH_2), 28.49 (2 x CH_2), 25.76 (2 x C10), 22.53 (2 x CH_2), 14.05 (2 x C1); IR (oil, cm^{-1}) 3463 (w), 2970 (m) 1744 (s), 1720 (s); MS (CI+) m/z (relative intensity): 455 ([M+H], 50), 228 (100), 194 (60); Exact Mass Calcd for $[\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_4\text{S}_2]+\text{H}$ requires m/z 455.2038 Found 455.2019 (CI+); m.p. 104-106 °C.

^1H NMR

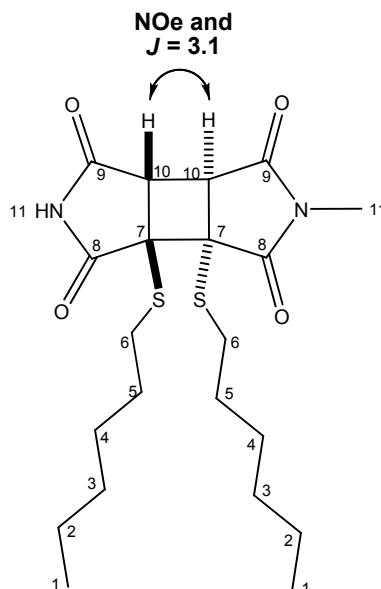


^{13}C NMR



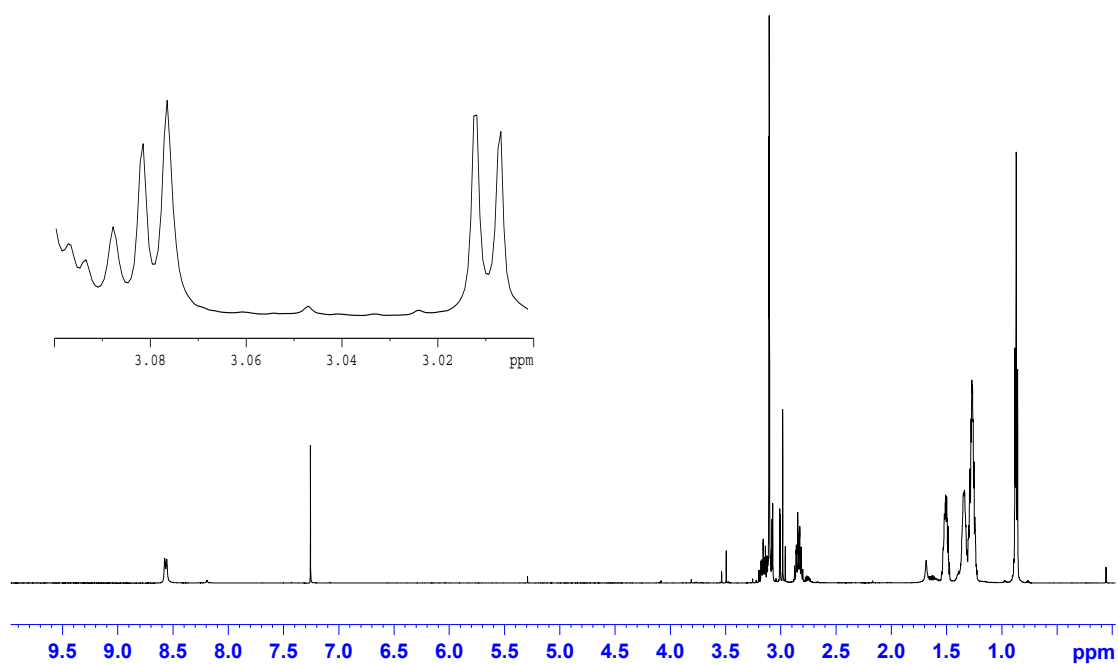
Dimer model

(4RS, 5RS, 9SR, 10SR) - 4, 5-Dihexylsulfanyl-2-methyl-2,7-diaza-bicyclo [3.5.0.0^{5,9}]decantetra-1,3,6,8-one. Stereochemistry and regiochemistry defined by analysis of coupling constants.

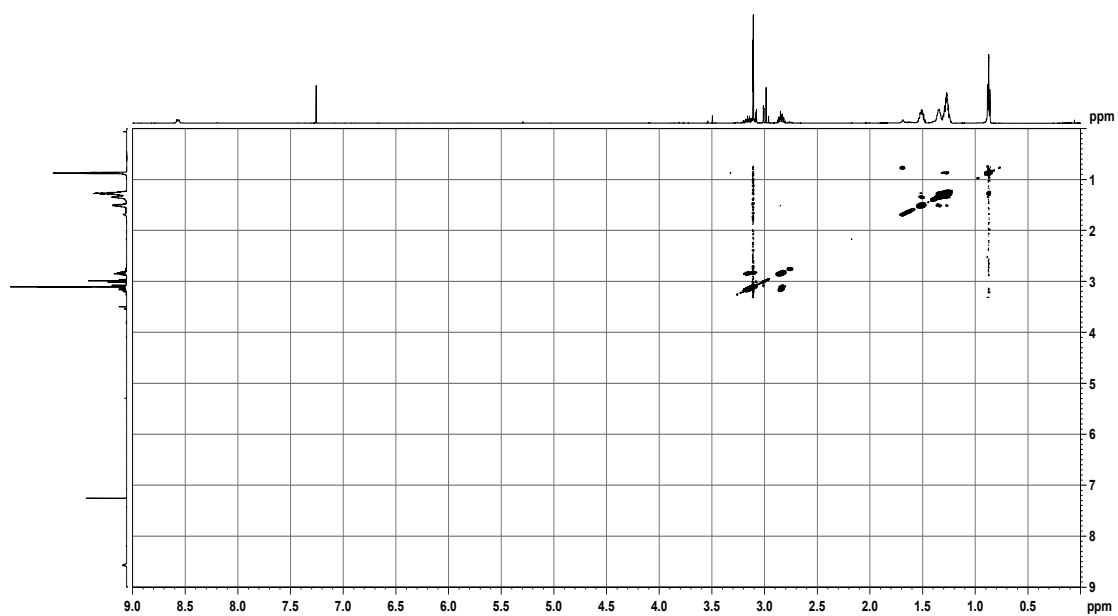


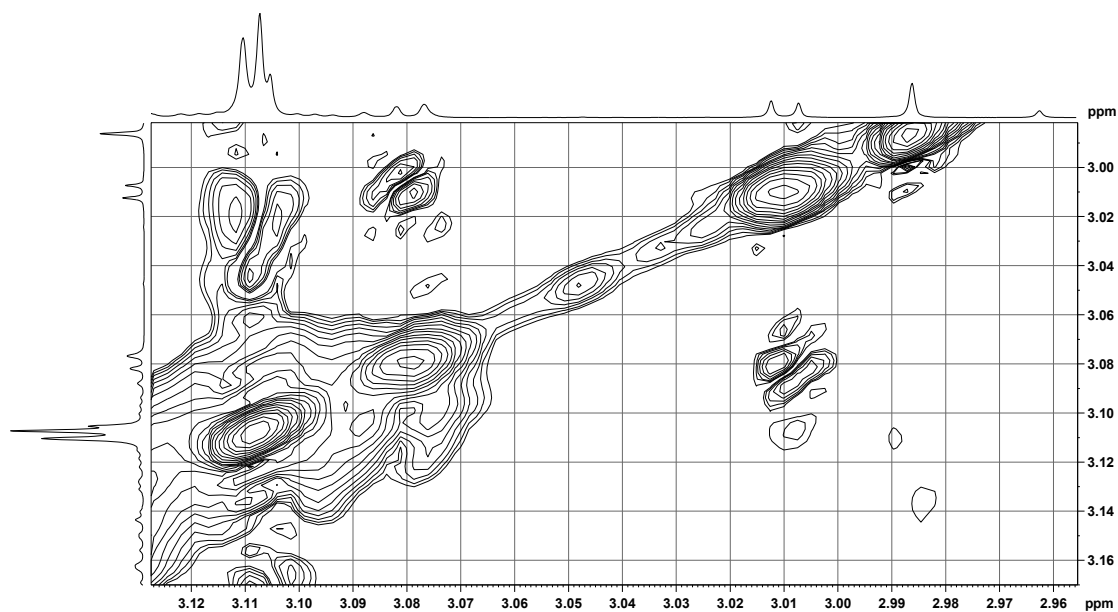
3 (12.5 mg, 0.058 mmol) and **5** (12.5 mg, 0.058 mmol) were dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* to afford an inseparable mixture of dimers **4** and **6**, alongside a product of the above structure. Full spectral analysis was not possible due to the complex mixture of structures but in an isolated area of the spectra, NOESY and coupling constant analysis indicated that the structure was of the stereochemistry show. A weak NOE between the indicated protons demonstrated that the dimer was head-to-head, whilst a coupling constant of 3.1 Hz arose from the *trans* configuration of the dimer.² (See also calculations of expected coupling constants on page S21).

^1H NMR

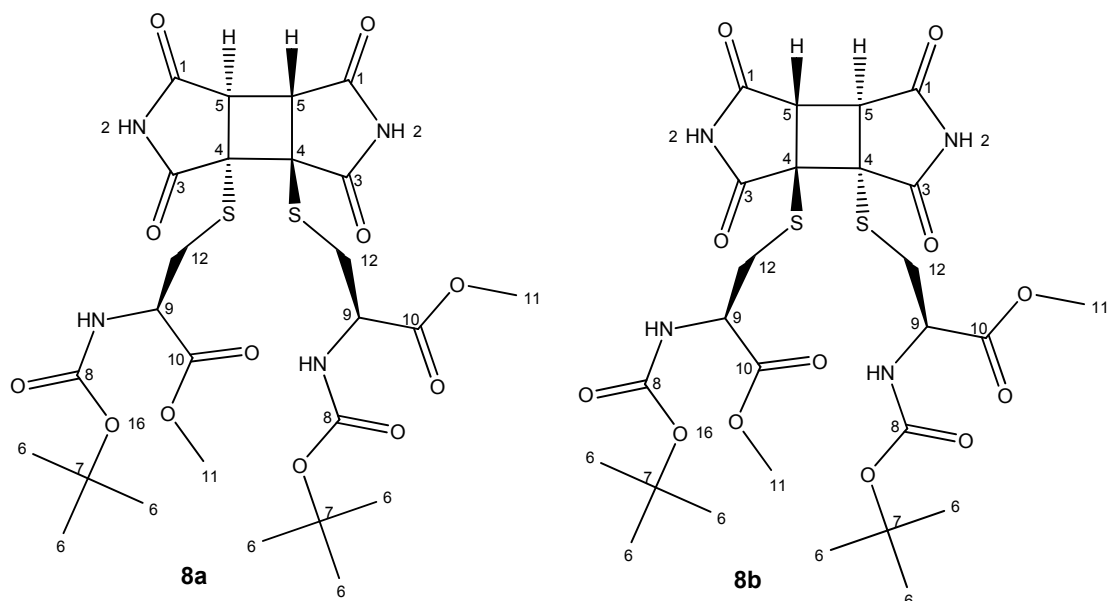


$^1\text{H}, ^1\text{H}$ -NOESY





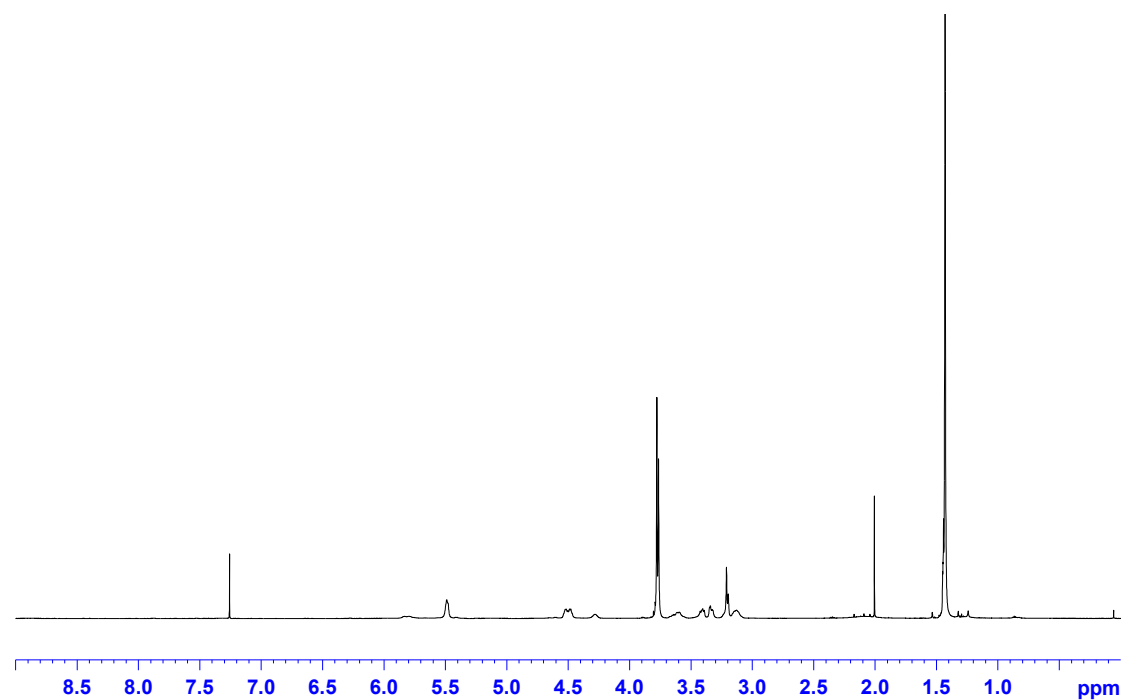
8a. (9R, 10R) – 4S, 5S-Di[2R-*tert*-butoxycarbonylamino-3-sulfanyl-propionic acid methyl ester]-2,7-diaza-bicyclo [3.5.0.0^{5,9}]decantetra-1,3,6,8-one and **8b.** (9S, 10S) – 4R, 5R-di[2R-*tert*-butoxycarbonylamino-3-sulfanyl-propionic acid methyl ester]-2,7-diaza-bicyclo [3.5.0.0^{5,9}]decantetra-1,3,6,8-one. Stereochemistry and regiochemistry defined with analogy to **10**.



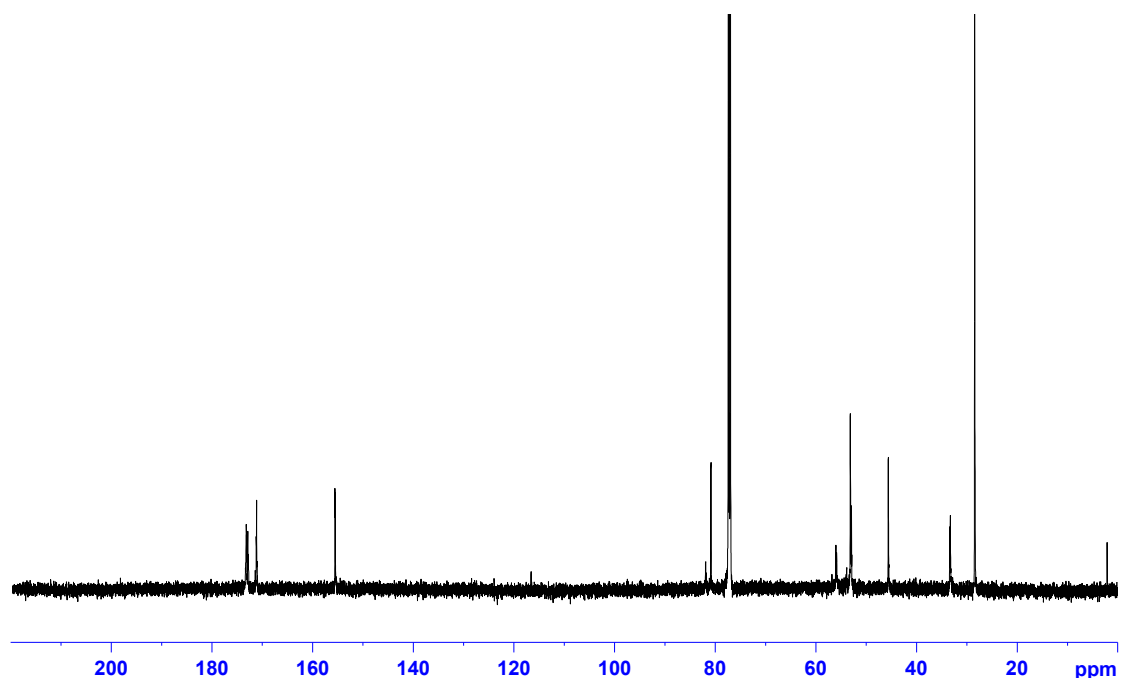
7¹ (39 mg, 0.117 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* to afford a mixture of **8a** and **8b** as a yellow solid (39 mg, 0.117 mmol) in 100% yield. NMR investigations showed the

mixture was a 1:1 ratio of **8a:8b**. δ_{H} (600 MHz, CDCl_3) 5.49 (s, 2H, 2 x 8-NH), 5.48 (s, 2H, 2 x 8-NH), 4.54-4.52 (m, 2H, 2 x H-9), 4.50-4.47 (m, 2H, 2 x H-9), 3.78 (s, 6H, 2 x H_3 -11), 3.76 (s, 6H, 2 x H_3 -11), 3.66-3.59 (m, 2H, 2 x HH-12), 3.42-3.39 (m, 2H, 2 x HH-12), 3.35-3.32 (m, 2H, 2 x HH-12), 3.21 (s, 4H, 4 x H-5), 3.16-3.11 (m, 2H, 2 x HH-12), 1.43 (s, 36H, 12 x H_3 -6); δ_{C} (150 MHz, CDCl_3) 173.17 (2 x C=O), 173.11 (2 x C=O), 172.85 (2 x C=O), 172.76 (2 x C=O), 171.11 (2 x C=O), 171.18 (2 x C=O), 155.53 (2 x C=O), 155.49 (2 x C=O), 80.82 (4 x C7), 55.83 (4 x C4), 53.11 (4 x C11), 52.89 (4 x C9), 45.57 (4 x C5), 33.34 (2 x C12), 33.22 (2 x C12), 28.40 (12 x C6); IR (film, cm^{-1}) 3171 (w), 2980 (w), 1721 (s); MS (ES+) m/z (relative intensity): 683 ([M+Na], 95), 505 (100); Exact Mass Calcd for $[\text{C}_{26}\text{H}_{36}\text{N}_4\text{O}_{12}\text{S}_2]+\text{Na}$ requires m/z 683.1669 Found 683.1666 (ES+). m.p. 144-146 °C;

^1H NMR

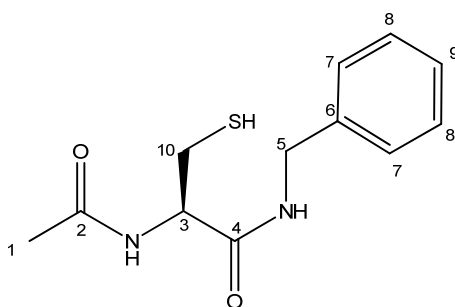


¹³C NMR



The ¹H NMR spectrum of this compound was not sufficiently resolved to distinguish ¹³C satellites and their splitting to aid characterisation of the dimer structure. Therefore, a second amino acid based thiomaleimide was synthesised and its dimer's spectra analysed to aid structural elucidation. Its synthesis and subsequent irradiation are described below.

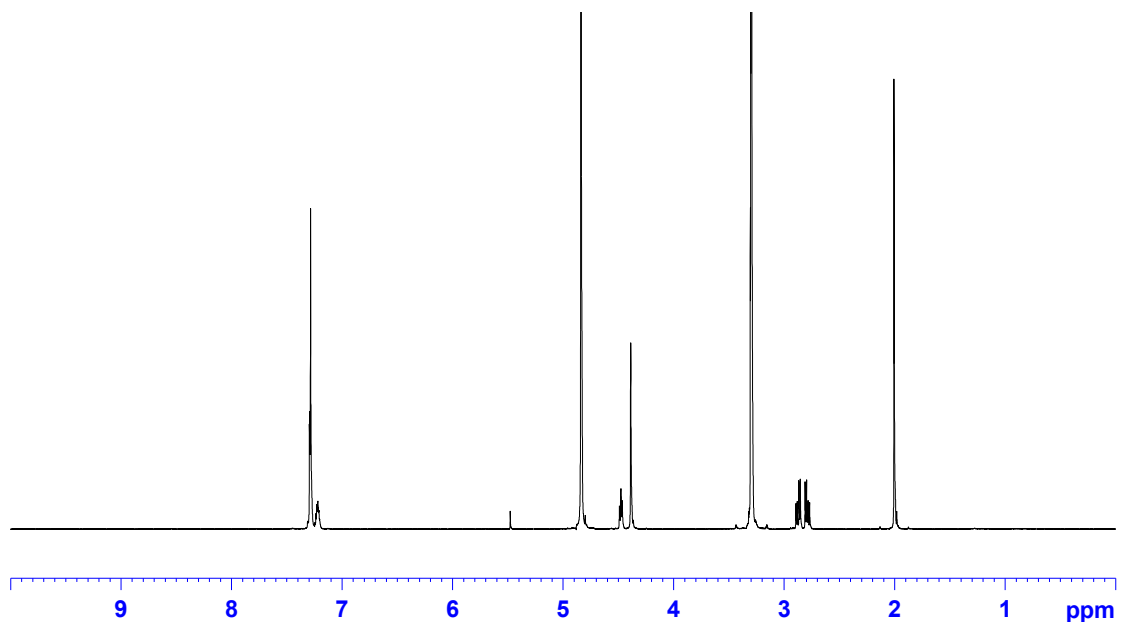
2R-Acetylamino-*N*-benzyl-3-mercapto-propionamide



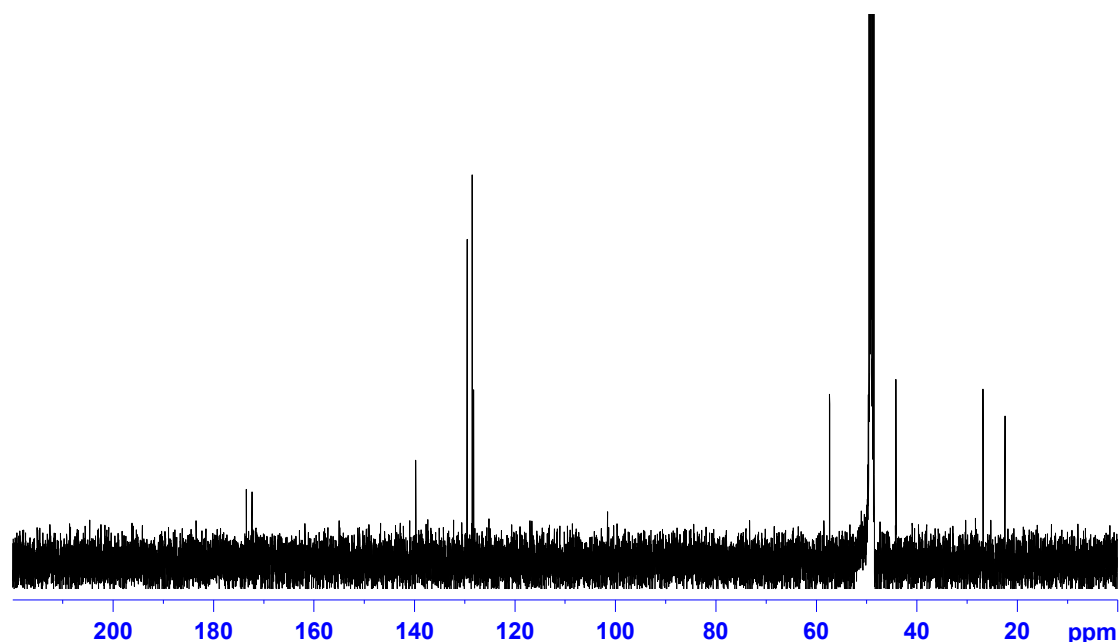
To 2S-acetylamino-3-mercapto-propionic acid (500 mg, 3.07 mmol) in dichloromethane (25 mL) and DMF (3 mL) at 0 °C, was added HOBt (456 mg, 3.38 mmol), benzylamine (0.50 mL, 4.60 mmol) and finally EDC (0.65 g, 3.38 mmol). The reaction was brought to room temperature and stirred for 16 hours. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in

dichloromethane to 3% methanol in dichloromethane) afforded 2R-acetylamino-*N*-benzyl-3-mercapto-propionamide as a white solid (434 mg, 1.72 mmol) in 56% yield. δ_{H} (500 MHz, MeOD) 7.29-7.23 (m, 5H, 5 x Ar-H), 4.48 (dd, 1H, $J = 7.1$ and 5.8, H-3), 4.39 (s, 2H, H₂-5), 2.87 (dd, 1H, $J = 13.9$ and 5.9, HH-10), 2.79 (dd, 1H, $J = 13.9$ and 7.1, HH-10), 2.01 (s, 3H, H₃-1); δ_{C} (125 MHz, MeOD) 173.48 (C=O), 172.36 (C=O), 139.70 (C6), 129.49 (2 x Ar-H), 128.47 (2 x Ar-H), 128.19 (C9), 57.32 (C3), 44.11 (C5), 26.83 (C10), 22.46 (C1); IR (oil, cm^{-1}) 3284 (m), 1630 (w); MS (CI+) m/z (relative intensity): 253 ([M+H], 12), 211 (15), 146 (20), 108 (100); Exact Mass Calcd for $[\text{C}_{12}\text{H}_{16}\text{NO}_2\text{S}]+\text{H}$ requires m/z 253.1011 Found 253.1017 (CI+); m.p. 164 – 166 °C.

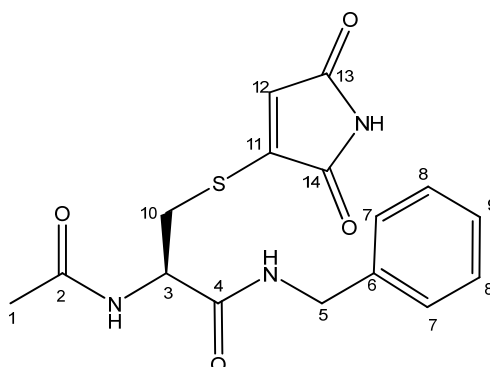
^1H NMR



¹³C NMR



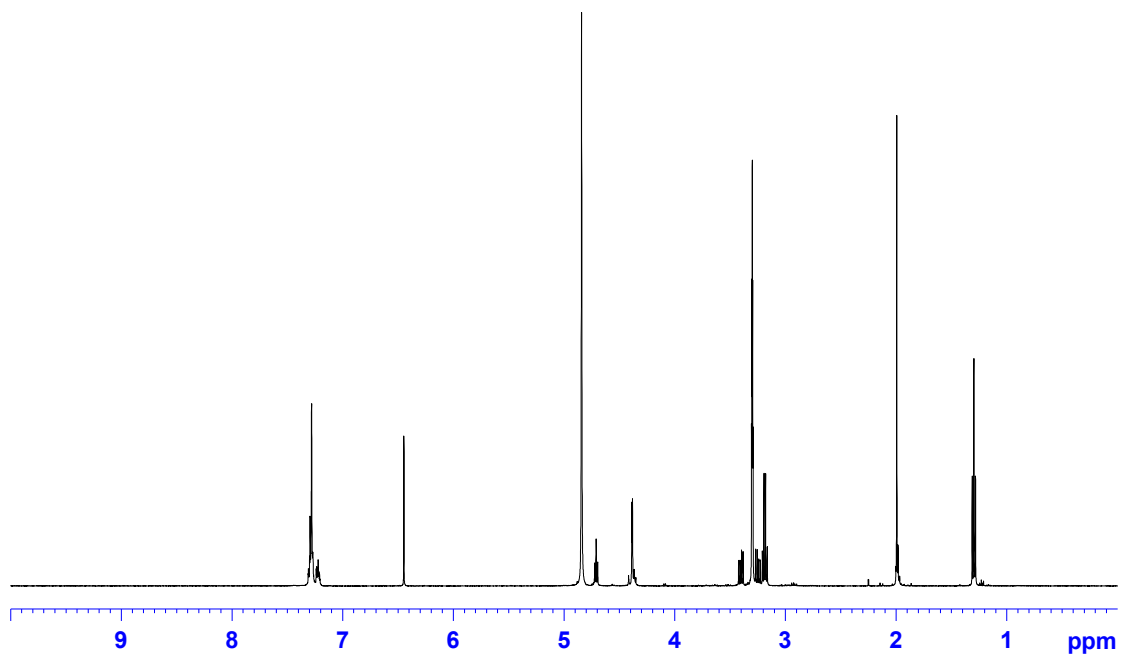
9. 2R-Acetylamino-*N*-benzyl-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-3-ylsulfanyl)-propionamide



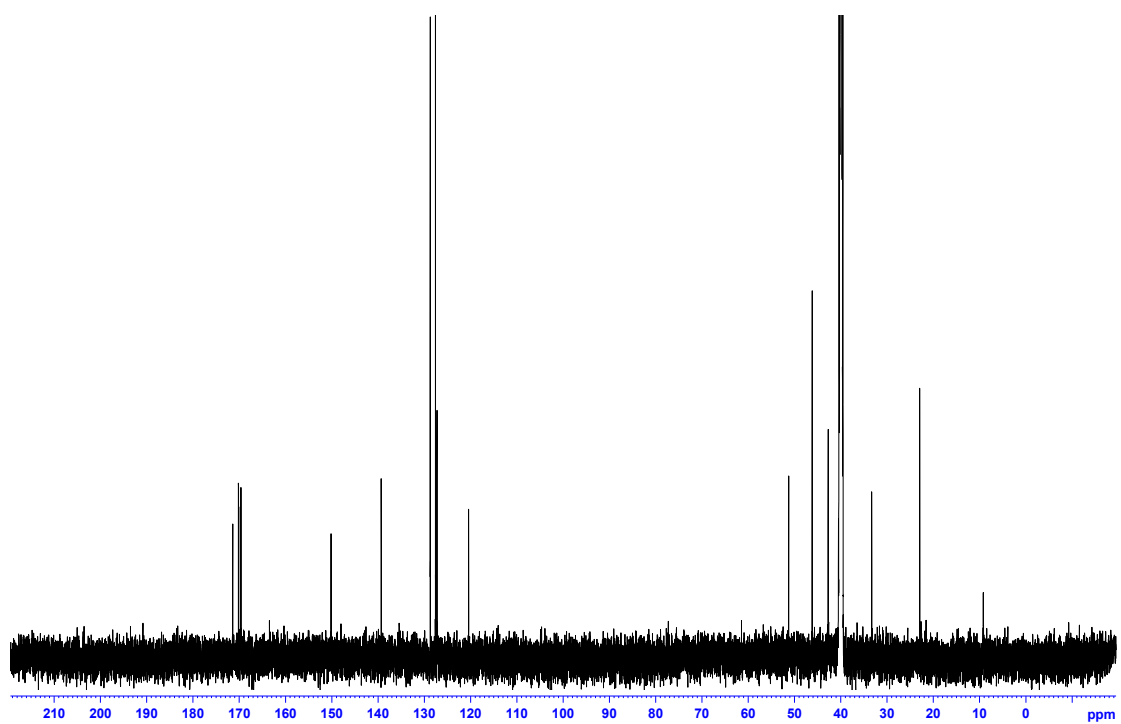
To 2R-acetylamino-*N*-benzyl-3-mercapto-propionamide (1.00 g, 4.00 mmol) in methanol (42 mL), was added bromomaleimide¹ (0.78 g, 4.37 mmol) in methanol (42 mL) dropwise over 5 minutes. After 10 minutes, the solvent was removed *in vacuo* and purification by flash chromatography (10% ethyl acetate in petroleum ether) afforded **9** as an off-white solid (429 mg, 1.2 mmol) in 30% yield and unreacted bromomaleimide¹ (700 mg, 2.8 mmol) in 70%. δ_{H} (500 MHz, MeOD) 7.32-7.20 (m, 5H, 5 x Ar-H), 6.45 (s, 1H, H-12), 4.71 (t, 1H, $J = 7.3$, H-3), 4.38 (d, 2H, $J = 2.7$, H₂-5), 3.40 (dd, 1H, $J = 13.6$ and 7.0 , HH-10), 3.25 (dd, 1H, $J = 13.6$ and 7.0 , HH-10), 1.99 (s, 3H, H₃-1); δ_{C} (125 MHz, MeOD) 173.51 (C=O), 172.22 (C=O), 171.44 (C=O), 170.51 (C=O), 151.58 (C11), 139.48 (C6), 129.54 (2 x Ar-H), 128.51 (2 x Ar-

H), 128.26 (C9), 121.01 (C12) 53.04 (C3), 44.25 (C5), 33.72 (C10), 22.42 (C1); IR (film, cm^{-1}) 3187 (w), 1717 (s), 1646 (s); MS (ES+) m/z (relative intensity): 370 ([M+Na], 20), 337 (50), 325 (90), 309 (100); Exact Mass Calcd for [C₁₆H₁₇N₃O₄S]+Na requires m/z 370.0873 Found 370.0852 (ES+); White solid decomposes above 180 °C; UV (Acetonitrile) $\epsilon_{213} = 19400$, $\epsilon_{247} = 4800$ and $\epsilon_{337} = 2700 \text{ cm}^{-1}\text{M}^{-1}$.

