SUPPLEMENTARY INFORMATION Part 1

Synthesis of models of the BC ring systems of MPC1001 and MPC1001F

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General Experimental Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made by from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. For high resolution mass spectra an orthogonal time of flight analyzer was used.

(2*S*)-2-{[(Benzyloxy)carbonyl]amino}butanedioic acid.[10]

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Aspartic acid (5 g, 37.6 mmol) was added to a solution of K_2CO_3 (10.4 g, 75.2 mmol) in water (100 mL) and the mixture was cooled in an ice bath. BnOCOCl (7.8 mL, 52.6 mmol) was added dropwise from a syringe over about 5 min with vigorous stirring. The ice bath was left in place but not recharged and stirring was continued for 18 h. The mixture was then extracted with Et_2O and the aqueous phase was acidified to pH 1 with hydrochloric acid (6 N). The acidified solution was extracted with EtOAc and the combined organic extracts were dried ($MgSO_4$) and evaporated to give (2*S*)-2-{[(benzyloxy)carbonyl]amino}butanedioic acid (10 g, 100%) which was used directly in the next step.

1,4-Di-*tert*-Butyl (2*S*)-2-{[(Benzyloxy)carbonyl]amino}butanedioate.[11,12]

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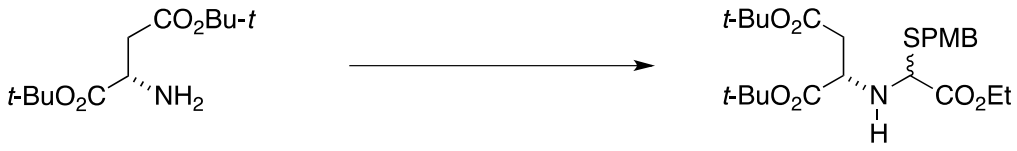
t-BuOAc (52 mL, 384 mmol) was added to a flask containing (2*S*)-2-{[(benzyloxy)carbonyl]amino}butanedioic acid (10.0 g, 37.6 mmol) and the mixture was stirred to produce a slurry. $BF_3.Et_2O$ (0.95 mL, 7.7 mmol) was added at a fast dropwise rate from a syringe, the flask was closed with a stopper and stirring was continued for 8 h. The mixture was quenched by rapid addition of water (100 mL) and the solution was adjusted to pH 10 by addition of aqueous NaOH (10 N). At this stage three layer had formed and the top layer was collected and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm), using 5:1 hexane-EtOAc, then 2:1 hexane-EtOAc, gave 1,4-di-*tert*-butyl (2*S*)-2-{[(Benzyloxy)carbonyl]amino}butanedioate (6.68 g, 47%) as an oil, which was used directly in the next step: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.44 (d, *J* = 9.6 Hz, 18 H), 2.71 (dd, *J* = 16.9, 4.5 Hz, 1 H), 2.87 (dd, *J* = 16.9, 4.7 Hz, 1 H), 4.42–4.50 (m, 1 H), 5.12 (s, 2 H), 5.74 (d, *J* = 8.7 Hz, 1 H), 7.27–7.37 (m, 5 H).

1,4-Di-*tert*-Butyl (2*S*)-2-Aminobutanedioate (19).[12]

- **19**

A solution of 1,4-di-*tert*-butyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}butanedioate (6.68 g, 17.6 mmol) in EtOAc (60 mL) was added to a mixture of 5%Pd on C (627 mg) and water (25 mL) in a Parr bottle which was then filled with hydrogen at 60 psi. Hydrogenation was then conducted overnight at room temperature and the mixture was filtered through a pad of Celite (6 x 2 cm), using EtOAc as a rinse. Evaporation of the solvent gave **19** (4.2 g, 98%) as an oil which was used immediately for the next step. After storage in a refrigerator the material solidifies completely but becomes a colorless oil at room temperature: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.45 (dd, J = 2.5, 1.1 Hz, 18 H), 1.78 (br, 2 H), 2.52–2.71 (m, 2 H), 3.61 (t, J = 5.8 Hz, 1 H).

1,4-Di-*tert*-Butyl (2*S*)-2-[(2-Ethoxy-1-{[(4-methoxyphenyl)methyl]sulfanyl}-2-oxo-ethyl)amino]butanedioate (20).



19 **20**

A solution of EtO_2CCHO (50%w/w in PhMe, 486 μL, 2.45 mmol) was added to a solution of **19** from the above experiment (600 mg, 2.45 mmol) in PhMe (4 mL) and the mixture was stirred for 15 min. At that point *p*-$MeOC_6H_4CH_2SH$[13] (341 μL, 2.45 mmol) was added and stirring was continued for 4 h (Ar atmosphere). Sufficient $MgSO_4$ was added until no further clumping together of the $MgSO_4$ occurred and stirring was continued overnight. The mixture was filtered, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the filtrate over silica gel (3 × 20 cm), using 5:1 hexane-EtOAc, gave **20** (950 mg, 99%) as a mixture of isomers, which was used in the next step.

The less polar isomer was obtained pure: mp 60–61.5 °C; FTIR ($CDCl_3$, cast) 3351, 2978, 1732, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (t, *J* = 7.1 Hz, 3 H), 1.41 (s, 9 H), 1.46 (s, 9 H), 2.43–2.51 (m, 2 H), 3.01 (dd, *J* = 12.1, 5.6 Hz, 1 H), 3.69 (t, *J* = 12.1 Hz, 3 H), 3.75 (s, 3 H), 4.15 (dd, *J* = 9.7, 7.1 Hz, 2 H), 4.39 (d, *J* = 12.2 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 28.0 (q), 32.7 (t), 39.2 (t), 54.5 (d), 55.3 (q), 61.3 (d), 63.6 (q), 80.9 (s), 81.8 (s), 113.9 (d), 129.5 (s), 130.2 (d), 158.7 (s), 169.3 (s), 169.9 (s), 172.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{38}NO_7S$ $(M + H)^+$ 484.2363, found 484.2361.

1,4-Di-*tert*-Butyl (2*S*)-2-[2-Bromo-*N*-(2-Ethoxy-1-{[(4-methoxyphenyl)methyl]sulfanyl}-2-oxoethyl)acetamido]butanedioate (21).

20 **21**

$BrCH_2COBr$ (0.8 mL, 9.2 mmol) in dry CH_2Cl_2 (10 mL) was was added at a fast dropwise rate to a stirred and cooled (–78 °C, large silvered Dewar basin) solution of **20** (mixture of isomers, 2.3 g, 4.5 mmol) in CH_2Cl_2 (50 mL). The cooling bath was left in place and recharged periodically so the the temperature remained at –78 °C for 20 h. [With the silvered Dewar we used the temperature remained at –78 C overnight.] At this point a small amount of **20** still remained (TLC, silica, 1:4 EtOAc-hexane). The mixture was quenched with water and partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm), using 1:5 EtOAc-hexane, gave **21** (2.54 g, 88%) as an oil: **This compound should be stored in a freezer and used within a few days**. FTIR ($CDCl_3$, cast) 2977, 2925, 1733, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (mixture of rotamers) 1.28 (ddd, *J* = 13.8, 7.0, 2.1 Hz, 3 H), 1.47 (dt, *J* = 9.8, 2.2 Hz, 18 H), 2.50 (d, *J* = 17.3 Hz, 1 H), 2.69–2.79 (m, 1 H), 2.92 (ddd, *J* = 17.1, 4.3, 2.2 Hz, 1 H), 3.39 (ddd, *J* = 17.2, 8.7, 2.1 Hz, 1 H), 3.58 (ddd, *J* = 59.5, 11.4, 2.1 Hz, 2 H), 3.81 (d, *J* = 2.1 Hz,

2 H), 3.89 (t, *J* = 2.5 Hz, 1 H), 4.03–4.27 (m, 4 H), 4.60–4.69 (m, 1 H), 5.05 (dt, *J* = 8.8, 2.6 Hz, 1 H), 5.35 (d, *J* = 2.1 Hz, 1 H), 6.88 (dd, *J* = 8.7, 2.2 Hz, 2 H), 7.28–7.44 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of rotamers) 14.1 (q), 14.3 (q), 26.2 (t), 28.1 (q), 28.1 (q), 28.2 (q), 28.2 (q), 28.2 (q), 28.9 (t), 35.3 (t), 37.0 (t), 37.4 (t), 49.9 (d), 55.1 (d), 55.5 (q), 62.8 (d), 64.2 (q), 80.6 (s), 82.0 (s), 82.3 (s), 82.9 (s), 114.4 (d), 128.0 (s), 130.6 (d), 159.4 (s), 165.4 (s), 166.4 (s), 167.5 (s), 168.7 (s), 169.3 (s), 170.0 (s), 170.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{39}NO_8S$ $(M + H)^+$ 604.1574, found 604.1563.

