The Synthesis of Spirotetramates via a Diels-Alder Approach

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SUPPORTING INFORMATION

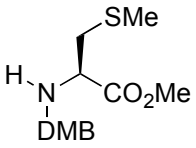
EXPERIMENTAL DETAILS

Contents

General experimental details

Commercially available reagents were used throughout without purification, except tetrahydrofuran and dichloromethane, which were freshly distilled. Light petroleum refers to the fraction with bp 40-60 °C and ether refers to diethyl ether. Thin layer chromatography was carried out on aluminum foil backed plates, visualized under UV light (at 254 and/or 360 nm) or by vanillin or permanganate stains. Chromatography was carried out using silica gel, with the eluent specified. Fully characterized compounds are chromatographically homogeneous. Infrared spectra were recorded on an FTIR spectrometer, in the range 4000-600 cm^{-1} using chloroform as solvent, or as solids in attenuated total reflectance (ATR) mode. NMR spectra were recorded at 300, 400 and 500 MHz (^{1}H frequencies, corresponding ^{13}C frequencies 75, 100 and 125 MHz). Chemical shifts are quoted in ppm and are referenced to residual H in the deuterated solvent as the internal standard. *J* values are recorded in Hz. In the ^{13}C spectra, signals corresponding to CH, CH_2, or Me groups, as assigned from DEPT, are noted; all others are quaternary C. High and low resolution mass spectra were recorded on a time-of-flight mass spectrometer. Microwave reactions were carried out in a CEM Discover™ reactor with IR temperature sensor.

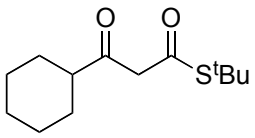
(*R*)-Methyl 2-(2,4-dimethoxybenzylamino)-3-(methylthio)propanoate 7



To a solution of *S*-methyl-(*R*)-methyl cysteine hydrochloride **6** (4.8 g, 26.0 mmol) in dichloromethane (150 mL) was added triethylamine (3.6 mL, 26.0 mmol) and 2,4-dimethoxybenzaldehyde (2.9 g, 17.5 mmol), and the reaction mixture stirred for 35 min at room

temperature. Sodium triacetoxyborohydride (7.3 g, 33.5 mmol) was then added in one portion and the reaction mixture stirred at room temperature for 16 h. Saturated sodium hydrogen carbonate (30 mL) was added and organic phase separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organics layers were combined, washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (30% ethyl acetate in light petroleum) to give the *title compound* (4.4 g, 84%) as a pale yellow oil; (Found: M + Na^+, 300.1267. $C_{14}H_{22}NO_5S$ + Na^+ requires 300.1264); $[\alpha]_D^{21}$ +20.8 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3003, 2839, 1734, 1613, 1507, 1464, 1289, 1158, 1037; δ_H (400 MHz; $CDCl_3$) 7.12 (1 H, d, *J* 8.0, ArH), 6.43-6.40 (2 H, m, ArH), 3.80 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.79-3.78 (1 H, m, ArC<u>H</u>HN), 3.69 (3 H, s, O<u>Me</u>), 3.69-3.68 (1 H, m, ArCH<u>H</u>N), 3.43 (1 H, dd, *J* 7.0, 6.3, C<u>H</u>CH_2SMe), 2.82-2.71 (2 H, m, NHCHC<u>H_2</u>S), 2.33 (1 H, br, NH), 2.02 (3 H, s, SMe); δ_c (100 MHz; $CDCl_3$) 174.1 (C), 160.2 (C), 158.6 (C), 130.4 (CH), 119.9 (C), 103.6 (CH), 99.4 (CH), 59.4 (CH), 55.3 (Me), 55.2 (Me), 51.9 (Me), 47.0 (CH_2), 37.0 (CH_2), 15.5 (Me); *m/z* (ESI) 300 (MNa^+, 100%).

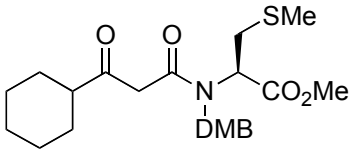
S-tert-Butyl 3-cyclohexyl-3-oxopropanethioate 8



A solution of 1,1'-carbonyldiimidazole (279 mg, 1.7 mmol) and cyclohexanecarboxylic acid (200 mg, 1.6 mmol) in THF (5 mL) was stirred at room temperature overnight. The solution was used directly in the next reaction. A solution of *N,N*-diisopropylamine (677 μL, 4.8 mmol) in THF (5 mL) was cooled to 0 °C and *n*-butyllithium (2.5 M solution in hexanes; 1.87 mL, 4.7 mmol) was added. The mixture was stirred at room temperature for 30 min, cooled to -78 °C and *tert*-butyl