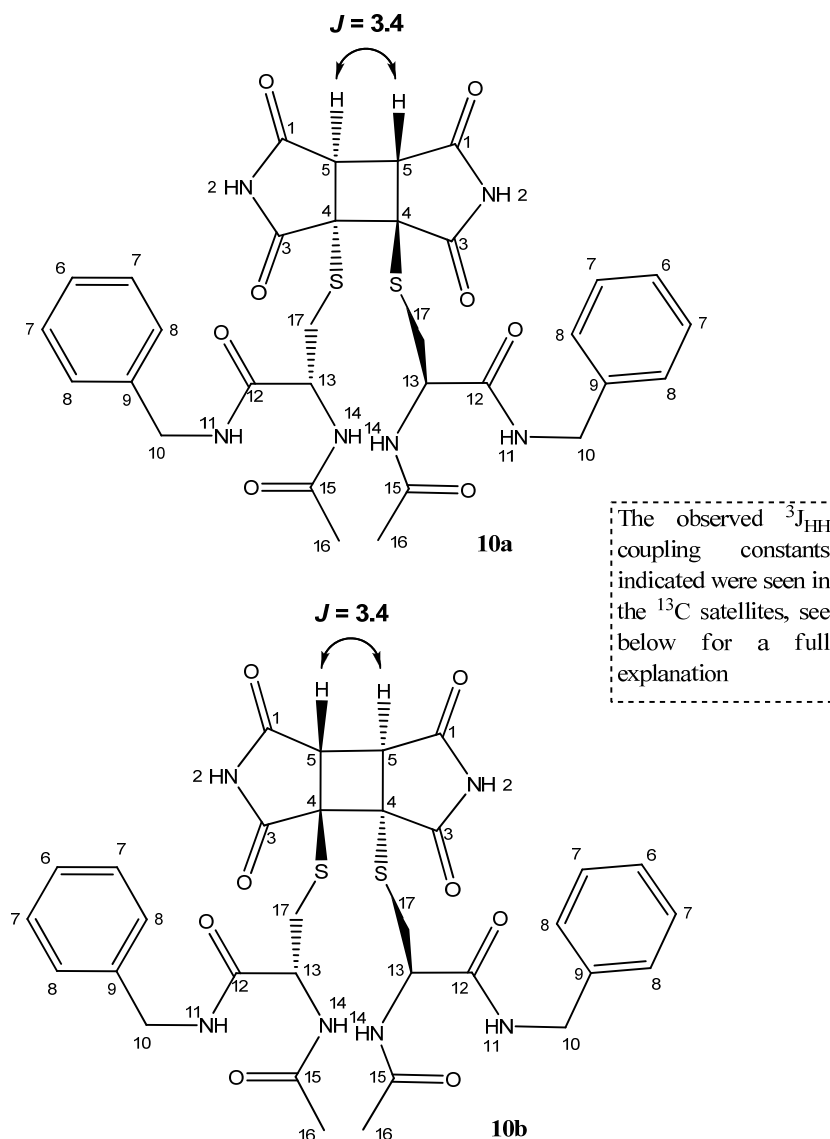
¹H NMR



¹³C NMR



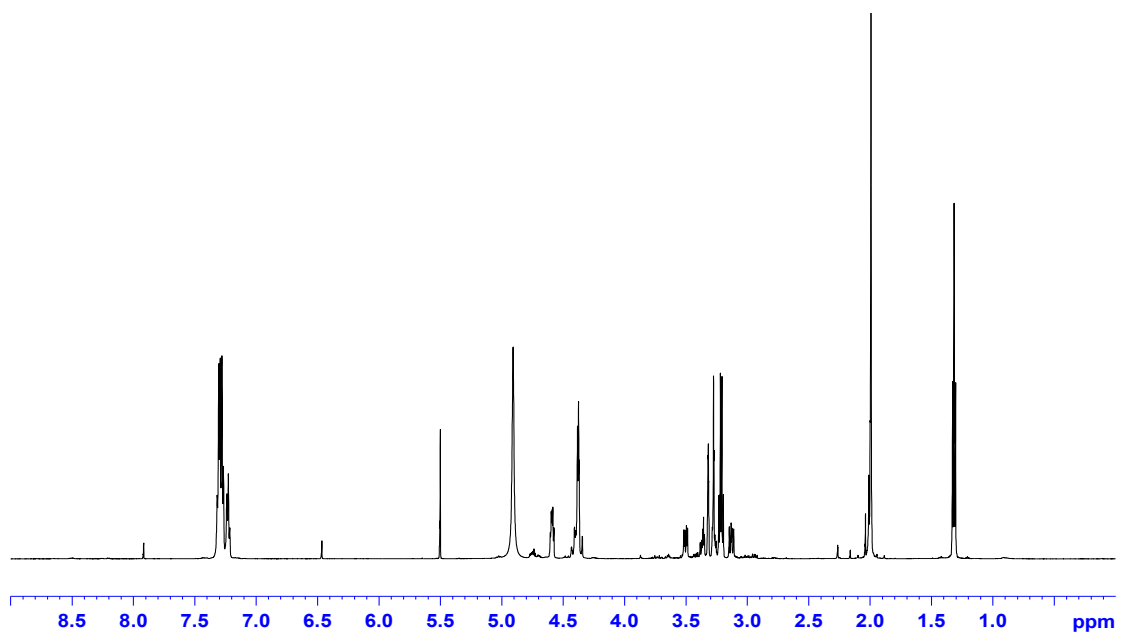
10a. (9R, 10R) – 4S, 5S-Di[2R-acetylamino-*N*-benzyl-3-sulfanyl-propionamide]-2,7-diaza - bicyclo [3.5.0.0^{5,9}]decantetra - 1,3,6,8 - one and **10b.** (9S, 10S) – 4R, 5R - di[2R - acetylamino-*N*-benzyl-3-sulfanyl-propionamide]-2,7-diaza-bicyclo [3.5.0.0^{5,9}]decantetra-1,3,6,8-one.



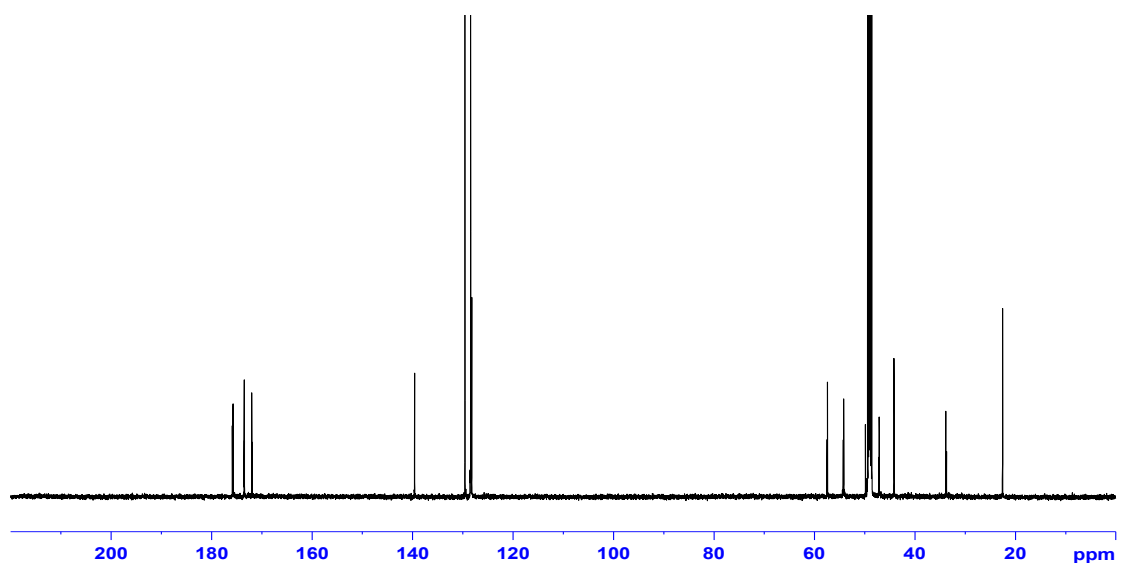
9 (55 mg, 0.16 mmol) was dissolved in acetonitrile (50 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in 30% ethyl acetate in petroleum ether to 10% methanol in ethyl acetate) afforded **10a** and **10b** as a colourless oil (55 mg, 0.16 mmol) in 100% yield. NMR investigations showed the mixture was a 1:1 ratio of the two products. δ_{H} (600 MHz, CDCl_3) 7.37-7.23 (m, 16H, 16 x Ar-H), 7.21 (d, 4H, $J = 7.1$, 4 x H-6), 4.58 (dt, 4H, $J = 7.7$ and 5.0, 4 x H-13), 4.38-4.36 (m, 8H, 4 x H₂-10), 3.49 (dd, 2H, $J = 12.8$

and 5.3, 2 x *HH*-17), 3.35 (s, 2H, 2 x H-5), 3.31-3.30 (m, 4H, 2 x H₂-17) 3.27 (s, 2H, 2 x H-5), 3.12 (dd, 2H, *J* = 12.8 and 8.7, 2 x *HH*-17), 1.99 (s, 12H, 4 x H₃-16); δ_C (150 MHz, CDCl₃) 175.85 (C=O), 175.74 (C=O), 175.72 (C=O), 173.50 (C=O), 173.45 (C=O), 171.98 (C=O), 171.88 (C=O) 139.57 (4 x C9), 129.55 (8 x Ar-H), 128.48 (8 x Ar-H), 128.20 (4 x Ar-H), 57.50 (2 x C4), 57.40 (2 x C4), 54.27 (2 x C13), 54.18 (2 x C13), 47.20 (2 x C5), 47.10 (2 x C5), 44.16 (2 x C10), 44.14 (2 x C10), 33.86 (2 x C17), 33.70 (2 x C17), 22.56 (4 x C16) One carbon signal is missing due to overlap of the diastereomers; IR (oil, cm⁻¹) 3437 (w), 1726 (s); MS (FAB+) *m/z* (relative intensity): 695 ([M+H], 10), 439 (10), 286 (100); Exact Mass Calcd for [C₃₂H₃₄N₆O₈S₂]+H requires *m/z* 695.1958 Found 695.1964 (FAB+).

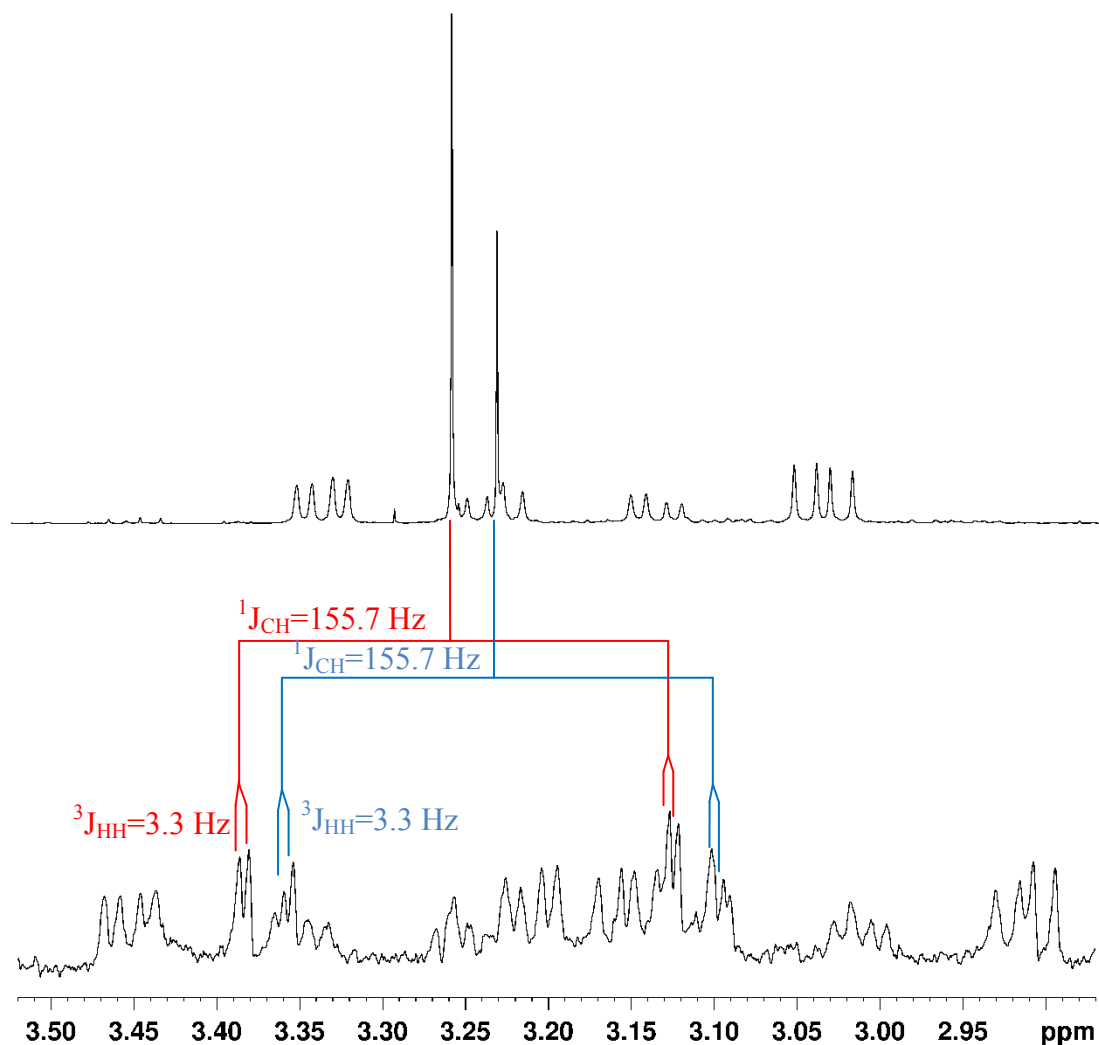
¹H NMR



¹³C NMR



^{13}C satellites in ^1H NMR spectrum in CD_3CN (600 MHz).

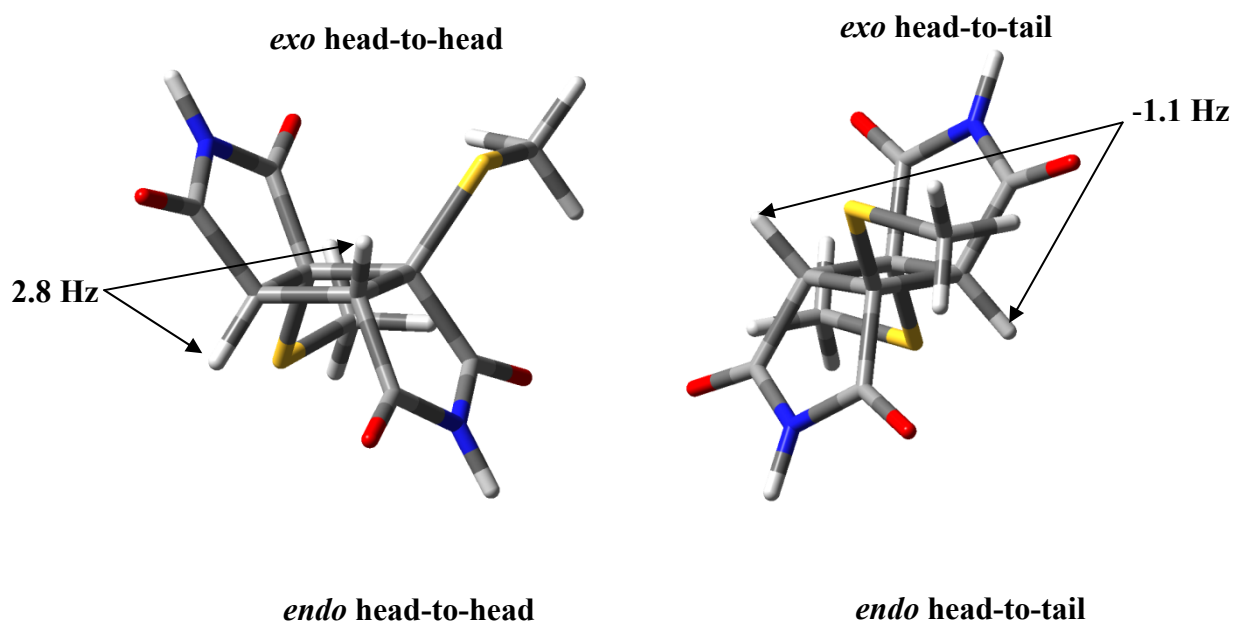


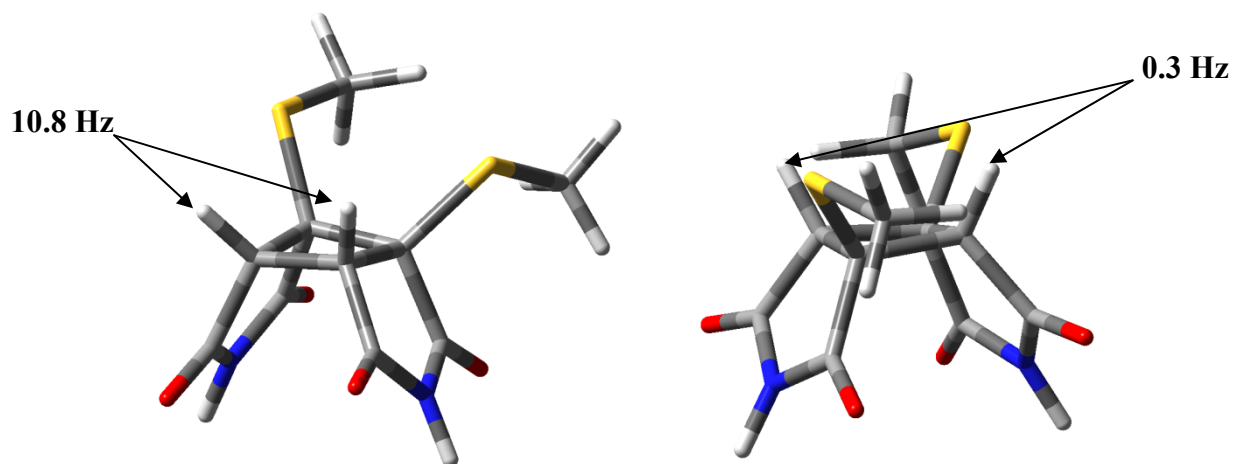
The ^1H spectrum recorded in CD_3CN (top spectrum) showed a relatively large chemical shift difference of 16 Hz for the cyclobutane CH singlets at 3.26 and 3.23 ppm due to two diastereomers with the integral intensity ratio of 3:2. As the two cyclobutane protons are equivalent in **10a** and **10b**, ^{13}C satellites were used for the measurement of the J_{HH} -coupling between them, since the presence of a ^{13}C nucleus (at the natural abundance level) in the cyclobutane ring of **10** introduces the needed inequivalence of the two cyclobutane protons. The spectrum recorded with the suppression of the ^1H signals bonded to ^{12}C and showing only ^{13}C satellite peaks (bottom spectrum, recorded using the one-dimensional version of the HSQC pulse sequence) revealed doublet of doublets (155.7 and 3.3 Hz) for each of the diastereomers. The value of the $^1J_{\text{CH}}$ coupling (155.7 Hz) was additionally confirmed using the proton-coupled ^{13}C spectrum of **10**. The value of the J_{HH} coupling (3.3 Hz)

in both diastereomers indicates that the amino acid containing thiomaleimides also dimerise in head-to-head *exo* fashion (see also section below, titled “Quantum mechanical calculations of NMR J-couplings”).

Quantum Mechanical Calculations of NMR J-couplings.

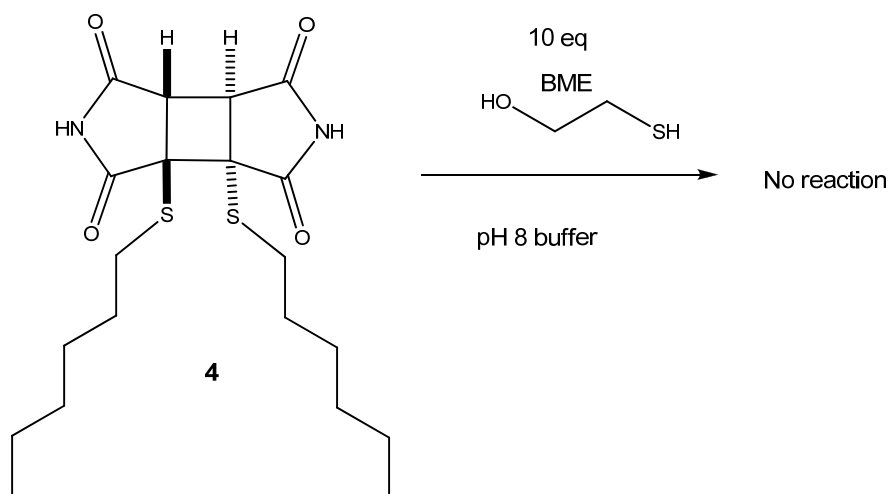
In order to verify the stereochemical dependence of the NMR J-coupling between two cyclobutane protons quantum mechanical calculations of four model molecules were carried out using *Gaussian 09*.³ The geometry optimisations of structures shown below were done using DFT B3LYP/6-31G(d) calculations. Chloroform solvent effects were introduced in all the quantum mechanical calculations using the reaction field method IEFPCM.⁴ Additional frequency calculations were also undertaken in order to verify that the optimized geometries correspond to true minima. The optimised molecular geometries were then used for NMR *J*-coupling calculations, which were computed at the B3LYP/6-311+G(2d,p) level of theory. Within the expected accuracy of ca. ± 1 Hz of the B3LYP/6-311+G(2d,p) calculations of ^1H - ^1H J-couplings,⁵ the value of 2.8 Hz predicted for the *exo* head-to-head configuration of the cyclobutane dimer is in agreement with the experimentally measured values of 3.1 Hz in the dimer model (see page S10) and 3.3 Hz in **10**.



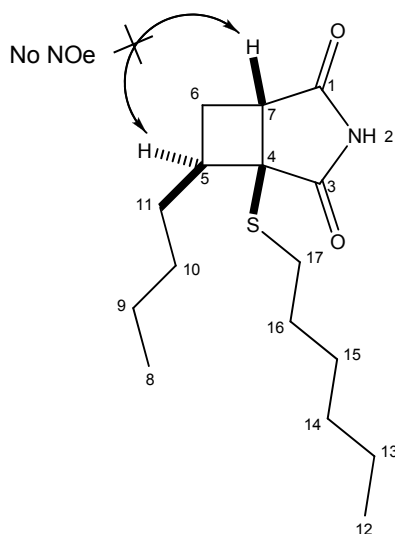


Stability of dimerised thiomaleimides to reducing conditions.

Cyclobutane **4** (5 mg, 0.012 mmol) was dissolved in buffer (2 mL, 150 mM NaCl, 100 mM NaH₂PO₄, pH 8.0) and β -mercaptoethanol (8 μ L, 0.122 mmol) added. No reaction was observed after 1 h, monitored by ¹H NMR.

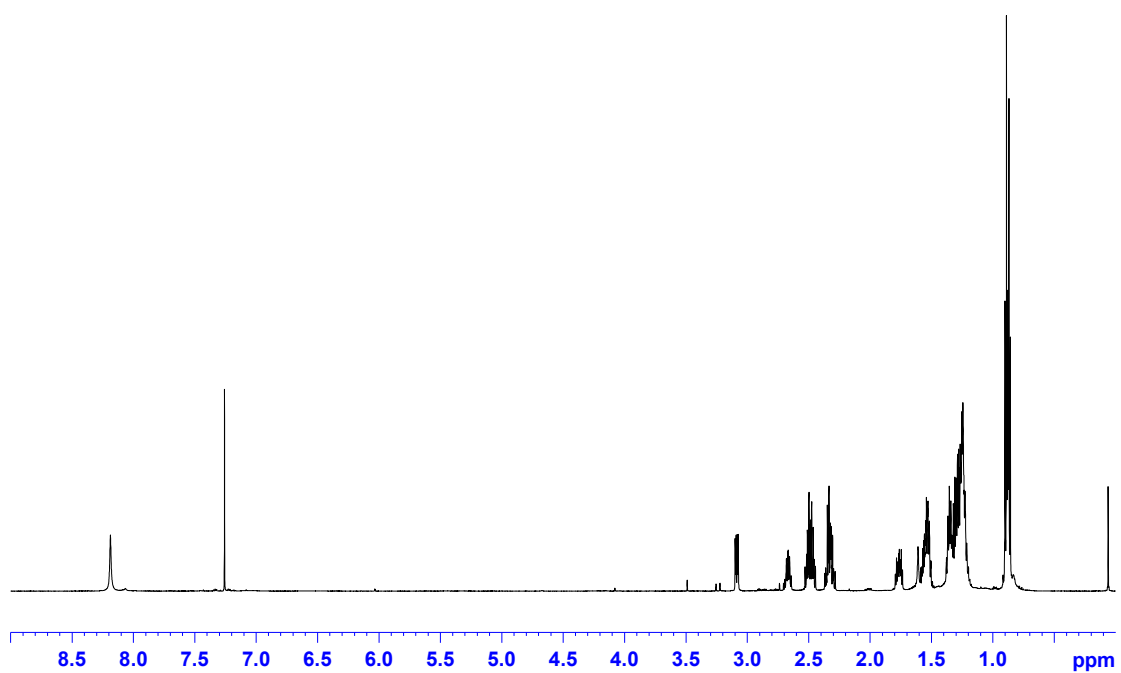


11. (4RS, 5RS, 7SR)-2-Aza-4-hexylsulfanyl-5-butyl-bicyclo[3.2.0]heptan-1,3-dione

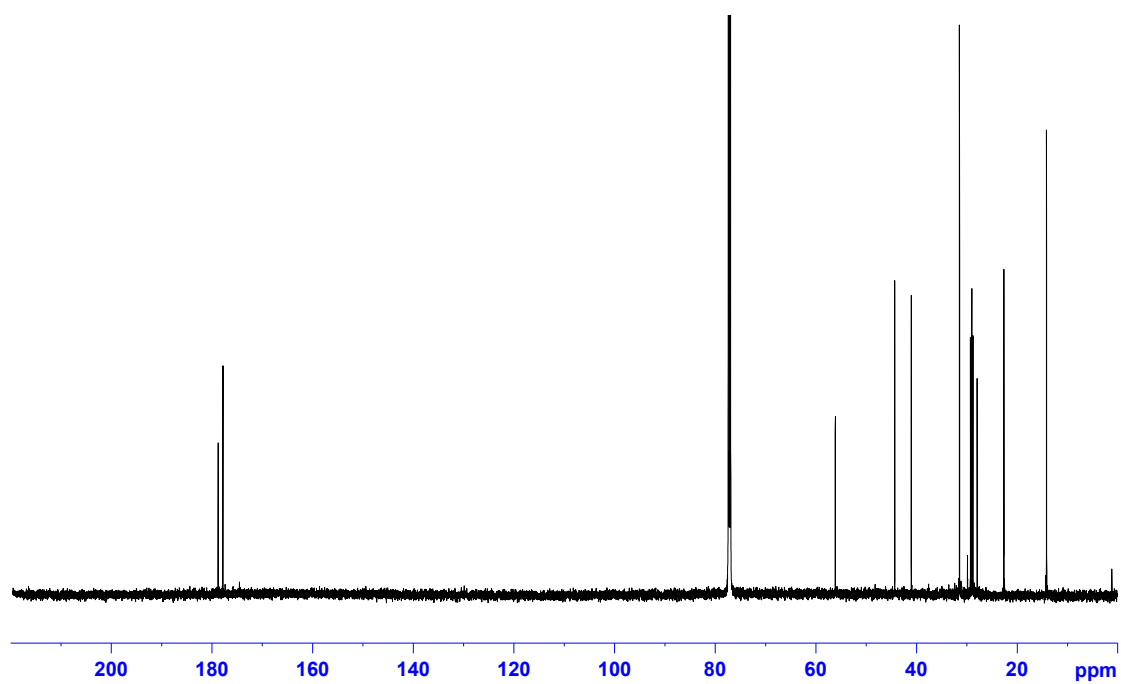


3 (25 mg, 0.116 mmol) was dissolved in acetonitrile (20.7 mL) and hex-1-ene (4.3 mL, 11.6 mmol). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **11** as a colourless oil (14 mg, 0.047 mmol) in 41% yield. δ_{H} (600 MHz, CDCl_3) 8.19 (s, 1H, H-2), 3.09 (dd, 1H, $J = 10.2$ and 4.5, H-7), 2.70-2.64 (m, 1H, H-5), 2.53-2.45 (m, 2H, H_2 -17), 2.37-2.28 (m, 2H, H_2 -6), 1.80-1.73 (m, 1H, HH -11), 1.59-1.50 (m, 2H, HH -11 and HH -10), 1.38-1.20 (m, 11H, HH -10 and 5 x CH_2), 0.90 (t, 3H, $J = 7.1$, CH_3), 0.87 (t, 3H, $J = 7.3$, CH_3); δ_{C} (150 MHz, CDCl_3) 178.73 (C=O), 177.81 (C=O), 56.10 (C4), 44.29 (C7), 40.99 (C5), 31.42 (C17), 29.24 (CH_2), 28.99 (CH_2), 28.90 (CH_2), 28.74 (CH_2), 28.73 (CH_2), 27.92 (CH_2), 22.59 (CH_2), 22.58 (CH_2), 14.12 (CH_3), 14.09 (CH_3); IR (oil, cm^{-1}) 3209 (w), 2927 (m) 1774 (w), 1711 (s); MS (CI+) m/z (relative intensity): 298 ([M+H], 100); Exact Mass Calcd for $[\text{C}_{16}\text{H}_{27}\text{NO}_2\text{S}] + \text{H}$ requires m/z 298.1841 Found 298.1845 (CI+).