1,4-Di-*tert*-Butyl (2*S*)-2-(2-{[(4-Methoxyphenyl)methyl]sulfanyl}-4-methyl-3,6-dioxopiperazin-1-yl)butanedioate (22).

21 **22**

A solution of **21** (680 mg, 1.12 mmol) in MeCN (26 mL) was added at a fast dropwise rate to a stirred and cooled (–30 °C) solution made up from $MeNH_2$ (2 M in THF, 1.60 mL, 3.37 mmol) in MeCN (24 mL). The cold bath was left in place but not recharged and stirring was continued for 6 h, before which time the mixture had reached room temperature. The solvent was evaporated and the residue was partitioned between water and EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 2:3 EtOAc-hexane, gave the less polar isomer of **22** (73 mg, 12.8%), a mixture of the two isomers (127 mg, 22.2%) and the more polar isomer (330 mg, 57.8%), all as oils: ^{1}H NMR on the crude product indicted a 2:1 ratio of isomers. The more polar isomer had: FTIR ($CDCl_3$, cast) 2978, 2933, 1732, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42 (dd, *J* = 11.1, 0.9 Hz, 18 H), 2.36 (ddd, *J* = 16.7, 5.4, 0.8 Hz, 1 H), 2.96 (d, *J* = 0.8 Hz, 3 H), 3.11 (ddd, *J* = 16.7, 8.4, 0.8 Hz, 1 H), 3.72–3.85 (m, 5 H), 4.01 (d, *J* = 13.3 Hz, 1 H), 4.18 (d, *J* = 17.1 Hz, 1 H), 4.43 (ddd, *J* = 8.4, 5.4, 0.8 Hz, 1 H), 4.67 (s, 1 H), 6.81–6.92 (m, 2 H), 7.33 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.0 (q), 28.1 (q), 33.9 (q), 35.5 (t), 35.6 (t), 51.7 (t), 55.4

(q), 57.1 (d), 61.4 (d), 81.2 (s), 82.7 (s), 114.2 (d), 128.2 (s), 130.5 (d), 159.2 (s), 163.8 (s), 164.4 (s), 167.5 (s), 169.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{37}N_2O_7S$ $(M + H)^+$ 509.2316, found 509.2307. The less polar isomer had: FTIR ($CDCl_3$, cast) 2978, 2933, 1733, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40 (s, 18 H), 2.58 (ddd, *J* = 17.4, 9.4, 0.9 Hz, 1 H), 2.83 (ddd, *J* = 17.3, 4.8, 0.9 Hz, 1 H), 2.96 (d, *J* = 0.9 Hz, 3 H), 3.70–3.84 (m, 5 H), 3.97 (d, *J* = 13.4 Hz, 1 H), 4.21 (d, *J* = 16.8 Hz, 1 H), 4.62 (ddd, *J* = 9.4, 4.8, 0.8 Hz, 1 H), 4.74 (d, *J* = 0.8 Hz, 1 H), 6.81–6.87 (m, 2 H), 7.32–7.37 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.9 (q), 28.1 (q), 33.9 (q), 35.0 (t), 35.2 (t), 51.9 (t), 55.4 (q), 55.9 (q), 60.9 (d), 81.4 (s), 82.9 (s), 114.1 (d), 128.4 (s), 130.6 (d), 159.1 (s), 164.0 (s), 164.7 (s), 167.5 (s), 169.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{37}N_2O_7S$ $(M + H)^+$ 509.2316, found 509.2319.

***tert*-Butyl (6*S*,8a*R*)-8a-{[(4-Methoxyphenyl)methyl]sulfanyl}-2-methyl-1,4,8-trioxo-octahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (23)**.

22 **23**

LDA was prepared as follows: *n*-BuLi (2.5 M in hexanes, 1.6 mL, 4.0 mmol) was added at a fast dropwise rate to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.62 mL, 4.4 mmol) in THF (5.78 mL). Stirring at –78 °C was continued for 20 min. A portion (0.9 mL) of this stock solution was transferred rapidly by syringe to an argon-filled flask immersed in a cold bath (–78 °C). Dry HMPA (216 μL, 1.24 mmol) was injected and the mixture was stirred for 10 min (–78 °C). A solution of **22** (a 1:2 mixture of isomers, 210 mg, 0.41 mmol) in THF (12 mL) was injected over 5 min with continued stirring. After the addition stirring at –78 °C was continued for 1.2 h and then another aliquot of the stock LDA solution (which had in the meantime been kept at –78 °C) (200 μL, 0.10 mmol) was injected and stirring at –78 °C was continued for 30 min. The mixture was quenched by quickly injecting a solution of AcOH (0.9 mL) in THF (3 mL). Stirring at –78 °C was continued for 5 min, the mixture was removed from the cold bath

and aqueous $NaHCO_3$ (5% w/v) was added slowly to adjust the pH to 7. Stirring was continued for 30 min and most of the THF was then evaporated at room temperature. The residue was extracted with EtOAc and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 1:1 EtOAc-hexane and then EtOAc, gave **23** (75 mg, 42%) as a colorless oil, and recovered **22** (a 1:1 mixture of isomers, 73 mg, 35%) so that the corrected yield of **23** was 64%. Compound **23** had: $[\alpha]^{25}_{D}$ –28.7° (*c* 0.56, CH_2Cl_2); FTIR ($CDCl_3$, cast) 2978, 1772, 1692, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9 H), 2.93 (s, 4 H), 3.17 (dd, *J* = 19.3, 3.9 Hz, 1 H), 3.73–3.83 (m, 4 H), 4.00–4.09 (m, 2 H), 4.40 (d, *J* = 16.7 Hz, 1 H), 4.81 (dd, *J* = 10.9, 3.9 Hz, 1 H), 6.81 (d, *J* = 8.7 Hz, 2 H), 7.17 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.0 (q), 34.2 (d), 34.8 (t), 36.6 (t), 52.3 (q), 52.6 (s), 55.4 (q), 62.5 (s), 83.6 (s), 114.1 (d), 127.3 (s), 130.5 (d), 159.1 (s), 160.3 (s), 163.8 (s), 168.0 (s), 195.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{27}N_2O_6S$ $(M+H)^+$ 435.1584, found 435.1592.

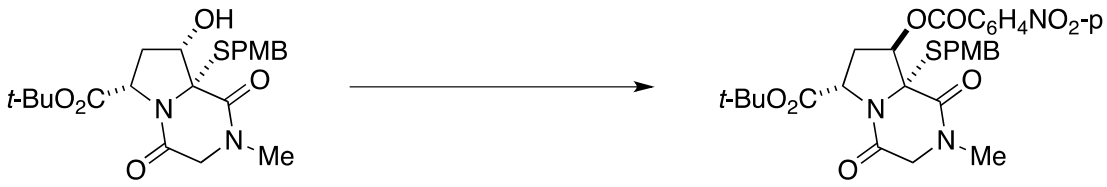
***tert*-Butyl (6*S*,8*S*,8a*R*)-8-Hydroxy-8a-{[(4-methoxyphenyl)methyl]sulfanyl}-2-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (24)**.