thioacetate (682 mg, 5.2 mmol) added. After 5 min, the cyclohexyl imidazolide solution was added *via* cannula and the mixture stirred at room temperature for 3 h. The reaction mixture was quenched with hydrochloric acid (10%; 10 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by column chromatography (silica, 30% dichloromethane in light petroleum) to give the *title compound* as a red oil (263 mg, 68%); (Found: C, 64.2; H, 9.1%. $C_{13}H_{22}O_2S$ requires C, 64.4, H, 9.2%); (Found: M + Na^+, 265.1229. $C_{13}H_{22}O_2S$ + Na^+ requires 265.1233); ν_{max} ($CHCl_3$)/ cm^{-1} 1671, 1611. In $CDCl_3$ at room temperature this compound exists as a (3 : 1) keto : enol mixture; $\delta_{H\ keto}$ (400 MHz; $CDCl_3$); 3.60 (2 H, s, COC$\underline{H_2}$CO), 2.51–2.44 (1 H, m, CyCHCO), 1.89-1.76 (4 H, m, CyH), 1.68-1.63 (1 H, m, CyH), 1.47 (9 H, s, $SCMe_3$), 1.38-1.15 (5 H, m, CyH); $\delta_{C\ keto}$ (100 MHz; $CDCl_3$) 205.4 (C), 192.7 (C) 56.3 (CH_2) 51.0, (CH), 48.9 (C), 29.6 (Me) 25.8 (CH_2), 25.7 (CH_2), 25.4 (CH_2); $\delta_{H\ enol}$ (400 MHz; $CDCl_3$) 5.30 (1 H, s, =CH), 2.05-1.99 (1 H, m, CH), 1.89-1.76 (4 H, m, CyH), 1.68-1.63 (2 H, m, CyH), 1.51 (9 H, s, $SCMe_3$) 1.38-1.14 (4 H, m, CyH); $\delta_{C\ enol}$ (100 MHz; $CDCl_3$) 196.4 (C), 182.8 (C), 97.6 (CH), 48.1 (C), 43.4 (CH), 30.1 (CH_2), 29.9 (CH_2), 28.1 (Me), 25.6 (CH_2); *m/z* (ESI) 265 (MNa^+, 100%).

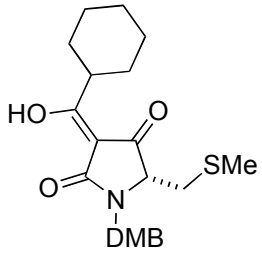
Methyl (*R*)-2-[(3-cyclohexyl-3-oxopropanoyl)(2,4-dimethoxybenzyl)amino]-3-(methylsulfanyl)propanoate 9



To a solution of *S-tert*-butyl 3-cyclohexyl-3-oxopropanethioate **8** (467 mg, 1.93 mmol) in THF (5 mL) was added a solution of amine **7** (865 mg, 2.89 mmol) in THF (5 mL) *via* cannula.

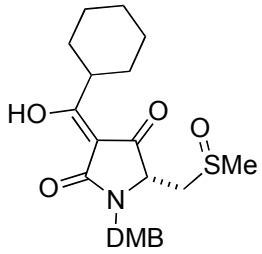
Triethylamine (1.1 mL, 7.7 mmol) was added and the reaction mixture stirred for 10 min at 0 °C. Silver trifluoroacetate (849 mg, 3.86 mmol) was added in one portion and the solution stirred at room temperature for 3 h. Solvent was removed under reduced pressure and the residue purified by column chromatography (25% ethyl acetate in light petroleum) to give the *title compound* (801 mg, 92%) as a yellow oil; (Found: M + Na^+, 474.1925. $C_{23}H_{33}NO_6S$ + Na^+ requires 474.1921; $[\alpha]_D^{21}$ +8.14, (*c* 1.0, $CHCl_3$) ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2935, 2856, 1739, 1617, 1508, 1465, 1181. In $CDCl_3$ at room temperature this compound exists as a (4 : 1) keto : enol mixture; $\delta_{H\ keto}$ (400 MHz; $CDCl_3$) 7.21 (1 H, d, *J* 8.8, ArH), 6.48-6.45 (2 H, m, ArH), 4.49 (2 H, s, NC$\underline{H}_2$Ar), 4.33 (1 H, dd, *J* 7.7, 6.4, C$\underline{H}$CH_2S), 3.82 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.70 (2 H, d, *J* 3.1, COCH_2CO), 3.61 (3 H, s, OMe), 3.23-3.18 (1 H, dd, *J* 7.7, 6.4, CHC$\underline{H}_2$S), 2.87-2.81 (1 H, dd, *J* 7.7, 6.4, CHC$\underline{H}_2$S), 2.56-2.49 (1 H, m, CHCO), 2.03 (3 H, s, SMe), 1.90-1.63 (5 H, m, CyH), 1.38-1.14 (5 H, m, CyH); $\delta_{c\ keto}$ (100 MHz; $CDCl_3$) 207.5 (C), 170.2 (C), 168.0 (C), 161.0 (C), 158.6 (C), 130.0 (CH), 116.1 (C), 103.7 (CH), 98.6 (CH), 58.0 (CH), 55.4 (Me), 52.3 (Me), 55.2 (Me), 50.5 (CH), 48.4 (CH_2), 47.2 (CH_2), 33.7 (CH_2), 30.1 (CH_2), 28.2 (CH_2), 25.5 (CH_2), 16.0 (Me); $\delta_{H\ enol}$ (400 MHz; $CDCl_3$) 7.24-7.22 (1 H, m, ArH), 6.48-6.46 (2 H, m, ArH), 5.14 (1 H, s, COHC$\underline{H}$CON), 4.63 (1 H, dd, *J* 7.6, 6.6, C$\underline{H}$CH_2S), 4.52-4.51 (2 H, m, NC$\underline{H}_2$Ar), 3.82 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.63 (3 H, s, OMe), 3.20 (1 H, dd, *J* 7.6, 6.6, CHC$\underline{H}_2$S), 2.85 (1 H, dd, *J* 7.6, 6.6, CHC$\underline{H}_2$S), 2.55-2.49 (CHCO), 2.07 (SMe), 1.90-1.76 (5 H, m, CyH), 1.38 (5 H, m, CyH); $\delta_{c\ enol}$ (100 MHz; $CDCl_3$) 129.3 (CH), 116.7 (C), 103.8 (CH), 98.2 (CH), 85.2 (CH), 57.9 (CH), 55.41 (Me), 55.3 (Me), 52.3 (Me), 46.2 (CH_2), 44.3 (CH_2), 34.0 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 16.1 (Me); *m/z* (ESI) 474 (MNa^+, 100%), 452 (MH^+, 31%).