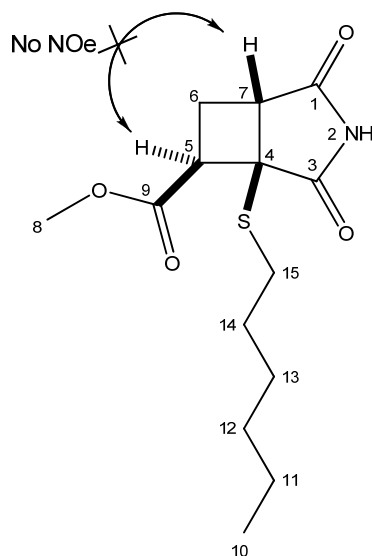
^1H NMR



^{13}C NMR

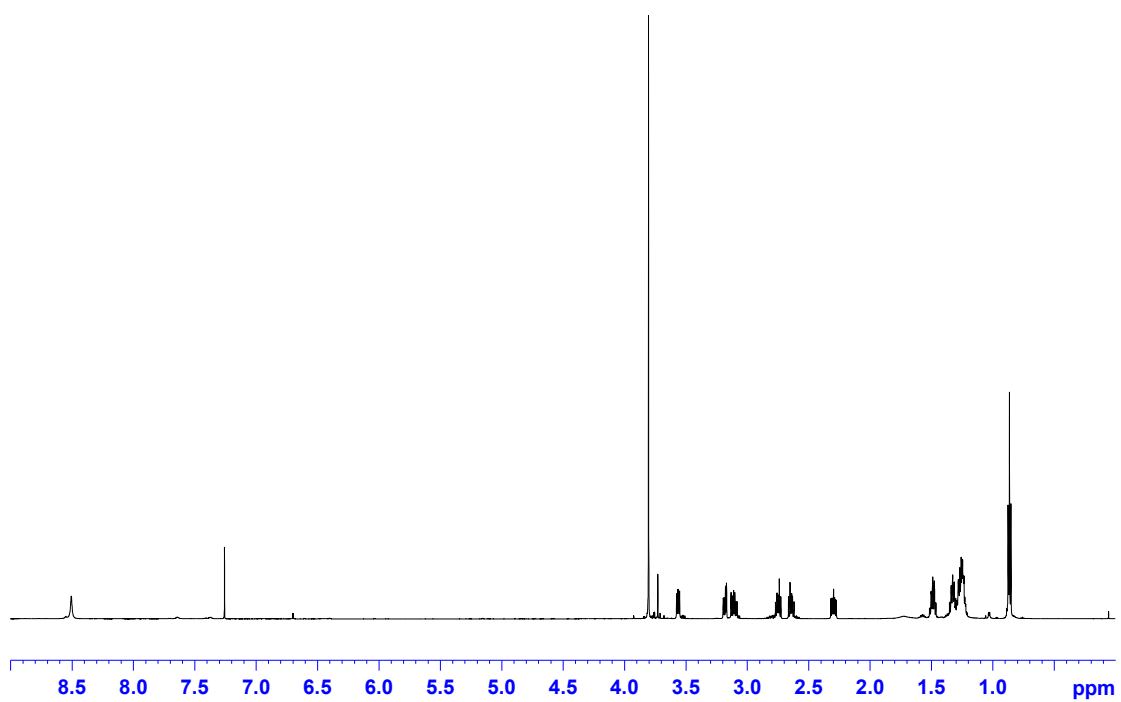


12. (4*RS*, 7*RS*, 5*RS*)-2-Aza-4-hexylsulfanyl-5-carboxylic acid methyl ester-bicyclo[3.2.0]heptan-1,3-dione

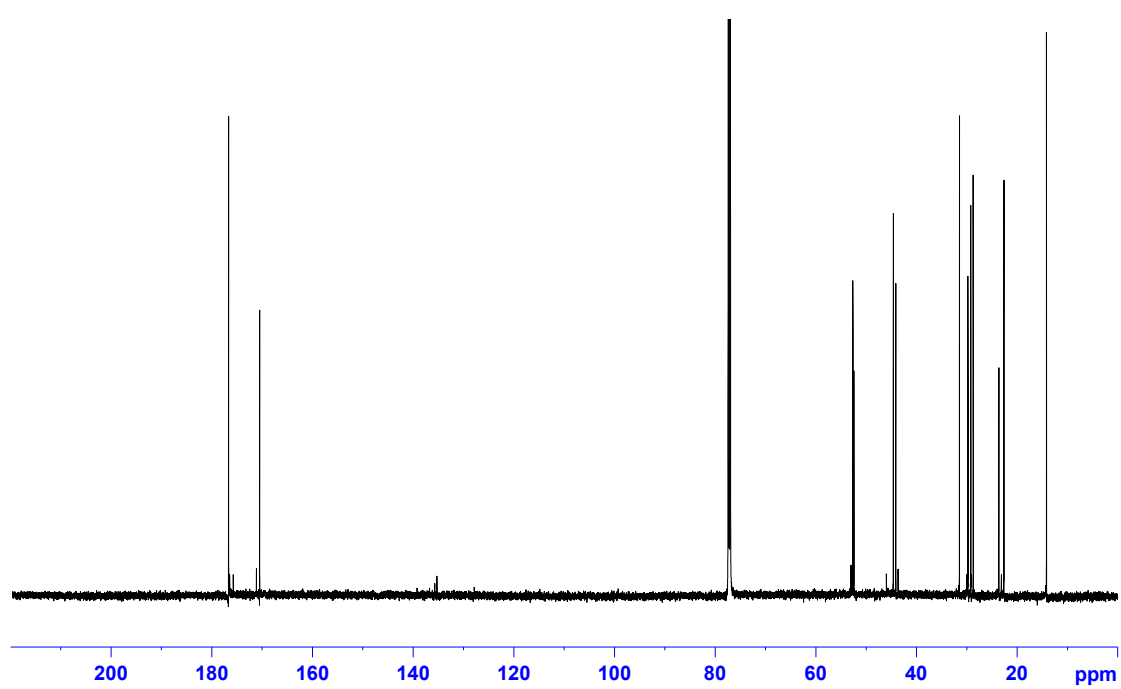


3 (25 mg, 0.12 mmol) was dissolved in acetonitrile (21.9 mL) and methyl acrylate (3.1 mL, 36 mmol). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in 10% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) afforded **12** as a thick colourless oil (17 mg, 0.056 mmol) in 49% yield. δ_{H} (600 MHz, CDCl_3) 8.50 (s, 1H, NH), 3.81 (s, 3H, H_3 -8), 3.57 (dd, 1H, $J = 8.5$ and 5.8 , H-5), 3.18 (dd, 1H, $J = 10.7$ and 5.0 , H-7), 3.11 (ddd, 1H, $J = 12.9$, 10.0 and 5.5 , HH -6), 2.73 (td, 1H, $J = 11.5$ and 7.5 , HH -15), 2.64 (td, 1H, $J = 11.5$ and 7.5 , HH -15), 2.29 (ddd, 1H, $J = 13.2$, 8.5 and 5.2 , HH -6), 1.52-1.47 (m, 2H, H_2 -14), 1.35-1.30 (m, 2H, H_2 -13), 1.29-1.21 (m, 4H, H_2 -11 and H_2 -12), 0.87 (t, 3H, $J = 6.7$, H_3 -10); δ_{C} (150 MHz, CDCl_3) 176.65 (C=O), 171.13 (C=O), 170.48 (C=O), 52.59 (C8), 52.39 (C4), 44.56 (C7), 44.06 (C5), 31.41 (C15), 29.73 (CH_2), 29.16 (CH_2), 28.68 (CH_2), 23.57 (C12), 22.57 (C11), 14.11 (C10); IR (oil, cm^{-1}) 3244 (w), 2928 (w) 1778 (w), 1714 (s); MS (FAB+) m/z (relative intensity): 322 ($[\text{M}+\text{Na}]$, 100), 300 (30), 214 (25); Exact Mass Calcd for $[\text{C}_{14}\text{H}_{21}\text{NO}_4\text{S}]+\text{Na}$ requires m/z 322.1089 Found 322.1082 (FAB+).

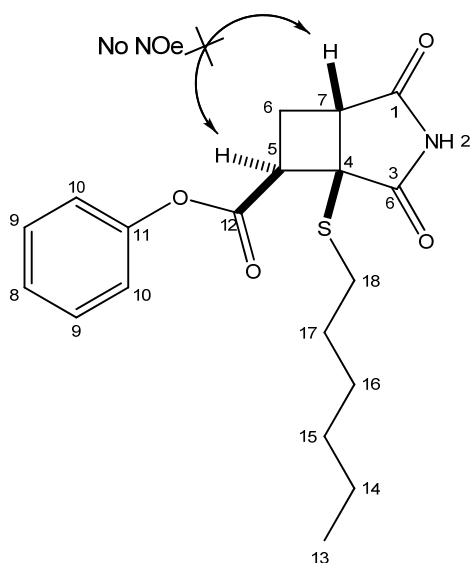
^1H NMR



^{13}C NMR

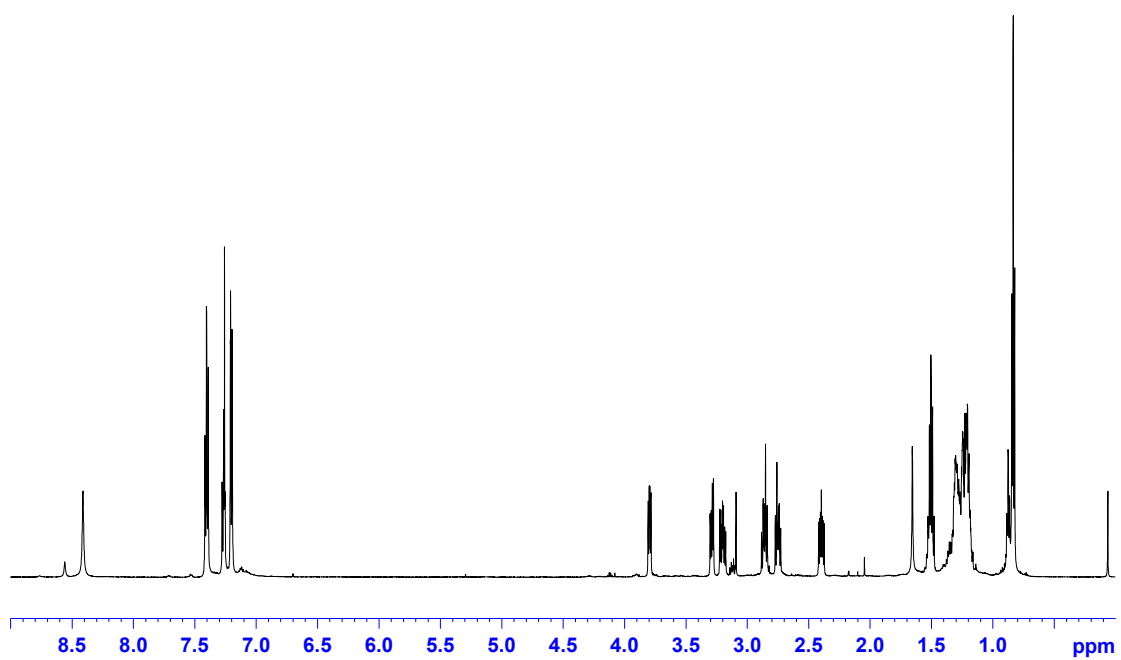


13. (4*RS*, 5*RS*, 7*RS*)-2-Aza-4-hexylsulfanyl-5-carboxylic acid phenyl ester-bicyclo [3.2.0]heptan-1,3-dione

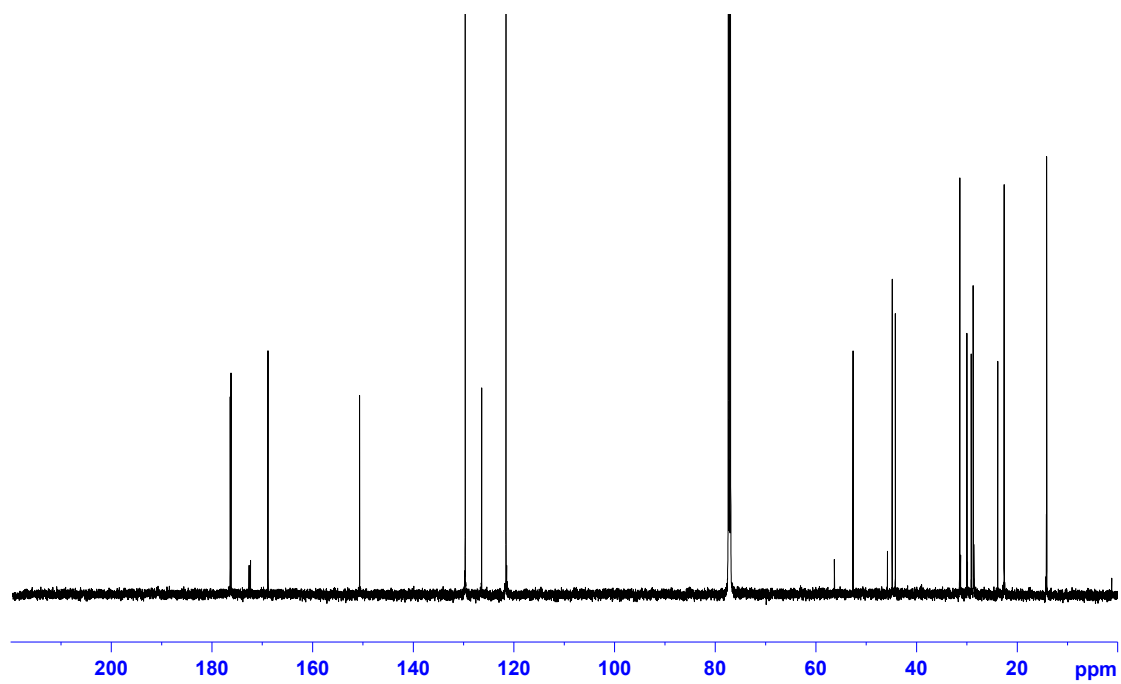


3 (25 mg, 0.12 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes, phenyl acrylate (160 μ L, 1.20 mmol) added and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **13** as a thick colourless oil (21 mg, 0.058 mmol) in 48% yield and dimer **4** (12 mg, 0.028 mmol) in 48% yield (data matched that obtained above for **4**). δ_{H} (600 MHz, CDCl_3) 8.41 (s, 1H, NH), 7.41-7.39 (m, 2H, 2 x Ar-H), 7.27-7.25 (m, 1H, H-8), 7.20 (d, 2H, $J = 7.8$, 2 x Ar-H), 3.80 (dd, 1H, $J = 8.5$ and 5.1, H-5), 3.29 (dd, 1H, $J = 10.7$ and 5.1, H-7), 3.20 (ddd, 1H, $J = 13.0$, 10.9 and 5.5, HH -6), 2.73 (td, 1H, $J = 11.5$ and 7.5, HH -18), 2.62 (td, 1H, $J = 11.5$ and 7.5, HH -18), 2.40 (ddd, 1H, $J = 13.5$, 8.8 and 5.6, HH -6), 1.54-1.48 (m, 2H, H_2 -17), 1.33-1.16 (m, 6H, H_2 -14, H_2 -15 and H_2 -16), 0.84 (t, 3H, $J = 6.9$, H_3 -13); δ_{C} (150 MHz, CDCl_3) 176.35 (C=O), 176.19 (C=O), 168.85 (C=O), 150.66 (C11), 129.64 (2 x Ar-H), 126.34 (C8), 121.54 (2 x Ar-H), 52.59 (C4), 44.78 (C7), 44.17 (C5), 31.36 (CH_2), 29.94 (C18), 29.09 (CH_2), 28.68 (CH_2), 23.83 (C6), 22.56 (CH_2), 14.08 (C13); IR (oil, cm^{-1}) 3213 (w), 2927 (w) 1757 (m), 1715 (s); MS (CI^+) m/z (relative intensity): 362 ($[\text{M}+\text{H}]$, 35), 268 (100), 149 (25); Exact Mass Calcd for $[\text{C}_{19}\text{H}_{23}\text{NO}_4\text{S}]+\text{H}$ requires m/z 362.1426 Found 362.1431 (CI^+).

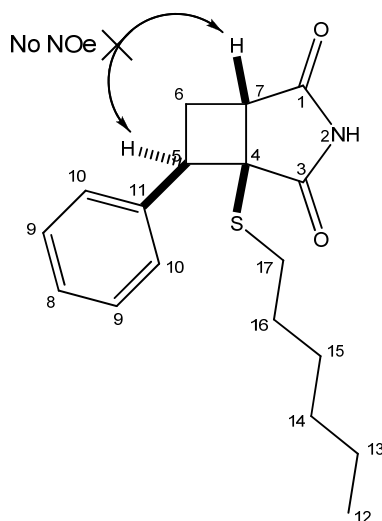
^1H NMR



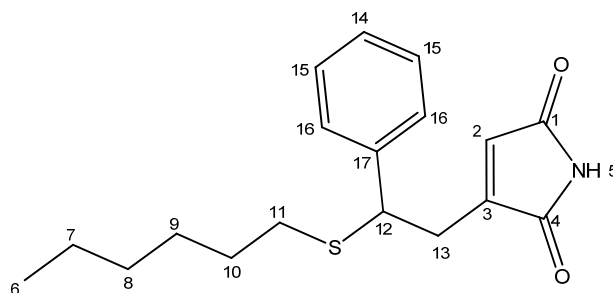
^{13}C NMR



14. (4RS, 5SR, 7SR)-2-Aza-4-hexylsulfanyl-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione



17. 3-(2-Hexylsulfanyl-2-phenyl-ethyl)-pyrrole-2,5-dione

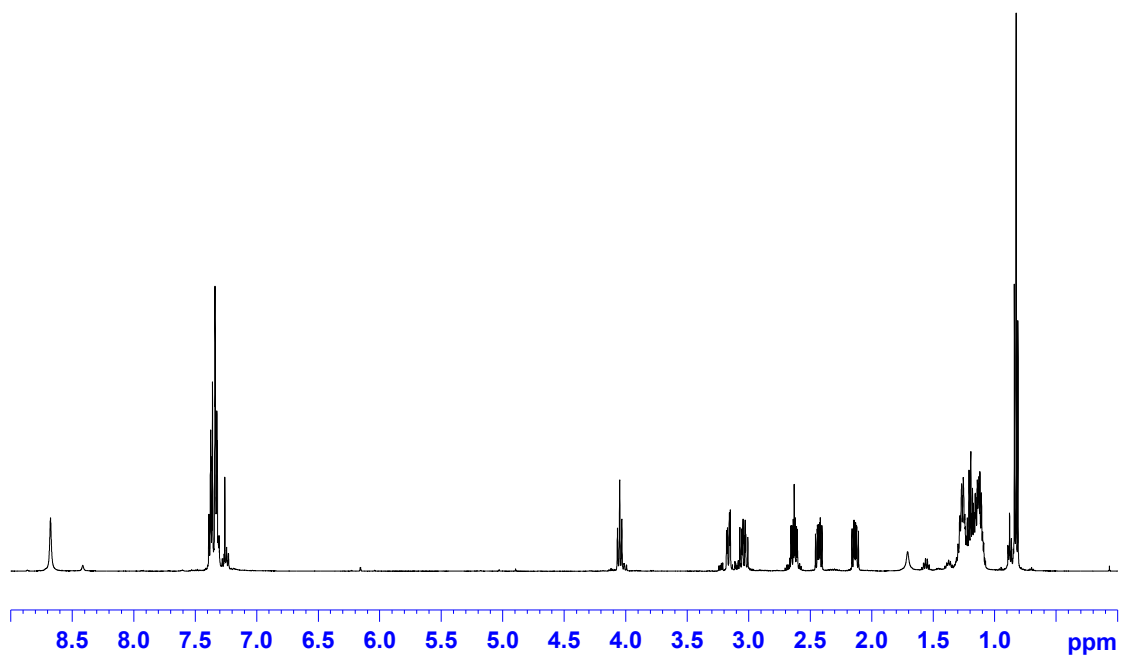


3 (25 mg, 0.12 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes, styrene (133 μ L, 1.2 mmol) added and the solution irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **17** as a thick yellow oil (11 mg, 0.034 mmol) in 30% yield and **14** as an off-white paste (26 mg, 0.082 mmol) in 70% yield.

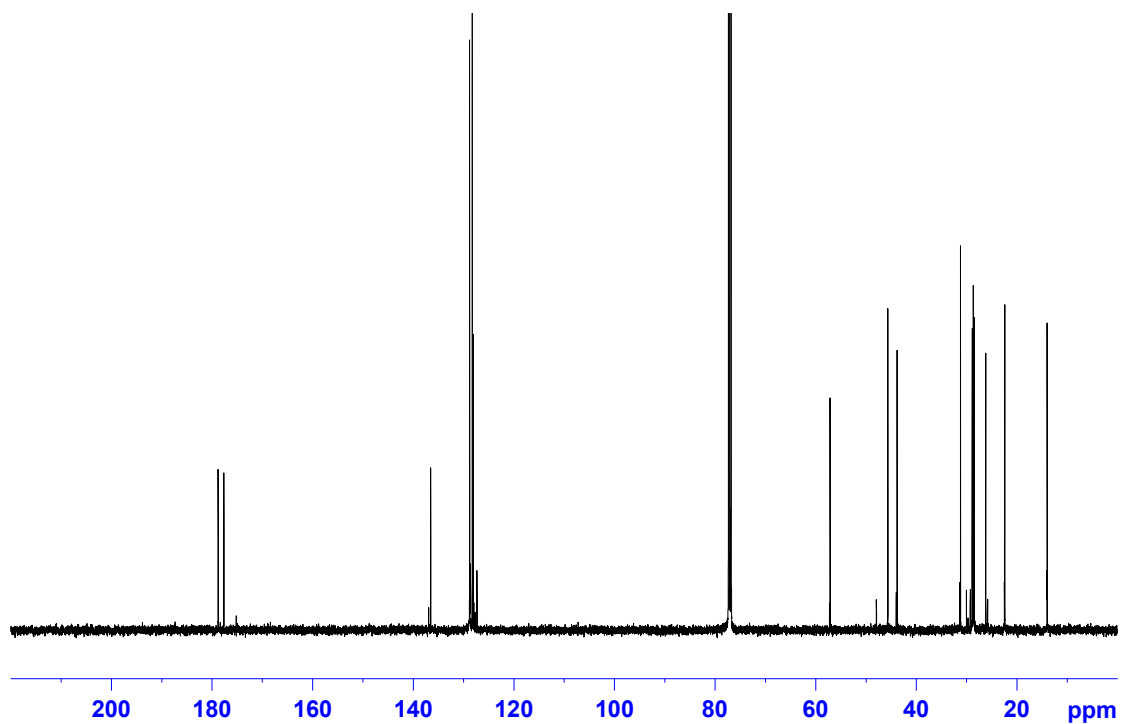
14. δ_{H} (600 MHz, CDCl_3) 8.77 (s, 1H, NH), 7.39-7.31 (m, 5H, 5 x Ar-H), 4.05 (app t, 1H, $J = 8.8$, H-5), 3.17 (dd, 1H, $J = 10.9$ and 3.4, H-7), 3.04 (ddd, 1H, $J = 12.7$, 11.1 and 8.4, *HH*-6), 2.63 (ddd, 1H, $J = 12.8$, 9.0 and 3.6, *HH*-6), 2.43 (ddd, 1H, $J = 11.3$, 7.9 and 6.7, *HH*-17), 2.13 (ddd, 1H, $J = 11.3$, 8.0 and 6.6, *HH*-17), 1.30-1.08 (m, 8H, H_2 -13, H_2 -14, H_2 -15 and H_2 -16), 0.83 (t, 3H, $J = 7.3$, H_3 -12); δ_{C} (150 MHz, CDCl_3) 178.76 (C=O), 177.62 (C=O), 136.51 (C11), 128.77 (2 x Ar-H), 128.70 (2 x Ar-H), 128.03 (C8), 57.17 (C4), 45.70 (C5), 43.87 (C7), 31.26 (C17), 28.70 (CH_2), 28.65 (CH_2), 28.52 (CH_2), 26.22 (C6), 22.46 (CH_2), 14.10 (C12); IR (oil, cm^{-1}) 3218 (w),

2926 (w) 1771 (m), 1703 (s); MS (FAB+) m/z (relative intensity): 340 ([M+Na], 20), 199 (25), 176 (100); Exact Mass Calcd for [C₁₆H₂₃NO₂S]+Na requires m/z 340.1347 Found 340.1357 (FAB+). Elemental analysis: Calc for C₁₆H₂₃NO₂S: C: 68.10, H: 7.31, N: 4.41 Found: C: 68.31, H: 7.41, N: 4.34.

¹H NMR

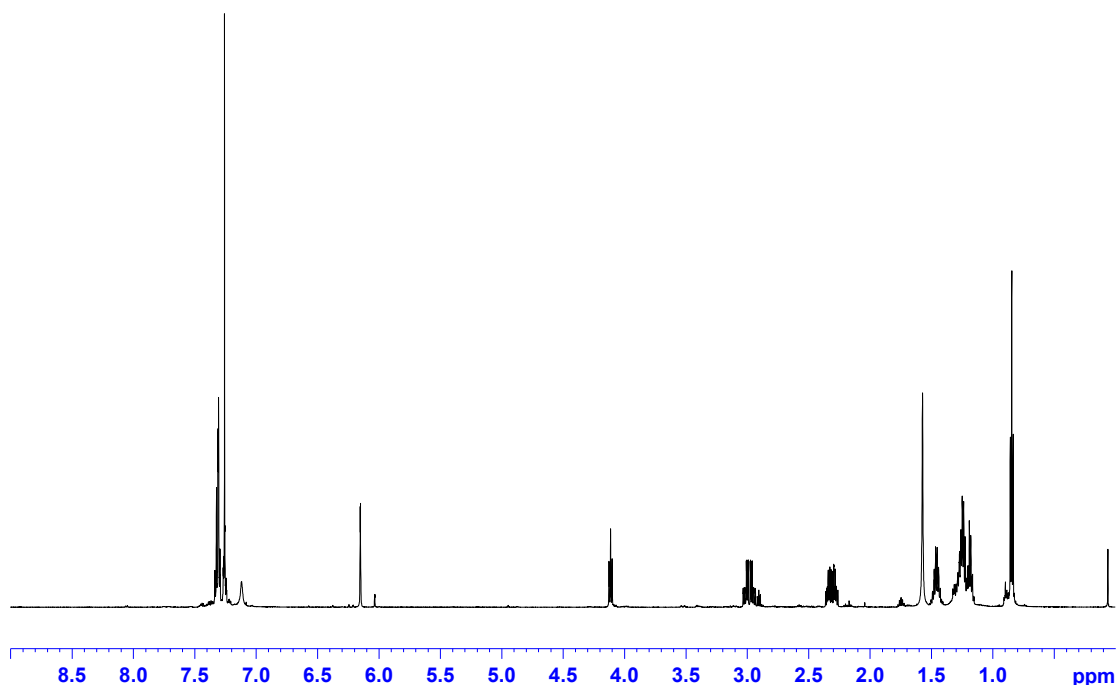


¹³C NMR

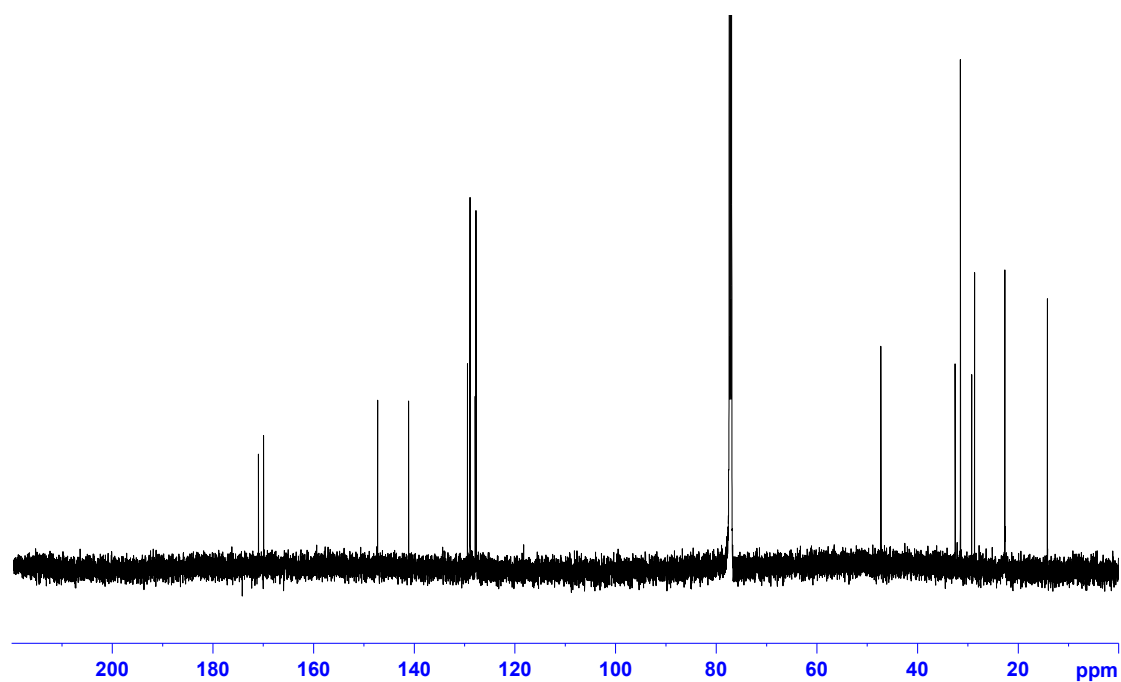


17. δ_{H} (600 MHz, CDCl_3) 7.34-7.24 (m, 5H, 5 x Ar-H), 7.22 (d, 1H, $J = 1.5$, H-5), 6.15 (app q, 1H, $J = 1.5$, H-2), 4.11 (t, 1H, $J = 7.7$, H-12), 3.01 (ddd, 1H, $J = 15.8$, 7.8 and 1.5, HH-13), 2.96 (ddd, 1H, $J = 15.6$, 7.8 and 1.5, HH-13), 2.36-2.26 (m, 2H, H₂-11), 1.50-1.41 (m, 2H, H₂-10), 1.35-1.33 (m, 6H, H₂-7, H₂-8 and H₂-9), 0.85 (t, 3H, $J = 7.0$, H₃-6); δ_{C} (150 MHz, CDCl_3) 170.96 (C=O), 169.95 (C=O), 147.26 (C3), 141.10 (C17), 129.41 (C2), 128.89 (2 x Ar-H), 127.86 (C14), 127.71 (2 x Ar-H), 47.24 (C12), 32.47 (C11), 31.43 (CH₂), 31.31 (CH₂), 29.19 (CH₂), 28.61 (CH₂), 22.60 (CH₂), 14.10 (C6); IR (oil, cm^{-1}) 3288 (w), 2928 (w), 1775 (w), 1717 (s); MS (FAB+) m/z (relative intensity): 340 ([M+Na], 20), 329 (35), 207 (20), 176 (100); Exact Mass Calcd for $[\text{C}_{16}\text{H}_{23}\text{NO}_2\text{S}]+\text{Na}$ requires m/z 340.1347 Found 340.1351 (FAB+).

