Preparation of Novel Bridged Bicyclic Thiomorpholines as Potentially Useful Building Blocks in Medicinal Chemistry

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Abstract: Thiomorpholine and thiomorpholine 1,1-dioxide are important building blocks in medicinal chemistry research, and some analogues containing these moieties have entered human clinical trials. Analogues containing bridged bicyclic thiomorpholines have also shown interesting biological profiles. 3-Thia-6-azabicyclo[3.1.1]heptane, 3-thia-8-azabicyclo[3.2.1]octane, and their corresponding 1,1-dioxide counterparts were prepared as novel bicyclic thiomorpholine building blocks. Each heterocycle was synthesized from an inexpensive starting material by straightforward chemistry.

Key words: stereoselective synthesis, heterocycles, bicyclic compounds, pyrroles, hydrogenation

Thiomorpholine (TM) and thiomorpholine 1,1-dioxide (TMD) are important building blocks in drug discovery research. Numerous biologically active analogues containing a TM or TMD ring have been described in the medicinal chemistry literature.[1] Of these, artemisone[2] and sutezolid[3] are currently undergoing human clinical trials for the treatment of malaria and tuberculosis, respectively (Figure 1).

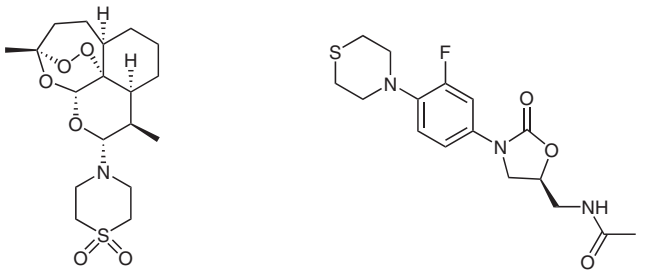

Figure 1 Drugs containing a thiomorpholine ring that are undergoing clinical trials in humans

Biologically active analogues incorporating a bridged bicyclic TM or TMD ring have also been described in the medicinal chemistry literature and patent literature; some recent examples are shown in Figure 2.[4] In general, rigid bicycles are important ring systems in medicinal chemistry because, in many instances, analogues containing a rigid bicyclic system show superior biological activity and/or metabolic stability in comparison with the corresponding monocyclic analogues.[5]

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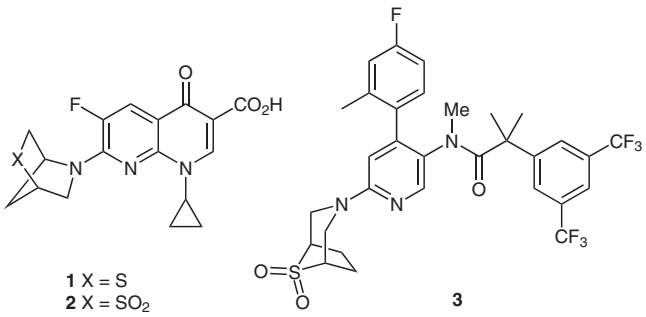


Figure 2 Biologically active compounds containing bridged bicyclic thiomorpholine rings

Of the parent bridged bicyclic TM and TMD ring systems shown in Figure 3, syntheses of **5**,[6] **6**[4a] and **7**,[7] and an analogue incorporating **8**[4b] have previously been reported. As part of our continued interest in preparing new bicyclic heterocycles as useful building blocks in medicinal chemistry,[8] we became interested in preparing 3-thia-6-azabicyclo[3.1.1]heptane (**9**), 3-thia-8-azabicyclo[3.2.1]octane (**11**), and their corresponding *S*,*S*-dioxides (**10** and **12**, respectively). Compared with building blocks **5** and **6**, an attractive feature of compounds **9**–**12** is that they all have *meso* stereochemistry, so there is no need to separate and test individual enantiomers. Below, we describe practical syntheses of heterocycles **9**–**12** as their tosylate salts, which, to the best of our knowledge, are the first syntheses of these potentially useful medicinal chemistry building blocks.