(*R*)-3-(Cyclohexyl(hydroxy)methylene)-1-(2,4-dimethoxybenzyl)-5-(methylthiomethyl)-pyrrolidine-2,4-dione 10



To a solution of ester **9** (801 mg, 1.78 mmol) in methanol (60 mL) was added a solution of sodium methoxide (1 M; 8.9 mmol, 8.9 mL) in methanol and the reaction mixture stirred at room temperature for 1 h. The solution was acidified to pH4 (hydrochloric acid; 2 M) and extracted with dichloromethane (3 × 50 mL). The organic phases were combined, washed with brine (20 mL) and dried ($MgSO_4$). Solvent was removed under reduced pressure to give the *title compound* (702 mg, 94%) as a pale red solid which was used without further purification; mp 89-91 °C; (Found: M + Na^+, 442.1649. $C_{22}H_{29}NO_5S$ + Na^+ requires 442.1659); ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2858, 2360, 2341, 1701, 1611, 1508, 1465, 1242, 1036; $[\alpha]_D^{21}$ -100.97 (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.23(1 H, d, *J* 8.0, ArH), 6.48-6.44 (2H, m, ArH), 4.98 (1 H, d, *J* 14.8, ArC<u>H</u>HN), 4.17 (1 H, d, *J* 14.8, ArC<u>H</u>HN), 3.80 (6 H, s, OMe), 3.41-3.36 (1 H, m, C<u>H</u>CH_2SMe), 3.12-3.00 (2 H, m, CHC<u>H_2</u>SMe), 2.08 (3 H, s, SMe), 1.85-1.70 (4 H, m, CyH), 1.55-1.24 (6 H, m, CyH); δ_c (100 MHz; $CDCl_3$) 193.3 (C), 191.3 (C), 174.2 (C), 160.9 (C), 158.5 (C), 131.6 (CH), 116.2 (C), 104.5 (CH), 100.3 (C), 98.5 (CH), 63.9 (CH), 55.4 (Me), 55.3 (Me), 40.9 (CH), 38.0 (CH_2), 33.4 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 25.6 (CH_2), 17.1 (Me); *m/z* (ESI) 442 (MNa^+, 100%), 420 (MH^+, 46%).

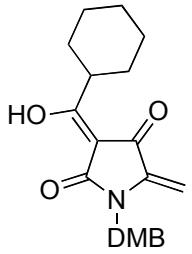
(5*R*)-3-(Cyclohexyl(hydroxy)methylene)-1-(2,4-dimethoxybenzyl)-5-(methylsulfinylmethyl)-pyrrolidine-2,4-dione 11



To a solution of sulfide **10** (500 mg, 1.2 mmol) in methanol and dichloromethane (2:1; 8 mL) was added hydrogen peroxide in water (30% by weight; 2.7 mL, 36 mmol) and the mixture stirred at room temperature for 20 h. Water (3 mL) was added and the solution extracted with dichloromethane (3 × 15 mL). The organic phases were combined, washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the *title compound* (458 mg, 88%) as a pale red gum which was used without further purification; (Found: M + Na^+, 442.1649. $C_{22}H_{29}NO_5S$ + Na^+ requires 442.1659); ν_{max} ($CHCl_3$)/cm^{-1} 2962, 2932, 2861, 1719, 1601, 1463, 1291. In $CDCl_3$ at room temperature this compound exists as a (2 : 1) mixture of enols; $\delta_{H\ enol\ 1}$ (400 MHz; $CDCl_3$) 7.26 (1 H, d, *J* 8.0, ArH), 6.48-6.45 (2 H, m, ArH), 5.00 (1 H, d, *J* 14.9, NC<u>H</u>HAr), 4.37 (1 H, d, *J* 14.9, NCH<u>H</u>Ar), 4.06-4.03 (1 H, m, C<u>H</u>CH_2S), 3.82 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.36-3.27 (2 H, m, CHC<u>H</u>HS + C<u>H</u>CO), 3.20 (1 H, dd, *J* 12.0, 4.0, CHCH<u>H</u>S), 2.60 (3 H, s, SOMe), 1.83-1.70 (5 H, m, CyH), 1.54-1.24 (5 H, m, CyH); $\delta_{c\ enol\ 1}$ (100 MHz; $CDCl_3$) 193.1 (C), 191.9 (C), 174.1 (C), 161.0 (C), 158.6 (C), 131.7 (CH), 116.0 (C), 104.5 (CH), 99.2 (C), 98.6 (CH), 60.5 (CH), 55.5 (Me), 55.4 (Me), 55.1 (CH_2), 41.3 (CH), 40.1 (Me), 39.0 (CH_2), 28.5 (CH_2), 25.5 (CH_2), 24.5 (CH_2); $\delta_{H\ enol\ 2}$ (400 MHz; $CDCl_3$) 7.28-7.25 (1 H, m, ArH), 6.49-6.46 (2 H, m, ArH), 4.96 (1 H, d, *J* 14.8, NC<u>H</u>HAr), 4.34 (1 H, d, *J* 14.8, NCH<u>H</u>Ar), 4.00 (1 H, dd, *J* 7.2, 3.5, C<u>H</u>CH_2S), 3.83 (OMe), 3.80 (OMe), 3.39-3.27 (2 H, m, CHC<u>H</u>$_2$S),

