Supporting Information

All experiments sensitive to air and/or to moisture were carried out under an argon atmosphere in dried glassware assembled under a stream of argon. Nuclear magnetic resonance spectra were recorded on Bruker Ultrashield Avance (1H, 300 or 400 MHz; 13C, 75 or 100 MHz) spectrometers. All reagents and solvents, unless otherwise noted, were purchased from commercial vendors and used without further purification. All reported compounds had a purity of >95%, as judged by 1H-NMR, unless otherwise stated.

1-Methyl-bicyclo[3.2.1]octane-2,4-dione (7)

A round bottom flask was successively charged with a diethyl ether solution of 1.8 g of diazomethane (42 mmol, prepared from 12.7 g Diazald, with the Diazald kit available from Aldrich) and 150 mL of a 5% solution of KOH. This mixture was cooled to 0 °C and stirred and a solution of compound 6 (2.62 g, 19 mmol) in diethyl ether (30 mL) was slowly added. The reaction was stirred for 1 h at 0 °C and then quenched with AcOH (1 mL). The aqueous layer was extracted two times with Et2O, the combined Et2O extracts were dried (Na2SO4) and concentrated to give the methyl enol ether of compound 7a. The methyl enol ether 7a was then dissolved in THF (5 mL), aqueous 1N HCl (2 mL) was added and the mixture was stirred for 16 h at room temperature. The mixture was partially concentrated to remove the THF and then extracted three times with CH2Cl2. The combined organic layers were dried (Na2SO4) and concentrated to give compound 7 (950 mg).

The previous basic aqueous layer was acidified with aqueous 4 N HCl and extracted three times with CH2Cl2. The combined CH2Cl2 fractions were dried (Na2SO4) and concentrated under vacuum to give an additional amount of 800 mg of compound 7. Total yield: 1.75 g (51%).

1H NMR (300 MHz, CDCl3): δ = 3.40 (d, J = 20Hz, 1H), 3.21 (d, J = 20Hz, 1H) 3.05 (m, 1H), 2.25 (m, 1H), 2.0-1.75 (m, 5H), 1.28 (s, 3H).

3-[1,3]Dithian-2-yl-cyclopentanone (9)

1,3 Dithiane (24.1 g, 200 mmol) was dissolved in THF (300 mL) and cooled to -78 °C. A cyclohexane solution of nBuLi (2 M, 100 mL, 200 mmol) and hexamethyolphosphoramide (71.7 g, 400 mmol) were added dropwise keeping the temperature below -60 °C. The reaction mixture was stirred for 0.5 h, and then cyclopentenone (16.32 g, 200 mmol) was added dropwise. The reaction was stirred for an additional 0.5 h at -78 °C. MeOH (20 mL) was added and the reaction was warmed to room temperature, poured into a saturated aqueous NH4Cl-solution (200 mL). The resulting mixture was extracted three times with a 1:1 Et2O / hexane mixture. The combined organic extracts were washed with brine, dried over Na2SO4 and concentrated. The crude product was crystallized from ethyl acetate / hexane to give 22.1 g (55%) of compound 9. The remaining material was purified by chromatography (SiO2, ethyl acetate / hexane = 1:4 to 1:3) to give 11.8 g (29%) of compound 9.

Mp (from ethyl acetate / hexane) = 48-49 °C.

1H NMR (300 MHz, CDCl3): δ = 4.1 (d, J = 7.5Hz, 1H), 2.85 (m, 4H), 2.6-2.05 (m, 7H), 1.85 (m, 2H).

13C NMR (75 MHz, CDCl3): δ = 218.6, 53.7, 44.2, 43.1, 40.1, 31.8, 31.8, 28.6, 27.4.

2-(3-Methylene-cyclopentyl)-[1,3]dithiane (10)

Methyltriphenylphosphonium bromide (58.9 g, 165 mmol) was suspended in freshly distilled THF (197 mL) and cooled to -15 °C. A solution of nBuLi (1.6 M in hexane, 103 mL, 165 mmol) was added dropwise and the resulting orange solution was stirred for 10 min. A solution of compound 9 (15.2 g, 75 mmol in 39 mL THF) was slowly added during 30 min at -15 °C and then stirred at room
temperature for 18 h. The reaction mixture was poured into an aqueous solution of NH₄Cl (200 mL) and extracted with hexane (200 mL) and hexane / Et₂O (10:1, 200 mL). The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated in vacuum. The resulting crude material (21.8 g) was purified by chromatography (SiO₂, Et₂O / hexane = 1:10) to give pure compound 10 (6.1 g, 40%).