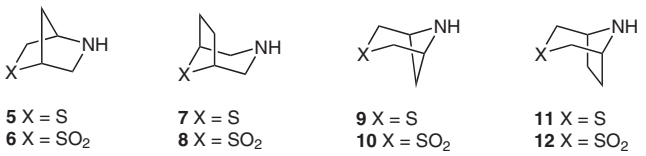
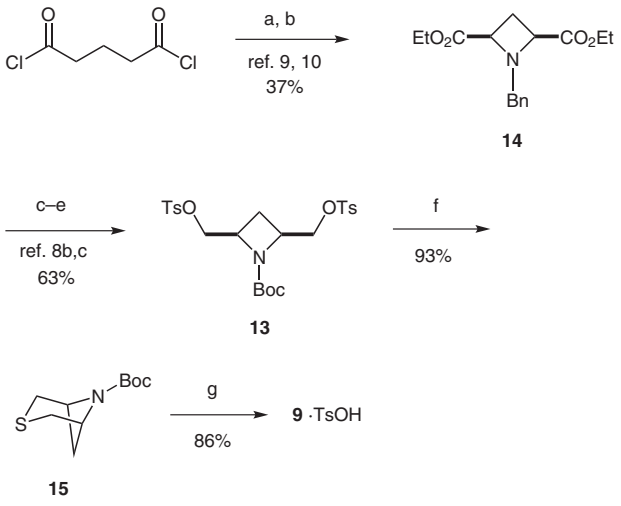


Figure 3 Synthetic targets **9**–**12**, together with various bridged bicyclic thiomorpholines and thiomorpholine *S*,*S*-dioxides used in medicinal chemistry

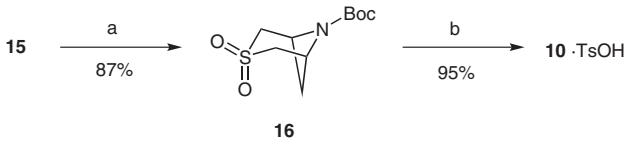
We began our synthesis of 3-thia-6-azabicyclo[3.1.1]heptane hydrotosylate (**9**·TsOH) from the known bistosylate **13**[8c] (Scheme 1). Compound **13** can be obtained in three steps (63% overall yield) from the azetidine diester **14**.[8b,c] Compound **14** can, in turn, be prepared in two steps and 37% yield from inexpensive glutaryl chloride.[9,10] Treatment of bistosylate **13** with sodium sulfide effected ring closure to give the bicyclic thiomorpholine **15**. The struc-

ture of **15** was confirmed by ^{1}H NMR spectroscopy and LC/MS. Cleavage of the *tert*-butoxycarbonyl group in **15** with 4-toluenesulfonic acid gave the bridged thiomorpholine **9**·TsOH directly.



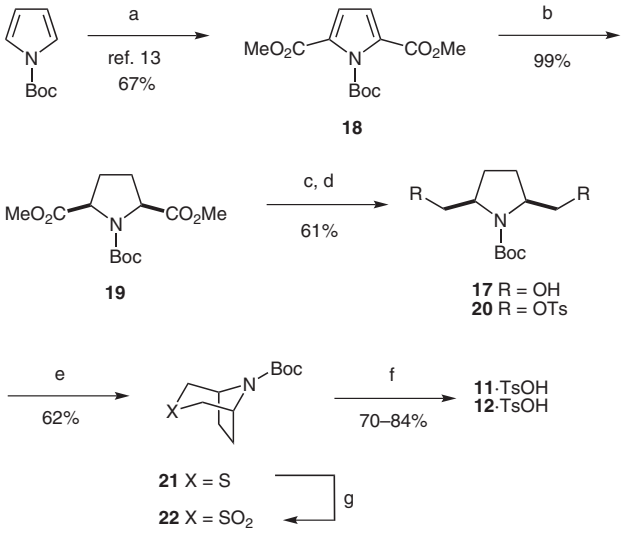
Scheme 1 *Reagents and conditions:* (a) Br_2, *hv*, 80 °C, 6 h; EtOH, 0 °C to r.t., 24 h; (b) $BnNH_2$ (3.0 equiv), DMF, 80 °C, 10 h; (c) H_2 (60 psi), 20% $Pd(OH)_2$/C, $(Boc)_2O$ (1.2 equiv), EtOH, 24 h; (d) $CaCl_2$ (3.0 equiv), $NaBH_4$ (5.0 equiv), EtOH–MeOH (9:1), r.t., 5 h; (e) Ts_2O, py, 0 °C, 4 h; (f) $Na_2S·9H_2O$ (3.0 equiv), EtOH–H_2O (1:1), 90 °C, 2 h; (g) TsOH·H_2O (1.2 equiv), EtOH, 85 °C, 1 h.