23 **24**

$NaBH_4$ (ca 1.5 mg, 0.04 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **23** (17 mg, 0.039 mmol) in 2:1 THF-MeOH (1.5 mL). Stirring at 0 °C was continued for 10 min and the mixture was then diluted with water and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 12 cm), using EtOAc, gave **24** (15 mg, 99%) as an oil: $[\alpha]^{25}_{D}$ –67.6° (*c* 0.10, CH_2Cl_2); FTIR ($CDCl_3$, cast) 3419, 2978, 1772, 1660, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.49 (s, 9 H), 2.30 (ddd, *J* = 12.7, 10.7, 9.5 Hz, 1 H), 2.61 (ddd, *J* = 12.7, 8.7, 7.1 Hz, 1 H), 2.73 (s, 3 H), 3.44 (d, *J* = 2.7 Hz, 1 H), 3.64 (d, *J* = 17.1 Hz, 1 H), 3.77 (s, 3

H), 3.97 (s, 2 H), 4.14 (d, *J* = 17.1 Hz, 1 H), 4.33–4.39 (m, 1 H), 4.40–4.48 (m, 1 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 7.27–7.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.1 (q), 31.6 (t), 33.1 (t), 33.5 (d), 52.9 (t), 55.2 (q), 55.4 (q), 72.6 (s), 75.5 (d), 82.6 (s), 114.0 (d), 128.6 (s), 130.0 (d), 158.9 (s), 163.1 (s), 166.4 (s), 168.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{28}N_2NaO_6S$ $(M + Na)^+$ 459.1560, found 459.1551.

***tert*-Butyl (6*S*,8*R*,8a*R*)-8a-{[(4-Methoxyphenyl)methyl]sulfanyl}-2-methyl-8-(4-nitrobenzoyloxy)-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (25)**.



24 **25**

Compound **24** (15 mg, 0.0344 mmol), Ph_3P (46 mg, 0.175 mmol) and *p*-$O_2NC_6H_4CO_2H$ (26 mg, 0.155 mmol) were tipped into a round bottomed flask containing a magnetic stirring bar. The flask was then closed by a septum and dry THF (2 mL) was injected. The flask was immediately lowered into a cold bath (–20 °C, ice-NaCl) and the reaction mixture was stirred for 10 min. Di-isopropyl diazodicarboxylate (34 μL, 0.172 mmol) was injected over about 1 min. The cold bath was left in place but not recharged and stirring was continued for 23 h during which time the temperature rose to room temperature. The solvent was then evaporated (water pump vacuum) and flash chromatography of the residue over silica gel (1 × 17 cm), using 1:2 EtOAc-hexane, gave **25** (19 mg, 95%): $[\alpha]^{25}_D$ –107.5° (*c* 2.03, CH_2Cl_2); FTIR ($CDCl_3$, cast) 3352, 2925, 1734, 1684, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.49 (s, 9 H), 2.50 (dd, *J* = 14.4, 8.1 Hz, 1 H), 2.77 (ddd, *J* = 14.1, 9.9, 4.0 Hz, 1 H), 2.87 (s, 3 H), 3.79 (s, 4 H), 3.89–4.05 (m, 2 H), 4.31 (d, *J* = 16.6 Hz, 1 H), 4.61 (dd, *J* = 9.8, 8.1 Hz, 1 H), 5.84 (d, *J* = 3.8 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 8.01 (d, *J* = 8.8 Hz, 2 H), 8.25 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.1 (q), 32.4 (t), 33.9 (d), 35.1 (t), 52.9 (t), 55.4 (q), 58.9 (q), 74.2 (s), 78.1 (d), 82.9 (s), 114.2 (d), 123.7 (d), 128.6 (s), 130.3 (d), 130.9 (d), 135.0 (s),

150.8 (s), 159.1 (s), 162.2 (s), 163.16 (s), 163.22 (s), 168.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{28}H_{31}N_3NaO_9S$ $(M + Na)^+$ 608.1673, found 608.1675.

***tert*-Butyl (6*S*,8*R*,8a*R*)-8-Hydroxy-8a-{[(4-methoxyphenyl)methyl]sulfanyl}-2-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (13)**.

25 **13**

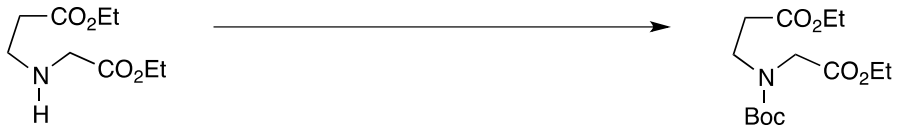
A solution of $LiOH.H_2O$ (29 mg, 0.68 mmol) in water (2.5 mL) was added to a stirred solution of **25** (200 mg, 0.34 mmol) in THF (5 mL) and stirring was continued for 30 min. The solution was diluted with water (5 mL) and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using EtOAc, gave **13** (120 mg, 80%): $[\alpha]^{25}_D$ –134.7° (*c* 0.49, CH_2Cl_2); FTIR ($CDCl_3$, cast) 3411, 2976, 1744, 1684, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9 H), 2.33 (dd, *J* = 13.6, 8.1 Hz, 1 H), 2.45 (tdd, *J* = 9.9, 4.4, 2.2 Hz, 1 H), 2.89 (s, 3 H), 3.26 (d, *J* = 2.1 Hz, 1 H), 3.68 (dd, *J* = 16.6, 0.6 Hz, 1 H), 3.78 (d, *J* = 0.6 Hz, 3 H), 3.88 (d, *J* = 2.8 Hz, 2 H), 4.31 (d, *J* = 16.6 Hz, 1 H), 4.45–4.51 (m, 1 H), 4.53–4.61 (m, 1 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 7.22–7.27 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.1 (q), 32.9 (t), 33.9 (d), 34.8 (t), 53.0 (t), 55.4 (q), 59.6 (q), 75.9 (s), 76.6 (d), 82.3 (s), 114.0 (d), 129.0 (s), 130.1 (d), 159.0 (s), 163.4 (s), 164.6 (s), 169.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{28}N_2NaO_6S$ $(M + Na)^+$ 459.1560, found 459.1549.

Ethyl 3-[(2-Ethoxy-2-oxoethyl)amino]propanoate (27).[15]

26 **27**

Ethyl acrylate (9.7 g, 97 mmol) and Et_3N (21 mL, 97 mmol) were added to a stirred solution of glycine ethyl ester hydrochloride (20 g, 145 mmol) in EtOH (150 mL). The resulting solution was stirred for 2 days at room temperature and then evaporated at room temperature. The residue was partitioned between EtOAc (80 mL) and water (80 mL) and the aqueous layer was extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and evaporated. Flash chromatography over silica gel (5 × 12 cm), gave **27** (15.4 g, 78%) as a colorless liquid: FTIR (CH_2Cl_2, cast) 3340, 2983, 1736, 1187, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) □ 1.22−1.27 (m, 6 H), 1.86 (s, 1 H), 2.48 (t, J = 6.4 Hz, 2 H), 2.88 (t, J = 6.0 Hz, 2 H), 3.38 (s, 2 H), 4.10−4.19 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 34.8 (t), 44.7 (t), 50.7 (t), 60.3 (t), 60.6 (t), 172.1 (s), 172.3 (s); exact mass (electrospray) *m/z* calcd for $C_9H_{18}NO_4$ $(M + H)^+$ 204.1230, found 204.1230.