1H NMR (300 MHz, CDCl₃): δ = 4.85 (m, 2H), 4.00 (d, J = 7.5Hz, 1H), 2.85 (m, 4 H), 2.6 (m, 1H), 2.4 (m, 1H), 2.23 (m, 3H), 2.05 (m, 2H), 1.9 (m, 1H), 1.6 (m,1H).

2-(3-Methylene-cyclopentyl)-2-(2-nitro-ethyl)-[1,3]dithiane (11)

Compound 10 (418 mg, 2.09 mmol) was dissolved in freshly distilled THF (8.4 mL). The resulting solution was cooled to -20°C, a solution of nBuLi (1.6 M in hexane, 2.19 mmol) was added dropwise and the reaction mixture was stirred for 1.5 h at -20 °C. A solution of nitroethene (229 mg, 3.13 mmol) in THF (3 mL) was added, stirring was continued for 5 min at -20 °C and 45 min without cooling. An aqueous NH₄Cl solution (50 mL) was added and the resulting mixture was extracted two times with Et₂O. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄ and concentrated in vacuum. The crude product (525 mg) was purified by chromatography (SiO₂, Et₂O / hexane = 2:98 to 1:10) to give pure compound 11 (281 mg, 49%).

1H NMR (300 MHz, CDCl₃): δ = 4.82 (bs, 2H), 4.60 (m, 2H), 2.95 (m, 2H), 2.76 (m, 4H), 2.5 (m, 3H), 2.25 (m, 2H), 2.05 (m, 1H), 1.85 (m, 3H).

3-Oxa-4-azatricyclo[6.2.1.0₁,₅]undec-4-enyl-7-spiro-[1,3]dithiane (12)

Compound 11 (15.0 g, 55 mmol) was dissolved in toluene (300 mL) and Boc₂O (29.8 g, 137 mmol) and DMAP (670 mg, 5.47 mmol) were added. The resulting mixture was heated at 90 °C. After 35 min reaction time gas evolution was observed. After 1.5 h the reaction was cooled to room temperature and concentrated in vacuum. After chromatography (SiO₂, Et₂O / hexane = 2:98 to 1:10), 13.8 g (99%) of an oil were obtained. Crystallization from Et₂O gave pure compound 12 (11.2 g, 80%).

1H NMR (500 MHz, CDCl₃): δ = 4.28 (d, J = 8Hz, 1H), 4.15 (d, J = 8Hz, 1H), 3.32 (d, J = 16Hz, 1H), 2.59 (dt, J = 12Hz, J = 2Hz, 1H), 2.23 (m, 1H), 2.04 (m, 1H), 1.95 (m, 2H), 1.82 (m, 2H), 1.66 (dd, J = 12Hz, J = 5Hz, 1H).

13C NMR (75 MHz, CDCl₃): δ = 159.9, 73.2, 59.2, 54.7, 45.0, 38.5, 33.4, 31.7, 26.6, 26.3, 24.8, 24.5.

MS (ES+): 256.3 (M+H⁺).

7,7-Dimethoxy-3-oxa-4-azatricyclo[6.2.1.0₁,₅]undec-4-ene (13)

and

7-[3-(3a-Ethyl-5-methyl-3,3a,4,5,6,7-hexahydro-benzo[c]isoxazol-6-ylsulfanyl)-propylsulfanyl]-3-oxa-4-aza-tricyclo[6.2.1.0₁,₅]undec-4-ene (14)

Compound 12 (3.26 g, 12.8 mmol) was dissolved in MeOH (65 mL) and treated with PhI(OOCCF₃)₂ (8.23 g, 19.2 mmol) in portions at 19 °C. The reaction mixture was stirred at room temperature for 40 min, and poured onto an aqueous NaHCO₃ /brine mixture. The resulting mixture was extracted three times with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, concentrated in vacuum and purified by chromatography (120 g SiO₂, EtOAc / hexane = 1:2:3) to give compound 13 (1.19 mg, 44%) and compound 14 (730 mg, 22%).