Oxidation of sulfide **15** with tetrapropylammonium perruthenate[11] gave an 87% yield of sulfone **16** (Scheme 2), which on treatment with 4-toluenesulfonic acid in ethanol gave **10**·TsOH. The spectral properties of **10**·TsOH were in complete agreement with the proposed structure.



Scheme 2 *Reagents and conditions*: (a) $Pr_4N^+RuO_4^-$ (0.06 equiv), NMO (3.0 equiv), powdered 4 Å MS, MeCN, 40 °C, 3 h; (b) TsOH·H_2O (1.2 equiv), EtOH, 85 °C, 1 h.

Our next synthetic targets were 3-thia-8-azabicyclo[3.2.1]octane hydrotosylate (**11**·TsOH) and its corresponding *S,S*-dioxide (**12**·TsOH). We conceived a route in which the thiomorpholine ring of **11** would be constructed from the known bis(hydroxymethyl)pyrrolidine **17**[12] by a strategy similar to that used for the construction of thiomorpholine **9** (Scheme 3). Before addressing this key reaction, we focused on the synthesis of diol **17**. Under the conditions developed by Donohoe and co-workers,[13] biscarbomethoxylation of commercial *N*-(*tert*-butoxycarbonyl)pyrrole smoothly gave diester **18**.[14] Catalytic hydrogenation (5% Rh/Al_2O_3, AcOH, 60 psi, 8 h) of pyrrole **18** gave pyrrolidine **19** as a single stereoisomer in 99% yield. The use of a conventional low-pressure Parr hydrogenation apparatus with rhodium/alumina as the catalyst was crucial to the success of this transformation. Other catalysts, such as platinum[15] or palladium on carbon, gave no reaction, whereas rhodium/carbon led only to partial reduction. Diol **17** was obtained in 86% yield by treatment of the diester **19** with calcium borohydride. Under these conditions, no reduction of the *tert*-butoxycarbonyl group occurred. Lithium aluminum hydride has also been shown to convert **19** into **17** (84%),[16] but in our hands, significant cleavage of the *tert*-butoxycarbonyl group also occurred.



Scheme 3 *Reagents and conditions*: (a) LTMP (2.5 equiv), THF, –78 °C, 3 h; $ClCO_2Me$ (3.0 equiv), –78 °C, 30 min.; (b) H_2 (60 psi), 5% Rh/Al_2O_3, AcOH, r.t., 8 h; (c) $CaCl_2$ (3.0 equiv), $NaBH_4$ (5.0 equiv), EtOH–MeOH (9:1), r.t., 5 h; (d) Ts_2O, py, 0 °C, 4 h; (e) $Na_2S·9H_2O$ (3.0 equiv), EtOH–H_2O (1:1), 90 °C, 2 h; (f) TsOH·H_2O (1.2 equiv), EtOH, 85 °C, 1 h; (g) $Pr_4N^+RuO_4^-$ (0.06 equiv), NMO (3.0 equiv), powdered 4 Å MS, MeCN, 40 °C, 3 h (93%).

Having prepared **17**, we focused our efforts on the formation of the thiomorpholine ring. Toward this end, diol **17** was transformed in 71% yield into the corresponding bistosylate **20**. Treatment of **20** with sodium sulfide gave a 62% yield of the bicyclic thiomorpholine **21**. Cleavage of the *tert*-butoxycarbonyl group with 4-toluenesulfonic acid gave **11**·TsOH, the spectral properties of which were in complete agreement with proposed structure. Oxidation of sulfide **21** with tetrapropylammonium perruthenate,[11] followed by treatment with 4-toluenesulfonic acid, gave the corresponding sulfone **12**·TsOH.

