Synthesis of (±)-8-Oxa-3-azabicyclo[3.2.1]octan-2-thione and (±)-2-Oxa-5-azabicyclo[2.2.1]heptan-6-thione: Potential Synthons for the Preparation of Novel Heteroaryl-Annulated Bicyclic Morpholines

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Abstract: The bridged bicyclic morpholinethiones (±)-8-oxa-3-azabicyclo[3.2.1]octane-2-thione and (±)-2-oxa-5-azabicyclo[2.2.1]heptane-6-thione have been prepared in five and eight steps, respectively. Both compounds were derived from a respective requisite *cis*-disubstituted tetrahydrofuran, which was stereoselectively prepared via hydrogenation of the corresponding disubstituted furan derivatives.

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

Morpholines are utilized extensively in drug discovery research. Numerous drugs possessing a directly linked morpholine have been approved by the FDA and other regulatory agencies; a snapshot of recently marketed drugs is shown in Figure 1, including linezolid (Zyvox®),[1] gifitinib (Iressa®),[2] and reboxetine.[3]

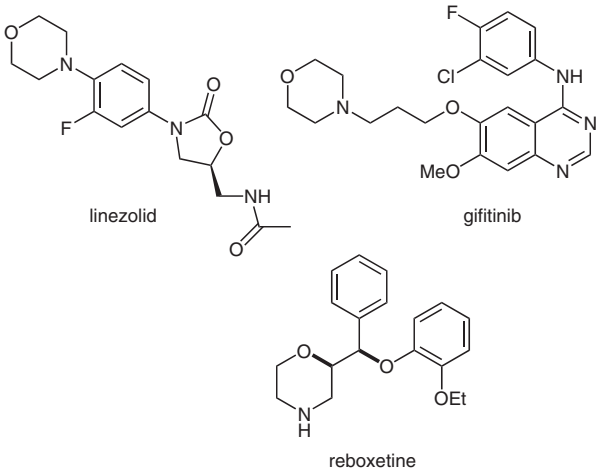

Figure 1 Drugs possessing a directly linked morpholine ring

Analogues incorporating a fused morpholine ring have also shown potential for treating various human diseases; some recent preclinical and clinical candidates are shown in Figure 2, including BLI-489,[4] finafloxacin,[5] and AGN 193080.[6]

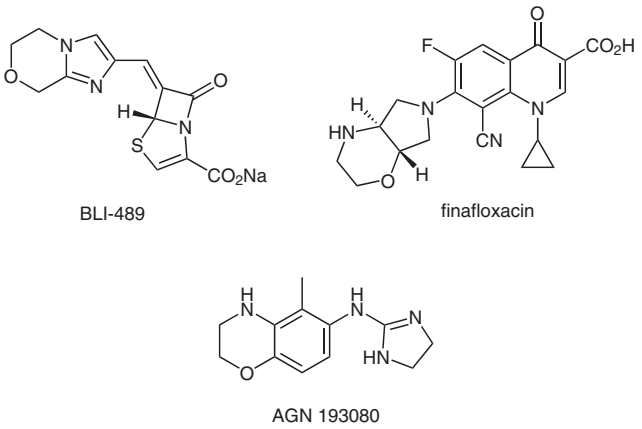

Figure 2 Clinical (BLI-489 and finafloxacin) and preclinical (AGN 193080) candidates possessing a fused morpholine ring

In addition, a number of reports detailing analogues incorporating a bridged bicyclic morpholine (e.g., **1** and **2**, Figure 3) have been reported in the medicinal chemistry literature.[7] In some instances, the bicyclic analogue showed enhanced biological activity compared to the corresponding morpholine analogue.[7c–e]

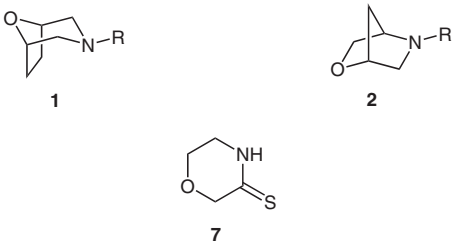

Figure 3 Bridged bicyclic morpholine templates **1** and **2** utilized in medicinal chemistry research programs, and structure of compound **7**