1H NMR (300 MHz, CDCl₃): δ = 4.27 (d, J = 8Hz, 1H), 4.15 (d, J = 8Hz, 1H), 3.22 and 3.17 (2 s, 6H), 3.0 (d, J = 14Hz, 1H), 2.57 (br t, J = 7Hz, 1H), 2.27 (d, J = 14Hz, 1H), 1.85 (m, 5H), 1.64 (dd, J = 12Hz, J = 5Hz, 1H).

Compound 14 1H NMR (500 MHz, CDCl₃): δ = 5.88 (s, 1H), 4.39 (d, J = 9Hz, 1H), 4.18 (d, J = 9Hz, 1H), 2.89 (m, 2H, CH₂S), 2.79 (t, J = 6.5Hz, 2H, CH₂SS), 2.65 (dd, J = 5Hz, J = 4Hz, 1H), 2.12-1.75 (m, 8H).
1-Hydroxymethyl-4,4-dimethoxy-bicyclo[3.2.1]octan-2-one (16)
Compound **13** (1.19 g, 5.6 mmol) and **HBr** (0.70 g, 11.3 mmol) were dissolved in MeOH (31 mL) and H2O (2 mL) and degassed with an argon stream. Raney Ni (36 mg) was added and the reaction atmosphere was exchanged with hydrogen gas. The reaction mixture was stirred in an autoclave at 25 °C at 1.5 atm H2. The reaction was terminated when hydrogen up-take stopped (92.4%, 2 h). The reaction atmosphere was changed to argon, and the mixture was filtered and concentrated in vacuum. Brine was added and the resulting mixture was extracted 4 times with EtOAc. The organic fractions were dried over Na2SO4 and concentrated to give compound **16** (841 mg, 70%) in sufficient purity for further processing.

**Compound 16**
**1H NMR** (300 MHz, CDCl3): δ = 3.70 (2s, 2H), 3.15 and 3.20 (2s, 6H), 2.65 (d, J = 14Hz, 1H), 2.65 (bt, partially overlapping with previous signal, 1H), 2.53 (bt, J = 7.5Hz, 1H), 2.47 (d, J = 14Hz, 1H), 2.0 (m, 2H), 1.85-1.50 (m, 4H).

**MS (ES+):** 451.2 (2M+Na+), 446.3 (2M+NH4+), 232.3 (M+NH4+), 183.2 (M-CH3-O-).

1-Hydroxymethyl-4-methoxy-bicyclo[3.2.1]oct-3-en-2-one (17)
Compound **16** (800 mg, 3.74 mmol) was dissolved in dichloroethane (10 mL) and treated with camphorsulfonic acid (several crystals). The resulting mixture was stirred for 4 h at room temperature. The reaction mixture was quenched with aqueous NaHCO3-solution, partially concentrated and extracted three times with ethyl acetate. The organic layers were washed with brine, dried over Na2SO4 and concentrated in vacuum to give compound **17** (462 mg, 68%).

**1H NMR** (300 MHz, CDCl3): δ = 5.1 (s, 1H), 3.8 (s, 2H), 3.7 (s, 3H), 2.9 (t, J = 6Hz, 1H), 2.77 (bs, 1H), 2.14 (m, 1H), 2.05 (d, J = 11Hz, 1H), 1.80 (m, 3H), 1.45 (dd, J1 = 11Hz, J2 = 4Hz, 1H). The NMR spectrum showed some minor signals, which are consistent with the isomeric enol ether of the 1,3-dione.

1-Methoxymethyl-bicyclo[3.2.1]octane-2,4-dione (18)
NaH (69 mg, 55% dispersion in mineral oil, 1.57 mmol) was washed with hexane to remove the mineral oil. THF (3 mL) was added and the resulting suspension was treated with a solution of compound **17** (191 mg, 1.05 mmol) in THF (2 mL). The reaction liberated hydrogen gas and was stirred for 40 min at room temperature, until no further gas evolution was observed. The mixture was cooled to 0 °C and treated with MeI (223 mg, 1.57 mmol). The reaction was stirred for 72 h at room temperature, and then poured into brine and extracted two times with ethyl acetate. The organic layers were dried over Na2SO4 and concentrated in vacuum to give compound **18** (92 mg, white crystals, 66% yield).

**1H NMR** (300 MHz, CDCl3): δ = 3.72 (d, J = 9Hz, 1H), 3.54 (d, J = 9Hz, 1H), 3.52 (d, J = 15Hz, 1H), 3.40 (s, 3H), 3.30 (d, J = 15Hz, 1H), 3.04 (bt, J = 5Hz, 1H), 2.3-1.7 (m, 6H). A small singlet at 5.30 ppm was indicative of the keto-enol tautomer.