In summary, we have developed concise syntheses of 3-thia-6-azabicyclo[3.1.1]heptane hydrotosylate (**9**·TsOH), 3-thia-8-azabicyclo[3.1.1]octane hydrotosylate (**11**·TsOH), and the corresponding sulfones **10**·TsOH and **12**·TsOH. Building block **9**·TsOH was prepared in seven steps and 18% overall yield, **10**·TsOH was prepared in eight steps and 17% overall yield, **11**·TsOH was prepared in six steps and 21% overall yield, and **12**·TsOH was prepared in seven steps and 16% overall yield. Each synthesis began with inexpensive starting materials and involved straightforward chemistry. The achiral nature of the bicyclic thio-

morpholines **9**–**12** and their structural similarity to thiomorpholine and thiomorpholine 1,1-dioxide suggest that these new isosteres might be useful building blocks in medicinal chemistry research.

^{1}H and ^{13}C NMR spectra were recorded at r.t. on a Bruker Avance 400 spectrometer with a 5-mm DUL probe. Chemical shifts are reported in ppm (δ) relative to TMS (δ = 0.0 ppm), and are referenced to residual solvent resonances ($CDCl_3$, δ = 7.27 or 77.00 ppm; CD_3OD, δ = 3.31 or 49.15 ppm; DMSO-d_6, δ = 2.50 or 39.51 ppm). Low-resolution ESI mass spectra were recorded on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph–mass spectrometer. IR spectra were recorded on a Bio-Rad Excalibur FTS 3000MX with a diamond anvil cell. Combustion analyses were performed by Robertson Microlit, Ledgewood, NJ. Melting points were recorded on a Stanford Research Systems OptiMelt apparatus and are uncorrected. Reactions were monitored by TLC on Analtech silica gel GF 250 micron plates visualized by staining with ninhydrin or $KMnO_4$ dip stains, or by reversed-phase HPLC on an Agilent 1100 chromatograph equipped with a an Agilent XDB-C18 (1.8 μm, 4.6 × 50 mm) column and diode array detector tuned to 210–254 nm. Flash chromatography was performed in a glass column on SiliCycle silica gel (230–400 mesh). All reagents were purchased from the Aldrich Chemical Co. and used without further purification. All solvents were of HPLC grade unless otherwise stated; anhydrous solvents were purchased from Aldrich Chemical Co. and were used as supplied.

tert-Butyl 3-Thia-6-azabicyclo[3.1.1]heptane-6-carboxylate (15)
$Na_2S{\cdot}9\ H_2O$ (5.76 g, 24.0 mmol) was added to a stirred suspension of azetidine **13**[8b,c] (4.2 g, 8.0 mmol) in 1:1 EtOH–H_2O (64 mL), and the mixture was heated to 90 °C. After 20 min at 90 °C, all the solids dissolved. After 2 h, the mixture was cooled to r.t., the solvent was removed in vacuo, and the residue was treated with H_2O (30 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (20 mL) and the organic layers were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. This crude product was purified by flash chromatography [silica gel, hexanes–EtOAc (90:10)] to give a white solid; yield: 1.6 g (93%); mp 54–56 °C; R_f = 0.60 (hexanes–EtOAc, 75:25).

IR (neat): 3000, 2960, 1681, 1433, 1374, 1175, 1147 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 4.27 (br d, J = 4.85 Hz, 2 H), 3.51–3.39 (br m, 2 H), 2.84 (br t, J = 9.60 Hz, 2 H), 2.63 (ddd, J = 9.35, 7.07, 7.07 Hz, 1 H), 1.70 (d, J = 9.35 Hz, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ (two rotamers; 1:1) = 158.5, 81.50, 61.20, 60.21, 29.64, 29.30, 28.84, 28.59.

MS (ESI+): m/z = 115.9 [M – Boc + 2H]$^+$

Anal. Calcd for $C_{10}H_{17}NO_2S$ (215.27): C, 55.79; H, 7.90; N, 6.51. Found: C, 56.04; H, 8.13; N, 6.52.

3-Thia-6-azabicyclo[3.1.1]heptane Hydrotosylate (9·TsOH)
$TsOH{\cdot}H_2O$ (530 mg, 2.8 mmol) was added to a stirred solution of **15** (500 mg, 2.3 mmol) in absolute EtOH (18 mL), and the mixture was heated at 85 °C for 1 h. The mixture was then cooled to r.t., and the solvent was removed in vacuo. The remaining oil was triturated with THF (5 mL) for 3 h, which caused a white precipitate to form. The precipitate was collected by filtration, washed with THF (2 mL) and Et_2O (10 mL), and dried in vacuo to give a white solid; yield: 575 mg (86%); mp 155–157 °C.