Ethyl 3-{[(*tert*-Butoxy)carbonyl](2-ethoxy-2-oxoethyl)amino}propanoate (28).[15]

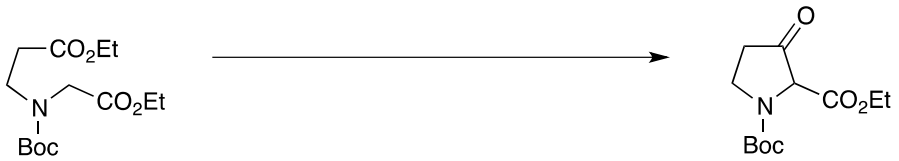


27 **28**

$(Boc)_2O$ (14.8 g, 68 mmol) was added to a stirred solution of (**27**) (10 g, 50 mmol) in $CHCl_3$ (100 mL) at 0 °C. An aqueous solution of NaOH (6 g, 150 mmol) in water (300 mL) was added slowly over 10 min; the ice bath was removed and stirring was continued overnight. The aqueous layer was extracted with $CHCl_3$ (2 × 60 mL) and the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 × 14 cm), gave **28** (13.9 g, 92%) as a colorless liquid: FTIR (CH_2Cl_2, cast) 2980, 2935, 1736, 1704, 1368, 1199, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (mixture of two rotamers) 1.21−1.28 (m, 6 H), 1.40 (s, 4.5 H), 1.46 (s, 4.5 H), 2.57−2.63 (m, 2 H), 3.49−3.56 (m, 2 H), 3.93 (s, 1 H), 4.00 (s, 1 H), 4.07−4.18 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of two rotamers) 14.1 (q), 14.17 (q), 14.24 (q), 28.2 (q), 28.3 (q), 33.7 (t), 34.2 (t), 44.8

(t), 44.9 (t), 50.1 (t), 50.9 (t), 60.5 (t), 60.6 (t), 60.9 (t), 61.0 (t), 80.3 (s), 80.5 (s), 155.0 (s), 155.5 (s), 170.1 (s), 170.3 (s), 172.1 (s), 172.4 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{25}NNaO_6$ $(M + Na)^+$ 326.1574, found 326.1574.

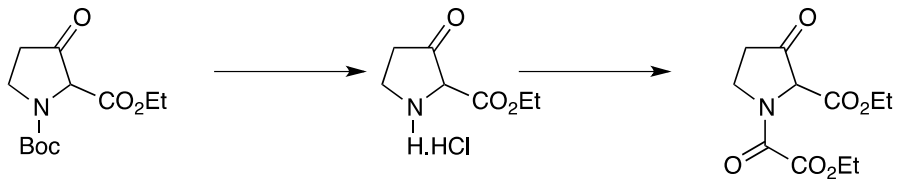
1-*tert*-Butyl 2-Ethyl 3-Oxopyrrolidine-1,2-dicarboxylate (29).[15]



28 **29**

A solution of **28** (5.8 g, 19 mmol) in THF (25 mL) was added dropwise over 15 min to a stirred and cooled (–78 °C) solution of $(Me_3Si)_2NLi$ (22.8 ml, 1.0 M) in dry THF (70 mL). The cold bath was left in place, but not recharged, and stirring was continued for 4 h, by which time the temperature had risen to –30 °C. The mixture was then poured into ice cold hydrochloric acid (1N, 100 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 × 14 cm), gave **29** (4.4 g, 89%) as colorless oil: FTIR (CH_2Cl_2, cast) 2980, 2935, 1774, 1742, 1708, 1394, 1237, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (mixture of rotamers) 1.29 (t, J = 6.8 Hz, 3 H), 1.43 (s), 1.49 (s, 9 H), 2.67 (t, J = 7.6 Hz, 2 H), 3.76−3.91 (m, 2 H), 4.20−4.26 (m, 2 H), 4.46 (s), 4.53 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of rotamers) 14.0 (q), 14.2 (q), 28.1 (q), 28.2 (q), 36.4 (t), 37.1 (t), 41.6 (t), 42.2 (t), 62.1 (t), 65.4 (d), 65.8 (d), 80.9 (s), 81.0 (s), 153.8 (s), 154.0 (s), 166.1 (s), 166.3 (s), 204.1 (s), 204.6 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{19}NNaO_5$ $(M + Na)^+$ 280.1155, found 280.1155.

Ethyl 1-(2-Ethoxy-2-oxoacetyl)-3-oxopyrrolidine-2-carboxylate (31).

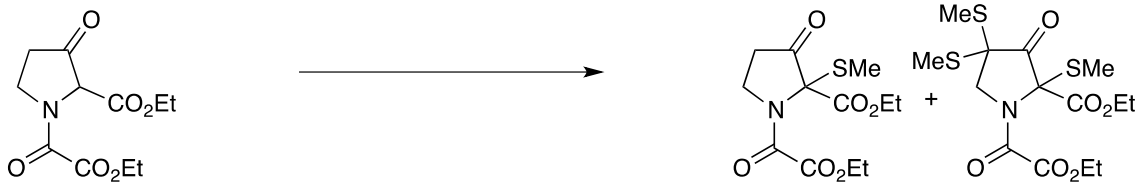


29 **30** **31**

Concentrated hydrochloric acid (3.2 mL) was added to a stirred solution of **29** (2.5 g, 9.7 mmol) in 3:1 CH_2Cl_2-Et_2O (16 mL) at room temperature and stirring was continued for 8 h, by which time all the starting material had reacted (TLC, silica, 1:1 EtOAc-hexane). The solvent was evaporated (rotary evaporator, water pump) and the residue was kept under oil pump vacuum to give the hydrochloride salt **30** as a gum, which was used directly for the next step.

Et_3N (4.1 mL, 29.3 mmol) was added to a stirred and cooled (0 °C) solution of above amine-hydrochloride salt **30** in CH_2Cl_2 (12.5 mL). After 10 min., EtOCOCOCl (1.625 mL, 14.5 mmol) was added slowly to the reaction mixture. The cold bath was left in place, but not recharged, and stirring was continued for 14 h. Hydrochloric acid (1 N, 3.2 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 30 cm), using 1:3 EtOAc-hexane and then 1:2 EtOAc-hexane, gave **31** (1.9 g, 78%) as an oil: FTIR (CH_2Cl_2, cast) 2985, 2940, 1775, 1740, 1672, 1445, 1368, 1257, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (mixture of rotamers) 1.27−1.41 (m, 6 H), 2.68 (dd, J = 8.4, 7.2 Hz, 1.3 H), 2.78−2.82 (m, 0.7 H), 3.88−4.15 (m, 0.6 H), 4.17−4.40 (m, 5.4 H), 4.75 (s) and 5.11 (s, 1 H in all); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of rotamers) 13.8 (q), 13.9 (q), 14.0 (q), 14.1 (q), 34.5 (t), 36.9 (t), 42.6 (t), 43.8 (t), 62.7 (t), 62.8 (t), 62.9 (t), 63.0 (t), 65.1 (d), 66.9 (d), 158.0 (s), 158.7 (s), 160.3 (s), 160.5 (s), 164.3 (s), 165.1 (s), 201.8 (s), 202.9 (s); exact mass (electrospray) *m/z* calcd for $C_{11}H_{16}NO_6$ $(M + H)^+$ 258.0972, found 258.0972.

Ethyl 1-(2-Ethoxy-2-oxoacetyl)-2-(methylthio)-3-oxopyrrolidine-2-carboxylate (32).

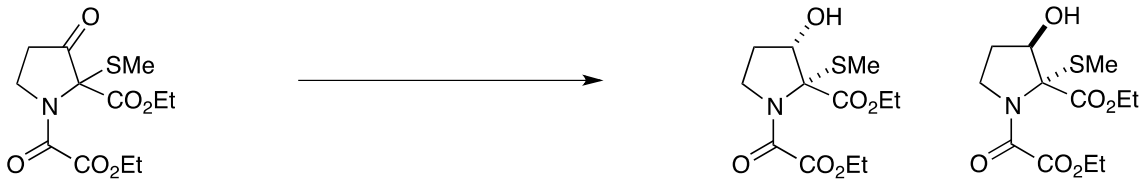


31 major **32** minor **32a**

Oven dried anhydrous Na_2CO_3 (212 mg, 2 mmol) was added to a stirred solution of **31** (544 mg, 2.2 mmol) and 1-(methylthio)pyrrolidine-2,5-dione[18] (290 mg, 2 mmol) in MeCN (6 mL) at room temperature. Stirring was continued for 6 h, and the solvent was evaporated. Hydrochloric acid (1 N, 4 mL) and CH_2Cl_2 (10 mL) were added to the residue and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:2 EtOAc-hexane, gave the major product (**32**) (384 mg, 63%) and the minor product (**32a**) (63 mg, 8%), both as a pale yellow liquids: The major product had: FTIR (CH_2Cl_2, cast) 2984, 2929, 1773, 1745, 1672, 1422, 1248, 1180, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (mixture of rotamers) 1.24−1.30 (m, 3 H), 1.33−1.39 (m, 3 H), 2.06 (s) and 2.25 (s, 3 H in all), 2.67−2.73 (m, 0.4 H), 2.81−2.94 (m, 1.6 H), 3.93−3.98 (m, 0.4 H), 4.03−4.15 (m, 1 H), 4.21−4.29 (m, 3 H), 4.32−4.38 (m, 1.6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of rotamers) 12.8 (q), 13.6 (q), 13.7 (q), 13.9 (q), 13.95 (q), 13.97 (q), 33.3 (t), 35.1 (t), 42.1 (t), 43.3 (t), 62.9 (t), 63.3 (t), 63.7 (t), 73.0 (s), 75.1 (s), 158.4 (s), 160.3 (s), 160.6 (s), 161.1 (s), 164.1 (s), 165.1 (s), 199.1 (s), 202.6 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{17}NNaO_6S$ $(M + Na)^+$ 326.0669, found 326.0669.