1-(2-Methoxy-ethoxymethyl)-bicyclo[3.2.1]octane-2,4-dione (19)
NaH (69 mg, 55% dispersion in mineral oil, 1.50 mmol) was washed with hexane to remove the mineral oil. THF (3 mL) was added and the resulting suspension was treated with a solution of compound **17** (191 mg, 1.05 mmol) in THF (2 mL). The reaction liberated hydrogen gas and was stirred for 40 min at room temperature, until no further gas evolution was observed. The mixture was cooled to 0 °C and treated with methoxyethyl bromide (208 mg, 1.50 mmol). The reaction was stirred for 6 h at room temperature. NaH (69 mg) was added and the reaction was stirred for an additional 30
min at room temperature and then treated with methoxyethyl bromide (208 mg, 1.50 mmol), and stirring was continued for 16 h and the same amounts of reagent were added again. After 6 h stirring, the mixture was poured onto brine and extracted two times with ethyl acetate. The organic layers were dried over Na$_2$SO$_4$ and concentrated to give 220 mg of crude product. This material was dissolved in THF (3 mL) and treated with 1 N HCl (1.5 mL). The reaction mixture was stirred for 7 h at room temperature, poured onto brine and extracted two times with ethyl acetate. The organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuum. The crude material (181 mg) was purified by chromatography (SiO$_2$, ethyl acetate), to give compound 19 (88 mg, 42% yield).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.85$ (d, $J = 8$Hz, 1H), 3.65 (m, 3H), 3.55 (m, 2H), 3.4-3.15 (m, 5H), 3.05 (t, $J = 5$Hz, 1H), 2.3-1.7 (m, 6H).

1-Fluoromethyl-bicyclo[3.2.1]octane-2,4-dione (20)

Compound 17 (255 mg, 1.40 mmol) was dissolved in CH$_2$Cl$_2$ (5 mL) and cooled to -78 °C. Diethylaminosulfur trifluoride (338 mg, 2.10 mmol) was added with a syringe to the reaction mixture and stirring was continued at -78 °C for 40 min. Additional diethylaminosulfur trifluoride (24 mg, 0.15 mmol) was added, stirring was continued at -78 °C for 30 min and the reaction mixture was warmed to room temperature. The reaction mixture was added to aqueous NaHCO$_3$ solution and extracted 2 times with CH$_2$Cl$_2$. The organic layers were dried with Na$_2$SO$_4$ and concentrated in vacuum. Chromatography (SiO$_2$, ethyl acetate / hexane = 2:3) of the crude product (276 mg) gave 116 mg (45%) of the pure enol ether.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 5.13$ (s, 1H), 4.85 (dd, $J^1 = 46$Hz, $J^2 = 10$Hz, 1H), 4.57 (dd, $J^1 = 46$Hz, $J^2 = 10$Hz, 1H), 3.68 (s, 3H), 2.90 (t, 5Hz, 1H), 2.15 (m, 1H), 2.05-1.5 (m, 5H).

MS (ES+): 185 (M+H$^+$).

The intermediate enol ether (110 mg, 0.6 mmol) was dissolved in THF (2 mL) and treated with 2 N HCl (1 mL). The resulting mixture was stirred at room temperature for 20 h, poured onto brine and extracted 2 times with ethyl acetate. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuum to give crystalline compound 20 (106 mg, quantitative yield).

$^1$H NMR (300 MHz, CDCl$_3$:CD$_3$OD (10:1): mixture of the two keto-enol tautomers in ratio of 2.7:1 $\delta = 5.10$ (s, 0.1H (majority exchanged with D), 4.85 (dd, $J^1 = 46$Hz, $J^2 = 9$Hz, 0.73H), 4.78 (dd, $J^1 = 46$Hz, $J^2 = 9$Hz, 0.27H), 4.62 (dd, $J^1 = 46$Hz, $J^2 = 9$Hz, 0.27H), 4.52 (dd, $J^1 = 46$Hz, $J^2 = 9$Hz, 0.73H), 3.1 (t, $J = 6$Hz, 0.27H), 2.90 (t, $J = 5$Hz, 0.73H), 2.36-1.53 (m, 6H).

MS (ES+): 171 (M+H$^+$), 193 (M+Na$^+$).

MS (ES-): 169 (M-H$^-$).