3.05-3.02 (1 H, m, CHCO), 2.63 (3 H, s, SMe), 1.83-1.74 (5 H, m, CyH), 1.58-1.19 (5 H, m, CyH); $\delta_{c\ enol\ 2}$ (100 MHz; $CDCl_3$) 192.5 (C), 191.9 (C), 174.2 (C), 161.1 (C), 158.5 (C), 131.9 (CH), 115.8 (C), 104.7 (CH), 99.2 (C), 98.5 (CH), 60.3 (CH), 55.5 (Me), 55.4 (Me), 55.1 (CH_2), 41.0 (CH), 39.8 (Me), 38.4 (CH_2), 28.6 (CH_2), 25.6 (CH_2), 25.5 (CH_2); *m/z* (ESI) 458 (MNa^+, 100%), 436 (MH^+, 26%).

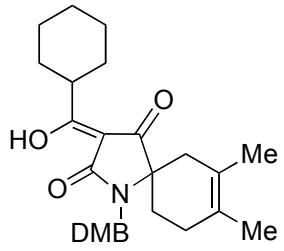
3-(Cyclohexyl(hydroxy)methylene)-1-(2,4-dimethoxybenzyl)-5-methylenepyrrolidine-2,4-dione 12



A solution of sulfoxide **11** (500 mg, 1.2 mmol) in toluene (8 mL) was heated under reflux for 3 h. The solvent was removed under reduced pressure and residue purified by column chromatography (10% light petroleum in dichloromethane) to give the *title compound* (300mg, 67%) as a pale yellow oil; (Found: M + Na^+, 394.1601. $C_{21}H_{25}NO_5$ + Na^+ requires 394.1625); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1706, 1613, 1509, 909. In $CDCl_3$ at room temperature this compound exists as a mixture of enols; $\delta_{H\ enol\ 1}$ (400 MHz; $CDCl_3$) 7.07 (1 H, d, *J* 8.0, ArH), 6.46-6.42 (2 H, m, ArH), 5.26 (1 H, d, *J* 1.8, C=C<u>H</u>H), 4.78 (2 H, s, NCH_2Ar), 4.69 (1 H, d, *J* 1.8, C=CH<u>H</u>), 3.84 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.53-3.48 (1 H, s, CyC<u>H</u>), 1.90-1.72 (5 H, m, CyH), 1.57-1.27 (5 H, m, CyH); $\delta_{C\ enol\ 1}$ (100 MHz; $CDCl_3$) 191.0 (C), 181.1 (C), 172.7 (C), 160.5 (C), 157.9 (C), 142.2 (C), 129.4 (C), 115.6 (C), 104.4 (CH), 99.1 (C), 98.4 (CH), 93.3 (CH_2), 55.4 (Me), 40.8 (CH), 37.1 (CH_2), 28.7 (CH_2), 25.5 (CH_2), 25.4 (CH_2); $\delta_{H\ enol\ 2}$ (300 MHz; $CDCl_3$) 7.06 (1 H, d, *J*

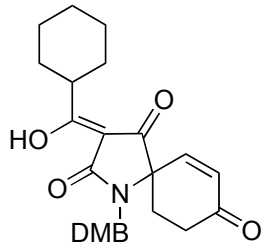
8.0, ArH), 6.46-6.42 (2 H, m, ArH), 5.23 (1 H, d, *J* 1.8, C=C<u>H</u>H), 4.77 (2 H, s, NC<u>H</u>$_2$Ar), 4.69 (1 H, d, *J* 1.8, C=CH<u>H</u>), 3.84 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.56-3.47 (1 H, s, CyC<u>H</u>), 190-1.72 (5 H, m, CyH), 1.58-1.23 (5 H, m, CyH); $\delta_{C\ enol\ 2}$ (100 MHz; $CDCl_3$) 196.0 (C), 186.1 (C), 165.3 (C), 160.3 (C), 157.8 (C), 140.0 (C), 129.4 (CH), 116.5 (C), 104.4 (CH), 101.8 (C), 98.4 (CH), 93.5 (CH_2), 55.4 (Me), 41.8 (CH), 36.7 (CH_2), 28.7 (CH_2), 25.7 (CH_2), 25.6 (CH_2); *m/z* (ESI) 394 (MNa^+, 100%), 372 (MH^+, 38%).