The minor product (**32a**) had: FTIR (CH_2Cl_2, cast) 2985, 2924, 1739, 1673, 1420, 1244, 1126, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (mixture of rotamers) 1.24−1.37 (m, 6 H), 2.10 (s), 2.11 (s), 2.13 (s, 4.5 H), 2.16 (s), 2.17 (s, 3 H), 2.24 (s), 2.31 (s, 1.5 H), 4.18 (s, 1 H), 4.22−4.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of rotamers) 12.7 (q), 13.0 (q), 13.2 (q), 13.3 (q), 13.7 (q), 13.8 (q), 13.88 (q), 13.90 (q), 13.94 (q), 14.0 (q), 56.2 (t), 56.6 (t), 57.5 (s), 59.7 (s), 62.9 (t), 63.1 (t), 63.4 (t), 63.9 (t), 72.9 (s), 76.0 (s), 157.3 (s), 159.9 (s), 160.2 (s), 161.0 (s), 163.2 (s), 164.6 (s), 189.3 (s), 193.3 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{22}NO_6S_3$ $(M + H)^+$ 396.0604, found 396.0605.

(2*R,3*S**)-Ethyl 1-(2-Ethoxy-2-oxoacetyl)-3-hydroxy-2-(methylthio)pyrrolidine-2-carboxylate (Major) (33) and (2*R**,3*R**)-Ethyl 1-(2-Ethoxy-2-oxoacetyl)-3-hydroxy-2-(methylthio)pyrrolidine-2-carboxylate (Minor) (33a).**



32 **33** **33a**

$NaBH_4$ (161 mg, 4.36 mmol) was added to a stirred and cooled (–78 °C) solution of ketone **32** (880 mg, 2.9 mmol) in EtOH (15 mL). Stirring at –78 °C was continued for 2 h. The reaction mixture was removed from the cold bath and the stirred solution was immediately quenched by adding hydrochloric acid (1 N, 5 mL). The solvent was then evaporated (room temperature, waterpump), and the residue was extracted with EtOAc (5 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using successively 1:2-, 2:3- and 1:1 EtOAc-hexane, gave the major (less polar) alcohol **33** (600 mg, 67.7%) and the minor alcohol **33a** (128.4 mg, 14.5%) as colorless gums. The major alcohol (**33**) (OH and SMe syn) had: FTIR (CH_2Cl_2, cast) 3469, 2985, 2931, 1740, 1771, 1426, 1243, 1159, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (mixture of rotamers) 1.24−1.37 (m, 6 H), 1.84−1.91 (m, 0.4 H), 2.02−2.09 (m, 1.6 H), 2.13 (s, 2 H), 2.23−2.34 (m, 1 H), 3.13 (d, J = 4.5 Hz, 0.3 H), 3.24 (d, J = 4.5 Hz, 0.7 H), 3.81−3.89 (m, 2 H), 4.22−4.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of rotamers) 13.7 (q), 13.8 (q), 13.9 (q), 14.0 (q), 29.8 (t), 31.5 (t), 46.0 (t), 47.2 (t), 62.5 (t), 62.9 (t), 63.0 (s), 76.9 (d), 79.6 (d), 79.4 (s), 79.8 (s), 158.5 (s), 160.9 (s), 161.2 (s), 161.6 (s), 168.0 (s), 169.6 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{19}NNaO_6S$ $(M + Na)^+$ 328.0825, found 328.0820.

The minor alcohol (**33a**) (OH and SMe anti) had: FTIR (CH_2Cl_2, cast) 3453, 2984, 2924, 1738, 1656, 1431, 1244, 1115, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (mixture of rotamers) 1.24−1.38 (m, 6 H), 1.95 (s, 1.4 H), 2.11−2.30 (m, 3.6 H), 2.91 (s), 2.98 (s, 1 H), 3.44−3.50 (m, 0.5 H), 3.69−3.74 (m, 0.5 H), 3.95−4.03 (m, 1 H), 4.13−4.36 (m, 4 H), 4.37−4.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (mixture of rotamers) 11.2 (q), 13.7 (q), 14.00 (q), 14.04 (q), 14.08 (q), 14.12 (q), 27.4 (t), 31.0 (t), 45.4 (t), 46.9 (t), 62.4 (t), 62.5 (t), 62.8 (t), 77.1 (d), 78.6 (d), 77.5 (s), 78.0 (s), 158.6 (s), 161.0 (s), 161.2 (s), 161.6 (s), 166.6 (s), 168.0 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{19}NNaO_6S$ $(M + Na)^+$ 328.0825, found 328.0830.

(2*R,3*S**)-Ethyl 1-(2-Ethoxy-2-oxoacetyl)-3-(methoxymethoxy)-2-(methylthio)pyrrolidine-2-carboxylate (34).**

33 **34**

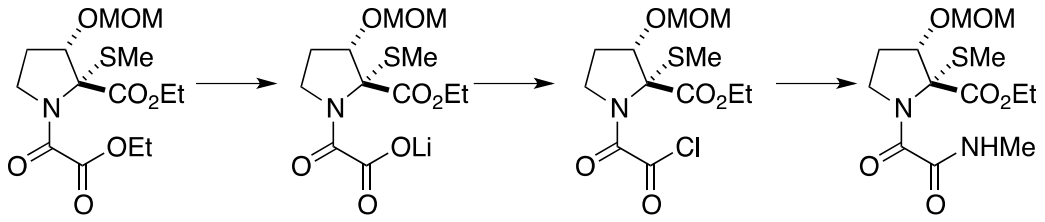
i-Pr_2NEt (511 mg, 3.96 mmol), $MeOCH_2Br$ (520 mg, 4.2 mmol) and Bu_4NI (1.46 g, 3.96 mmol) were added sequentially to a stirred and cooled (0 °C) solution of the major alcohol **33** (600 mg, 1.98 mmol) in CH_2Cl_2 (14 mL) and stirring was continued for 10 min. The cold bath was removed and stirring was continued for 16 h. Hydrochloric acid (1 N, 4.6 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:2 EtOAc-hexane, gave **34** (639 mg, 93%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2983, 2901, 1740, 1672, 1424, 1242, 1154, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (mixture of rotamers) 1.24−1.37 (m, 6 H), 1.83−1.90 (m, 0.3 H), 2.07 (s, 0.7 H), 2.20−2.30 (m, 4 H), 3.37 (s), 3.39 (s, 3 H), 3.65−3.76 (m, 0.2 H), 3.76−3.87 (m, 0.8 H), 3.87−3.93 (m, 1 H), 4.17−4.35 (m, 4 H), 4.47 (t, *J* = 6.5 Hz, 0.2 H), 4.55 (t, *J* = 7.5 Hz, 0.8 H), 4.65 (dd, *J* = 22.5, 6.5 Hz, 1.6 H), 4.81 (dd, *J* = 22.5, 6.5 Hz, 0.4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers) δ 13.67 (q), 13.75 (q), 13.8 (q), 13.9 (q), 14.0 (q), 29.2 (t), 29.9 (t), 45.2 (t), 45.5 (t), 55.9 (q), 56.2 (q), 62.3 (t), 62.4 (t), 62.8 (t), 62.9 (t), 77.8 (s), 78.1 (s), 82.2 (d), 83.8 (d), 96.2 (t), 96.6 (t), 158.9 (s), 161.0 (s), 161.3 (s), 162.0 (s), 167.9 (s), 170.2 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{24}NO_7S$ $(M + H)^+$ 350.1268, found 350.1273.