^1H NMR

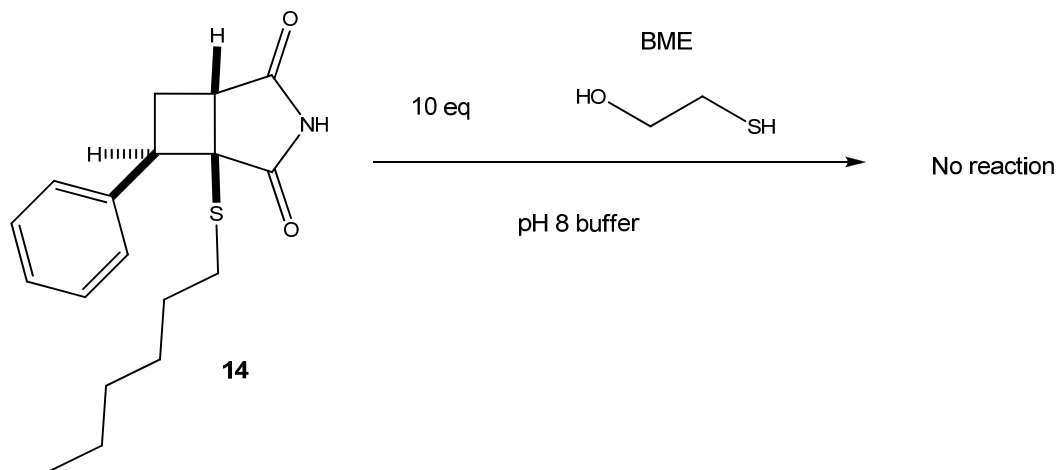


¹³C NMR

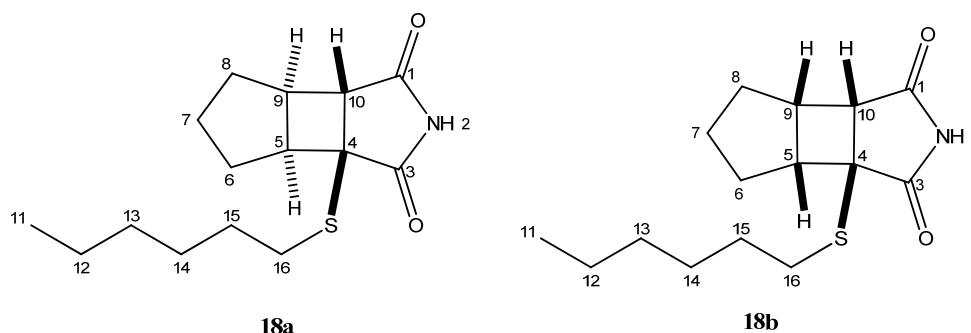


Stability of cyclobutanes to reducing conditions.

Cyclobutane **14** (5 mg, 0.016 mmol) was dissolved in buffer (2 mL, 150 mM NaCl, 100 mM NaH₂PO₄, pH 8.0) and β-mercaptoethanol (11 μL, 0.122 mmol) added. No reaction was observed after 1 h, monitored by ¹H NMR.



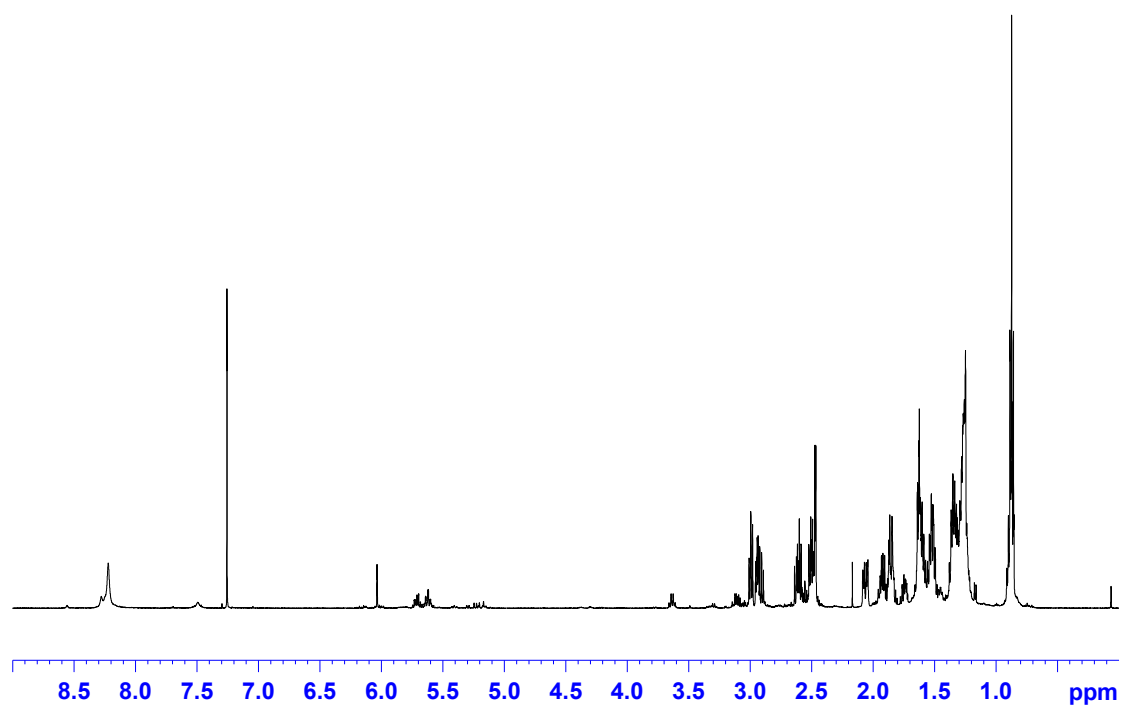
18a. (4RS, 5RS, 9SR, 10SR) - 2-Aza-4-hexylsulfanyl-2-aza-tricyclo[3.5.0.0^{5,9}]di-1,3-one and **18b.** (4RS, 5SR, 9RS, 10SR) - 2-aza-4-hexylsulfanyl-2-aza-tricyclo[3.5.0.0^{5,9}]di-1,3-one



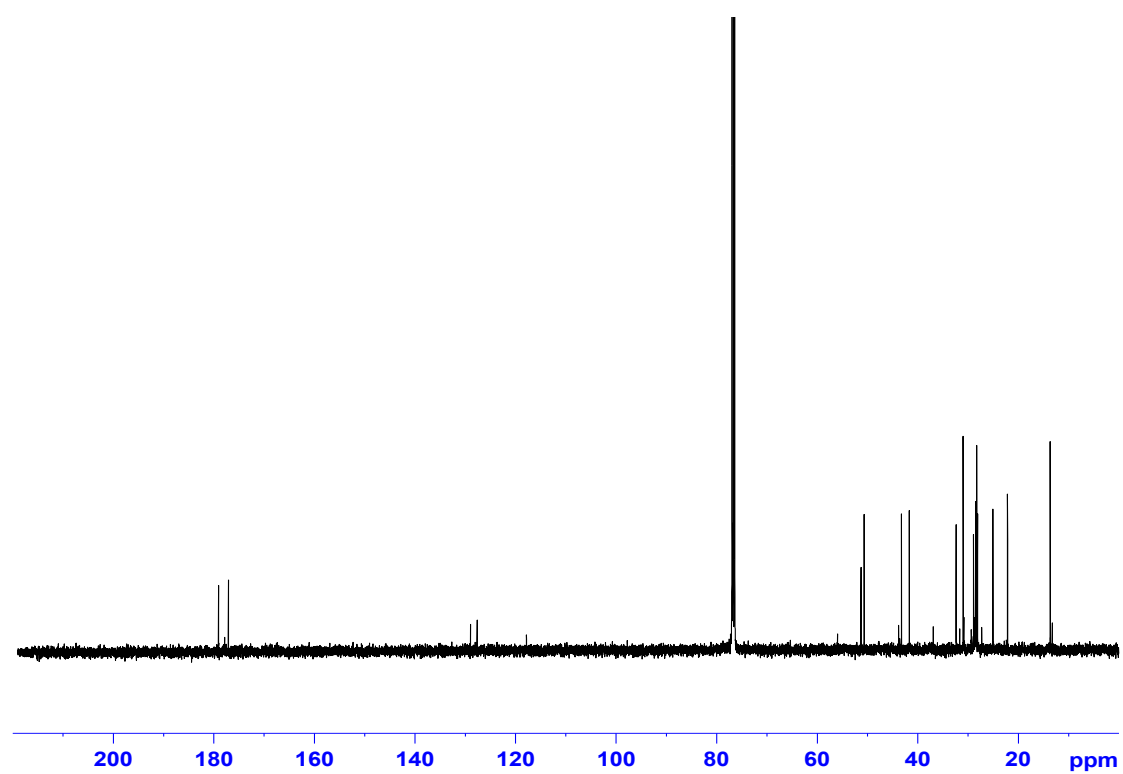
3 (25 mg, 0.12 mmol) was dissolved in acetonitrile (22.5 mL) and cyclopentene (3 mL, 36 mmol). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution 10% ethyl acetate in petroleum ether to 50% ethyl acetate in petroleum ether) afforded **18a** and **18b** as a thick colourless oil (12 mg, 0.045 mmol) in 78% yield, a 1:1 mix of two diastereomers. Two further purifications of the oil by the same column chromatography method afforded samples of the separated diastereomers, spectra given below combined data.

δ_{H} (500 MHz, CDCl_3) 3.15-3.07 (m, 2H, H-5_b and H-10_b), 3.00 (app t, 1H, $J = 6.8$, H-5_a), 2.97), 2.97-2.82 (m, 3H, H-9_a, H-9_b and HH-16), 2.64-2.59 (m, 1H, HH-16), 2.52-2.47 (m, 3H, H-10_a, HH-16 and HH-16), 2.07 (dd, 2H, $J = 6.9$ and 6.3, 2 x HH-15), 1.96-1.89 (m, 2H, 2 x HH-15) 1.88-1.82 (m, 4H, 2 x H₂-7) 1.64-1.50 (m, 8H, 2 x H₂-6 and 2 x H₂-8), 1.38-1.25 (m, 12H, 2 x H₂-12, 2 x H₂-13 and 2 x H₂-14), 0.89-0.86 (m, 6H, 2 x H₃-11), _a-signals shown as part of the same CH₂ by HMQC data, _b-signals shown as part of the same CH₂ by HMQC data; δ_{C} (125 MHz, CDCl_3) 179.09 (C=O), 177.12 (C=O), 176.93 (C=O), 171.83 (C=O), 51.31 (C4), 51.33 (C4), 50.68 (C10), 45.32 (C10), 43.26 (C9), 41.70 (C5), 32.38 (CH₂), 30.98 (CH₂), 30.95 (CH₂), 30.78 (CH₂), 28.92 (CH₂), 28.50 (CH₂), 28.30 (CH₂), 28.22 (CH₂), 28.10 (CH₂), 28.13 (CH₂), 25.09 (CH₂), 22.14 (CH₂), 22.11 (CH₂), 13.66 (2 x C11) Two diastereomers are indicated, thus five carbon signals are missing due to overlap of the diastereomers; IR (oil, cm^{-1}) 3120 (w), 2927 (m), 1711 (s), 1627 (s); MS (ES-) m/z (relative intensity): 280 ([M-H], 50), 212 (100); Exact Mass Calcd for [C₁₅H₂₃NO₂S]-H requires m/z 280.1371 Found 280.1382 (ES-).

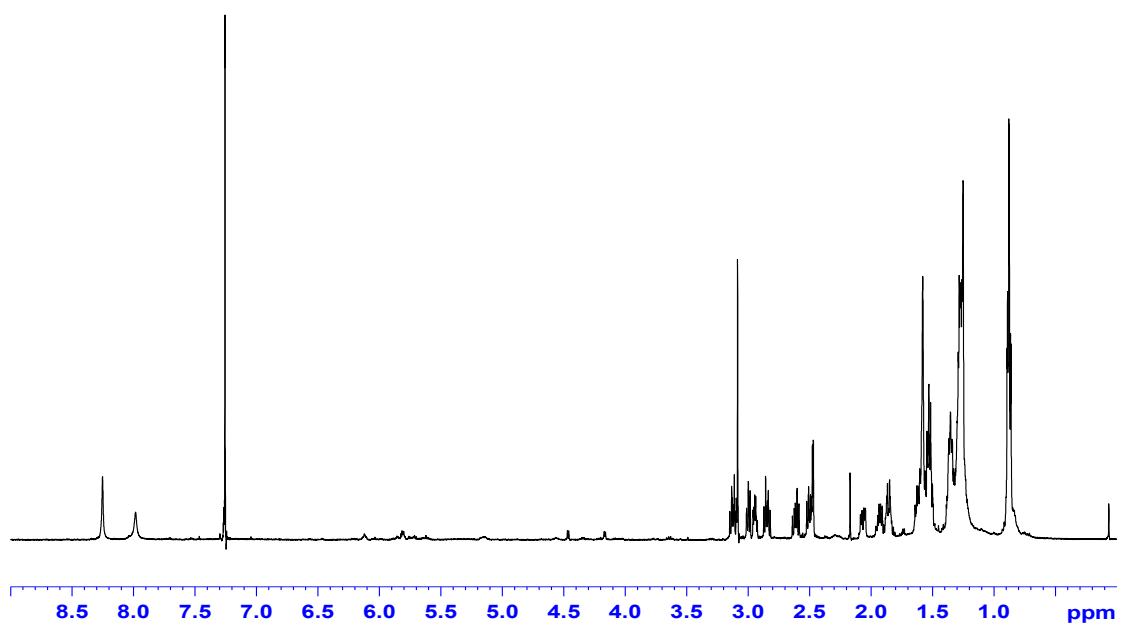
18a: ^1H NMR



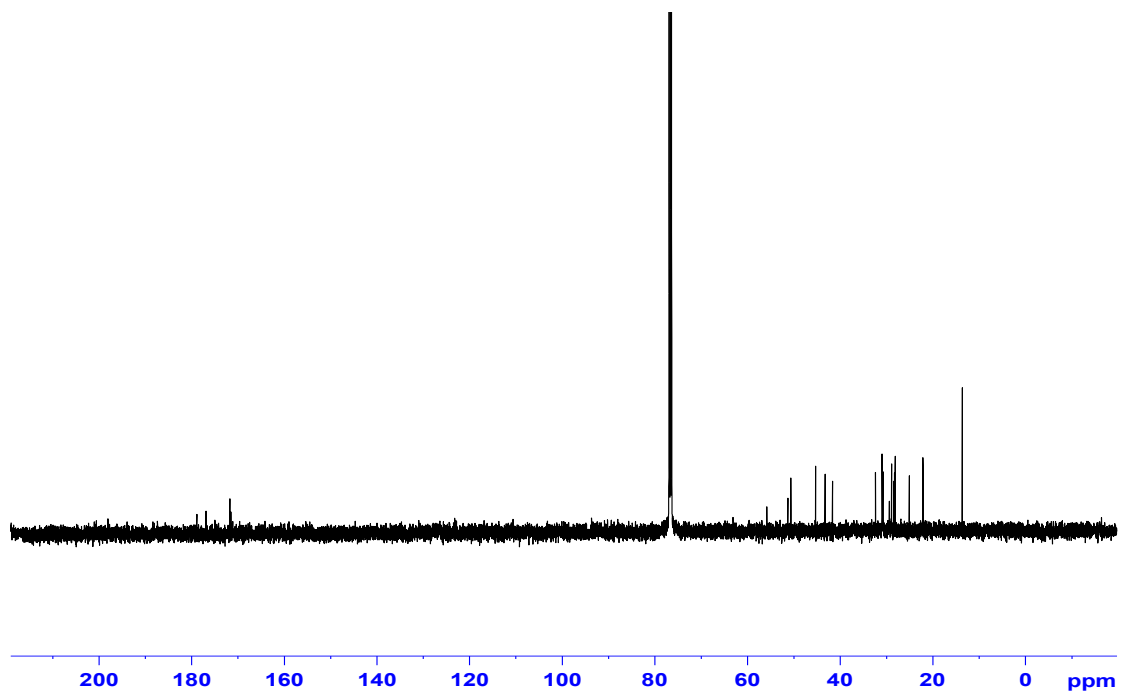
^{13}C NMR



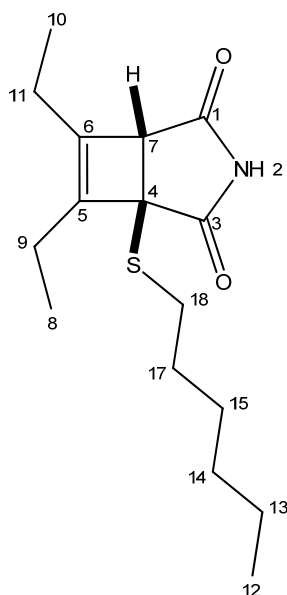
18b: ^1H NMR



^{13}C NMR



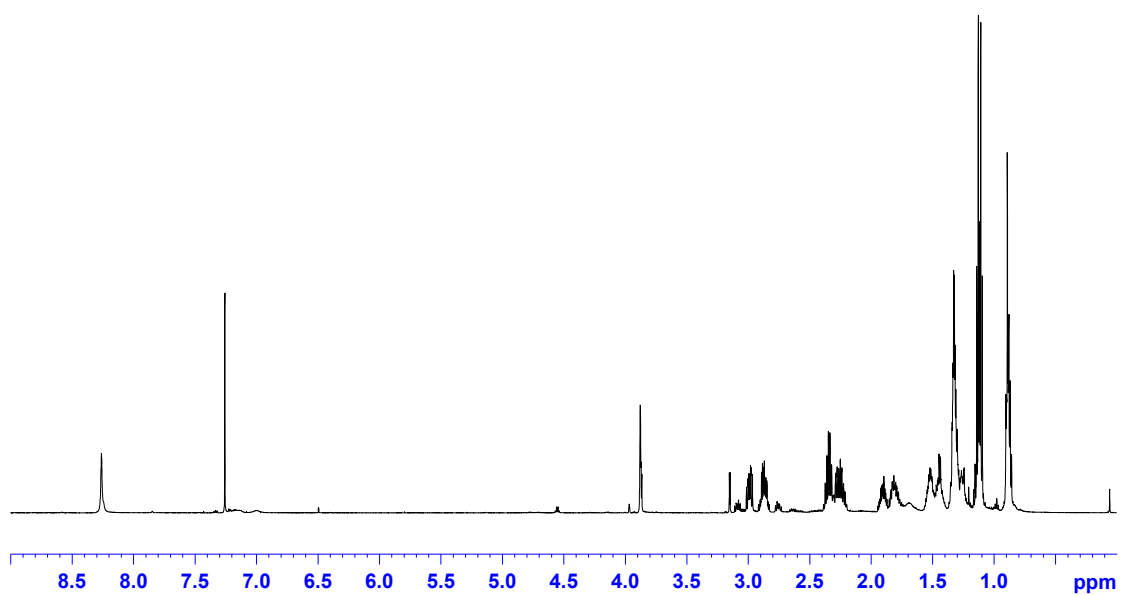
19. (4*RS*, 7*RS*)-2-Aza-4-hexylsulfanyl-5-ethyl-6-ethyl-bicyclo[3.2.0]hept-5-ene-1,3-dione



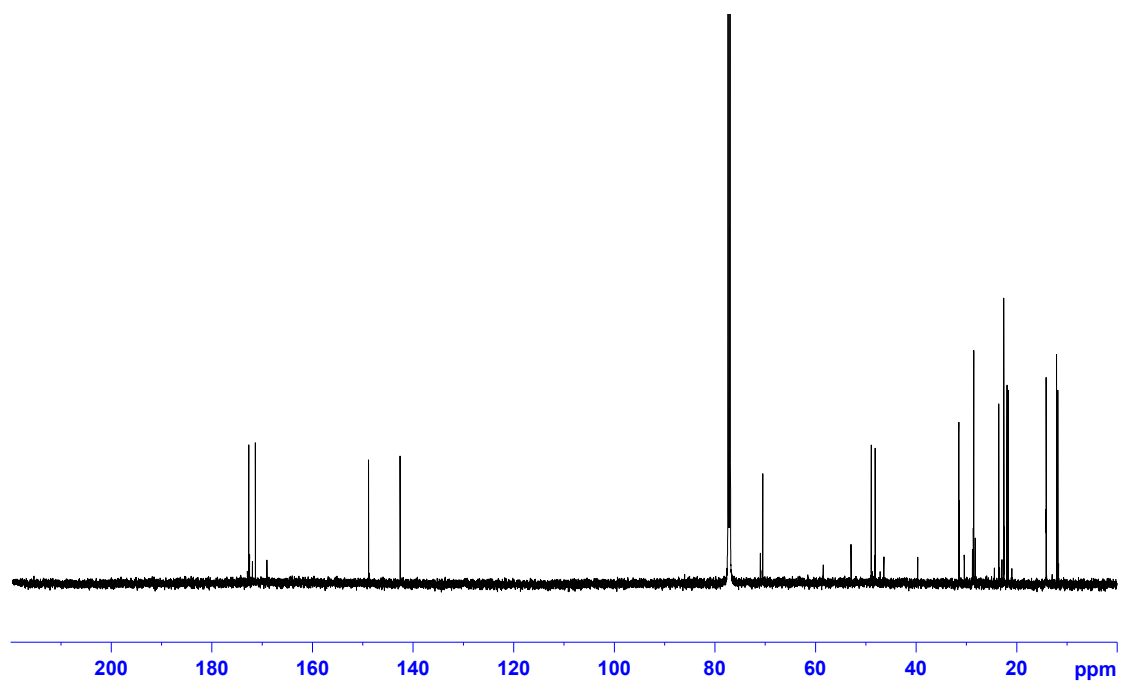
3 (25 mg, 0.116 mmol) was dissolved in acetonitrile (21.1 mL) and hex-3-yne (3.9 mL, 11.6 mmol). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **19** as a colourless oil (17 mg, 0.057 mmol) in 49% yield.

δ_{H} (600 MHz, CDCl_3) 8.26 (s, 1H, NH), 3.88 (s, 1H, H-7), 2.99 (ddd, 1H, $J = 12.8$, 9.1 and 7.5, *HH*-18), 2.87 (ddd, 1H, $J = 12.9$, 8.7 and 5.1, *HH*-18), 2.39-2.20 (m, 2H, *HH*-9 and *HH*-11), 1.95-1.75 (m, 2H, *HH*-9 and *HH*-11), 1.56-1.10 (m, 8H, 4 x CH_2), 0.90-0.86 (m, 9H, H_3 -8, H_3 -10 and H_3 -12); δ_{C} (150 MHz, CDCl_3) 172.66 (C=O), 171.34 (C=O), 148.84 (C=C), 142.53 (C=C), 70.45 (C4), 48.86 (C18), 48.09 (C7), 31.45 (CH_2), 28.51 (CH_2), 23.53 (CH_2), 22.50 (CH_2), 21.89 (CH_2), 21.62 (CH_2) 14.09 (C12), 12.03 (CH_3), 11.84 (CH_3); IR (oil, cm^{-1}) 2931 (m) 1717 (s); MS (CI⁺) m/z (relative intensity): 312 ([M+OH], 100), 178 (100); Exact Mass Calcd for $[\text{C}_{16}\text{H}_{25}\text{NO}_2\text{S}]+\text{OH}$ requires m/z 312.1633 Found 312.1648 (CI⁺).

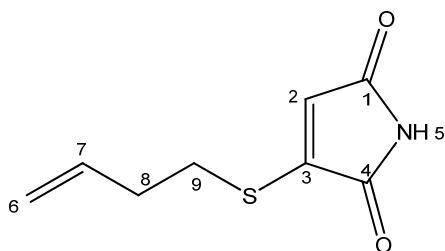
^1H NMR



^{13}C NMR



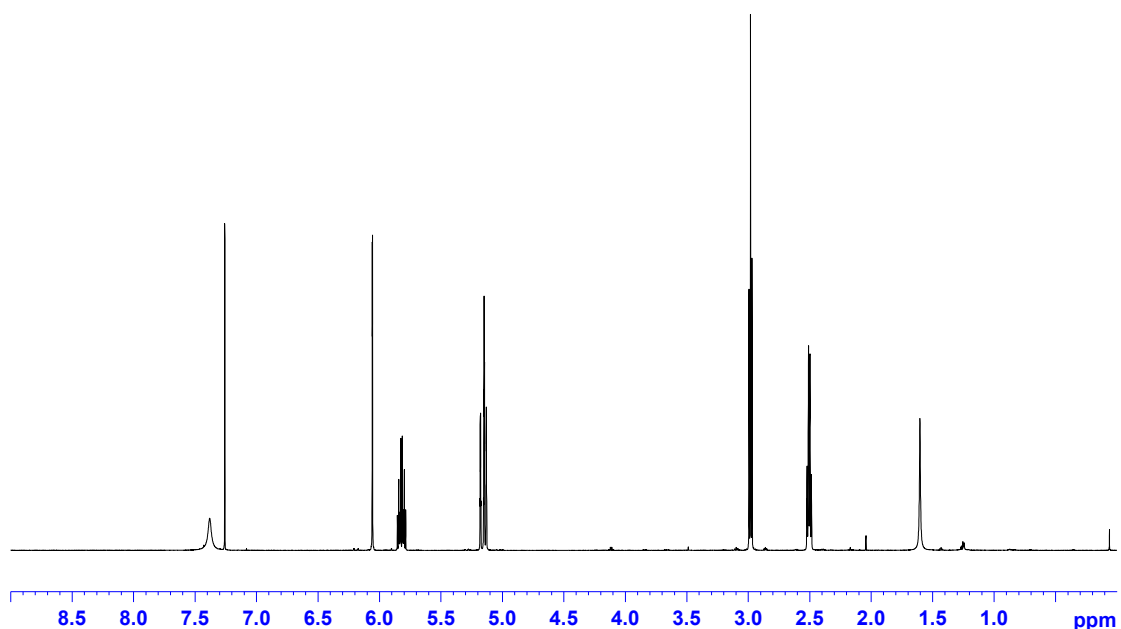
20. 3-But-3-enylsulfanyl-pyrrole-2,5-dione



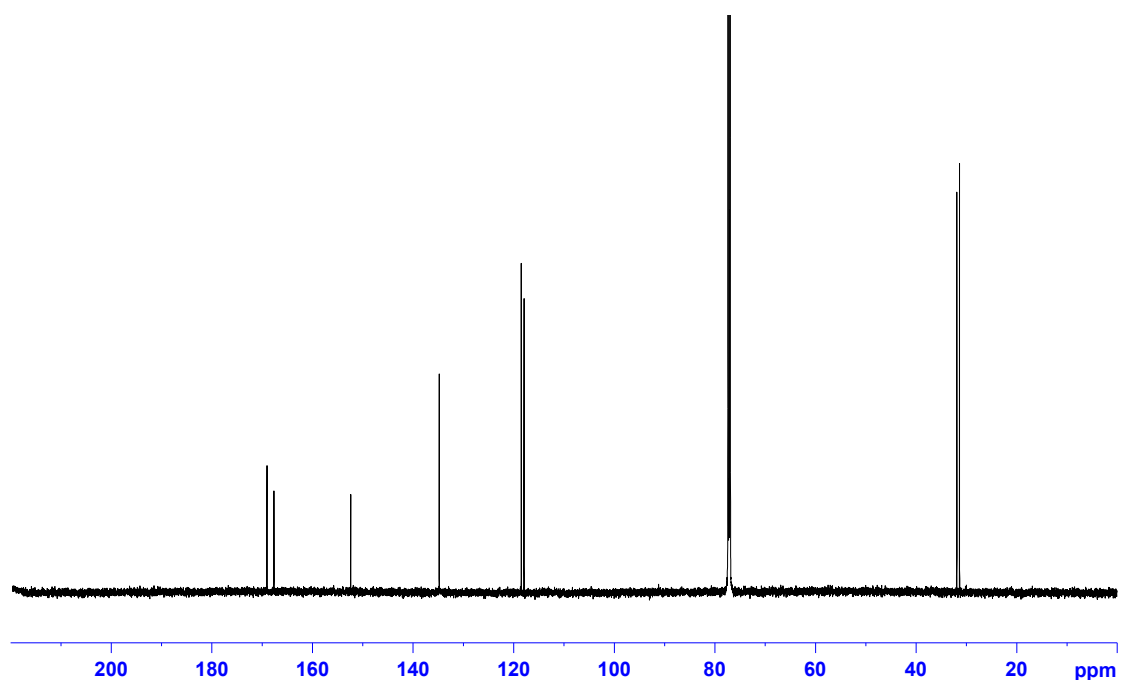
To a solution of sodium (22 mg, 0.96 mmol) in methanol (20 mL) at 0 °C was added thiobenzoic acid *S*-but-3-enyl ester⁹ (200 mg, 0.96 mmol) in methanol (5 mL) and the solution stirred for three hours. This solution was then added dropwise to a solution of bromomaleimide (170 mg, 0.96 mmol) in methanol (20 mL) at 0 °C and stirred for ten minutes. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 20% ethyl acetate in petroleum ether) afforded **20** as a pale yellow solid (72 mg, 0.39 mmol) in 41% yield.

δ_{H} (600 MHz, CDCl_3) 7.38 (s, 1H, H-5), 6.06 (s, 1H, H-2), 5.82 (ddt, 1H, $J = 17.0$, 10.2 and 6.6, H-7), 5.18-5.13 (m, 2H, H₂-6), 2.98 (t, 1H, $J = 7.4$, H₂-9), 2.52-2.49 (m, 2H, H₂-8); δ_{C} (125 MHz, CDCl_3) 169.03 (C=O), 167.64 (C=O), 152.37 (C3), 134.77 (C7), 118.46 (C2), 117.91 (C6), 31.88 (C8), 31.32 (C9); IR (solid, cm^{-1}) 3158 (m), 1762 (m), 1703 (s); MS (CI+) m/z (relative intensity): 184 ([M+H], 35), 105 (35), 86 (62), 84 (100); Exact Mass Calcd for $[\text{C}_8\text{H}_9\text{NO}_2\text{S}]+\text{H}$ requires m/z 184.0432 Found 184.0438 (ES-); m.p. 85-90 °C; UV (Acetonitrile) $\epsilon_{242} = 6800$ and $\epsilon_{344} = 4600 \text{ cm}^{-1}\text{M}^{-1}$.