3-(Cyclohexyl(hydroxy)methylene)-1-(2,4-dimethoxybenzyl)-7,8-dimethyl-1-azaspiro[4.5]dec-7-ene-2,4-dione 15



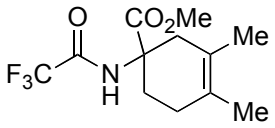
Method 1: To a solution of tetramic acid **12** (11 mg, 0.024 mmol) in 1,2-dichlorobenzene (0.2 mL) was added 2,3-dimethyl-1,3-butadiene (8.2 μL, 6 mg, 0.072 mmol) and the mixture heated with microwave irradiation (300 W) at 180 °C for 1 h in a sealed tube. Solvent was removed under reduced pressure and the residue purified by column chromatography (0.2% methanol in dichloromethane) to give the *title compound* (3 mg, 28%) as a pale yellow oil; data given below.

3-(Cyclohexyl(hydroxy)methylene)-1-(2,4-dimethoxybenzyl)-1-azaspiro[4.5]dec-6-ene-2,4,8-trione 16



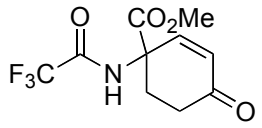
To tetramic acid **12** (80 mg, 0.22 mmol) in toluene (0.2 mL) was added *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (126 μL, 0.65 mmol) and the mixture heated under reflux conditions in a sealed tube for 16 h. The solvent was removed *in vacuo* and the residue dissolved in THF (2 mL) and hydrochloric acid (3 M; 2 mL) added and the reaction mixture was heated at 40 °C for 24 h. The mixture was extracted with ethyl acetate (3 × 5 mL) and the organic phases were combined, washed with brine (5 mL), dried ($MgSO_4$) and solvent evaporated *in vacuo*. The residue was purified by column chromatography (0.5 to 1% methanol in dichloromethane). The material was purified by column chromatography a second time (0.5% methanol in dichloromethane) to give the *title compound* (21 mg, 22%) as a red oil; (Found: M + Na^+, 462.1890. $C_{25}H_{29}NO_6$ + Na^+ requires 462.1887); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2937, 1701, 1603, 1509, 1455; δ_H (400 MHz; $CDCl_3$) 7.24 (1 H, d, *J* 8.4, ArH), 6.48 (1 H, d, *J* 8.4, ArH), 6.40-6.39 (1 H, m, ArH), 6.08 (1 H, d, *J* 8.0, CH=C<u>H</u>CO), 5.97 (1 H, d, *J* 8.0, C<u>H</u>=CHCO), 4.76 (1 H, d, *J* 15.2, NC<u>H</u>HAr), 4.47 (1 H, d, *J* 15.2, NCH<u>H</u>Ar), 3.80 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.36-3.33 (1 H, m, CyC<u>H</u>CO), 3.19-3.15 (1 H, m, CH_2C<u>H</u>HCO), 2.58-2.51 (1 H, m, CH_2CH<u>H</u>CO), 2.45-2.41 (1 H, m, C<u>H</u>HCH_2CO), 2.06-2.02 (1 H, m, CH<u>H</u>CH_2CO), 1.83-1.72 (5 H, m, CyH), 1.61-1.21 (5 H, m, CyH); δ_C (100 MHz; $CDCl_3$) 197.5 (C), 194.0 (C), 191.4 (C), 173.5 (C), 160.9 (C), 157.9 (C), 145.7 (CH), 131.9 (CH), 130.9 (CH), 117.2 (C), 104.7 (CH), 98.2 (CH), 97.4 (C), 68.9 (C), 55.4 (Me), 55.2 (Me), 41.3 (CH), 36.2 (CH_2), 33.3 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 25.6 (CH_2), 25.5 (CH_2); *m/z* (ESI) 440 (MH^+, 100%), 462 (MNa^+, 67%).

Methyl 3,4-dimethyl-1-(2,2,2-trifluoroacetamido)cyclohex-3-enecarboxylate 17



Methyl 2-(2,2,2-trifluoroacetamido)acrylate **13** (100 mg, 0.51 mmol) and 2,3-dimethyl-1,3-butadiene (0.5 mL) were heated at 100 °C for 24 h in a sealed tube. Excess 2,3-dimethyl-1,3-butadiene was evaporated under reduced pressure and the residue purified by column chromatography (10% ethyl acetate in light petroleum) to give the *title compound* (60 mg, 42%) as a colorless solid; mp 105-107 °C; (Found: M + Na^+, 302.0975. $C_{12}H_{16}F_3NO_3$ + Na^+ requires 302.0975); ν_{max} ($CHCl_3$)/cm^{-1} 3429, 3011, 1728, 1528, 1172; δ_H (400 MHz; $CDCl_3$) 6.33 (1 H, br, NH), 3.76 (3 H, s, OMe), 2.60 (1 H, d, *J* 17.6, CC<u>H</u>HC), 2.39-2.35 (1 H, m, CC<u>H</u>HCH_2C), 2.15 (1 H, d, *J* 17.6, CCH<u>H</u>C), 2.06-1.94 (3 H, m, CC<u>H</u>$_2$C<u>H</u>HC), 1.65 (6 H, s, Me); δ_C (100 MHz; $CDCl_3$) 172.4 (C), 156.7 (C, q, *J* 37), 128.4 (C), 120.4 (C), 115.5 (CF, q, *J* 287), 58.8 (C), 52.8 (Me), 39.6 (CH_2), 27.6 (CH_2), 26.8 (CH_2), 18.9 (Me), 18.7 (Me); *m/z* (ESI) 302 (MNa^+, 100%).