IR (neat): 2960, 1608, 1222, 1165, 1123 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.30 (br s, 1 H), 7.98 (br s, 1 H), 7.50 (d, J = 8.08 Hz, 2 H), 7.13 (d, J = 7.58 Hz, 2 H), 4.49–4.41 (m, 2 H), 3.45 (d, J = 12.13 Hz, 2 H), 3.16 (dd, J = 13.14, 3.03 Hz, 2 H), 2.81 (dt, J = 10.86, 7.07 Hz, 1 H), 2.29 (s, 3 H), 2.13 (dd, J = 10.62, 5.06 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.6, 137.7, 128.1, 125.5, 58.65, 29.42, 26.54, 20.80.

MS (ESI+): m/z = 115.9 [M + H]$^+$.

Anal. Calcd for $C_{12}H_{17}NO_3S_2$ (287.3): C, 50.16; H, 5.96; N, 4.88. Found: C, 50.13; H, 6.08; N, 4.82.

tert-Butyl 3-Thia-6-azabicyclo[3.1.1]heptane-6-carboxylate 3,3-Dioxide (16)
$Pr_4N^+RuO_4^-$ (33 mg, 0.09 mmol) was added to a stirred mixture of ester **15** (400 mg, 1.9 mmol), NMO (650 mg, 5.6 mmol), and powdered 4 Å MS (200 mg) in MeCN (10 mL), and the resulting mixture was warmed to 40 °C for 3 h. The solvent was removed in vacuo and the residue was passed through a short plug of silica gel with elution by hexanes–EtOAc (75:25) to give a white solid; yield: 400 mg (87%); mp 120–122 °C; R_f = 0.18 (hexanes–EtOAc, 75:25).

IR (neat): 2986, 2939, 1707, 1370, 1350, 1310, 1280, 1260, 1147, 1116 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 4.41 (br d, J = 6.82 Hz, 2 H), 4.12–3.85 (m, 2 H), 3.55 (br d, J = 13.13 Hz, 2 H), 2.84–2.76 (m, 1 H), 2.08 (d, J = 10.61 Hz, 1 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ (two rotamers; 1:1) = 156.2, 82.93, 61.38, 60.45, 58.12, 57.30, 28.71, 27.08.

MS (ESI+): m/z = 270.0 [M + Na]$^+$.

Anal. Calcd for $C_{10}H_{17}NO_4S$ (247.3): C, 48.57; H, 6.93; N, 5.67. Found: C, 48.56; H, 6.87; N, 5.68.

3-Thia-6-azabicyclo[3.1.1]heptane 3,3-Dioxide Hydrotosylate (10·TsOH)
$TsOH{\cdot}H_2O$ (230 mg, 1.2 mmol) was added to a stirred solution of ester dioxide **16** (250 mg, 1.0 mmol) in absolute EtOH (15 mL), and the mixture was heated at 85 °C for 1 h. The mixture was then cooled to r.t., and the solvent was removed in vacuo. The remaining solid was triturated with THF (3 mL) for 3 h to give a fine precipitate. The precipitate was collected by filtration and washed with THF (2 mL) and Et_2O (5 mL). The solid was dried in vacuo to give a white solid; yield: 307 mg (95%); mp 177–178 °C.

IR (neat): 2986, 2939, 1627, 1400, 1352, 1306, 1280, 1256, 1217, 1147, 1116 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.75–8.75 (br s, 2 H), 7.48 (d, J = 8.08 Hz, 2 H), 7.12 (d, J = 7.83 Hz, 2 H), 4.49 (br d, J = 6.31 Hz, 2 H), 3.99–3.87 (m, 4 H), 2.96 (dt, J = 11.87, 6.82 Hz, 1 H), 2.41 (d, J = 11.62 Hz, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.6, 137.7, 128.1, 125.5, 57.45, 56.58, 25.67, 20.80.

MS (ESI+): m/z = 148.0 [M + H]$^+$.