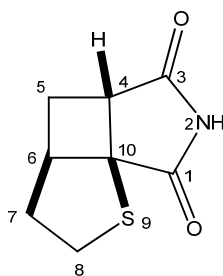
¹H NMR



¹³C NMR



21. (4RS, 6SR, 10SR)-2-Aza-9-thiatricyclo[5.3.0.0^{10,4}]decan-1,3-dione

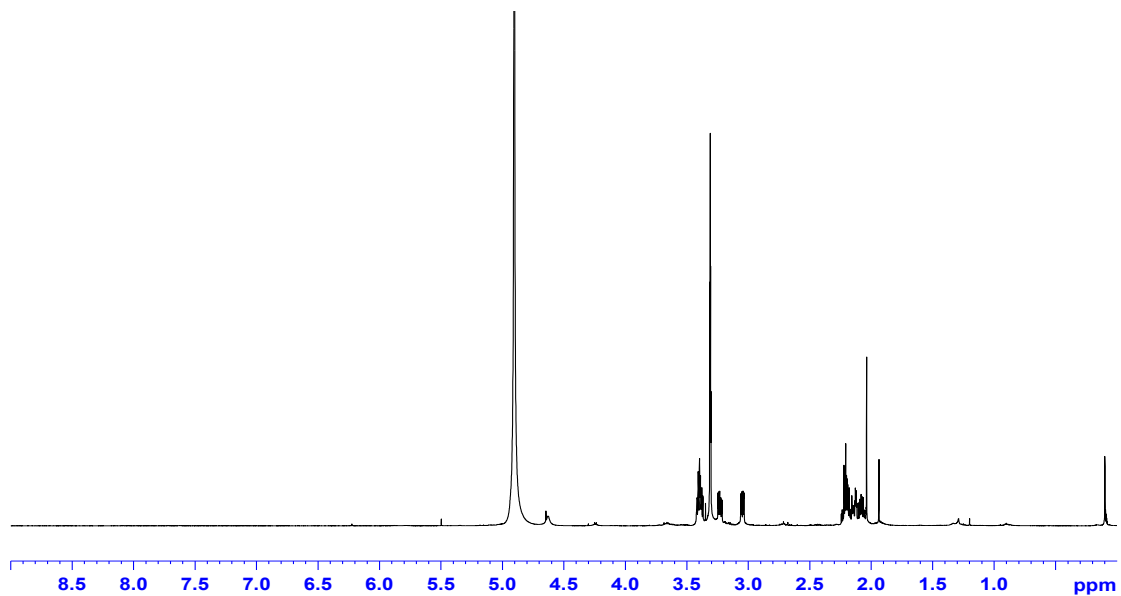


3-But-3-enylsulfanyl-pyrrole-2,5-dione (42 mg, 0.25 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes and irradiated in pyrex glassware for 4 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in ethyl acetate to 5% methanol in ethyl acetate) afforded **21** as an off-white solid (39 mg, 0.23 mmol) in 93% yield

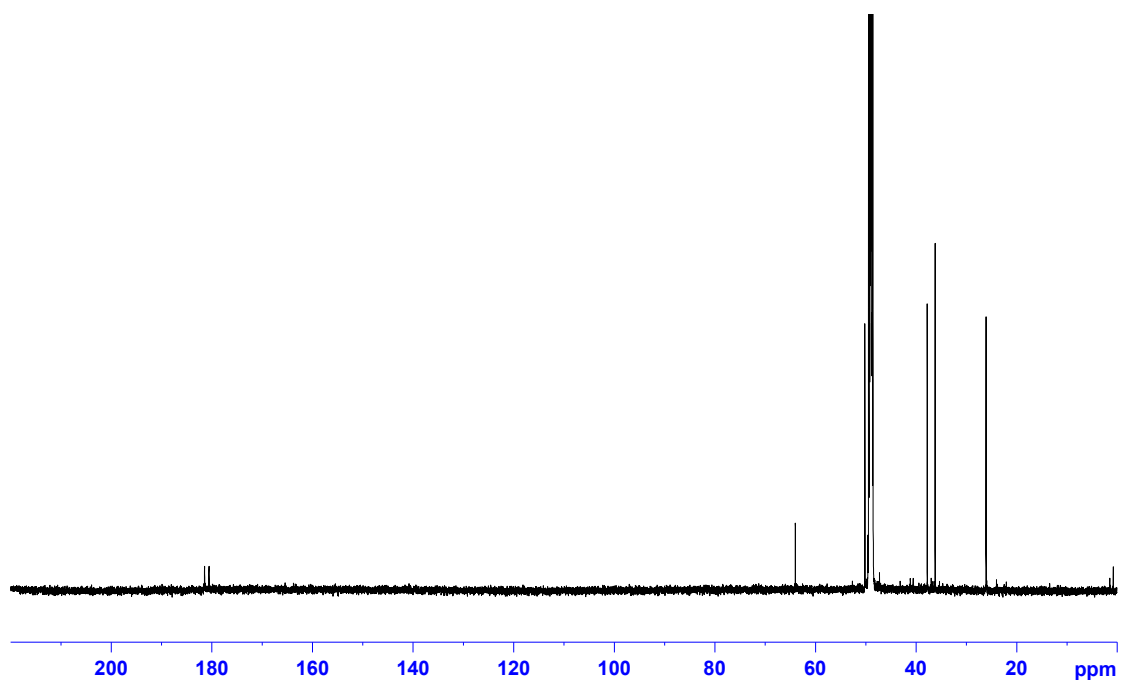
δ_{H} (500 MHz, CDCl_3) 3.50 (ddd, 1H, $J = 11.8, 4.8$ and 2.6 , HH-8), 3.18-3.12 (m, 2H, HH-8 and H-6), 2.98 (dd, 1H, $J = 10.7$ and 3.9 , H-4), 2.21 (ddd, 1H, $J = 13.2, 8.6$ and 4.0 , HH-5), 2.01 (ddd, 1H, $13.4, 10.5$ and 5.8 , HH-5), 1.79 (m, 2H, $\text{H}_2\text{-7}$); δ_{C} (150 MHz, MeOD) 181.44 (C=O), 180.54 (C=O), 64.01 (C10), 50.17 (C6), 48.95 (C4), 37.78 (C8), 36.20 (C7), 26.07 (C5); IR (solid, cm^{-1}) 3218 (w), 1768 (m), 1709 (s); MS

(EI) m/z (relative intensity): 166 (M^+ , 45), 125 (100); Exact Mass Calcd for $[C_8H_{10}N_2O_2]^+$ requires m/z 166.07387 Found 166.07386 (EI); m.p. 155-160 °C.

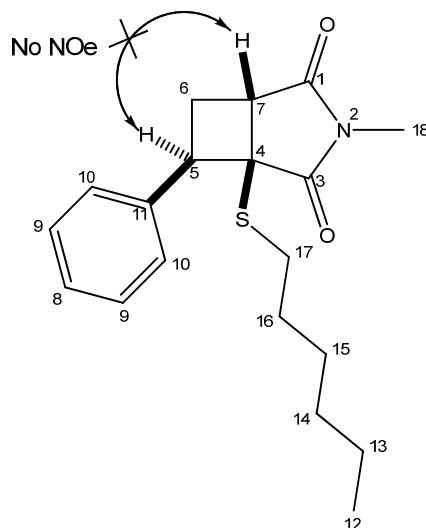
1H NMR



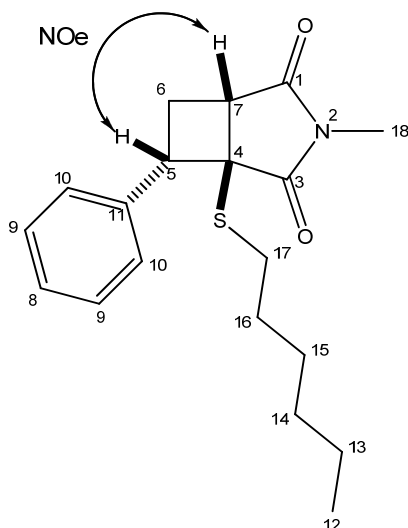
^{13}C NMR



22a. (4RS, 5SR, 7SR)-2-Aza-2-methyl-4-hexylsulfanyl-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione



22b. (4RS, 5RS, 7SR)-2-Aza-2-methyl-4-hexylsulfanyl-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione

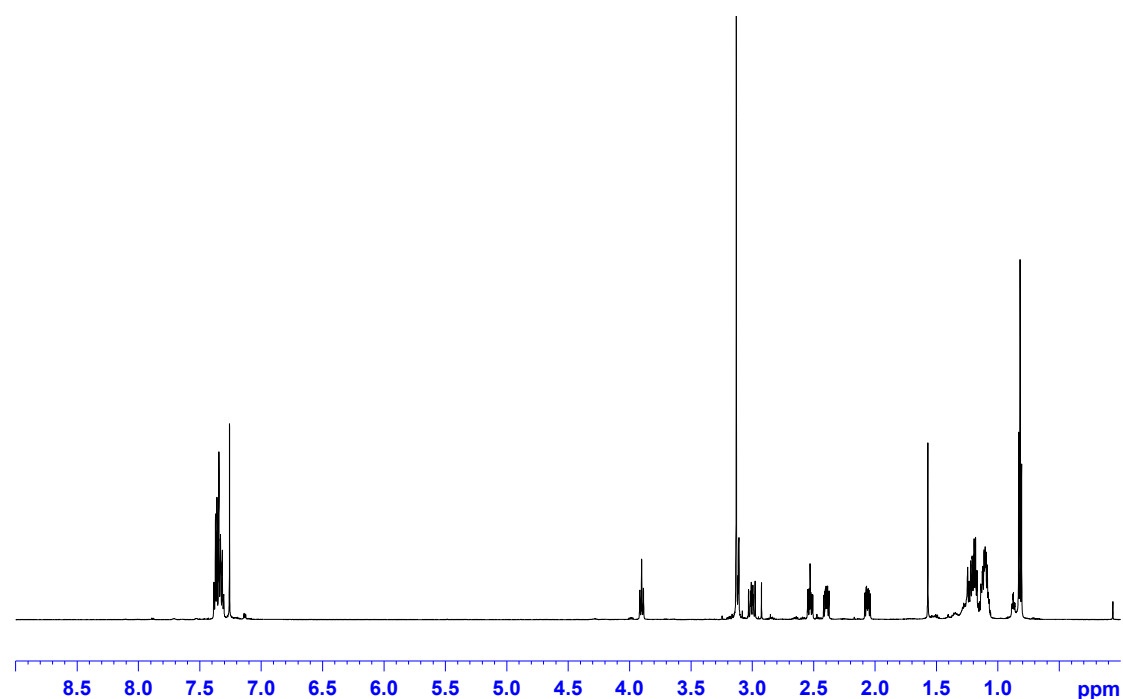


5 (27 mg, 0.119 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes, styrene (136 μ L, 1.19 mmol) added and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **22a** as a colourless oil (23 mg, 0.069 mmol) in 58% yield and **22b** as a colourless oil (5 mg, 0.015 mmol) in 12%

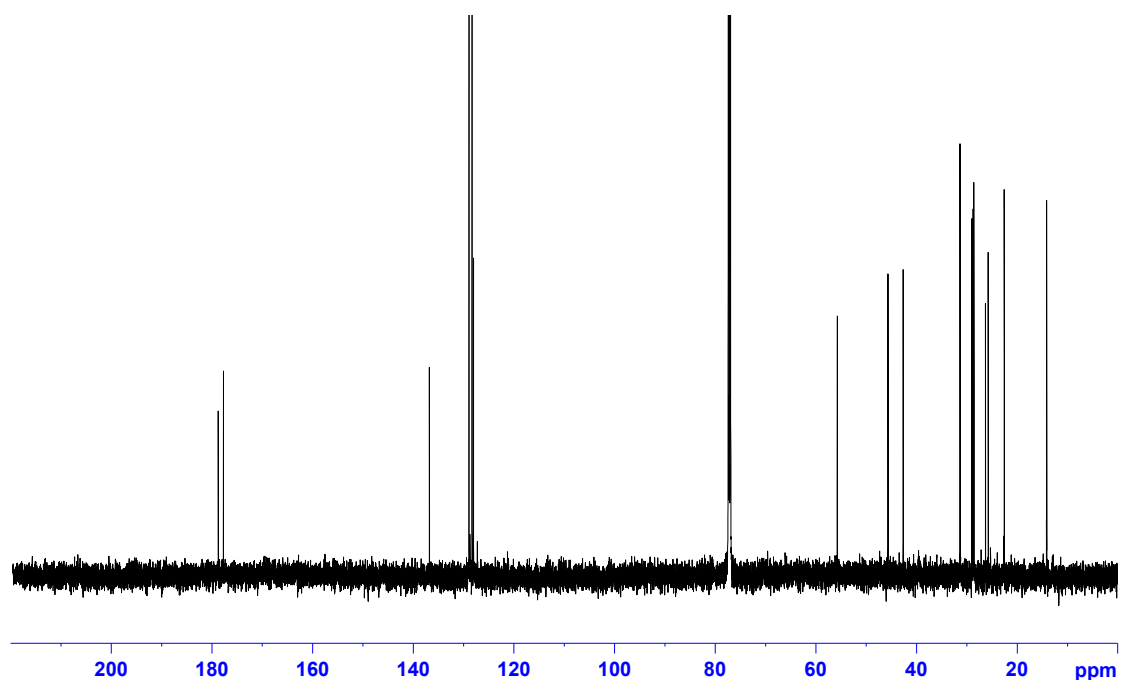
22a. δ_{H} (600 MHz, CDCl_3) 7.39-7.30 (m, 5H, 5 x Ar-H), 3.90 (app t, 1H, $J = 8.7$, H-5), 3.13-3.11 (m, 4H, H₃-18 and H-7), 3.00 (ddd, 1H, $J = 12.8$, 11.0 and 8.5, HH-6), 2.53 (ddd, 1H, $J = 12.8$, 9.1 and 3.7, HH-6), 2.40 (ddd, 1H, $J = 11.3$, 8.1 and 6.4, HH-

17), 2.06 (ddd, 1H, $J = 11.3, 8.3$ and 6.5 , $HH-17$), 1.25-1.08 (m, 8H, H_2-13, H_2-14, H_2-15 and H_2-16), 0.82 (t, 3H, $J = 7.4$, H_3-12); δ_C (150 MHz, $CDCl_3$) 178.73 (C=O), 177.70 (C=O), 136.77 (C11), 128.89 (2 x Ar-H), 128.27 (2 x Ar-H), 127.99 (C8), 55.69 (C4), 45.62 (C5), 42.61 (C7), 31.29 (CH_2), 28.94 (CH_2), 28.68 (CH_2), 28.55 (C17), 26.26 (C6), 25.70 (C18), 22.58 (CH_2), 14.09 (C12); IR (oil, cm^{-1}) 2927 (w) 1703 (s); MS (CI+) m/z (relative intensity): 332 ([M+H], 100); Exact Mass Calcd for $[C_{19}H_{25}NO_2S]+H$ requires m/z 332.1684 Found 332.1680 (CI+).

1H NMR

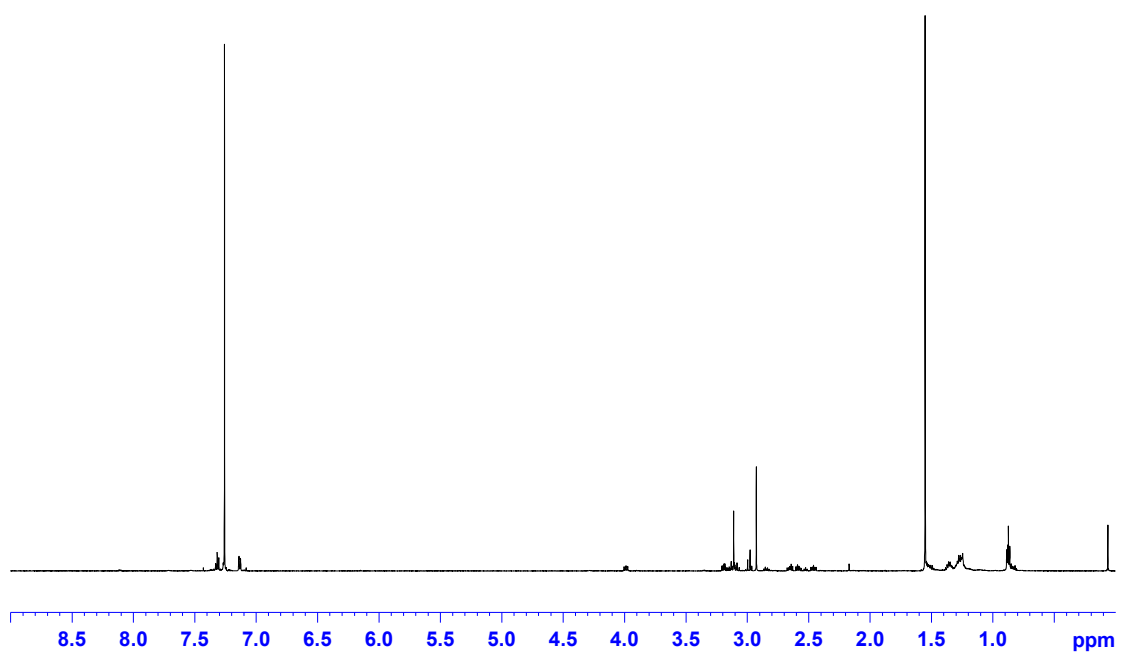


¹³C NMR

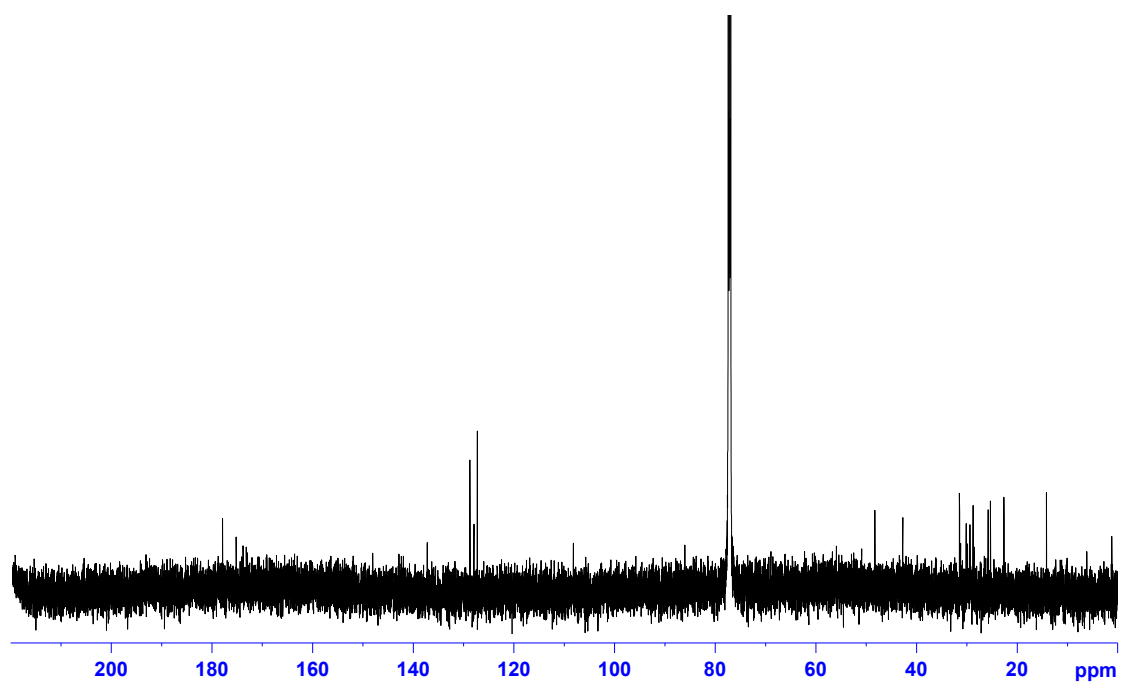


22b. δ_{H} (600 MHz, CDCl_3) 7.32-7.30 (m, 3H, 3 x Ar-H), 7.13 (d, 2H, $J = 7.9$, 2 x H-10), 3.99 (dd, 1H, $J = 10.2$ and 7.8, H-5), 3.20 (dd, 1H, $J = 10.3$ and 4.8, H-7), 3.13-3.07 (m, 1H, HH-6), 2.93 (s, 3H, H₃-18), 2.65 (dt, 1H, $J = 11.4$ and 7.5, HH-17), 2.58 (dt, 1H, $J = 11.8$ and 7.5, HH-17), 2.46 (ddd, 1H, $J = 12.0$, 7.7 and 4.9, HH-6), 1.55-1.25 (m, 8H, H₂-13, H₂-14, H₂-15 and H₂-16), 0.87 (t, 3H, $J = 7.0$, H₃-12); δ_{C} (150 MHz, CDCl_3) 177.78 (C=O), 175.17 (C=O), 137.21 (C11), 128.71 (2 x Ar-H), 127.93 (C8), 127.24 (2 x Ar-H), 55.39 (C4), 48.23 (C5), 42.71 (C7), 31.42 (CH₂), 30.07 (C17), 29.33 (CH₂), 28.69 (CH₂), 25.71 (CH₂), 25.25 (C18), 22.58 (CH₂), 14.12 (C12); IR (oil, cm^{-1}) 2927 (w) 1715 (s); MS (CI+) m/z (relative intensity): 332 ([M+H], 40), 228 (40), 86 (70), 84 (100); Exact Mass Calcd for $[\text{C}_{19}\text{H}_{25}\text{NO}_2\text{S}]+\text{H}$ requires m/z 332.1684 Found 333.1697 (CI+).

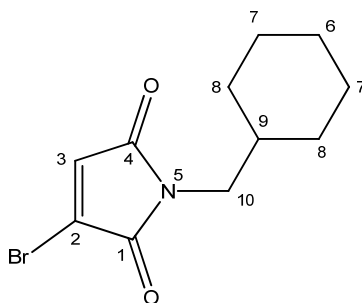
^1H NMR



^{13}C NMR

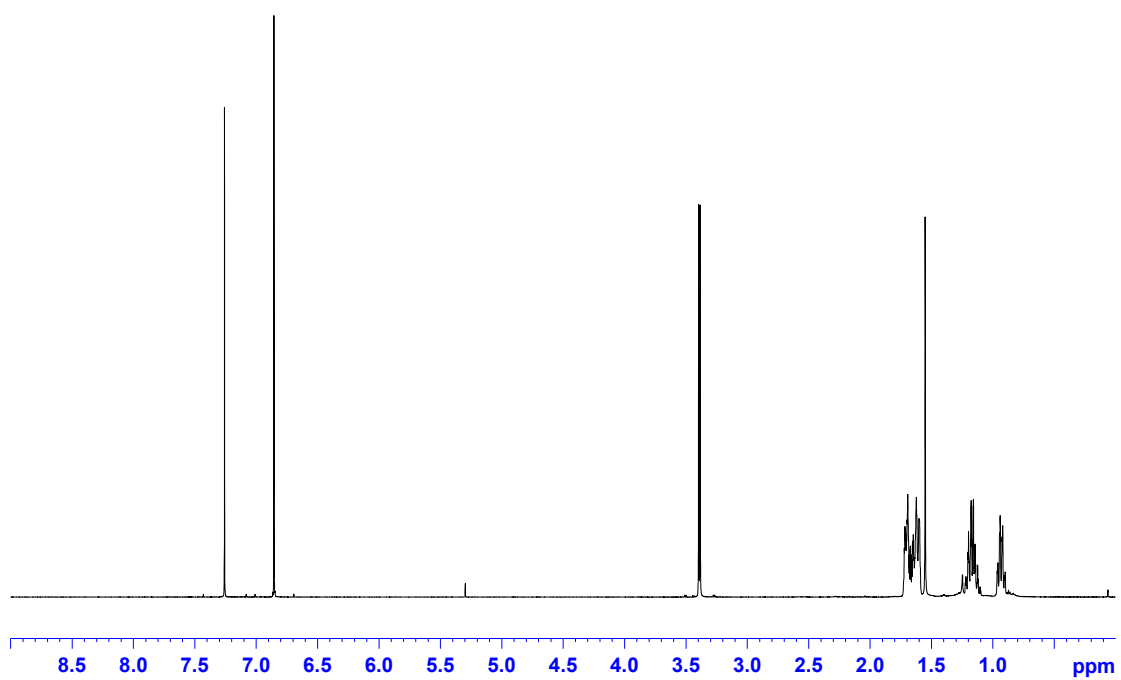


23. 3-Bromo-1-cyclohexylmethyl-pyrrole-2,5-dione

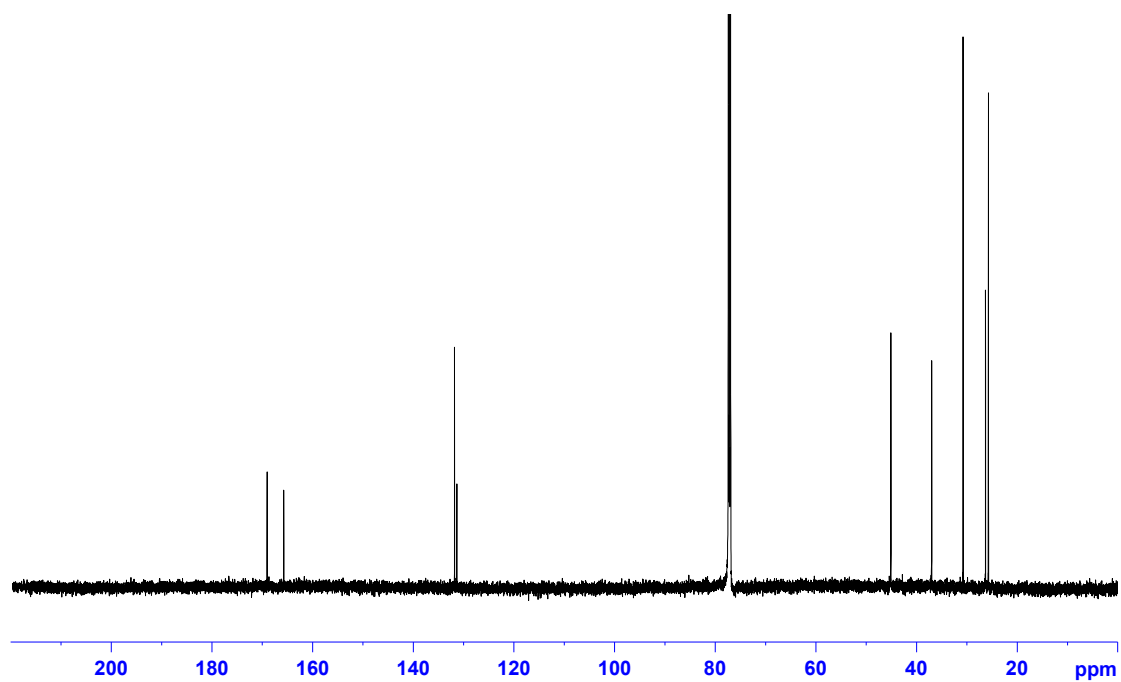


To bromomaleic anhydride (131 μL , 1.41 mmol) in acetic acid (20 mL) was added *N*-methylene cyclohexamine (183 μL , 1.41 mmol). The reaction mixture was stirred in a sealed tube for 3 hours at room temperature and then heated to 150 $^{\circ}\text{C}$ for 90 minutes. The solvent was removed *in vacuo* and purification by flash chromatography (petroleum ether) afforded **23** as a yellow powder (96 mg, 0.35 mmol) in 25% yield. δ_{H} (600 MHz, CDCl_3) 6.85 (s, 1H, H-3), 3.39 (d, 2H, $J = 7.3$, H₂-10), 1.72-1.59 (m, 7H, H₂-6, 2 x *HH*-7, 2 x *HH*-8 and H-9), 1.3-1.10 (m, 2H, 2 x *HH*-7), 0.98-0.90 (m, 2H, 2 x *HH*-8); δ_{C} (150 MHz, CDCl_3) 169.03 (C=O), 165.73 (C=O), 131.78 (C3), 131.32 (C2), 45.06 (C10), 36.95 (C9), 30.68 (2 x CH_2), 26.25 (C6), 25.66 (2 x CH_2); IR (solid, cm^{-1}) 2925 (w), 1713 (s); MS (EI) m/z , (relative intensity): 273 (M^+ , 60), 271 (M^+ , 60), 191 (90), 189 (90), 95 (100); Exact mass calcd for $[\text{C}_{11}\text{H}_{14}\text{O}_2\text{N}^{79}\text{Br}]^+$ requires 271.0202 Found 271.0192 (EI); m.p. 76-78 $^{\circ}\text{C}$; UV (Acetonitrile): $\epsilon_{237} = 20700$ and $\epsilon_{274} = 2790 \text{ cm}^{-1}\text{M}^{-1}$.

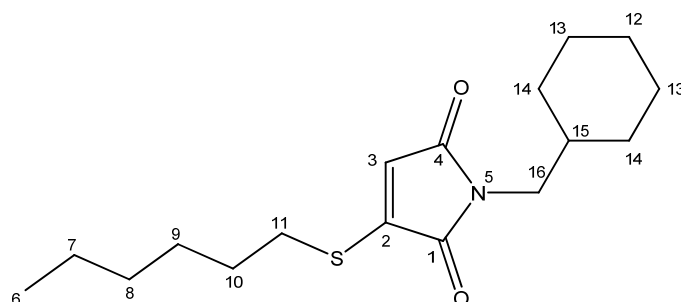
^1H NMR



^{13}C NMR

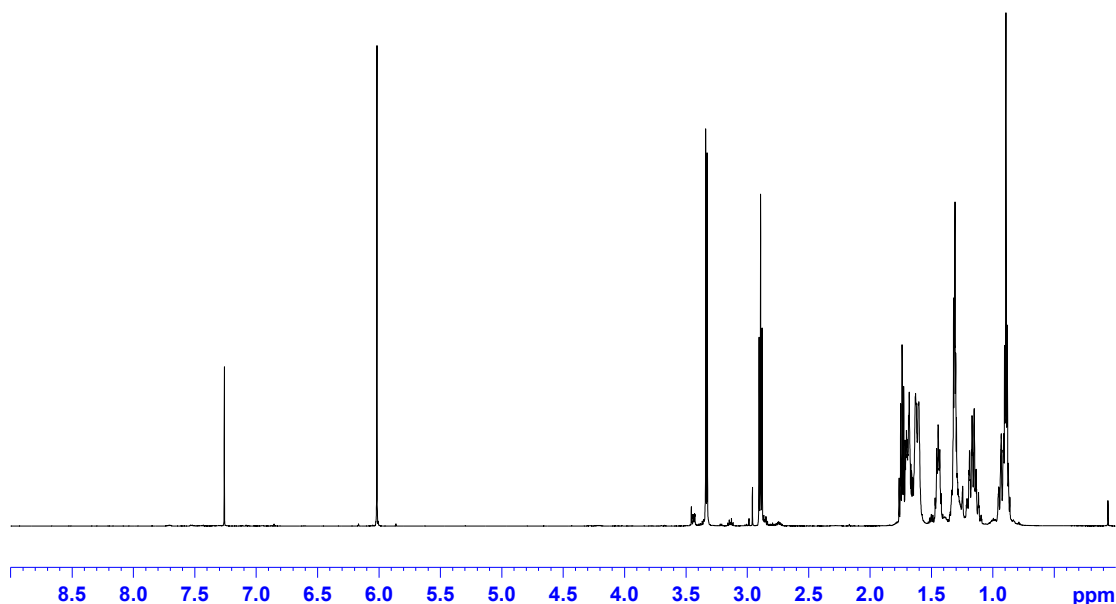


24. 1-Cyclohexylmethyl-3-hexylsulfanyl-pyrrole-2,5-dione

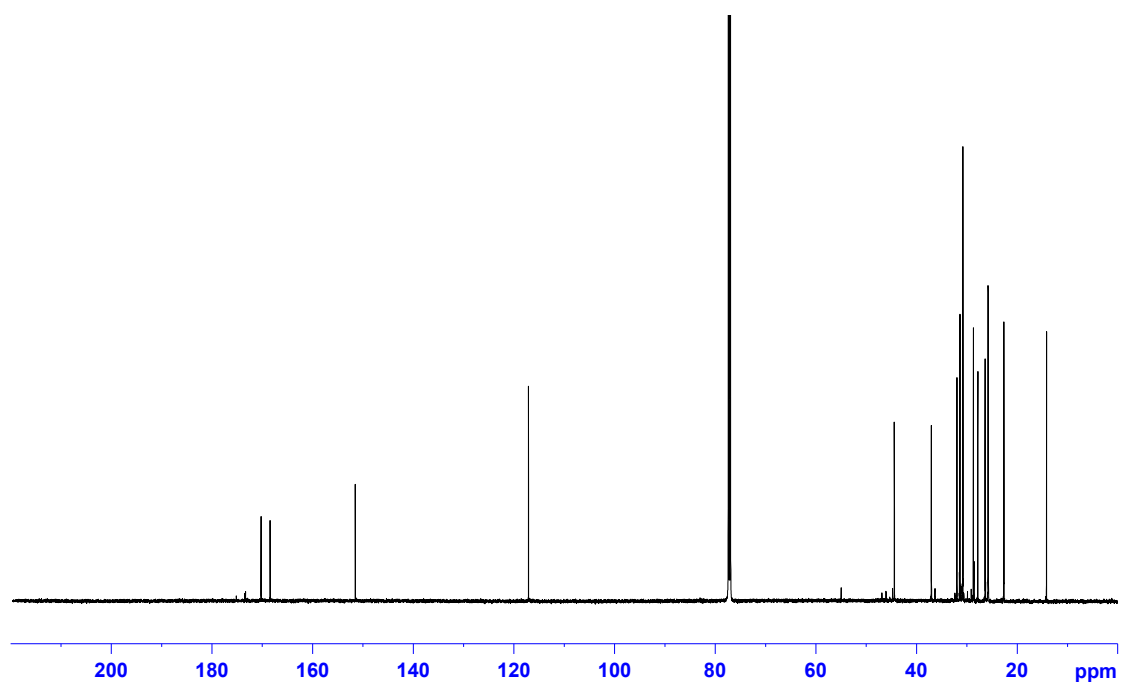


To **23** (50 mg, 0.19 mmol) in methanol (50 mL), was added hexanethiol (52 μ L, 0.37 mmol) and sodium acetate (50 mg, 0.37 mmol) in methanol (50 mL) dropwise over 5 minutes. After 10 minutes, the solvent was removed *in vacuo* and purification by flash chromatography (petroleum ether) afforded **24** as an off-white solid (29 mg, 0.09 mmol) in 84% yield. δ_{H} (600 MHz, CDCl_3) 6.01 (s, 1H, H-3), 3.33 (d, 2H, $J = 7.2$, H_2 -16), 2.89 (t, 2H, $J = 7.3$, H_2 -11), 1.76-1.60 (m, 8H, H_2 -10, H-15 and 5 x CHH), 1.45 (q, 2H, $J = 7.4$ H_2 -9), 1.33-1.29 (m, 4H, H_2 -7 and H_2 -8), 1.22-1.11 (m, 2H), 0.96-0.86 (m, 3H), 0.89 (t, 3H, $J = 6.9$, H_3 -6); δ_{C} (125 MHz, CDCl_3) 170.23 (C=O), 168.44 (C=O), 151.49 (C2), 117.08 (C3), 44.36 (C16), 37.00 (C15), 31.91 (2 x CH_2), 31.32 (2 x CH_2), 30.73 (CH_2), 28.66 (CH_2), 27.78 (CH_2), 26.33 (CH_2), 25.73 (CH_2), 22.58 (CH_2), 14.10 (C6); IR (solid, cm^{-1}) 2927 (m), 1701 (s); MS (ES+) m/z , (relative intensity): 310 ([M+H], 100), 180 (40); Mass calcd for $[\text{C}_{17}\text{H}_{27}\text{O}_2\text{NS}]+\text{H}$ requires 310.1841 Found 310.1828 (ES+); UV (Acetonitrile): $\epsilon_{254} = 6680$ and $\epsilon_{348} = 5040 \text{ cm}^{-1} \text{ M}^{-1}$.