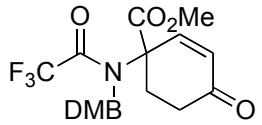
Methyl 1-(2,2,2-trifluoroacetamido)-4-oxocyclohex-2-enecarboxylate 18



To a solution of methyl 2-(2,2,2-trifluoroacetamido)acrylate **13** (100 mg, 0.51 mmol) in toluene (0.2 mL) was added *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (198 μL, 1.02 mmol) and the reaction mixture stirred at 120 °C for 24 h in a sealed tube. The solvent was removed *in vacuo* and the residue dissolved in THF (2 mL) and hydrochloric acid (3 M; 1.5 mL) was added and the reaction mixture stirred at 40 °C for 24 h. The solution was diluted with water (1 mL) and

extracted with ethyl acetate (3 × 3 mL). The organic phases were combined, washed with brine (2 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue purified by column chromatography (10 % ethyl acetate in light petroleum) to give the *title compound* (64 mg, 48 %) as a colorless oil; (Found: M + Na^+, 288.0468. $C_{10}H_{10}F_3NO_4$ + Na^+ requires 288.0454); ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3044, 2928, 1731, 1686, 1521, 1263, 1172, 820; δ_H (400 MHz; $CDCl_3$) 7.27 (1 H, s, br, NH), 6.87 (1 H, d, *J* 10.2, CHC<u>H</u>CO), 6.26 (1 H, d, *J* 10.2, C<u>H</u>CHCO), 3.89 (3 H, s, OMe), 2.72-2.62 (3 H, m, CyH), 2.52-2.49 (1 H, m, CyH); δ_C (100 MHz; $CDCl_3$) 196.1 (C), 169.8 (C), 156.7 (C, q, *J* 38) 144.0 (CH), 132.0 (CH), 116.7 (CF, q, *J* 287), 59.0 (C), 54.1 (Me), 33.6 (CH_2), 31.0 (CH_2); *m/z* (ESI) 288 (MNa^+, 100%).

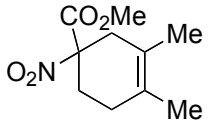
Methyl 1-(*N*-(2,4-dimethoxybenzyl)-2,2,2-trifluoroacetamido)-4-oxocyclohex-2-ene-carboxylate 19



To a solution of methyl 2-(N-(2,4-dimethoxybenzyl)-2,2,2-trifluoroacetamido)acrylate **14** (100 mg, 0.29 mmol) in 1,2-dichlorobenzene (0.3 mL) was added *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (168 μLg, 0.87 mmol) and the mixture heated with microwave irradiation (300 W) at 180 °C for 3 h in a sealed tube. The solvent was removed *in vacuo* and the crude material dissolved in THF (1.5 mL) and HCl (3 M; 1 mL) added. The reaction mixture was heated at 40 °C for 24 h and then water was added. The solution was extracted with ethyl acetate (3 × 3 mL). Organic phases were combined, dried ($MgSO_4$) and solvent evaporated *in vacuo*. The residue was purified by column chromatography (1% methanol in dichloromethane) to give the *title compound* (32 mg, 27%) as a colorless oil; (Found: M + Na^+, 438.1138. $C_{19}H_{20}F_3NO_6$ + Na^+

requires 438.1135); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2957, 1747, 1688, 1618, 1591, 1509, 1464, 1159, 823; δ_H (400 MHz; $CDCl_3$) 7.42 (1 H, d, *J* 8.4, CCH=C<u>H</u>CO), 6.64 (1 H, d, *J* 10.4, ArH), 6.55 (1 H, d, *J* 8.4, C<u>H</u>CHCO), 6.45 (1 H, s, ArH), 6.04 (1 H, d, *J* 10.4, ArH), 4.76 (1 H, d, *J* 18.8, ArC<u>H</u>HN), 4.55 (1 H, d, *J* 18.8, ArCH<u>H</u>N), 3.83 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.81 (3 H, s, OMe), 2.93-2.83 (2 H, m, COC<u>HH</u>CH_2), 2.50-2.46 (1 H, m, CCH<u>H</u>CH_2CO), 2.23-2.19 (1 H, m, CCH<u>H</u>CH_2CO); δ_C (100 MHz; $CDCl_3$) 196.8 (C), 169.1 (C), 160.6 (C), 158.9 (C, q, *J* 37), 156.6 (C), 143.2 (CH), 133.1 (CH), 127.9 (CH), 116.7 (C), 114.6 (CF, q, *J* 286), 104.2 (CH), 98.3 (CH), 66.2 (C), 55.4 (Me), 55.3 (Me), 53.3 (Me), 43.7 (CH_2), 34.3 (CH_2), 28.7 (CH_2); *m/z* (ESI) 438 (MNa^+, 100%).