(2*R,3*R**)-Ethyl 1-(2-Ethoxy-2-oxoacetyl)-3-(methoxymethoxy)-2-(methylthio)pyrrolidine-2-carboxylate (34a).**

33a **34a**

i-Pr_2NEt (103 mg, 0.799 mmol), $MeOCH_2Br$ (104 mg, 0.83 mmol) and Bu_4NI (295 mg, 0.799 mmol) were added sequentially to a stirred and cooled (0 °C) solution of the minor alcohol **33a** (120 mg, 0.399 mmol) in CH_2Cl_2 (2.5 mL) and stirring was continued for 10 min. The ice bath was removed and stirring was continued for 19 h. Hydrochloric acid (1 N, 1 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 1:2 EtOAc-hexane, gave **34a** (125 mg, 91%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2984, 1745, 1661, 1428, 1251, 1155, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (mixture of rotamers) 1.21−1.35 (m, 6 H), 1.95 (s, 1.5 H), 2.15−2.21 (m, 3.5 H), 3.34 (s) and 3.35 (s, 3 H), 3.40−3.46 (m, 0.5 H), 3.61−3.67 (m, 0.5 H), 3.92−3.99 (m, 1 H), 4.15−4.34 (m, 4 H), 4.49 (t, *J* = 7.0 Hz, 1 H), 4.57 (dd, *J* = 6.5, 2.5 Hz, 1 H), 4.87 (dd, *J* = 15.5, 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers) δ 11.4 (q), 13.6 (q), 13.8 (q), 13.96 (q), 14.04 (q), 14.1 (q), 27.0 (t), 30.2 (t), 45.6 (t), 47.2 (t), 55.8 (q), 62.39 (t), 62.44 (t), 62.5 (t), 76.2 (s), 76.9 (s), 80.6 (d), 82.4 (d), 96.1 (t), 96.2 (t), 158.2 (s), 161.0 (s), 161.1 (s), 161.5 (s), 166.1 (s), 167.6 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{24}NO_7S$ $(M + H)^+$ 350.1268, found 350.1267.

Ethyl (2*R,3*S**)-3-(Methoxymethoxy)-1-[(methylcarbamoyl)carbonyl]-2-(methylsulfanyl)pyrrolidine-2-carboxylate (37)**.



34 **35** **36** **37**

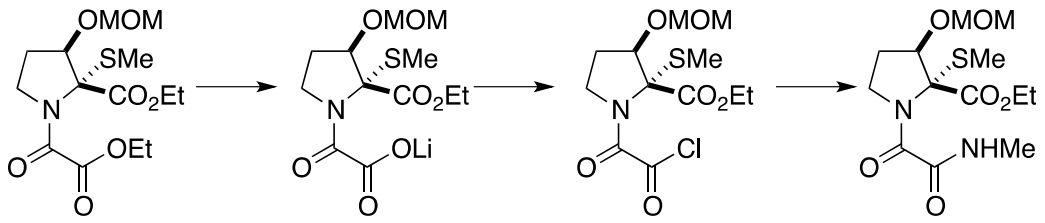
$LiOH.H_2O$ (56.5 mg, 1.35 mmol) was added to a stirred and cooled (0 °C) solution of **34** (427 mg, 1.223 mmol) in a mixture of THF (9.7 mL) and water (3.2 mL), and stirring was continued for 30 min, during which the reaction was monitored by TLC (silica, 1:1 EtOAc-hexane; the TLC plates were only partially developed so that several could be run at intervals during the 30-min reaction time). At the end of the reaction, the solvent was evaporated under water pump vacuum and and the residue was kept under oil pump vacuum for at least 1 h, to obtain the pure (^{1}H NMR) mono lithium salt **35**, which was used directly for the next step. Compound **35** had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, J = 7.1 Hz, 3 H), 2.22 (s, 3 H), 2.28 (dt, J = 7.8, 7.0 Hz, 2 H), 3.40 (s, 3 H), 4.15–4.36 (m, 4 H), 4.54 (t, J = 6.9 Hz, 1 H), 4.69 (d, J = 6.9 Hz, 1 H), 4.75 (d, J = 6.9 Hz, 1 H).

Anhydrous THF (13 mL) and DMF (8.6 μL) were added to salt **35** (Ar atmosphere) and the stirred solution was cooled to 0 °C. Oxalyl chloride (207 μL, 2.45 mmol) was added dropwise over 5 min and stirring was continued for 30 min. The ice bath was removed and stirring was continued for 20 min. The solvent and excess of oxalyl chloride were removed under water pump vacuum (protection from moisture) to give **36** as an oil.

The oil was dissolved in THF (16.2 mL) and the stirred solution was cooled to –78 °C. Methylamine (2 M in THF, 616 μL, 1.2 mmol) was added dropwise, and the reaction was monitored by TLC (silica, 1:1 EtOAc-hexane). After 10 min, another portion of methylamine solution (200 μL, 0.4 mmol) was added. Stirring was continued for another 10 min (TLC control), more methylamine solution (100 μL, 0.2 mmol) was added and the reaction flask was immediately connected via a drying tube packed with Drierite to a water pump so as to remove the $MeNH_2$ at –78 °C. After 5 min the cold bath was removed and the water pump vacuum was maintained for 10 min. A portion of flash chromatography silica gel (400 mg) was added and the solvents were evaporated on a rotary evaporator at room temperature. Flash chromatography of the residue over silica gel (2.2 × 25 cm), using EtOAc, gave **37** (300 mg, 73.4% over three steps) as yellowish oil: FTIR ($CDCl_3$, cast) 3350, 2979, 1743, 1401 cm^{-1}; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.30 (t, J = 7.1 Hz, 3 H), 2.19 (s, 3 H), 2.23–2.35 (m, 2 H), 2.85 (d, J = 5.2 Hz, 3 H), 3.39 (s, 3 H), 4.19–4.25 (m, 2 H), 4.27–4.35 (m, 2 H), 4.52 (dd, J = 8.4, 6.6 Hz, 1 H), 4.68 (d, J = 6.9 Hz, 1 H), 4.73 (d, J = 6.8 Hz, 1 H), 7.38 (s, 1 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 14.2 (q), 14.2 (q), 26.1 (q), 30.8 (t), 47.6 (t), 56.2 (q), 62.7 (t), 79.3 (t), 81.9 (d), 96.6 (s), 159.3 (s), 160.5 (s), 168.8

(s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{22}N_2NaO_6S$ $(M + Na)^+$ 357.1091, found 357.1095.

Ethyl (2*R,3*R**)-3-(Methoxymethoxy)-1-[(methylcarbamoyl)carbonyl]-2-(methylsulfanyl)pyrrolidine-2-carboxylate (37a)**.



34a **35a** **36a** **37a**

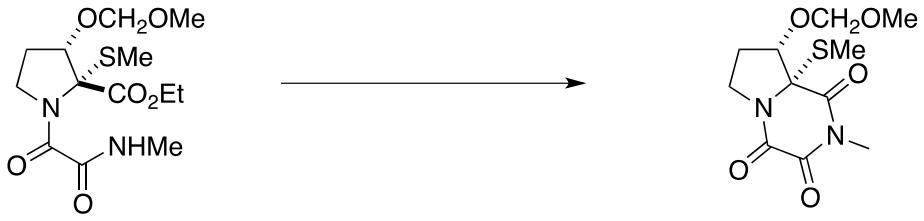
$LiOH.H_2O$ was added to a stirred and cooled (0 °C) solution of **34a** (75.2 mg, 0.217 mmol) in a mixture of THF (2.3 mL) and water (0.8 mL) and stirring was continued for 30 min during which the reaction was monitored by TLC (silica, 1:1 EtOAc-hexane; the TLC plates were only partially developed so that several could be run at intervals during the 30-min reaction time). At the end of the reaction, the solvent was evaporated under water pump vacuum and and the residue was kept under oil pump vacuum for at least 1 h, to obtain the mono lithium salt **35a**, which was used directly for the next step.