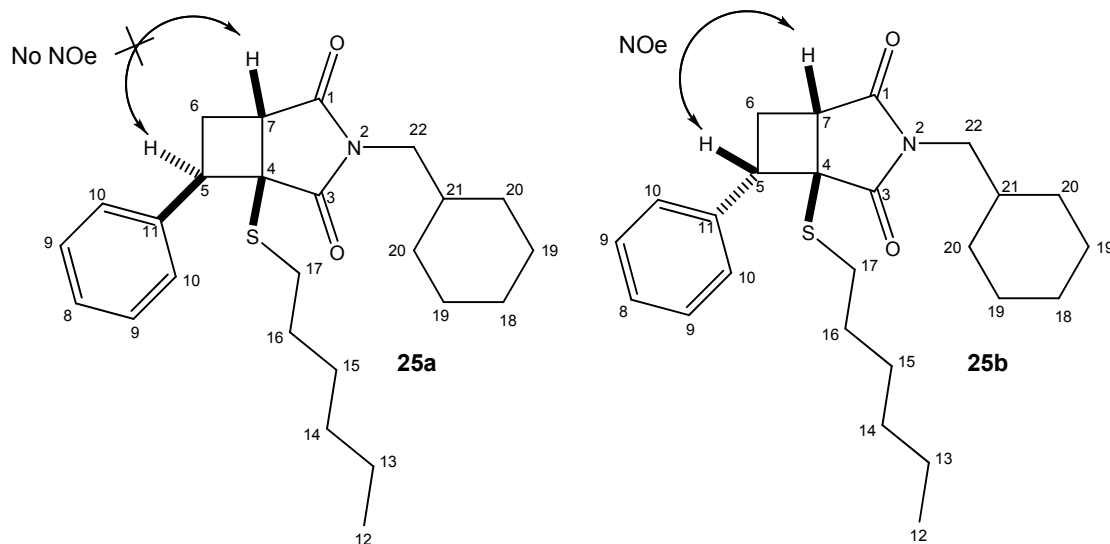
^1H NMR



^{13}C NMR



25a. (4*RS*, 5*SR*, 7*SR*)-2-Aza-2-methylenecyclohexane-4-hexylsulfanyl-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione and **25b.** (4*RS*, 5*RS*, 7*SR*)-2-aza-2-methylenecyclohexane-4-hexylsulfanyl-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione

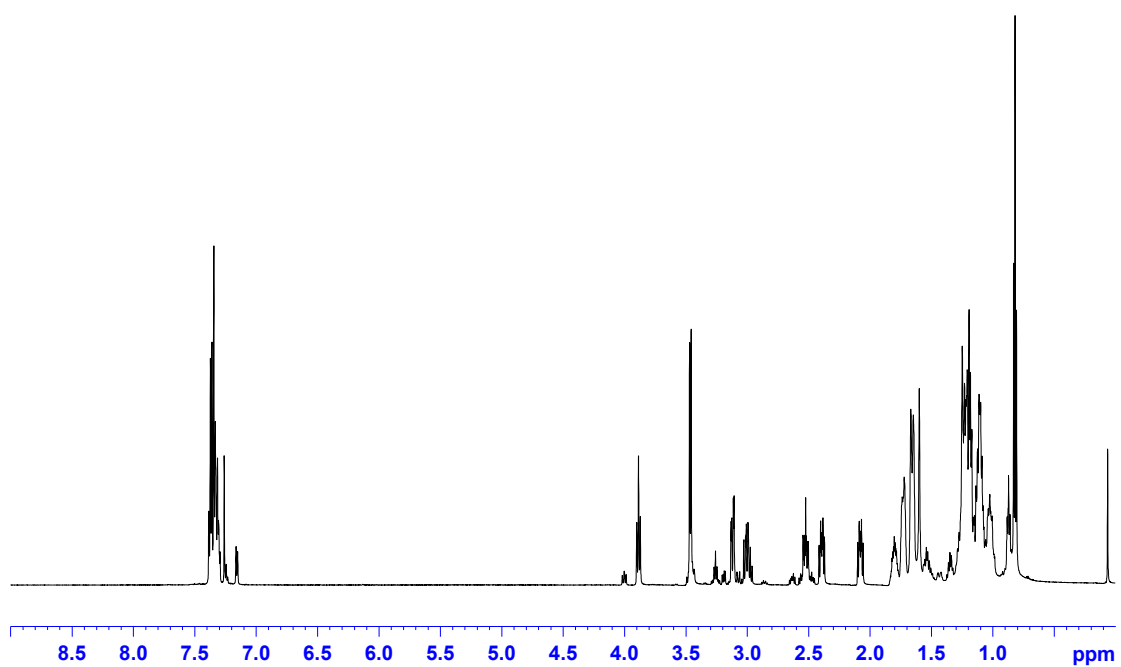


24 (25 mg, 0.116 mmol) was dissolved in acetonitrile (21 mL). The resulting solution was degassed for 30 minutes, styrene (133 μL , 1.16 mmol) added and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and

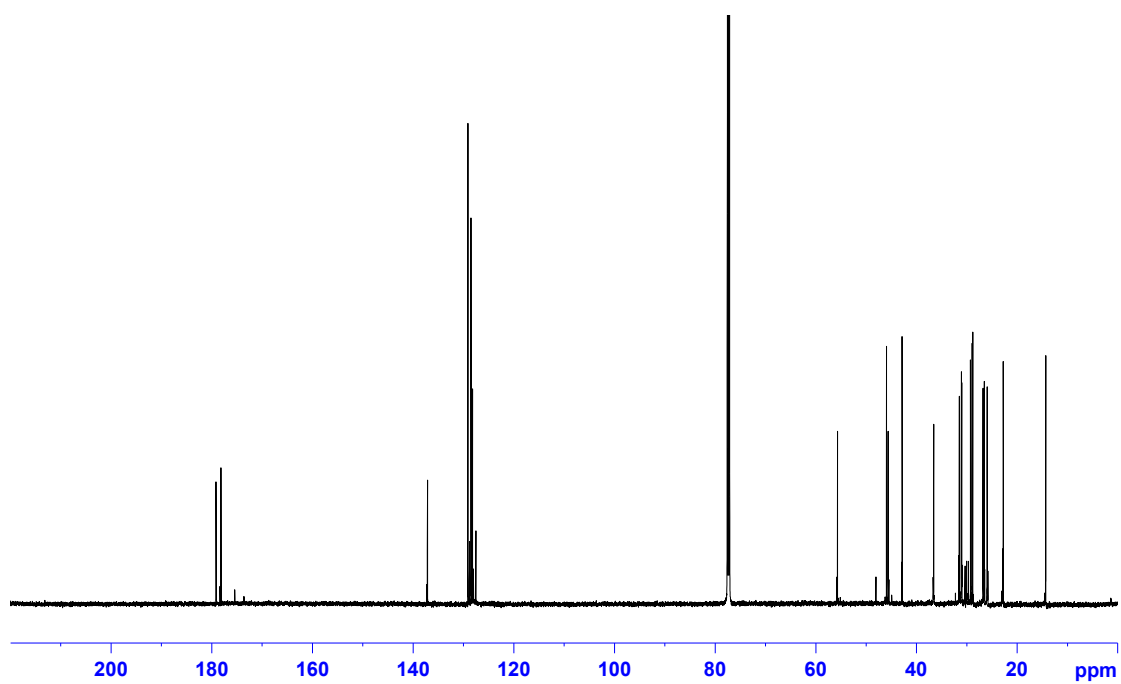
purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **25a** and **25b** as a colourless oil (30 mg, 0.075 mmol) in 64% yield as a mix of diastereoisomers. NMR investigations showed the mixture was a 1:10 ratio of **25a** to **25b**.

25a and **25b**. δ_{H} (600 MHz, CDCl_3) 7.39-7.29 (m, 7H, 5 x Ar-H_b and 2 x Ar-H_a), 7.24 (d, 1H, $J = 7.4$, H-8_a), 7.16 (d, 2H, $J = 7.4$, 2 x H-10_a), 4.00 (dd, 1H, $J = 10.5$ and 6.9, H-5_a), 3.89 (app t, 1H, $J = 8.7$, H-5_b), 3.46 (d, 4H, $J = 7.5$, H₂-22_b and H₂-22_a), 3.19 (dd, 1H, $J = 10.5$ and 6.9, H-7_a), 3.12 (dd, 1H, $J = 10.9$ and 3.5, H-7_b), 3.07 (app dt, 1H, $J = 12.0$ and 10.5, HH-6_a), 3.00 (ddd, 1H, $J = 12.6$, 11.5 and 8.5, HH-6_b), 2.64 (ddd, 1H, $J = 14.0$, 11.4 and 6.9, HH-17_a), 2.56 (app dt, 1H, $J = 12.0$ and 6.9, HH-6_a), 2.53 (ddd, 1H, $J = 12.9$, 9.1 and 3.3, HH-6_b), 2.48 (ddd, 1H, $J = 14.0$, 8.0 and 5.4, HH-17_a), 2.39 (dt, 1H, $J = 11.4$ and 7.4, HH-17_b), 2.08 (dt, 1H, $J = 11.4$ and 7.7, HH-17_b), 1.83-0.99 (m, 38H, 19H_b and 19H_a), 0.87 (t, 3H, $J = 7.0$, H₃-12_a), 0.82 (t, 3H, $J = 7.5$, H₃-12_b); δ_{C} (150 MHz, CDCl_3) 179.12 (C=O_b), 178.35 (C=O_a), 178.15 (C=O_b), 175.41 (C=O_a), 137.23 (C11_a), 137.12 (C11_b), 129.08 (2 x Ar-H_b), 128.76 (2 x Ar-H_a), 128.47 (2 x Ar-H_b), 128.16 (C8_b), 127.99 (C8_a), 127.51 (2 x Ar-H_a), 55.84 (C4_a), 55.69 (C4_b), 48.06 (C5_a), 45.97 (C5_b), 45.63 (C22_b), 45.48 (C22_a), 42.94 (C7_a), 42.83 (C7_b), 36.67 (C21_a), 36.58 (C21_b), 31.64 (CH₂-_a), 31.49 (CH₂-_b), 31.08 (CH₂-_b), 31.01 (CH₂-_b), 30.96 (CH₂-_a), 30.34 (CH₂-_a), 30.04 (CH₂-_a), 29.67 (CH₂-_a), 29.28 (CH₂-_b), 28.98 (CH₂-_b), 28.82 (CH₂-_b), 26.76 (CH₂-_a), 26.63 (CH₂-_a), 26.52 (CH₂-_b), 26.45 (CH₂-_a), 25.96 (CH₂-_b), 25.94 (CH₂-_b), 25.82 (CH₂-_a), 14.34 (C12_a), 14.31 (C12_b); IR (oil, cm^{-1}) 2925 (m) 1703 (s); MS (CI+) m/z (relative intensity): 414 ([M+H], 100), 309 (20); Exact Mass Calcd for $[\text{C}_{25}\text{H}_{35}\text{NO}_2\text{S}]+\text{H}$ requires m/z 414.2461 Found 414.2452 (CI+)

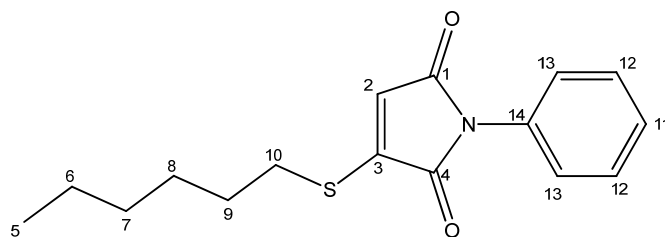
^1H NMR



^{13}C NMR

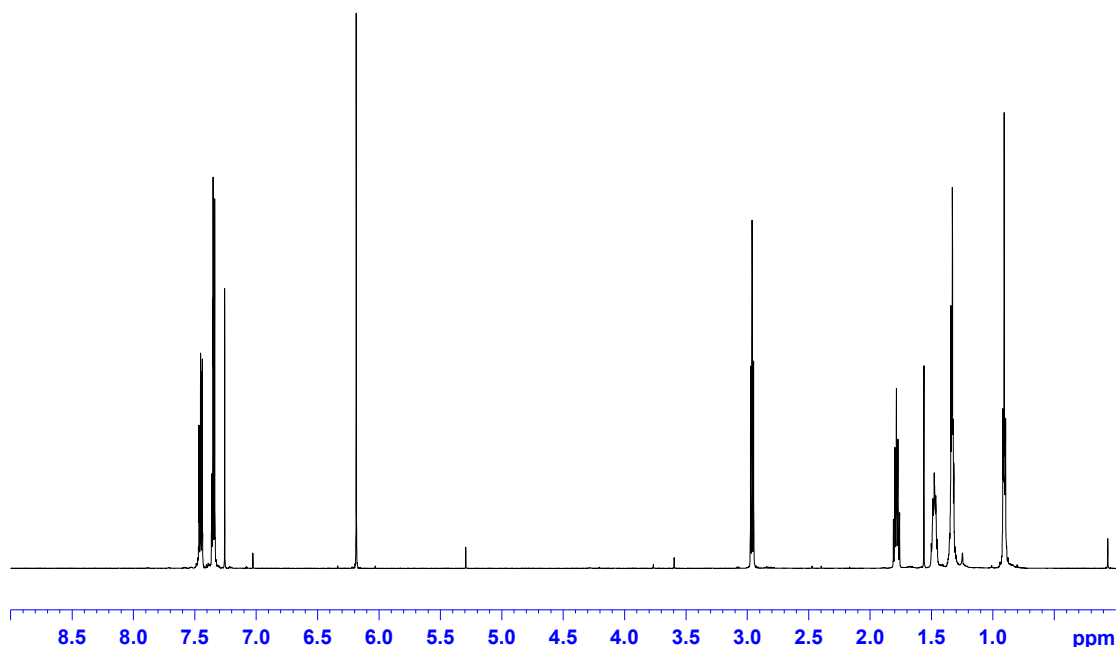


26. 3-Hexylsulfanyl-1-phenylpyrrole-2,5-dione

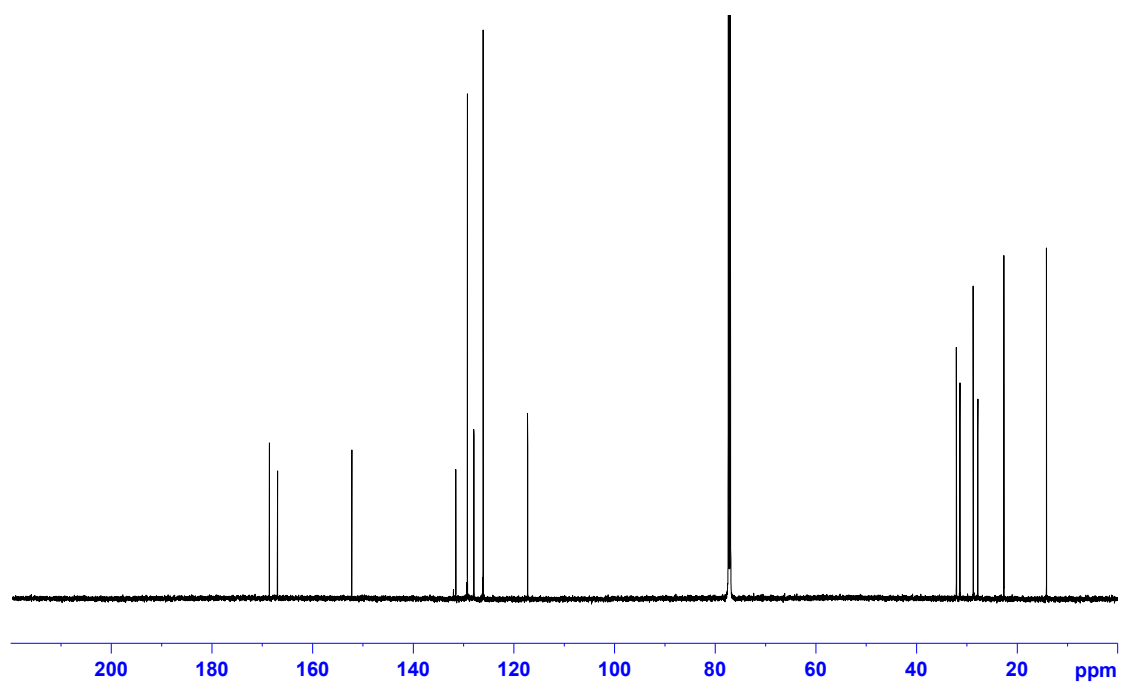


To N-phenyl bromomaleimide⁶ (200 mg, 0.79 mmol) in methanol (60 mL) was added hexanethiol (111 μ L, 0.79 mmol) and sodium acetate trihydrate (108 mg, 0.79 mmol) in methanol (60 mL) dropwise over 1 hour with vigorous stirring. After 5 minutes the solvent was removed *in vacuo*. Purification by flash chromatography (gradient elution in 10% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **26** as a pale yellow solid (109 mg, 0.38 mmol) in 48% yield. δ_{H} (600 MHz, CDCl_3) 7.45 (dd, 2H, $J = 8.0$ and 7.1 , 2 x H-12), 7.36 (t, 1H, $J = 7.1$, H-11), 7.35 (d, 2H, $J = 8.1$, 2 x H-13), 6.19 (s, 1H, H-2), 2.96 (t, 2H, $J = 7.9$, H₂-10), 1.81-1.76 (m, 2H, H₂-9), 1.50-1.45 (m, 2H, H₂-8), 1.34-1.32 (m, 4H, H₂-6 and H₂-7), 0.91 (t, 3H, $J = 6.9$, H₃-5); δ_{C} (125 MHz, CDCl_3) 168.59 (C=O), 166.96 (C=O), 152.20 (C3), 131.53 (C14), 129.21 (2 x Ar-H), 127.93 (C11), 126.09 (2 x Ar-H), 117.24 (C2), 32.03 (C10), 31.33 (CH₂), 28.68 (CH₂), 27.78 (CH₂), 22.59 (CH₂), 14.11 (C5); IR (oil, cm^{-1}) 2931 (w), 1703 (s); MS (CI⁺) m/z (relative intensity): 290 ([M+H], 100); Exact Mass Calcd for $[\text{C}_{16}\text{H}_{19}\text{NO}_2\text{S}]+\text{H}$ requires m/z 290.1215 Found 290.1224 (CI⁺); m.p. 102-104 $^{\circ}\text{C}$; UV (Acetonitrile): $\epsilon_{277} = 9150$ and $\epsilon_{346} = 5880 \text{ cm}^{-1}\text{M}^{-1}$.

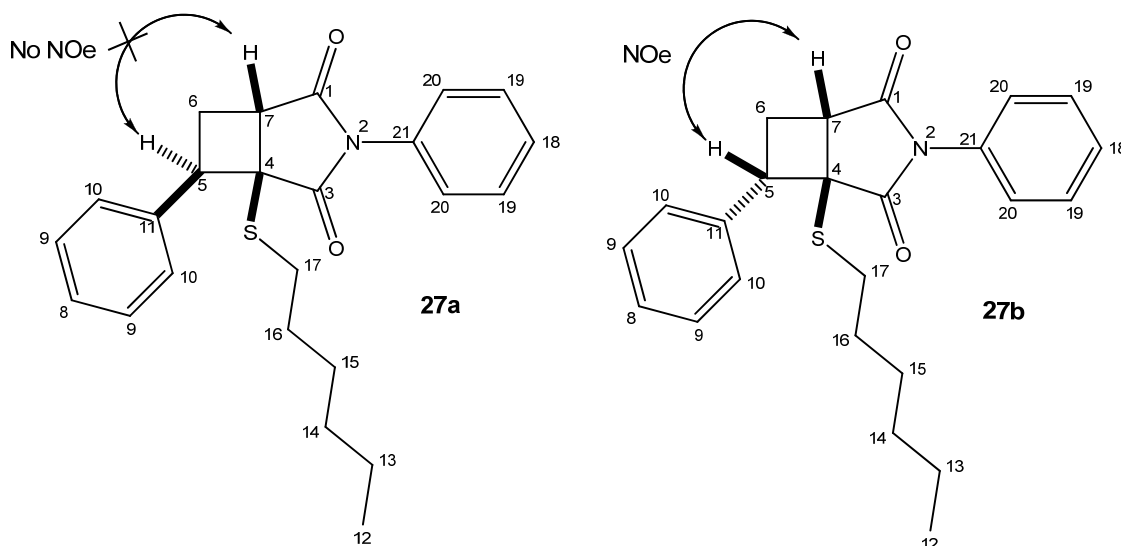
¹H NMR



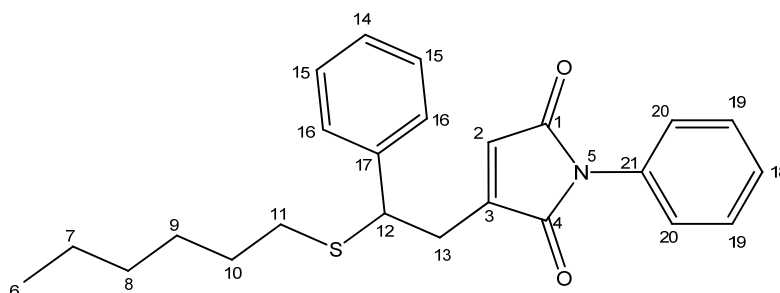
^{13}C NMR



27a. (4*RS*, 5*SR*, 7*SR*)-2-Aza-2-phenyl-4-hexylsulfanyl-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione and **27b.** (4*RS*, 5*RS*, 7*SR*)-2-aza-2-phenyl-4-hexylsulfanyl-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione



28. 3-(2-Hexylsulfanyl-2-phenyl-ethyl)-1-phenyl-pyrrole-2,5-dione

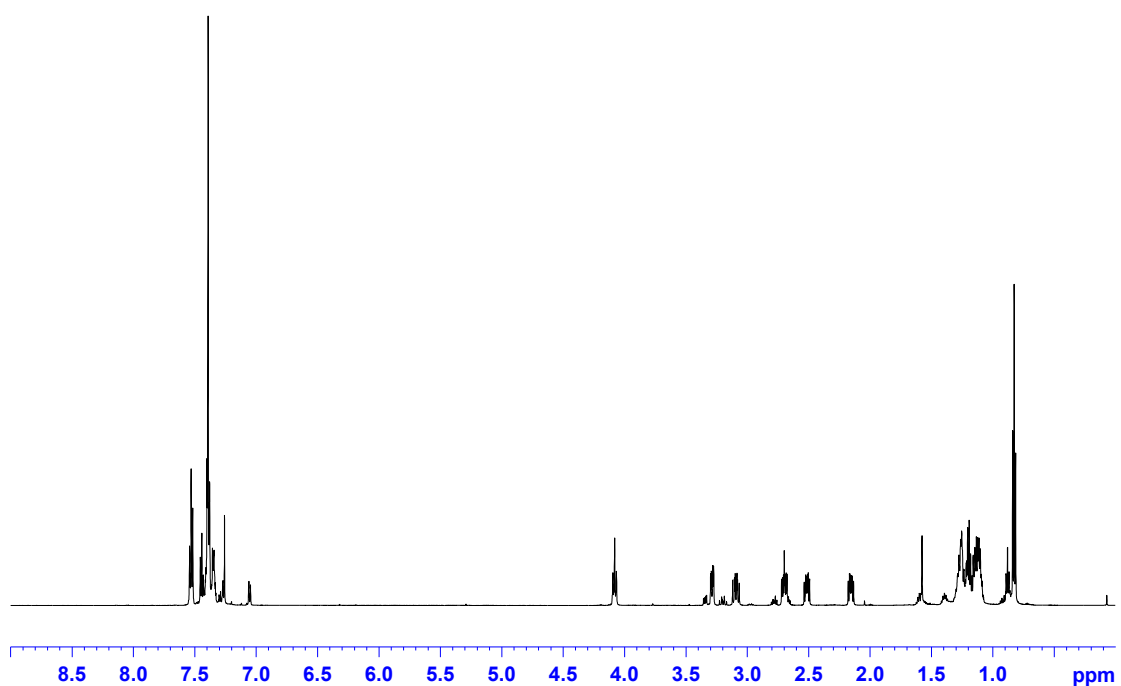


26 (34 mg, 0.12 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes, styrene (135 μ L, 1.18 mmol) added and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **27a** and **27b** as a colourless oil (37 mg, 0.94 mmol) in 80% (NMR investigations showed the mixture was a 1:11 ratio of a:b) and **28** as a colourless oil (0.5 mg, 0.001 mmol) in 1% yield.

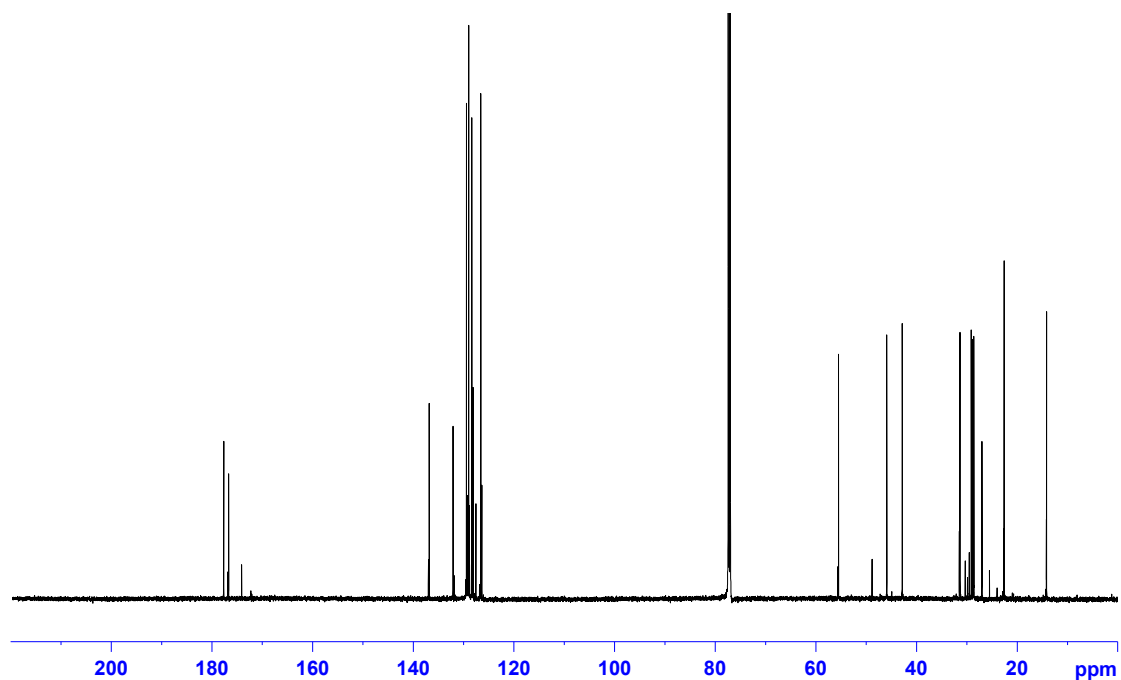
27a. and **27b.** δ_{H} (600 MHz, CDCl_3) 7.54-7.52 (m, 2H, 2 x Ar-H_b), 7.46-7.42 (m, 4H, 4 x Ar-H_a), 7.41-7.37 (m, 10H, 8 x Ar-H_b and 2 x Ar-H_a), 7.27-7.26 (m, 2H, 2 x Ar-H_a), 7.06-7.05 (m, 2H, 2 x Ar-H_a), 4.09 (app t, 1H, $J = 8.5$, H-5_a), 4.08 (app t, 1H, $J = 8.5$, H-5_b), 3.35 (dd, 1H, $J = 10.5$ and 4.7, H-7_a), 3.29 (dd, 1H, $J = 10.9$ and 4.0, H-7_b), 3.20 (ddd, 1H, $J = 13.3$, 10.3 and 8.5, HH-6_a), 3.09 (ddd, 1H, $J = 13.0$, 11.0 and 8.2, HH-6_b), 2.78 (dt, 1H, $J = 11.7$ and 7.4, HH-17_a), 2.72-2.68 (m, 2H, HH-6_b and HH-6_a), 2.66 (dd, 1H, $J = 7.4$ and 4.8, HH-17_a), 2.52 (ddd, 1H, $J = 11.4$, 8.2 and 6.5, HH-17_b), 2.16 (ddd, 1H, $J = 11.4$, 8.4 and 6.6, HH-17_b), 1.63-1.58 (m, 2H, H₂-16_a), 1.42-1.37 (m, 2H, H₂-15_a), 1.36-1.09 (m, 6H, 4 x CH₂-b and 2 x CH₂-a), 0.88 (t, 3H, $J = 6.7$, H₃-12_a), 0.83 (t, 3H, $J = 7.3$, H₃-12_b); δ_{C} (150 MHz, CDCl_3) 177.65 (C=O_b), 176.82 (C=O_a), 176.67 (C=O_b), 174.08 (C=O_a), 136.96 (C11_a), 136.82 (C11_b), 132.06 (C21_b), 131.86 (C21_a), 129.40 (2 x Ar-H_b), 129.22 (Ar-H_a), 128.96 (2 x Ar-H_b), 128.84 (Ar-H_a), 128.79 (Ar-H_a), 128.34 (2 x Ar-H_b), 128.08 (Ar-H_b), 127.51 (Ar-H_a), 126.56 (2 x Ar-H_b), 126.34 (Ar-H_a), 55.57 (C4_a), 55.47 (C4_b), 48.78 (C5_a), 45.87 (C5_b), 44.88 (C7_a), 42.79 (C7_b), 31.45 (C17_a), 31.31 (C17_b), 30.27 (CH₂-a), 29.46 (CH₂-a), 29.08 (CH₂-b), 28.75 (CH₂-a), 28.56 (CH₂-b), 26.95 (CH₂-b), 22.60 (CH₂-a), 22.52 (CH₂-b), 14.14 (C12_a), 14.10 (C12_b) Four carbon signals are missing due to overlap of the diastereomers; IR (oil, cm^{-1}) 2926 (w) 1709 (s); MS (CI⁺) m/z (relative

intensity): 394 ([M+H], 70), 290 (100), 105 (100); Exact Mass Calcd for [C₂₄H₂₇NO₂S]+H requires *m/z* 394.1841 Found 394.1834 (CI+).