Anal. Calcd for $C_{12}H_{17}NO_5S_2$ (319.3): C, 45.13; H, 5.37; N, 4.39. Found: C, 45.15; H, 5.38; N, 4.34.

1-_tert_-Butyl 2,5-Dimethyl 1_H_-pyrrole-1,2,5-tricarboxylate (18)
This compound was prepared by a slight modification of an established procedure.[13]

A 2.5 M solution of BuLi in hexanes (58.0 mL) was added dropwise from a syringe to a stirred solution of 2,2,6,6-tetramethylpiperidine (24.4 mL, 145 mmol) in anhydrous THF (180 mL) at –78 °C, and the mixture was stirred at –78 °C for 15 min. In a separate flask, *N*-(*tert*-butoxycarbonyl)pyrrole (9.63 g, 58 mmol) was dissolved in anhydrous THF (40 mL). The solution was cooled to –78 °C then slowly added through a cannula to the first solution. The resulting mixture was stirred at –78 °C for 3 h then transferred through a cannula to a solution of $ClCO_2Me$ (13.4 mL, 174 mmol) in THF (20 mL) at –78 °C, and the resulting mixture was stirred at –78 °C for 15 min. Sat. aq NH_4Cl (50 mL) was added, and the mixture was allowed to warm to r.t. Et_2O (200 mL) and H_2O (100 mL) were added,

and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL). The ethereal layers were combined, washed sequentially with 1.0 M aq HCl (2 × 50 mL) and brine (50 mL) then dried ($MgSO_4$), filtered, and concentrated in vacuo to give an orange semi-solid. This crude product was triturated with Et_2O–hexanes (80:20; 30 mL) to give a white precipitate. The precipitate was collected by filtration, washed with cold (0 °C) Et_2O–hexanes (80:20; 30 mL), and dried in vacuo to give a white solid; yield: 11.0 g (67%).

The spectral properties of **18** were identical in all respects to those reported in the literature.[13b]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 2 H), 3.87 (s, 6 H), 1.67 (s, 9 H).

1-*tert*-Butyl 2,5-Dimethyl (2*R,5*S**)-Pyrrolidine-1,2,5-tricarboxylate (19)**

A 500-mL Parr bottle was charged with 5% Rh/Al_2O_3 (0.500 g, 0.24 mmol). The bottle was flushed with argon, and a solution of tricarboxylate **18** (5.3 g, 19 mmol) in glacial AcOH (250 mL) was added. The mixture was hydrogenated at 60 psi for 8 h then filtered through Celite. The catalyst was washed with AcOH (100 mL) and the collected filtrate was concentrated in vacuo to give a white solid; yield: 5.35 g (99%); mp 69–71 °C; R_f = 0.38 (hexanes–EtOAc, 1:1).

The spectral properties of **19** were identical in all respects to those reported in the literature.[16,17]

^{1}H NMR (400 MHz, $CDCl_3$): δ (two rotamers; 1:1) = 4.45–4.35 (m, 1 H), 4.35–4.20 (m, 1 H), 3.76 (s, 6 H), 2.30–2.05 (m, 4 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (two rotamers; 1:1) = 172.5, 172.2, 153.5, 80.79, 60.00, 59.48, 52.20, 52.04, 29.50, 28.73, 28.16.

***tert*-Butyl (2*R**,5*S**)-2,5-Bis(hydroxymethyl)pyrrolidine-1-carboxylate (17)**

$CaCl_2$ (3.0 g, 27 mmol) and $NaBH_4$ (2.0 g, 53 mmol) were added to a stirred solution of tricarboxylate **19** (2.6 g, 9.0 mmol) in EtOH–MeOH (9:1; 100 mL) at r.t. The $NaBH_4$ was added in 5 × 400 mg portions at 30 min intervals, and MeOH (10 mL) was added every 2 h. When the mixture had been stirred for a total of 5 h, H_2O (15 mL) was added, and the mixture was stirred for a further 15 min. The mixture was then concentrated in vacuo until ~5 mL of liquid remained. H_2O (100 mL) and EtOAc (100 mL) were added to the remaining solid mass, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the organic layers were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. The crude product was purified by flash chromatography [silica gel, hexanes–EtOAc (4:1 to 1:1)] to give a colorless oil; yield: 1.8 g (86%); R_f = 0.11 (hexanes–EtOAc, 1:1).