Anhydrous THF (2.3 mL) and DMF (1.5 μL) were added to salt **35a** (Ar atmosphere) and the stirred solution was cooled to 0 °C. Oxalyl chloride (37 μL, 0.433 mmol) was added dropwise over 1 min and stirring was continued for 30 min. The ice bath was removed and stirring was continued for 10 min. The solvent and excess of oxalyl chloride were removed under water pump vacuum (protection from moisture) to give **36a** as an oil.

The oil was dissolved in THF (3 mL) and the stirred solution was cooled to –30 °C. Methylamine (2 M in THF, 184 μL, 0.36 mmol) was added dropwise, and the reaction was monitored by TLC (silica, 1:1 EtOAc-hexane). After 10 min, another portion of methylamine solution (100 μL, 0.2 mmol) was added. Stirring was continued for another 10 min and the reaction flask was connected via a drying tube packed with Drierite to a water pump so as to remove the $MeNH_2$ at –30 °C. After 5 min the cold bath was removed and the water pump

vacuum was maintained for 10 min. A portion of flash chromatography silica gel (200 mg) was added and the solvents were evaporated on a rotary evaporator at room temperature. Flash chromatography of the residue over silica gel (0.5 × 12 cm), using EtOAc, gave **37a** (46 mg, 64% over three steps) as a yellowish oil: FTIR ($CDCl_3$, cast) 3346, 2981, 1744, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 2.10 (s, 3 H), 2.16–2.29 (m, 2 H), 2.86 (d, *J* = 5.1 Hz, 3 H), 3.38 (s, 3 H), 3.89 (ddd, *J* = 12.3, 9.9, 7.0 Hz, 1 H), 4.25 (dd, *J* = 7.1, 2.8 Hz, 2 H), 4.48–4.54 (m, 1 H), 4.57 (dd, *J* = 8.8, 6.8 Hz, 1 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 4.92 (d, *J* = 6.7 Hz, 1 H), 7.40 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1 (q), 14.3 (q), 26.1 (q), 30.6 (t), 48.8 (t), 55.9 (q), 62.4 (t), 78.1 (t), 81.3 (d), 96.3 (s), 159.2 (s), 160.4 (s), 166.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{22}N_2NaO_6S$ $(M + Na)^+$ 357.1091, found 357.1088.

(8*S,8a*R**)-8-(Methoxymethoxy)-2-methyl-8a-(methylthio)tetrahydropyrrolo-[1,2-*a*]pyrazine-1,3,4(2*H*)-trione (38)**.

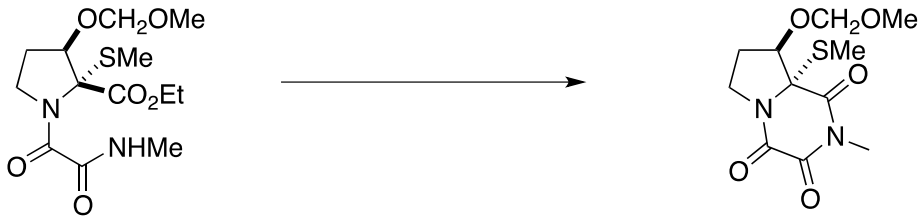


37 **38**

Et_3N (187 μL, 1.347 mmol) was added to a stirred solution of **37** (300 mg, 0.898 mmol) in MeOH (22.5 mL) at room temp. The reaction flask was lowered into an oil bath set at 45 °C and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 18 cm), using 2:1 EtOAc-hexane, gave **38** (236 mg, 91%) as a white solid: 140–141 °C; FTIR ($CDCl_3$, cast) 3412, 2957, 1698, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.04 (s, 3 H), 2.27–2.36 (m, 1 H), 2.38–2.51 (m, 1 H), 3.28 (s, 3 H), 3.42 (s, 3 H), 3.69–3.75 (m, 2 H), 4.60–4.66 (m, 1 H), 4.68 (d, *J* = 6.7 Hz, 1 H), 5.03 (d, *J* = 6.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.2 (q), 27.2 (t), 27.6 (q), 41.7 (t), 56.1 (q), 72.6 (t), 79.5 (d), 96.6 (s), 152.3 (s), 157.2 (s), 167.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{16}N_2NaO_5S$ $(M + Na)^+$ 311.0672, found 311.0675. For X-ray analysis a sample was crystallized from MeOH-Et_2O-

hexane. The material was dissolved in refluxing Et_2O-MeOH, then hexane was added and the mixture was allowed to cool slowly by keeping it in a Dewar vessel initially filled with hot water.

(8*R,8a*R**)-8-(Methoxymethoxy)-2-methyl-8a-(methylthio)tetrahydropyrrolo[1,2-*a*]pyrazine-1,3,4-trione (38a)**.



37a **38a**

Et_3N (5.1 mL, 0.037 mmol) was added to a solution of **37a** (11.2 mg, 0.0335 mmol) in MeOH (0.6 mL) at room temp and stirring was continued for 4 d. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 10 cm), using 1:1 EtOAc-hexane, gave **38a** [6.2 mg, 64% or ca 100% corrected for recovered **37a** (4 mg)]: FTIR ($CDCl_3$, cast) 3422, 2957, 1696, 1414 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 2.15 (s, 3 H), 2.19 (ddd, *J* = 8.5, 2.1, 0.7 Hz, 1 H), 2.54–2.65 (m, 1 H), 3.31 (s, 3 H), 3.37 (s, 3 H), 3.79 (ddd, *J* = 12.4, 10.2, 2.1 Hz, 1 H), 4.05 (dt, *J* = 12.4, 8.8 Hz, 1 H), 4.58 (d, *J* = 4.0 Hz, 1 H), 4.60 (d, *J* = 7.0 Hz, 1 H), 4.72 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 13.9 (q), 27.1 (t), 27.6 (q), 44.7 (t), 56.4 (q), 75.3 (t), 79.9 (d), 96.3 (s), 152.2 (s), 157.3 (s), 165.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{16}N_2NaO_5S$ $(M + Na)^+$ 311.0672, found 311.0677.

(8*S,8a*R**)-8-Hydroxy-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,3,4-trione (39)**.

38 **39**

Concentrated hydrochloric acid (87 μL) was added to a stirred solution of **38** (30 mg) in MeOH (3 mL) and the reaction flask was lowered into an oil bath set at 60 °C. Stirring was continued for 1 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (0.5 × 10 cm), using 40:1 CH_2Cl_2-MeOH, gave **39** (24 mg, 94.5%) as a colorless gum (which solidified in a freezer): FTIR (CD_3OD, cast) 3426, 2956, 1693, 1305 cm^{-1}; ^1H NMR (CD_3OD, 700 MHz) δ 2.04 (s, 3 H), 2.21 (dddd, *J* = 12.6, 10.5, 9.9, 9.2 Hz, 1 H), 2.35 (dddd, *J* = 12.6, 8.6, 7.7, 2.6 Hz, 1 H), 3.25 (s, 3 H), 3.63 (dddd, *J* = 12.6, 10.6, 2.7, 0.5 Hz, 1 H), 3.70 (ddd, *J* = 12.6, 9.3, 8.7 Hz, 1 H), 4.76 (dd, *J* = 10.0, 7.7 Hz, 1 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 12.5 (q), 27.4 (q), 28.7 (t), 42.7 (t), 74.4 (s), 76.1 (d), 154.6 (s), 159.2 (s), 169.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{12}N_2NaO_4S$ $(M + Na)^+$ 267.0410, found 267.0414.