¹H NMR



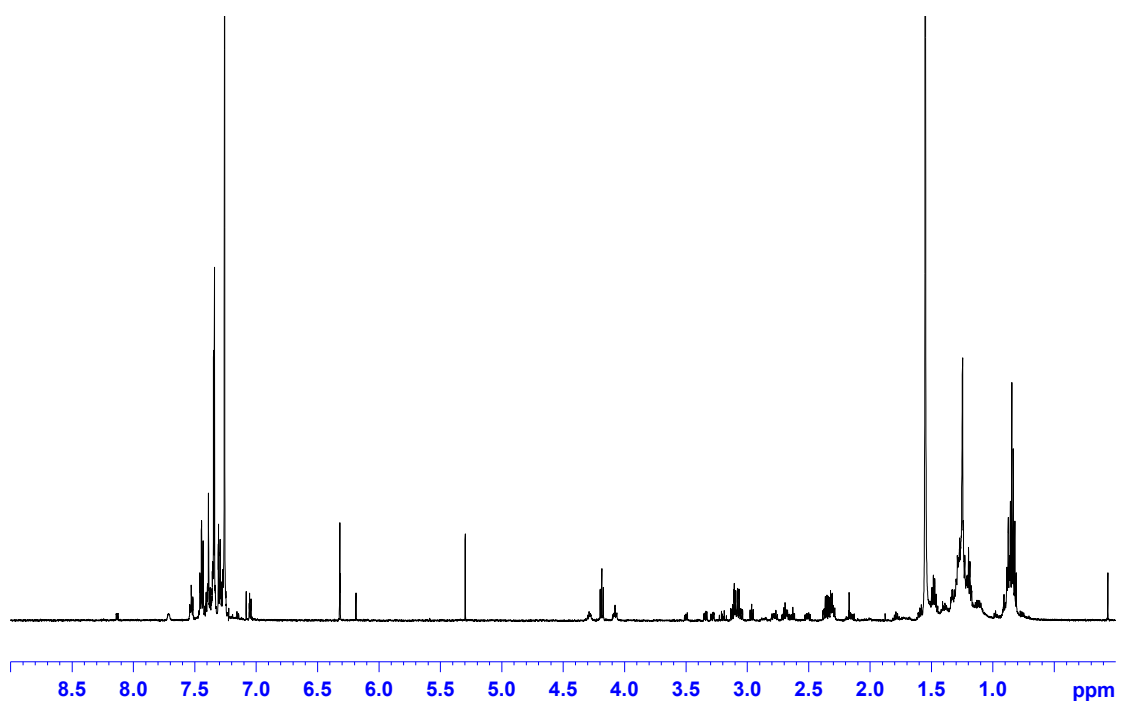
¹³C NMR



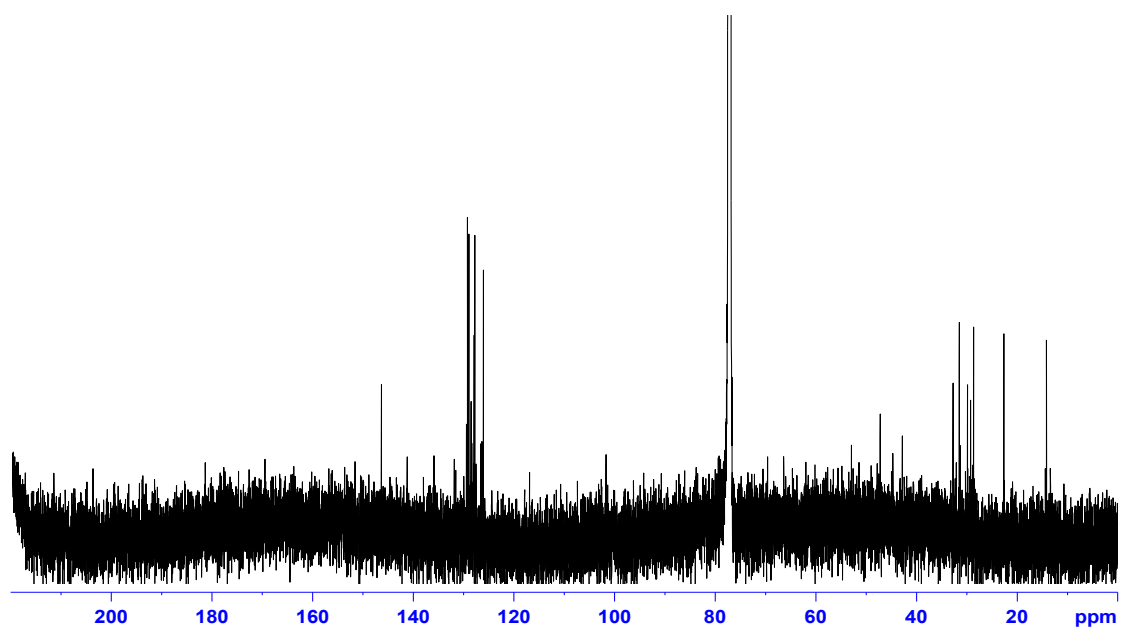
28. δ_{H} (600 MHz, CDCl₃) 7.54-7.27 (m, 10H, 10 x Ar-H), 6.32 (app t, 1H, *J* = 1.0, H-2), 4.19 (t, 1H, *J* = 8.0, H-12), 3.12 (ddd, 1H, *J* = 15.1, 7.5, and 1.0, HH-13), 3.07 (ddd, 1H, *J* = 15.6, 8.0 and 1.0, HH-13) 2.39-2.29 (m, 2H, H₂-11), 1.61-1.10 (m, 8H,

4 x CH₂), 0.89-0.81 (m, 3H, H₃₋₆); δ_C (150 MHz, CDCl₃) 172.61 (C=O), 169.60 (C=O), 130.19 (Ar), 129.41 (Ar), 129.20 (Ar-H), 128.93 (2 x Ar-H), 128.49 (2 x Ar-H), 127.90 (Ar-H), 127.76 (2 x Ar-H), 126.03 (2 x Ar-H), 47.19 (C12), 32.70 (CH₂), 31.43 (CH₂), 29.83 (CH₂), 29.20 (CH₂), 28.63 (CH₂), 22.61 (CH₂), 14.13 (C6); IR (oil, cm⁻¹) 2926 (m) 1715 (s); MS (CI+) *m/z* (relative intensity): 394 ([M+H], 40), 278 (100); Exact Mass Calcd for [C₂₄H₂₇NO₂S]+H requires *m/z* 394.1841 Found 394.1829 (CI+).

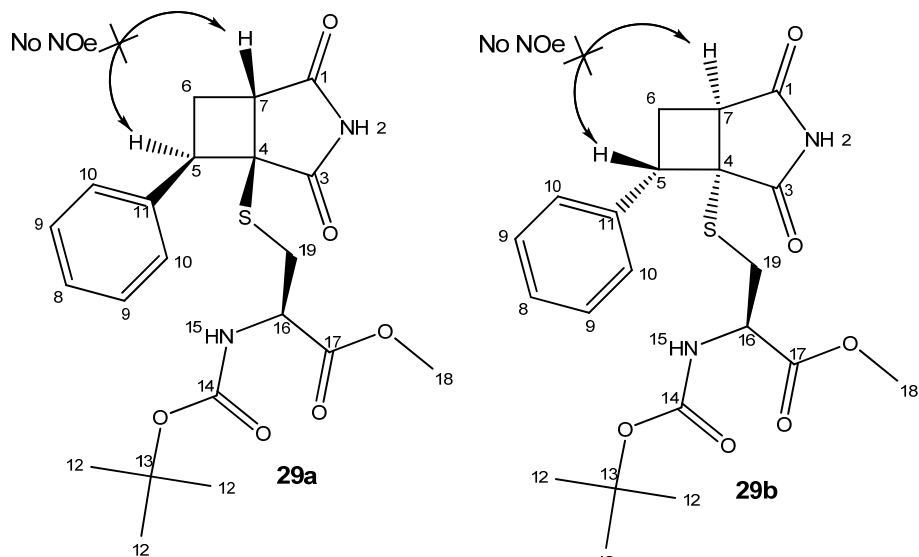
¹H NMR



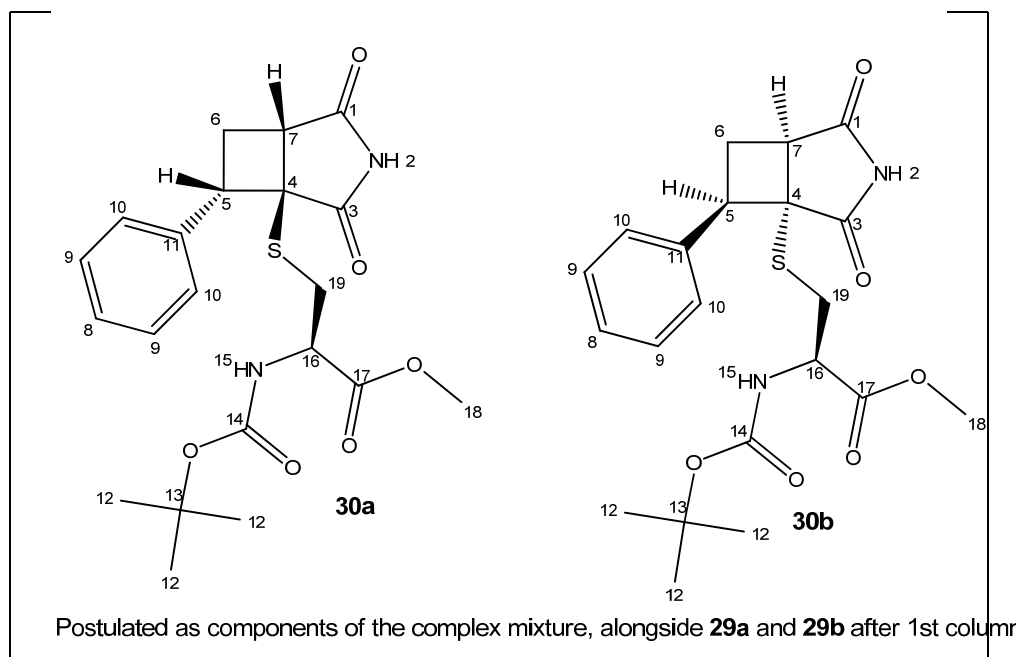
¹³C NMR



29a. (4S, 5R, 7R)-2-Aza-4-([2R-*tert*-butoxycarbonylamino-3-sulfanyl] propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione and **29b.** (4R, 5S, 7S)-2-aza-4-([2R-*tert*-butoxycarbonylamino-3-sulfanyl] propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione



30a. (4S, 5S, 7R)-2-Aza-4-([2R-*tert*-butoxycarbonylamino-3-sulfanyl] propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione and **30b.** (4R, 5R, 7S)-2-aza-4-([2R-*tert*-butoxycarbonylamino-3-sulfanyl] propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione

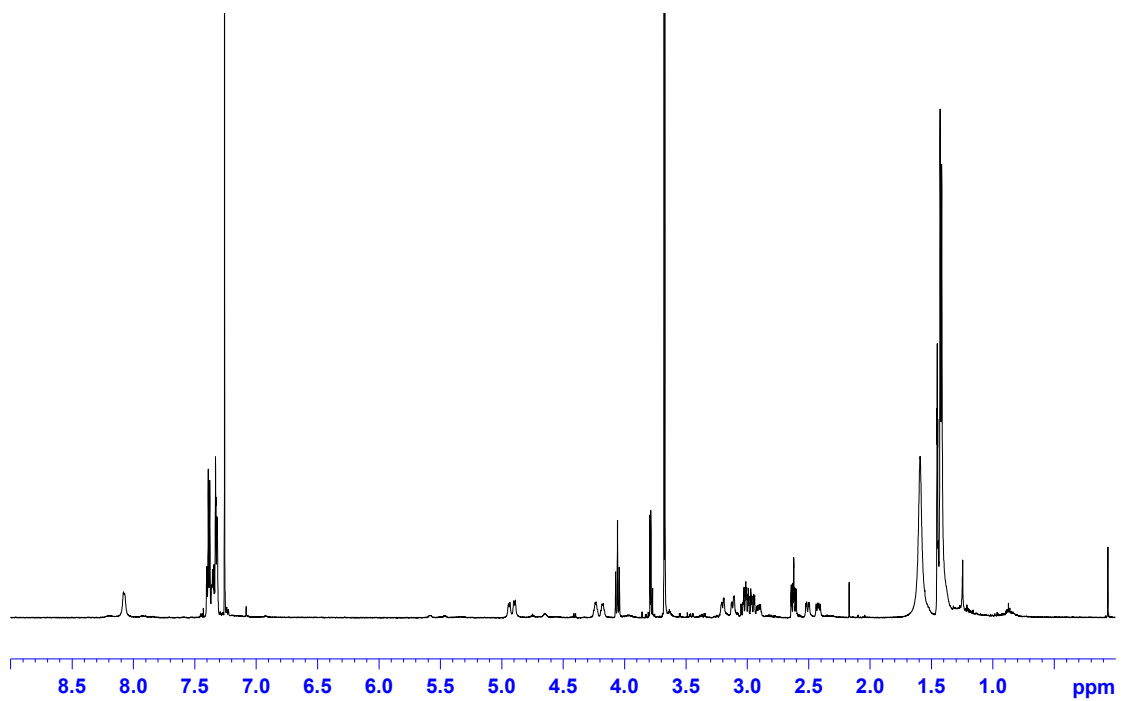


Method 1: **7¹** (39 mg, 0.12 mmol) was dissolved in acetonitrile (30 mL). The resulting solution was degassed for 30 minutes, styrene (13.6 μ L, 1.2 mmol) added and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and ¹H NMR indicated a complex mixture of diastereomers. Purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded a white solid (34 mg, 0.078 mmol) in 63% yield that was postulated as a mixture of four diastereomers shown, **29a**, **29b**, **30a** and **30b**, overlap of signals prevented NOE analysis at this stage. Further column chromatography afforded **29a** and **29b** as a white solid (12 mg, 0.028 mmol) in 23%. NMR investigations showed the mixture was 1:1 of **a:b**. Reanalysis of the crude suggests that almost all peaks are from these four compounds. δ_{H} (600 MHz, CDCl₃) 8.08 (s, 2H, 2 x H-2), 7.40-7.31 (m, 10H, 10 x Ar-H), 5.0 (d, 1H, $J = 8.2$, H-15), 4.9 (d, 1H, $J = 7.5$, H-15), 4.26-4.23 (m, 1H, H-16), 4.18-4.12 (m, 1H, H-16), 4.06 (app t, 2H, $J = 8.5$, 2 x H-5), 3.69 (s, 3H, H₃-18), 3.674 (s, 3H, H₃-18), 3.19 (ddd, 1H, $J = 11.0$ and 2.4, H-7), 3.11 (dd, 1H, $J = 11.0$ and 3.2, H-7) 3.04-2.93 (m, 3H, 2 x HH-6 and HH-19), 2.91 (dd, 1H, $J = 12.8$ and 6.6, HH-19), 2.64-2.60 (m, 2H, 2 x HH-6), 2.51 (dd, 1H, $J = 12.8$ and 4.6, HH-19), 2.43 (dd, 1H, $J = 13.0$ and 7.3, HH-19), 1.45 (s, 9H, 3 x H₃-12), 1.43 (s, 9H, 3 x H₃-12); δ_{C} (150 MHz, CDCl₃) 178.41 (C=O), 177.25 (C=O), 177.20 (C=O), 171.40 (C=O), 171.10 (C=O), 170.98 (C=O), 155.28 (C=O), 155.18 (C=O), 136.28 (C11), 136.25 (C11), 128.94 (2 x Ar-H), 128.93 (2 x Ar-H), 128.49 (2 x Ar-H), 128.46 (2 x Ar-H), 128.38 (C8), 128.33 (C8), 80.44 (2 x C13), 56.71 (C4), 56.48 (C4), 53.03 (C16), 52.87 (C16), 52.78 (C18), 52.75 (C18), 45.92 (C5), 45.82 (C5), 43.76 (C7), 43.61 (C7), 31.28 (C6), 31.09 (C6), 28.38 (6 x C12), 26.33 (C19), 26.21 (C19); IR (oil, cm⁻¹) 3215 (w), 2971 (w) 1738 (s), 1715 (s); MS (CI⁺) m/z (relative intensity): 435 ([M+H], 10), 379 (30), 335 (100); Exact Mass Calcd for [C₂₁H₂₆N₂O₆S]+H requires m/z 435.1590 Found 435.1576 (CI⁺); m.p. 78-90 °C.

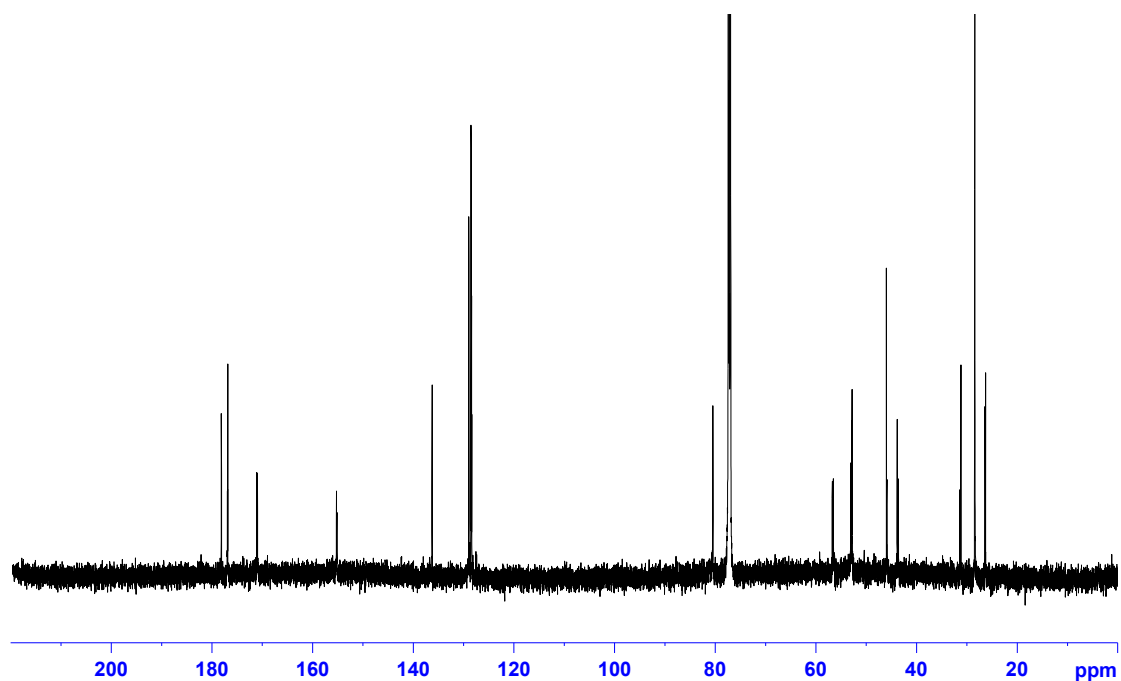
Method 2: **7¹** (39 mg, 0.12 mmol) was dissolved in acetonitrile (30 mL). The resulting solution was degassed for 30 minutes, styrene (13.6 μ L, 0.12 mmol) added and irradiated in pyrex glassware for 5 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded a white solid (27 mg, 0.062 mmol) in 52% yield as a mixture of the same four major diastereomers as

in Method 2, **29a**, **29b**, **30a** and **30b**. Further purification of this mixture was not undertaken.

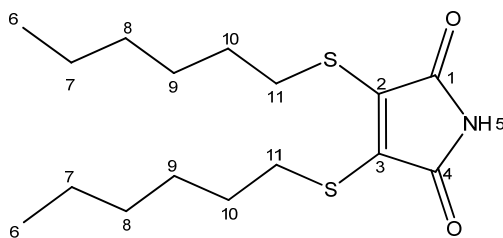
^1H NMR



^{13}C NMR

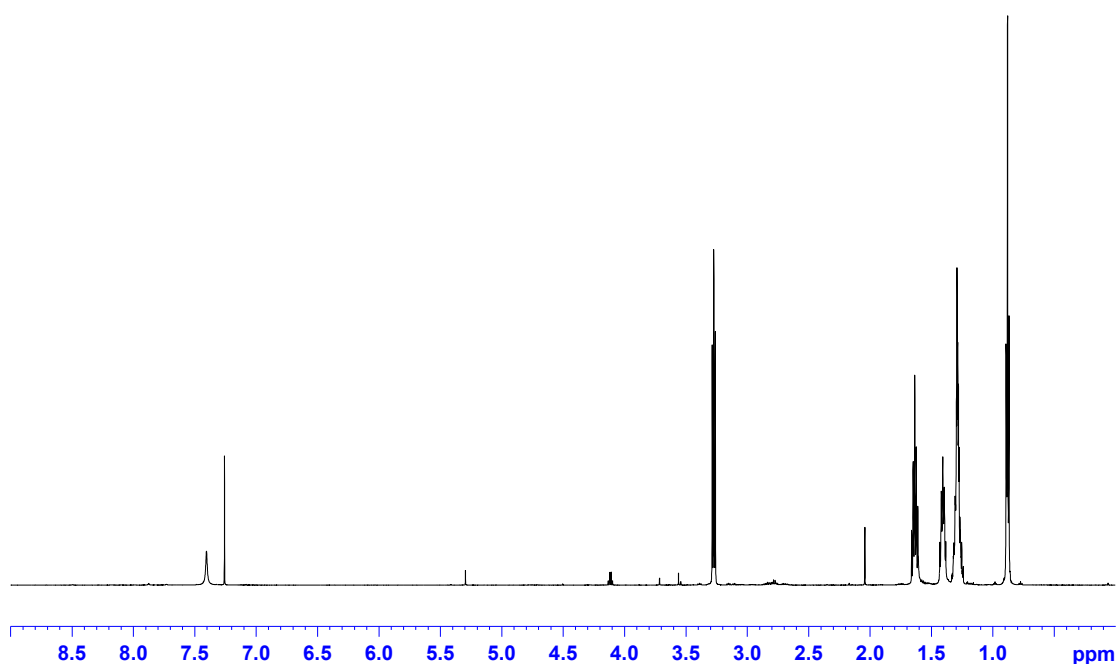


31. 3,4-Bis-hexylsulfanyl-pyrrole-2,5-dione

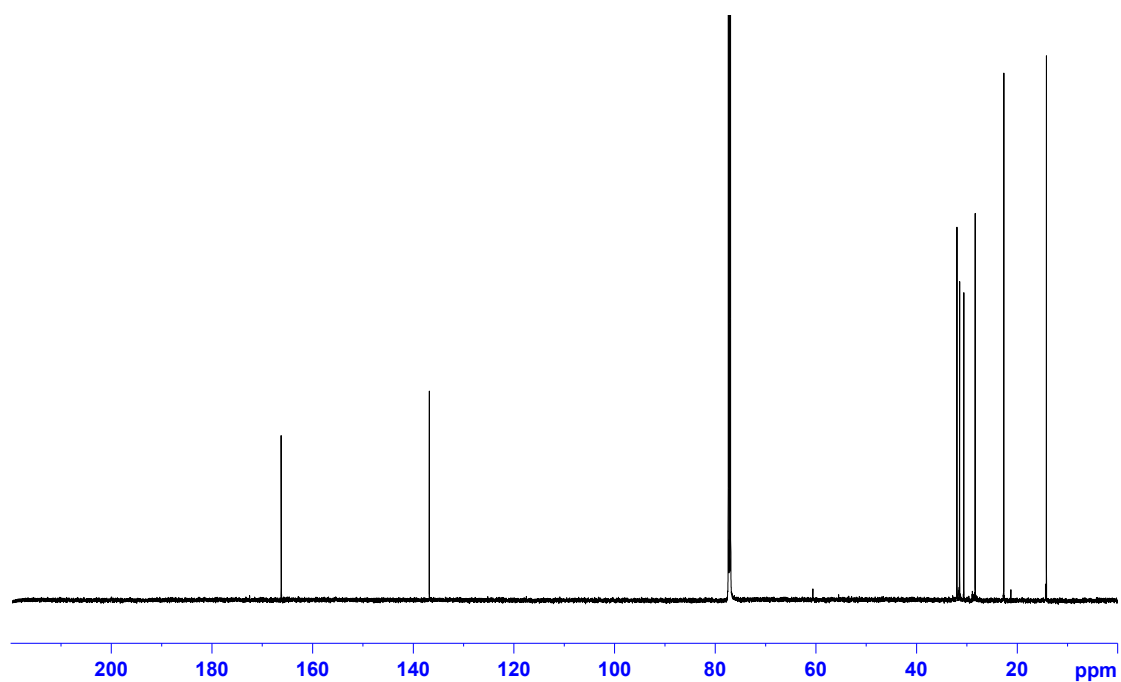


To 2,3-dibromomaleimide (300 mg, 1.17 mmol) and sodium acetate trihydrate (320 mg, 2.35 mmol) in methanol (100 mL) was added hexanethiol (328 μL , 2.34 mmol) in methanol (100 mL) dropwise over 1 hour with vigorous stirring. After 5 minutes the solvent was removed *in vacuo*. Purification by flash chromatography (gradient elution in 10% in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **31** as a bright yellow oil (215 mg, 0.65 mmol) in 55% yield. δ_{H} (600 MHz, CDCl_3) 7.40 (s, 1H, H-5), 3.27 (t, 4H, $J = 7.8$, 2 x H₂-11), 1.66-1.61 (m, 4H, 2 x H₂-10), 1.44-1.38 (m, 4H, 2 x H₂-9), 1.04 (m, 8H, 2 x H₂-8 and 2 x H₂-7), 0.88 (t, 6H, $J = 6.5$, 2 x H₃-6); δ_{C} (150 MHz, CDCl_3) 166.23 (C1 and C4), 136.80 (C2 and C3), 31.92 (2 x C11), 31.39 (2 x CH₂), 30.56 (2 x CH₂), 28.29 (2 x CH₂), 22.62 (2 x C7), 14.13 (2 x C6); IR (oil, cm^{-1}) 3271 (w), 2927 (m) 1770 (m), 1713 (s); MS (FAB+) m/z (relative intensity): 352 ([M+Na], 85), 329 (30), 176 (100); Exact Mass Calcd for $[\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_2\text{S}_2] + \text{Na}$ requires m/z 352.1381 Found 352.1385 (FAB+); UV (Acetonitrile) $\epsilon_{234} = 5400$ and $\epsilon_{398} = 4200 \text{ cm}^{-1}\text{M}^{-1}$.

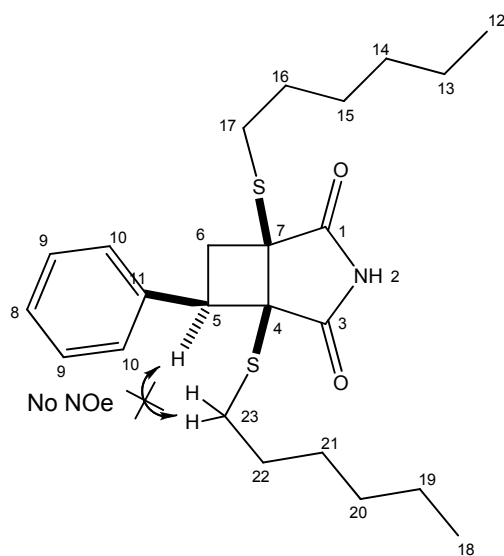
¹H NMR



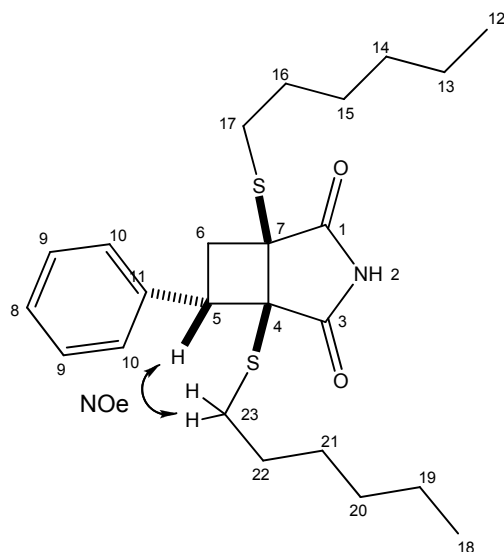
^{13}C NMR



32a. (4*RS*, 5*RS*, 7*SR*)-2-Aza-4-hexylsulfanyl-5-phenyl-7-hexylsulfanyl-bicyclo[3.2.0]heptan-1,3-dione



32b. (4*RS*, 5*SR*, 7*SR*)-2-Aza-4-hexylsulfanyl-5-phenyl-7-hexylsulfanyl-bicyclo[3.2.0]heptan-1,3-dione

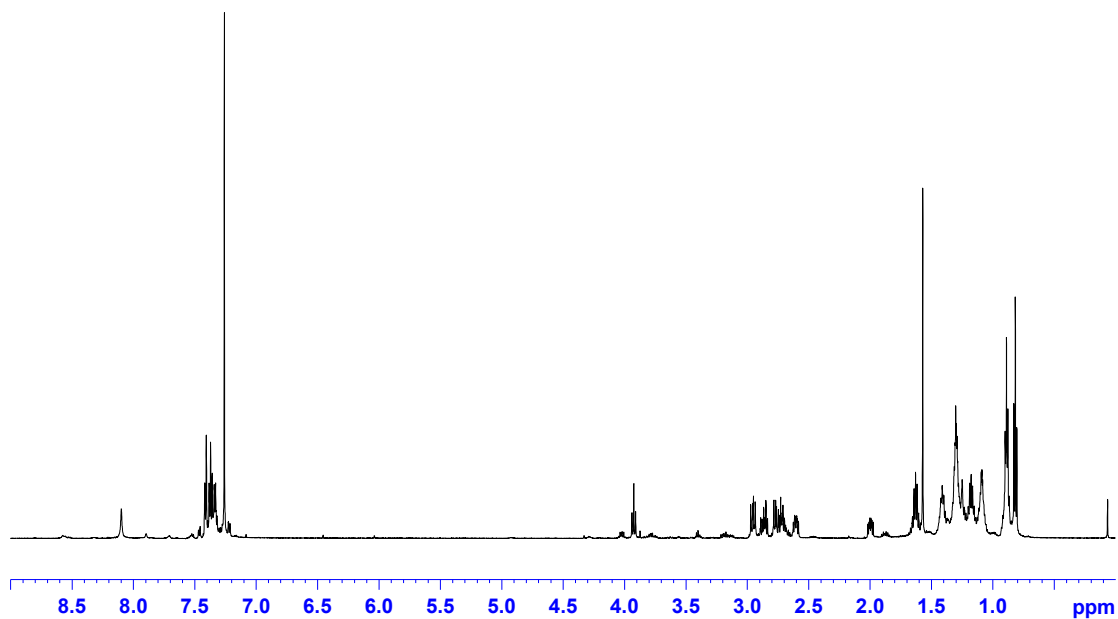


31 (38 mg, 0.115 mmol) was dissolved in acetonitrile (25 mL). The resulting solution was degassed for 30 minutes, styrene (133 μ L, 1.2 mmol) added and irradiated in pyrex glassware for 20 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in petroleum ether to 30% ethyl acetate in petroleum ether) afforded **32a** and **32b** together as a colourless oil (35 mg, 0.082 mmol) in 70%. NMR investigations showed the mixture was a 1:1 ratio of **32a** to **32b**. Further purification by flash chromatography afforded **32a** as a colourless oil (3 mg, 0.007 mmol) in 6% yield and **32b** as a colourless oil (3 mg, 0.007 mmol) in 6% yield. Diastereomers were tentatively assigned due to through space interactions seen *via* 2-D NMR and the lack thereof.