The spectral properties of **17** were identical in all respects to those reported in the literature.[12,16]

^{1}H NMR (400 MHz, CD_3OD): δ = 3.92–3.82 (m, 2 H), 3.70–3.50 (m, 4 H), 2.05–1.85 (m, 4 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ (two rotamers; 1:1) = 154.3, 82.58, 60.26, 59.74, 54.64, 54.26, 28.69, 28.26, 27.58.

***tert*-Butyl (2*R**,5*S**)-2,5-Bis[(tosyloxy)methyl]pyrrolidine-1-carboxylate (20)**

Ts_2O (5.3 g, 16 mmol) was added to a stirred solution of diol **17** (1.8 g, 7.8 mmol) in pyridine (25 mL) at 0 °C, and the mixture was stirred at 0 °C for 3 h. H_2O (5.0 mL) was added, and the mixture was allowed to warm to r.t. The volatiles were removed in vacuo, and the remaining oil was partitioned between H_2O (20 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL) and the organic layers were combined, washed sequentially with 1.0 M aq HCl (2 × 10 mL), sat. aq $NaHCO_3$ (20 mL), and brine (15 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. The crude product was purified by flash chromatography [silica gel, hexanes–EtOAc (70:30)] to give a white solid; yield: 3.0 g (71%); mp 82–84 °C; R_f = 0.19 hexanes–EtOAc (75:25).

IR (neat): 2985, 1695, 1396, 1173 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (two rotamers; 1:1) = 7.85–7.62 (m, 4 H), 7.42–7.31 (m, 4 H), 4.16–4.08 (m, 1 H), 4.08–3.95 (m, 4 H), 3.95–3.84 (m, 1 H), 2.47 (s, 6 H), 1.95–1.88 (m, 2 H), 1.88–1.80 (m, 2 H), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (two rotamers; 1:1) = 153.9, 144.9, 132.7, 129.9, 127.9, 80.70, 69.55, 69.33, 56.69, 28.17, 26.65, 25.45, 21.63.

MS (ESI+): *m/z* = 440.2 [M – Boc + 2 H]$^+$.

Anal. Calcd for $C_{25}H_{33}NO_8S_2$ (539.6): C, 55.64; H, 6.16; N, 2.60. Found: C, 55.54; H, 6.00; N, 2.57.

***tert*-Butyl 3-Thia-8-azabicyclo[3.2.1]octane-8-carboxylate (21)**

A solution of $Na_2S·9H_2O$ (1.67 g, 6.95 mml) in H_2O (10 mL) was added to a stirred solution of ester **20** (1.25 g, 2.32 mmol) in EtOH (10 mL). The cloudy mixture was heated under argon in an oil bath at 90 °C for 2 h. (After 45 min at 90 °C, the cloudy mixture became clear.) The mixture was then cooled to r.t., and the solvent was removed in vacuo. The remaining solid was partitioned between H_2O (15 mL) and Et_2O (25 mL). The aqueous layer was extracted with Et_2O (20 mL), and the ethereal layers were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography [silica gel, hexanes–EtOAc (90:10)] to give a white solid; yield: 330 mg (62%); mp 76–78 °C; R_f = 0.61 (hexanes–EtOAc, 75:25).

IR (neat): 2979, 1689, 1423, 1254 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 4.40–4.34 (m, 2 H), 3.15–3.05 (m, 2 H), 2.15 (br d, *J* = 12.8 Hz, 2 H), 2.11–2.03 (m, 4 H), 1.52 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ (two rotamers; 1:1) = 154.8, 81.39, 55.97, 55.14, 33.41, 32.73, 29.82, 29.18, 28.90.

MS (ESI+): *m/z* = 174.2 [M – *t*-Bu + 2H]$^+$.

Anal. Calcd for $C_{11}H_{19}NO_2S$ (229.3): C, 57.61; H, 8.35; N, 6.11. Found: C, 57.74; H, 8.07; N, 6.15.