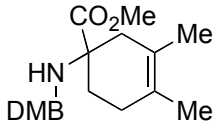
Methyl 3,4-dimethyl-1-nitrocyclohex-3-enecarboxylate 21



To a solution of methyl nitroacetate (166 μL/ 214 mg, 1.8 mmol) in THF (2.5 mL) was added 1,3-dimethylbutadiene (69 μL/ 100 mg, 0.6 mmol), glacial acetic acid (343 μL/ 360 mg, 6.0 mmol) and formalin (37 % weight in H_2O; 446 μL, 6.0 mmol), and the solution heated at 40 °C for 24 h. The volatiles were removed under reduced pressure and brine (10%; 2 mL) added. The solution was extracted with ether (3 × 4 mL), the organic layers combined, dried ($MgSO_4$) and solvent removed under reduced pressure. The residue was purified by column chromatography (30% ether in light petroleum) to give the *title compound* (70 mg, 55%) as a colorless oil; (Found: M + Na^+, 236.0891. $C_{10}H_{15}NO_4$ + Na^+ requires 236.0893); ν_{max} ($CHCl_3$)/cm^{-1} 3005, 1750, 1553, 1438, 1275; δ_H (400 MHz; $CDCl_3$) 3.83 (3 H, s, OMe), 2.92 (1 H, d, *J* 16.0, CC<u>H</u>HC), 2.75 (1 H, d, *J* 16.0, CCH<u>H</u>C), 2.62-2.55 (1 H, m, CCH<u>H</u>CH_2), 2.38 (1 H, m,

CC<u>H</u>HCH$_2$), 2.10-2.02 (2 H, m, CH$_2$), 1.69 (3 H, s, Me), 1.63 (3 H, s, Me); δ_c (100 MHz; $CDCl_3$) 167.7 (C), 125.0 (C), 121.0 (C), 92.0 (C), 53.6 (Me), 37.2 (CH$_2$), 29.1 (CH$_2$), 28.1 (CH$_2$), 18.7 (C), 18.6 (C); *m/z* (ESI) 236 (MNa^+, 100%).

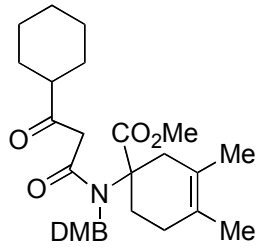
Methyl 1-(2,4-dimethoxybenzylamino)-3,4-dimethylcyclohex-3-enecarboxylate 22



To nitro compound **21** (40 mg, 0.19 mmol) in glacial acetic acid (1 mL) was added zinc powder (37 mg, 0.57 mmol) and the mixture stirred at room temperature for 48 h. The solution was filtered through Celite, washed with dichloromethane (10 mL) and water (5 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was dissolved in toluene (1 mL) and 2,4-dimethoxybenzaldehyde (28 mg, 0.17 mmol) added and the reaction mixture heated at reflux for 24 h. The toluene was evaporated under reduced pressure and the residue dissolved in dichloromethane (1 mL). Sodium triacetoxyborohydride (71 mg, 0.34 mmol) was added and the reaction mixture stirred at room temperature for 24 h. water (1 ml) was added and the mixture was extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), and solvent removed under reduced pressure. The residue was purified by column chromatography (15% ethyl acetate in light petroleum) to give the *title compound* (47 mg, 74%) as a pale yellow oil; (Found: $M + H^+$, 334.2012. $C_{19}H_{28}NO_4 + H^+$ requires 334.2013); ν_{max} ($CHCl_3$)/cm^{-1} 2951, 1725, 1615, 1508, 1465, 1289, 1157, 1038; δ_H (400 MHz; $CDCl_3$) 7.13 (1 H, d, *J* 8.0, ArH), 6.43-6.41 (2 H, m, ArH), 3.80 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.65 (1 H, d, *J* 12.0, ArC<u>H</u>HNH), 3.64 (3 H, s, OMe), 3.56 (1

H, d, *J* 12.0, ArCH<u>H</u>NH), 2.49 (1 H, d, *J* 16.6, CC<u>H</u>$_2$C), 2.98-1.89 (5 H, m, CyH), 1.62 (6 H, s, Me); δ_c (100 MHz; $CDCl_3$) 175.6 (C), 159.8 (C), 158.3 (C), 130.2 (CH), 124.4 (C), 122.1 (C), 120.4 (C), 103.5 (CH), 98.2 (CH), 60.6 (C), 55.0 (Me), 54.9 (Me), 51.3 (Me), 42.6 (CH_2), 39.7 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 18.8 (Me), 18.4 (Me); *m/z* (ESI) 334 (MNa^+, 100%), 151 (10%).

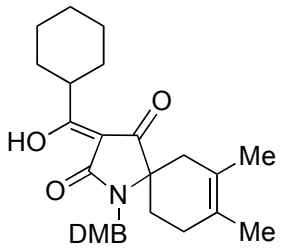
Methyl 1-(3-cyclohexyl-N-(2,4-dimethoxybenzyl)-3-oxopropanamido)-3,4-dimethylcyclohex-3-enecarboxylate 23