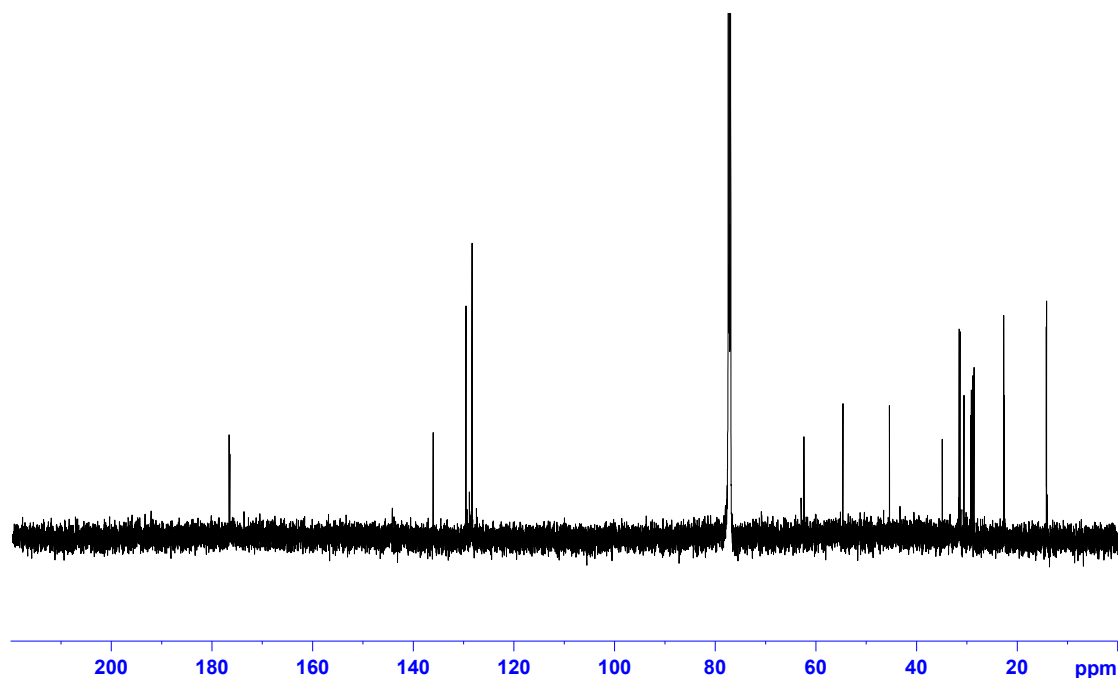
32a. δ_{H} (600 MHz, CDCl_3) 8.10 (s, 1H, NH), 7.41 (d, 2H, $J = 6.9$, 2 x Ar-H), 7.37 (t, 1H, $J = 6.9$, H-8), 7.33 (d, 2H, $J = 6.9$, 2 x Ar-H), 3.92 (app t, 1H, $J = 8.9$, H-5), 2.95 (dd, 1H, $J = 12.9$ and 8.9 , HH-6), 2.86 (td, 1H, $J = 14.2$ and 6.9 , -S-CHH-), 2.78-2.66 (m, 2H, HH-6 and -S-CHH-), 2.60 (ddd, 1H, $J = 10.9$, 8.3 and 6.3, -S-CHH-) 2.00 (ddd, 1H, $J = 10.7$, 8.6 and 5.6, -S-CHH-), 1.65-1.60 (m, 2H, HH-16 and HH-22), 1.43-1.06 (m, 14H, HH-16, HH-22 and 6 x CH_2), 0.88 (t, 3H, $J = 6.7$, CH_3), 0.82 (t, 3H, $J = 7.1$, CH_3); δ_{C} (150 MHz, CDCl_3) 176.59 (C=O), 176.44 (C=O), 136.03 (C11), 129.50 (2 x Ar-H), 128.83 (C8), 128.29 (2 x Ar-H), 62.32 (C4), 54.58 (C7), 45.33 (C5), 34.85 (C6), 31.48 (CH_2), 31.33 (CH_2), 30.51 (CH_2), 29.21 (CH_2), 29.06 (CH_2), 28.90 (CH_2), 28.76 (CH_2), 28.53 (CH_2), 22.62 (CH_2), 22.50 (CH_2), 14.16 (CH_3), 14.11

(CH₃); IR (oil, cm⁻¹) 3215 (w), 2926 (m) 1774 (w), 1715 (s); MS (CI+) *m/z* (relative intensity): 432 ([M-H], 5), 329 (60), 207 (100), 161 (60); Exact Mass Calcd for [C₂₄H₃₅NO₂S₂]-H requires *m/z* 432.2026 Found 432.2034 (CI+).

¹H NMR



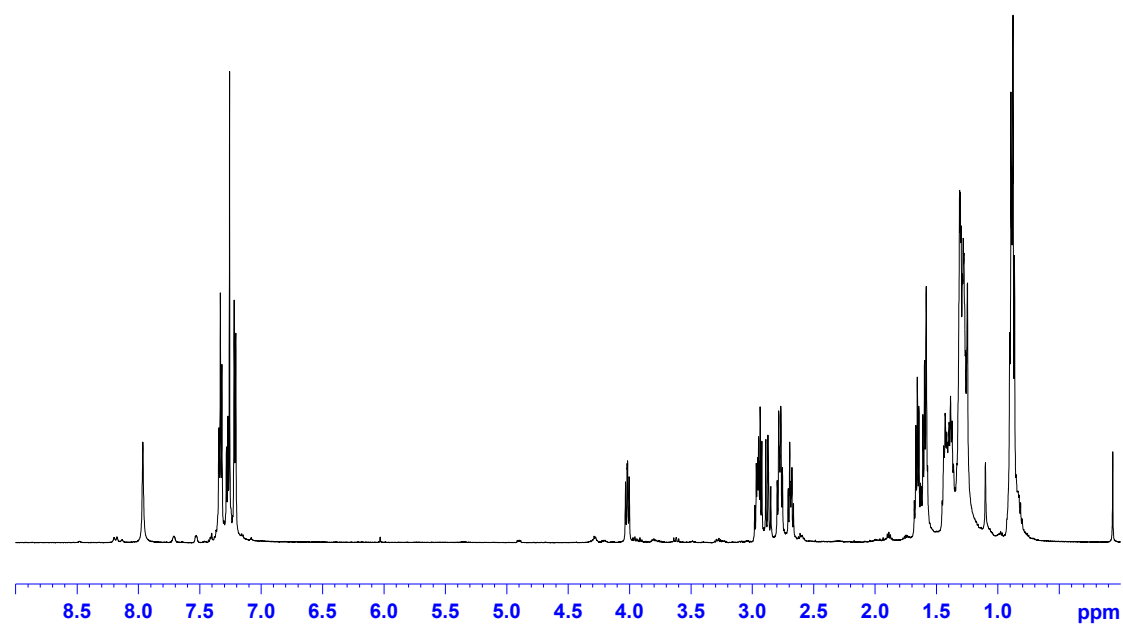
¹³C NMR



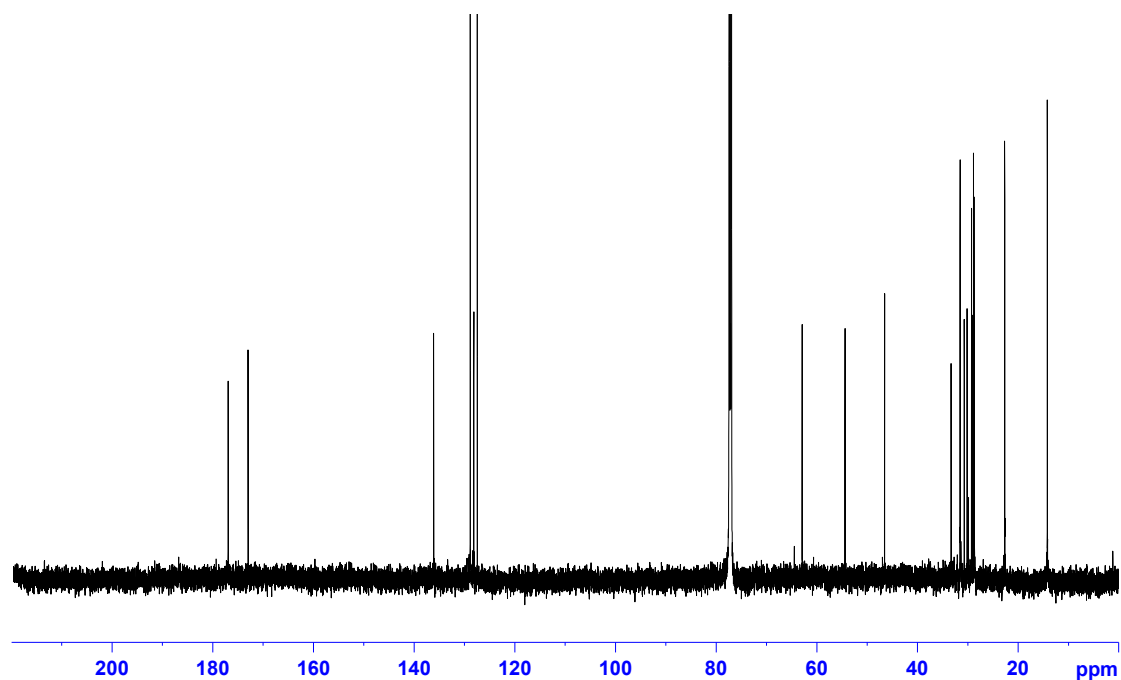
32b. δ_{H} (600 MHz, CDCl₃) 7.96 (s, 1H, NH), 7.33 (d, 2H, $J = 7.0$, 2 x Ar-H), 7.28 (t, 1H, $J = 7.0$, H-8), 7.21 (d, 2H, $J = 7.5$, 2 x Ar-H), 4.02 (app t, 1H, $J = 10.0$, H-5),

2.98-2.92 (m, 2H, *HH*-6 and *-S-CHH*-), 2.87 (dd, 1H, $J = 13.6$ and 10.8 , *HH*-6), 2.83-2.72 (m, 2H, *-S-CHH*- and *-S-CHH*-), 2.69 (td, 1H, $J = 10.8$ and 7.4 , *-S-CHH*-) 1.68-1.57 (m, 4H, H₂-16 and H₂-22), 1.45-1.31 (m, 4H, H₂-15 and H₂-21), 1.31-1.25 (m, 8H, H₂-13, H₂-14, H₂-19 and H₂-20), 0.86 (t, 6H, $J = 7.0$, H₃-12 and H₃-18); δ_C (150 MHz, CDCl₃) 176.91 (C=O), 172.96 (C=O), 136.09 (C11), 128.83 (2 x Ar-H), 128.13 (C8), 127.41 (2 x Ar-H), 62.86 (C4), 54.36 (C7), 46.49 (C5), 33.28 (C6), 31.51 (CH₂), 31.47 (CH₂), 30.65 (SCH₂), 30.09 (SCH₂), 29.22 (CH₂), 28.96 (CH₂), 28.80 (CH₂), 28.74 (CH₂), 22.63 (CH₂), 22.60 (CH₂), 14.17 (CH₃), 14.15 (CH₃); IR (oil, cm⁻¹) 3194 (w), 2928 (m) 1774 (w), 1722 (s); MS (CI+) m/z (relative intensity): 432 ([M-H], 5), 332 (50), 316 (95), 207 (100); Exact Mass Calcd for [C₂₄H₃₅NO₂S₂]-H requires m/z 432.2026 Found 432.2029 (CI+).

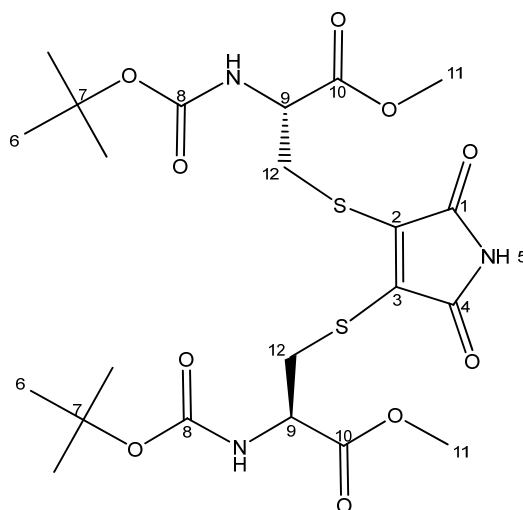
¹H NMR



¹³C NMR



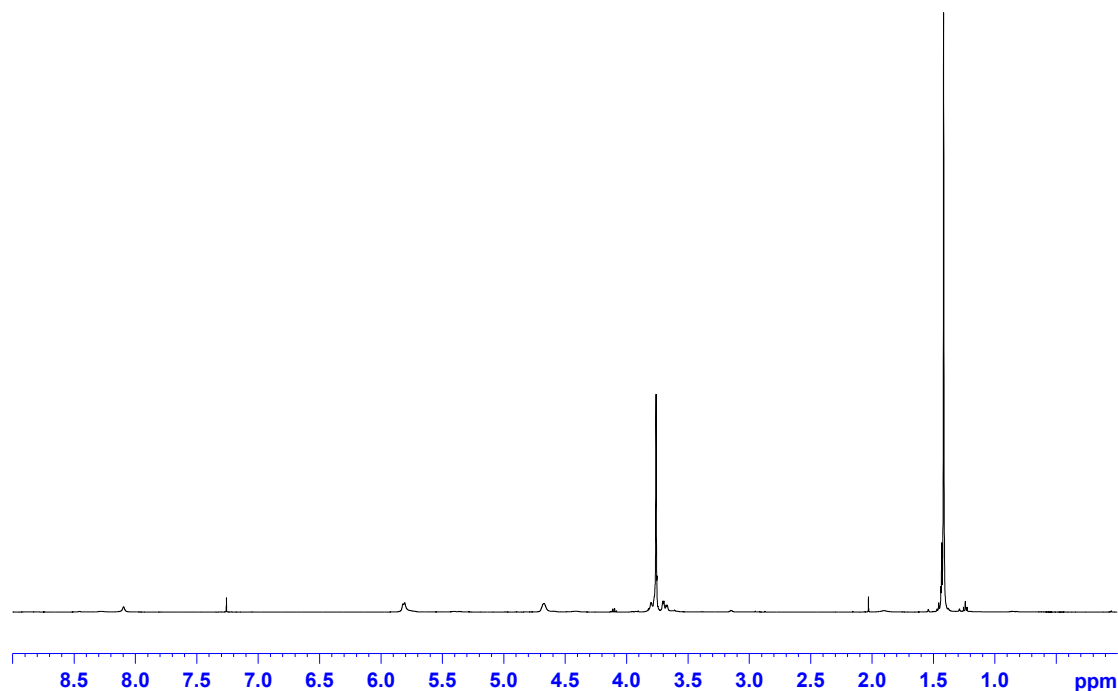
33. 2R-*tert*-Butoxycarbonylamino-3-[4-(2R-*tert*-butoxycarbonylamino-2-methoxycarbonyl-ethylsulfanyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-ylsulfanyl]-propionic acid methyl ester



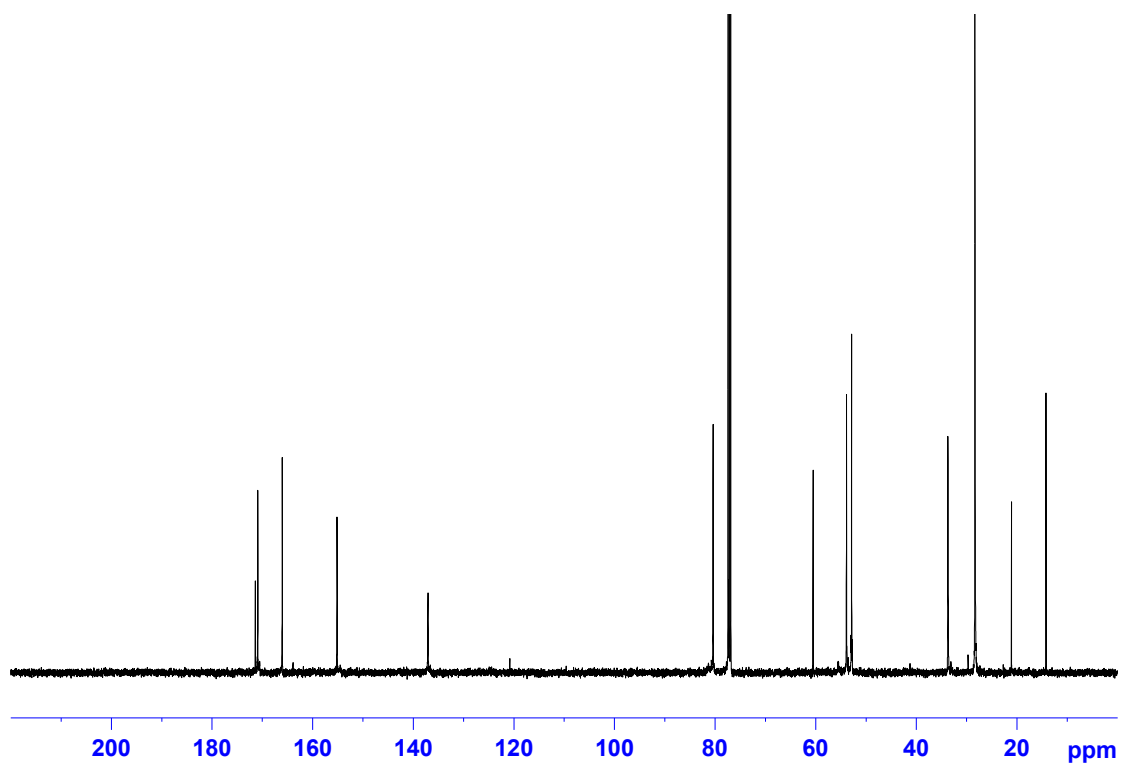
To 2,3-dibromomaleimide (50 mg, 0.19 mmol) in aqueous buffer (100 mM sodium phosphate, 150 mM NaCl, pH 8.0):DMF, 95:5 (54 mL) was added *N*-Boc-Cys-OMe (91 mg, 0.38 mmol). The reaction was stirred until all the cysteine was dispersed by the solvent and after a further 5 minutes the aqueous reaction mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers washed with saturated lithium chloride solution (aq.) (5 x 25 mL), water (25 mL) and brine (25 mL), dried

over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (gradient elution 20% ethyl acetate in petroleum ether to ethyl acetate) afforded **33** as a bright yellow sticky foam (108 mg, 0.19 mmol) in 100% yield. δ_{H} (500 MHz, CDCl_3) 8.10 (s, 1H, H-5), 5.81 (d, 2H, $J = 7.4$, 2 x 8-NH), 4.69-4.66 (m, 2H, 2 x H-9), 3.81-3.75 (m, 2H, 2 x HH-12), 3.76 (s, 6H, 2 x H₃-11), 3.69 (dd, 2H, $J = 14.3$ and 5.2 , 2 x HH-12), 1.42 (18H, s, 6 x H₃-6); δ_{C} (125 MHz, CDCl_3) 170.88 (2 x C=O), 166.02 (2 x C=O), 155.12 (2 x C=O), 137.05 (C2 and C3), 81.31 (2 x C7), 53.89 (2 x C9), 52.89 (2 x C11), 33.83 (2 x C12), 28.39 (6 x C6); IR (film, cm^{-1}) 3371 (w), 2978 (w), 1724 (s); MS (ES-) m/z (relative intensity): 562 ([M-H], 100); Exact Mass Calcd for $[\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_{10}\text{S}_2]\text{-H}$ requires m/z 562.1529 Found 562.1532 (ES-); m.p. 75-77 °C; UV (Acetonitrile) $\epsilon_{210} = 17400$, $\epsilon_{253} = 4200$ and $\epsilon_{393} = 3000 \text{ cm}^{-1}\text{M}^{-1}$.

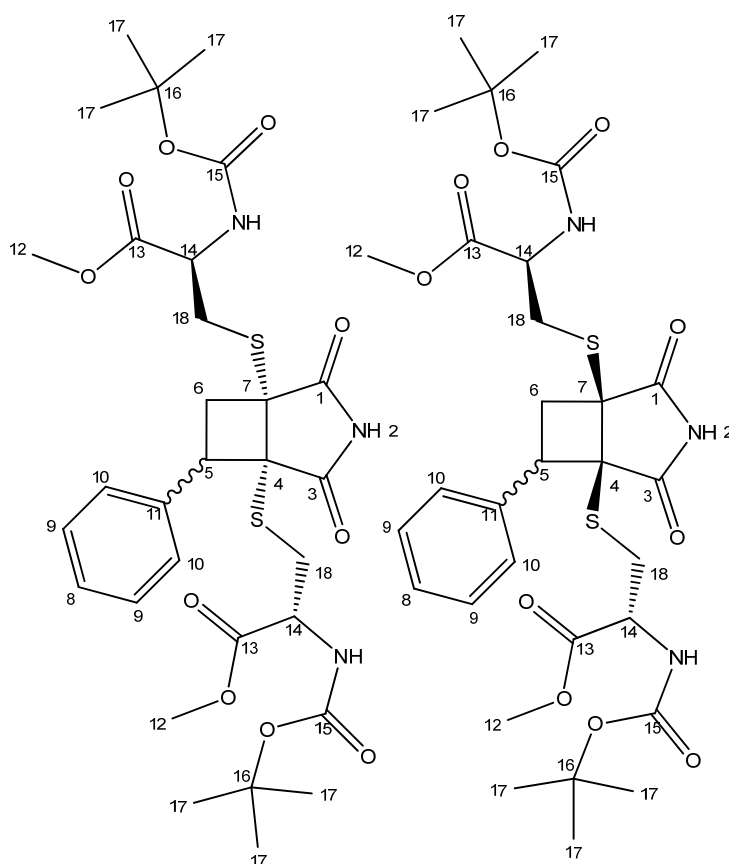
¹H NMR



^{13}C NMR



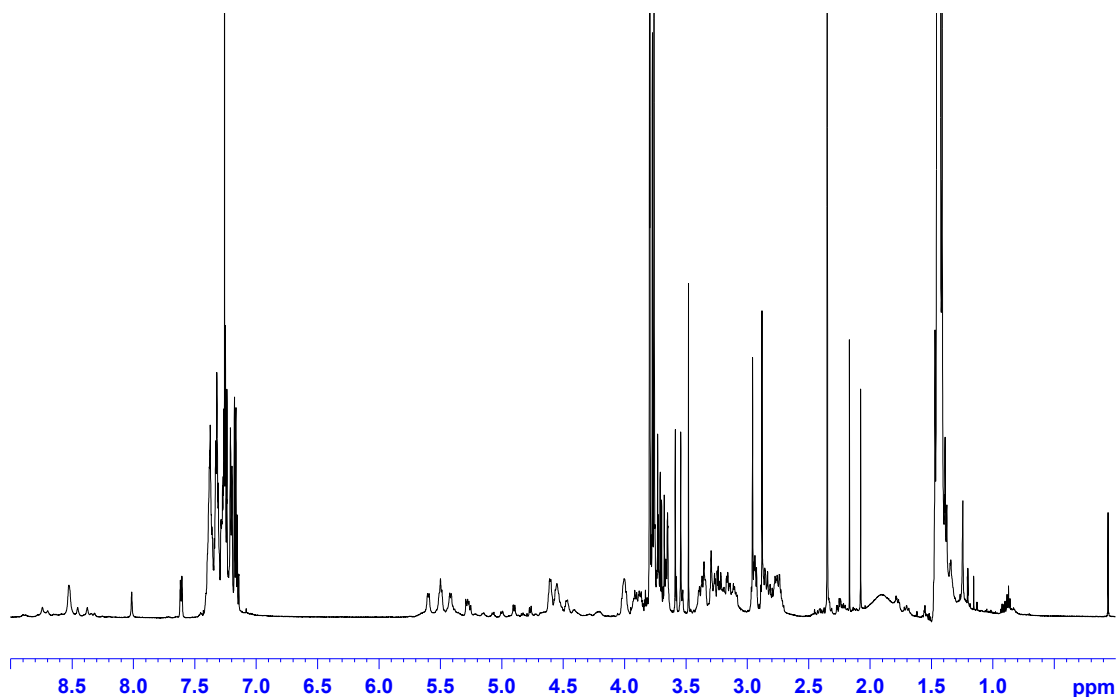
34 – a mixture of 4 diastereomers. (4R, 5R, 7S)-2-Aza-4,7-di(2R-*tert*-butoxycarbonylamino-3-sulfanyl propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione, (4R, 5S, 7S)-2-aza-4,7-di(2R-*tert*-butoxycarbonylamino-3-sulfanyl propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione, (4S, 5S, 7R)-2-aza-4,7-di(2R-*tert*-butoxycarbonylamino-3-sulfanyl propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione and (4S, 5R, 7R)-2-aza-4,7-di(2R-*tert*-butoxycarbonylamino-3-sulfanyl propionic acid methyl ester)-5-phenyl-bicyclo[3.2.0]heptan-1,3-dione.



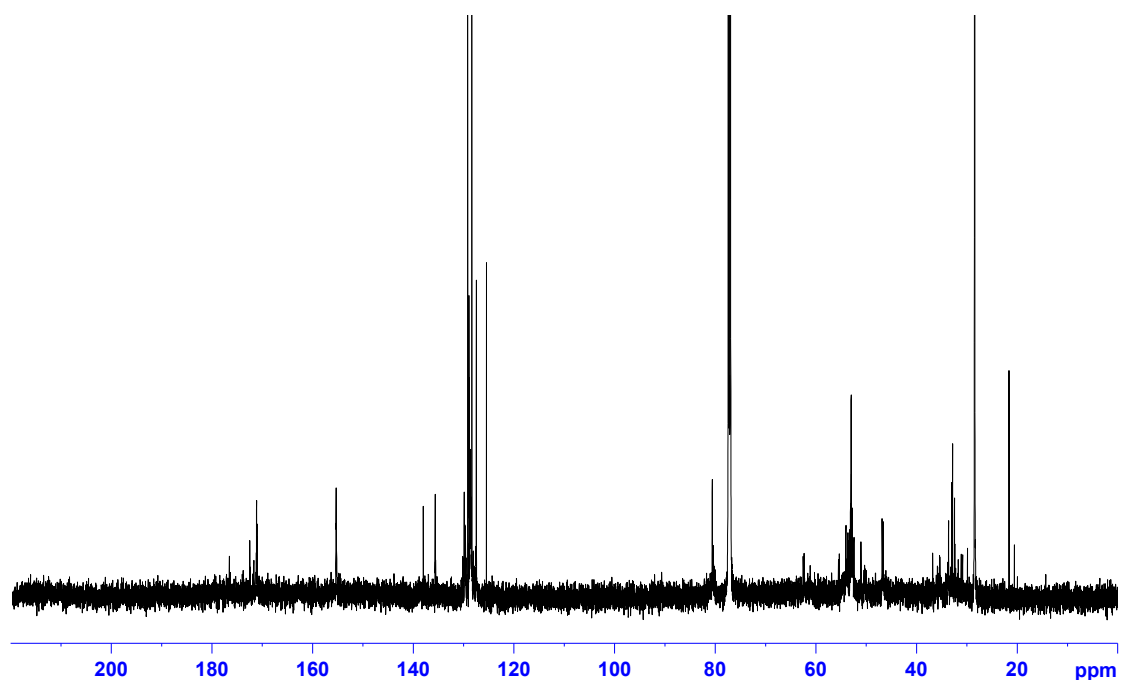
33 (76 mg, 0.135 mmol) was dissolved in acetonitrile (29 mL). The resulting solution was degassed for 30 minutes, styrene (148 μ L, 1.35 mmol) added and irradiated in pyrex glassware for 30 minutes with stirring. The solvent was removed *in vacuo* and purification by flash chromatography (gradient elution in 10% ethyl acetate in petroleum ether to 30% ethyl acetate in petroleum ether) afforded a mixture of diastereomers **34** as a colourless oil (47 mg, 0.070 mmol) in 60% yield. NMR spectra reported below but complexity of spectra prevents clear assignment of the peaks. MS confirmed the identity of the compounds as all having a mass that indicated conjugation had taken place. δ_{H} (600 MHz, CDCl_3) 8.18 (s, 2H, 2 x H-2), 7.95 (s, 2H,

2 x H-2), 7.40-7.26 (m, 16H, multiple Ar-H), 7.20 (d, 4H, $J = 7.5$, Ar-H), 5.56 (d, 2H, $J = 5.8$, 2 x 15-NH), 5.50-5.42 (m, 4H, 4 x 15-NH), 5.40 (d, 2H, $J = 7.3$, 2 x 15-NH), 4.74-4.55 (m, 6H, multiple H-14), 4.08-3.87 (m, 10H), 3.80-3.70 (m, 24H, 8 x H₃-12), 3.70-3.60 (m, 16H), 3.59 (d, 1H, $J = 4.0$), 3.53 (d, 1H, $J = 3.5$), 3.42-2.75 (m, 20H, contains multiple H-6 and H₂-18 by HMQC analysis), 1.46-1.42 (m, 74H, 24 x H₃-17); δ_c (150 MHz, CDCl₃) 175.94 (C=O), 175.84 (C=O), 175.82 (C=O), 171.10 (C=O), 171.04 (C=O), 170.95 (C=O), 155.28 (4 x C11), 129.63 (Ar-H), 129.50 (Ar-H), 128.96 (Ar-H), 128.88 (Ar-H), 128.80 (Ar-H), 128.75 (Ar-H), 128.59 (Ar-H), 128.53 (Ar-H), 128.41 (Ar-H), 80.51 (4 x C16), 80.22 (4 x C16), 55.97 (4 x C), 55.83 (4 x C), 52.97 (4 x C12), 52.93 (4 x C12), 52.71 (4 x C14), 52.61 (4 x C14), 45.25 (4 x C5), 32.92 (C18), 32.86 (C18), 31.19 (C18), 31.08 (C18), 29.83 (4 x C6), 28.42 (24 x C17) Four diastereomers are indicated, thus thirteen carbon signals are missing due to overlap of the diastereomers; IR (oil, cm⁻¹) 2924 (m), 1712 (s); MS (CI+) m/z (relative intensity): 666 ([M-H], 100); Exact Mass Calcd for [C₃₀H₄₁N₃O₁₀S₂]-H requires m/z 666.2155 Found 666.2188 (CI+).

¹H NMR



¹³C NMR



References.

1. Tedaldi, L. M.; Smith, M. E. B.; Nathani, R.; Baker, J. R. *Chem.Comm.* **2009**, 6583.
2. Karplus, M. *J. Am. Chem. Soc.* **1963**, 85, 18, 2870.
3. Gaussian 09, Revision A.2, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

4. Cances, E.; Mennucci, B. *J. Math. Chem.*, **1998**, *23*, 309.
5. Aliev, A.E.; Courtier-Murias, D. *J. Phys. Chem. B*, **2007**, *111*, 14034.
6. Sahoo, M. K.; Mhaske, S. B.; Argade, N. P. *Synthesis*, **2003**, *3*, 346.
7. Werner, F.; Weinzierl, R. O. *Mol. Cell*, **2002**, *10*, 635.
8. Grohmann, D.; Hirtreiter, A.; Werner, F. *Biochem. J.* **2009**, *421*, 339.
9. Nishi T., Higashi K., Takemura M. and Sato M., *J. Antibiot.*, 1993, **46**, 1740-1751.