3-Thia-8-azabicyclo[3.2.1]octane Hydrotosylate (11·TsOH)

A mixture of ester **21** (150 mg, 0.65 mmol) and $TsOH·H_2O$ (150 mg, 0.79 mmol) in EtOH (10 mL) was heated to 85 °C for 1 h. The mixture was then cooled to r.t. and the solvent was removed in vacuo to give a solid that was triturated with THF (1.5 mL) for 30 min. The resulting precipitate was collected by filtration, washed sequentially with THF (1 mL) and Et_2O (5 mL), and dried in vacuo to give a white solid; yield: 165 mg (84%); mp 185–187 °C.

IR (neat): 2952, 1221, 1167, 1124 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.00–8.55 (br s, 2 H), 7.50 (d, *J* = 7.80 Hz, 2 H), 7.13 (d, *J* = 7.80 Hz, 2 H), 4.20–4.10 (m, 2 H), 3.19 (dd, *J* = 13.8, 1.6 Hz, 2 H), 2.45 (dd, *J* = 13.8, 3.2 Hz, 2 H), 2.30 (s, 3 H), 2.01 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.3, 137.9, 128.2, 125.5, 54.29, 30.16, 26.50, 20.80.

MS (ESI+): *m/z* = 130.1 [M + H]$^+$.

Anal. Calcd for $C_{13}H_{19}NO_3S_2$ (301.3): C, 51.82; H, 6.36; N, 4.65. Found: C, 51.58; H, 6.21; N, 4.56.

***tert*-Butyl 3-Thia-8-azabicyclo[3.2.1]octane-8-carboxylate 3,3-Dioxide (22)**

Pr_4N^+ RuO_4^- (26 mg, 0.07 mmol) was added to a stirred mixture of ester **21** (260 mg, 1.13 mmol), NMO (389 mg, 3.32 mmol), and powdered 4 Å MS (160 mg) in MeCN (6.0 mL), and the resulting mixture was warmed to 40 °C for 3 h. The solvent was removed in vacuo and the residue was passed through a short plug of silica gel

with elution by hexanes–EtOAc (75:25) to give a white solid; yield: 275 mg (93%); mp 139–141 °C; R_f = 0.67 (hexanes–EtOAc, 1:1).

IR (neat): 2979, 1706, 1406, 1303, 1177, 1123 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 4.64–4.54 (m, 2 H), 3.43–3.32 (m, 2 H), 3.24 (br d, *J* = 14.2 Hz, 2 H), 2.35 (d, *J* = 8.33 Hz, 2 H), 2.20–2.05 (m, 2 H), 1.50 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ (two rotamers; 1:1) = 157.2, 81.38, 64.75, 64.40, 61.58, 28.88, 27.79, 27.43.

MS (ESI+): *m/z* = 206.2 $[M - t\text{-Bu} + 2H]^+$.

Anal. Calcd for $C_{11}H_{19}NO_4S$ (261.3): C, 50.56; H, 7.33; N, 5.36. Found: C, 50.34; H, 7.10; N, 5.30.

3-Thia-8-azabicyclo[3.2.1]octane 3,3-Dioxide Hydrotosylate (12·TsOH)

A mixture of **22** (185 mg, 0.71 mmol) and $TsOH·H_2O$ (161 mg, 0.84 mmol) in EtOH (8.0 mL) was heated to 85 °C for 1 h. The mixture was then cooled to r.t., and the solvent was removed in vacuo to afford a solid that was triturated with THF (1.0 mL) for 60 min. The resulting precipitate was collected by filtration, washed sequentially with THF (0.5 mL) and Et_2O (7 mL), and dried in vacuo to give a white solid; yield: 164 mg (70%); mp 241–242 °C.

IR (neat): 2958, 1602, 1321, 1250, 1153, 1113 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.49–9.30 (br s, 2 H), 7.50 (d, *J* = 8.08 Hz, 2 H), 7.13 (d, *J* = 7.8, 2 H), 4.49–4.39 (m, 2 H), 3.70–3.58 (m, 4 H), 2.40–2.30 (m, 2 H), 2.29 (s, 3 H), 2.15–2.00 (m, 2 H).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 145.2, 138.0, 128.2, 125.5, 56.19, 54.52, 24.80, 20.82.

MS (ESI+): *m/z* = 162.2 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{19}NO_5S_2$ (333.3): C, 46.84; H, 5.75; N, 4.20. Found: C, 46.86; H, 5.64; N, 4.15.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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