To a solution of amine **22** (20 mg, 0.062 mmol) in THF (1 mL) was added thioester **2** (10 mg, 0.041 mmol) and triethylamine (22 μL/16 mg, 0.16 mmol) and the mixture stirred at 0 °C for 10 min. Silver trifluoroacetate (18 mg, 0.082 mmol) was added and the reaction mixture stirred at room temperature for 5 h. Solvent was removed under reduced pressure and the crude material purified by column chromatography (15% ethyl acetate in light petroleum) to give the *title compound* (15 mg, 73%) as a colorless oil; (Found: M + Na^+, 508.2672. $C_{28}H_{39}NO_6$ + Na^+ requires 508.2670); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3011, 2337, 1733, 1601, 1239. In $CDCl_3$ at room temperature this compound exists as a (3 : 1) keto : enol mixture; $\delta_{H\ keto}$ (400 MHz; $CDCl_3$) 7.77 (1 H, d, *J* 8.3, ArH), 6.52 (1 H, dd, *J* 8.3, 2.2, ArH), 6.44 (1 H, d, *J* 2.2, ArH), 4.48 (1H, d, *J* 20.0, ArC<u>H</u>HN), 4.40 (1 H, d, *J* 20.0, ArCH<u>H</u>N), 3.82 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.45 (1 H, d, *J* 16.0, COC<u>H</u>HCO), 3.40 (1 H, d, *J* 16.0, COCH<u>H</u>CO), 2.45-2.32 (2 H, m, CyH), 2.08-1.95 (4 H, m, CyH), 1.82-1.73 (3 H, m, CyH), 1.66 (3 H, s, Me), 1.55 (3 H, s, Me), 1.31-1.19 (6 H, m, CyH), 0.91-0.87 (1 H, m, CyH); $\delta_{C\ keto}$ (100 MHz; $CDCl_3$) 208.1 (C), 174.7

(C), 168.8 (C), 160.0 (C), 156.8 (C), 127.8 (CH), 127.2 (C), 123.0 (C), 119.2 (C), 103.8 (CH), 98.2 (CH), 64.1 (C), 55.4 (Me), 55.2 (Me), 52.2 (Me), 50.9 (CH), 47.8 (CH_2), 43.3 (CH_2), 37.6 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 26.3 (CH_2), 25.5 (CH_2), 18.9 (Me), 18.2 (Me); $\delta_{H\ enol}$ (400 MHz; $CDCl_3$) 14.2 (1 H, s, OH), 7.54 (1 H. d, *J* 8.2, ArH), 6.53-6.51 (1 H, m, ArH), 6.45 (1 H, d, *J* 2.3, ArH), 4.90 (1 H, s, COC<u>H</u>CON), 4.56-4.49 (2 H, m, $ArCH_2N$), 3.82 (3 H, OMe), 3.78 (3 H, s, OMe), 3.76 (3 H, s, OMe), 2.08-1.95 (4 H, m, CyH), 1.82-1.73 (3 H, m, CyH), 1.62 (3 H, s, Me), 1.51 (3 H, s, Me), 1.31-1.19 (6 H, m, CyH), 0.91-0.87 (1 H, m, CyH); $\delta_{C\ enol}$ (100 MHz; $CDCl_3$) 182.3 (C), 174.9 (C), 173.7 (C), 159.8 (C), 156.6 (C), 128.4 (CH), 123.4 (C), 122.9 (C), 119.0 (C), 103.7 (CH), 97.9 (CH), 86.1 (CH), 63.5 (C), 55.4 (Me), 55.2 (Me), 52.3 (Me), 44.3 (CH), 42.5 (CH_2), 37.8 (CH_2), 32.0 (CH_2), 30.1 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 25.9 (CH_2), 18.8 (Me), 18.3 (Me); *m/z* (ESI) 508 (MNa^+, 100%), 227 (13%).

3-(Cyclohexyl(hydroxy)methylene)-1-(2,4-dimethoxybenzyl)-7,8-dimethyl-1-azaspiro[4.5]dec-7-ene-2,4-dione 15



Method 2: To a solution of amide **23** (15 mg, 0.031 mmol) in methanol (2 mL) was added sodium methoxide in methanol (1 M; 150 μL, 0.15 mmol) and the mixture stirred at room temperature for 1 h. The solution was acidified with aqueous hydrochloric acid (2 M; pH4) and extracted with dichloromethane (3 × 5 mL). The organic layers were combined, washed with brine (3 mL), dried ($MgSO_4$), and solvent evaporated under reduced pressure to give the *title compound* (8 mg, 57%) as a pale yellow oil; (Found: M + Na^+, 476.2406. $C_{27}H_{35}NO_5$ + Na^+

requires 476.2407); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2931, 2857, 1702, 1609, 1507, 1464; δ_H (400 MHz; $CDCl_3$) 7.05 (1 H, d, *J* 8.3. ArH), 6.47-6.43 (1 H, m, ArH), 4.59 (1 H, d, *J* 16.0, ArC<u>H</u>HN), 4.52 (1 H, d, *J* 16.0, ArCH<u>H</u>N), 3.80 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.47-3.41 (1 H, m, CyCH), 2.28-2.16 (2 H, m, CyH), 2.05-1.91 (3 H, m, CyH), 1.71-1.63 (5 H, m, CyH), 1.62 (3 H, s, CMe), 1.57-1.52 (2 H, m, CyH), 1.49 (3 H, s, CMe), 1.44-1.23 (4 H, m, CyH); δ_c (100 MHz; $CDCl_3$) 197.0 (C), 192.3 (C), 174.0 (C), 159.9 (C), 157.2 (C), 127.9 (CH), 125.3 (C), 121.1 (C), 118.3 (C), 104.0 (CH), 98.2 (CH), 98.0 (C), 68.2 (C), 55.4 (Me), 55.3 (Me), 40.9 (CH_2), 37.1 (CH_2), 36.4 (CH_2), 29.7 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.7 (CH2), 28.6 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 18.8 (Me), 18.7 (Me); *m/z* (ESI) 334 (MNa^+, 100%), 226 (58%), 157 (42%), 413 (23%), 430 (17%), 363 (16%), 159 (11%), 185 (10%).