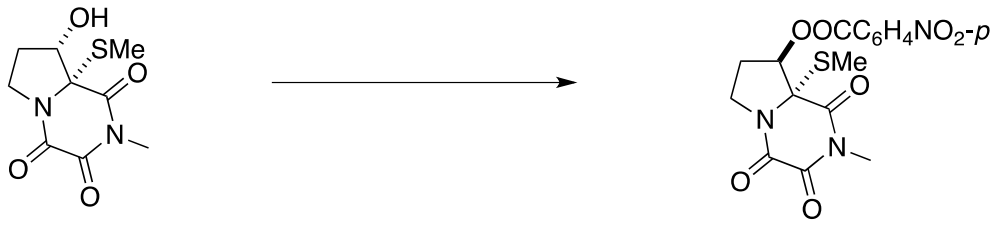
(8*R,8a*R**)-8-Hydroxy-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,3,4-trione (14)**.

38a **14**

Concentrated hydrochloric acid (18 μL) was added to a stirred solution of **38a** (6 mg) in MeOH (0.6 mL), and the reaction flask was lowered into an oil bath set at 60 °C. Stirring was continued for 40 min and the solvent was then evaporated. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 7 cm), using 40:1 CH_2Cl_2-MeOH, gave **14**

(4.3 mg, 85%) as a colorless gum (which solidified in a freezer): FTIR (CD_3OD, cast) 3426, 2956, 1693, 1305 cm^{-1}; ^1H NMR (CD_3OD, 700 MHz) δ 2.05 (dddd, *J* = 13.7, 8.6, 2.2, 0.6 Hz, 1 H), 2.16 (s, 3 H), 2.64 (dddd, *J* = 13.7, 10.4, 9.1, 4.4 Hz, 1 H), 3.27 (s, 3 H), 3.75 (ddd, *J* = 12.5, 10.4, 2.2 Hz, 1 H), 4.03 (dt, *J* = 12.5, 8.9 Hz, 1 H), 4.66 (d, *J* = 4.2 Hz, 1 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 13.5 (q), 27.5 (q), 30.0 (t), 45.5 (t), 76.2 (s), 77.3 (d), 153.1 (s), 158.8 (s), 169.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{12}N_2NaO_4S$ $(M + Na)^+$ 267.0410, found 267.0409.

(8*S,8a*R**)-2-Methyl-8a-(methylsulfanyl)-1,3,4-trioxooctahydropyrrolo[1,2-*a*]piperazin-8-yl 4-nitrobenzoate (40)**.



39 **40**

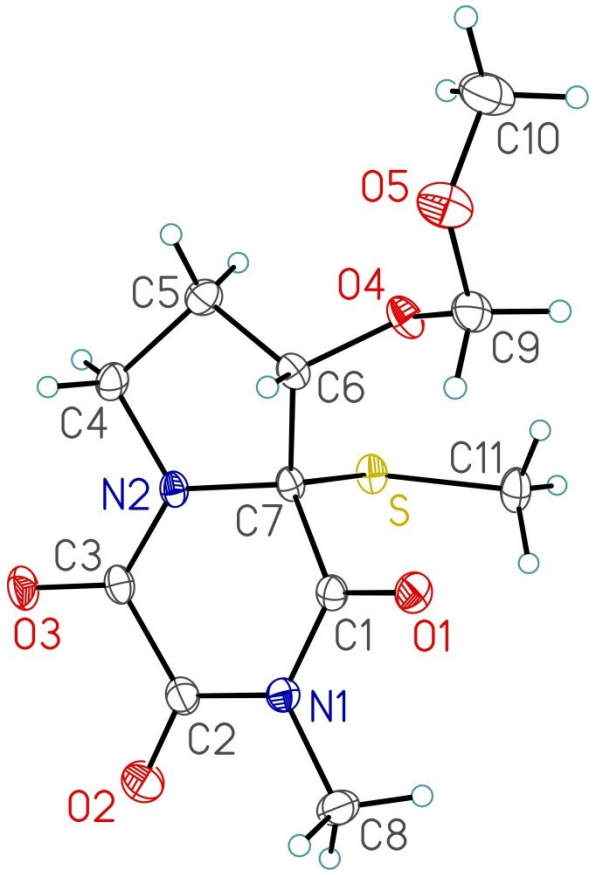
Alcohol **39** (24 mg, 0.098 mmol), Ph_3P (129 mg, 0.49 mmol) and *p*-$O_2NC_6H_4CO_2H$ (74 mg, 0.44 mmol) were tipped into a round bottomed flask containing a magnetic stirring bar. The flask was then closed by a septum and dry THF (2.5 mL) was injected. The flask was immediately lowered into a cold bath (–78 °C) and the reaction mixture was stirred for 10 min. Diisopropyl azodicarboxylate (97 μL, 0.49 mmol) was injected over about 1 min. The cold bath was removed and stirring was continued for 24 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 17 cm), using 100:1 to 40:1 CH_2Cl_2-acetone, gave **40** (31 mg, 79%) as a solid: mp 255–256 °C; FTIR (CD_3OD, cast) 3376, 2962, 1694, 1361 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 2.24 (s, 3 H), 2.33 (dddd, *J* = 14.9, 8.6, 2.5, 0.7 Hz, 1 H), 2.87–2.98 (m, 1 H), 3.26 (s, 3 H), 3.92 (ddd, *J* = 12.6, 10.3, 2.4 Hz, 1 H), 4.10 (dt, *J* = 12.6, 8.8 Hz, 1 H), 5.99 (d, *J* = 4.4 Hz, 1 H), 8.03 (d, *J* = 9.0 Hz, 2 H), 8.25 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 14.6 (q), 27.6 (q), 27.8 (t), 44.7 (t), 74.3 (s), 77.8 (d), 124.0 (d), 131.2 (d), 134.7 (s), 151.3 (s), 152.1 (s), 157.3 (s), 163.4 (s), 164.5 (s); exact mass (electrospray) *m*/*z* calcd

for $C_{16}H_{15}N_3NaO_7S$ $(M + Na)^+$ 416.0523, found 416.0524. For X-ray analysis a sample was crystallized from MeOH-hexane.

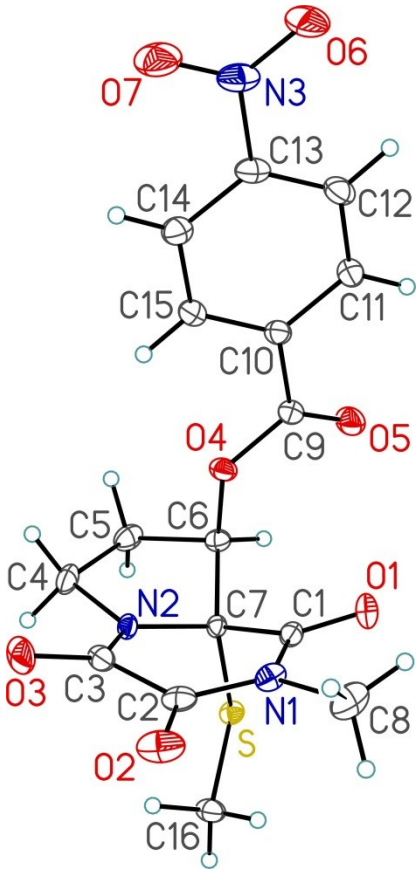
(8*R,8a*R**)-8-Hydroxy-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,3,4-trione (14)**.

40 **14**

A solution of **40** (16 mg, 0.041 mmol) and NaN_3[20] (11 mg, 0.163 mmol) in a mixture of dry MeOH (0.5 mL) and THF (0.25 mL) was stirred overnight at 50 °C (Ar atmosphere). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 10 cm), using 40:1 CH_2Cl_2-MeOH, gave **14** [7.6 mg, 76% or 87% corrected for recovered **40** (2 mg)] as a oil that was spectroscopically identical to material made from **38a**.



ORTEP diagram of compound **38**. Thermal ellipsoids of non-hydrogen atoms are illustrated at the 30% probability level. CCDC 1480572



ORTEP diagram of compound **40**. Thermal ellipsoids of non-hydrogen atoms are illustrated at the 30% probability level. CCDC 1480573