Given the promising biological profiles of analogues possessing a fused morpholine ring and the emerging potential of bridged bicyclic morpholine analogues, we became interested in preparing bridged bicyclic morpholines that were fused to an additional heteroaryl ring (e.g., **3** and **4**, Figure 4). The logical precursors to structures **3** and **4** would be thiolactams **5** and **6**, respectively. In general, thioamides and thiolactams are useful synthons for the preparation of a variety of fused heterocycles;[8] many of these heteroaryl-annulated analogues have shown interesting biological properties.[9] For instance, thiolactam **7**

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(Figure 3) is the precursor to the imidazo[2,1-*c*][1,4]oxazine skeleton contained in BLI-489.[4a] Hence, we have targeted the novel thiolactams **5** and **6** as synthons for the preparation of heteroaryl-annulated bicyclic morpholine analogues. While the bicyclo[3.2.1]octane skeleton in **5** restricts the morpholine ring in a pseudo-chair conformation, the bicyclo[2.2.1]heptane skeleton in **6** restricts the morpholine ring in a boat conformation. We detail below a racemic synthesis of the novel thiolactams **5** and **6**.

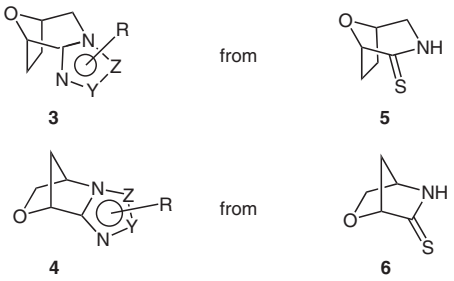
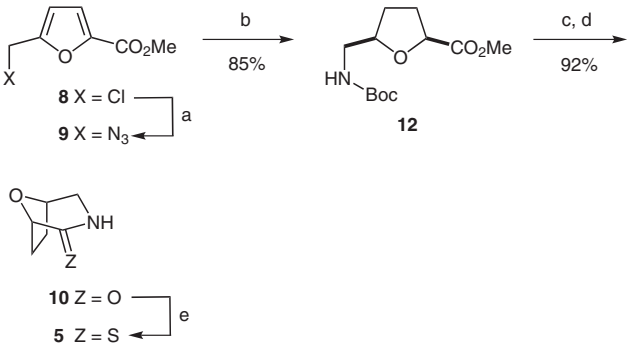


Figure 4 Novel heteroaryl-annulated bicyclic morpholine analogues **3** and **4** [Y = CH, CR, or N; Z = CH, CR, C(O), or N; R = H, alkyl, acyl, or aryl (see: refs 8 and 9)] and new synthetic targets **5** and **6**

The synthesis of bicyclic thiolactam **5** commenced from commercially available chloride **8** (Scheme 1). Azide **9** was prepared in a single step in near quantitative yield using a modification of the known procedure by Moore and Partain.[10] In that same study, the authors reported a direct conversion (H_2, 5% Rh/C, MeOH, 50 psi, 96 h, 70%) of azide **9** into bicyclic lactam **10**. Unfortunately, we were unable to repeat this procedure. In our hands, the major product, based on the crude ^{1}H NMR spectrum (500 MHz) and LCMS, was amine **11** (Figure 5). Presumably, the catalyst was being poisoned by the amine, preventing further hydrogenation from taking place. We reasoned that in situ protection of the amino group would resolve this issue. Indeed, hydrogenation of azide **9** in the presence of di-*tert*-butyl dicarbonate gave rise (85%) to tetrahydrofuran **12**. Under these conditions, none of the corresponding *trans*-product **13** (Figure 5) could be detected based on the crude ^{1}H NMR spectrum. This was somewhat surprising



Scheme 1 *Reagents and conditions*: (a) Bu_4NN_3 (1.05 equiv), 2-MeTHF, r.t., 1.5 h, 98%; (b) H_2, 5% Rh/C (cat.), $(Boc)_2O$ (1.5 equiv), MeOH, 50 psi, r.t., 36 h; (c) aq 4 M HCl in 1,4-dioxane (4.0 equiv), CH_2Cl_2, r.t.; (d) NaOAc (1.5 equiv), butan-2-ol, 100 °C, 3 h; (e) Lawesson's reagent, toluene, 90 °C, 1.5 h, 93%.

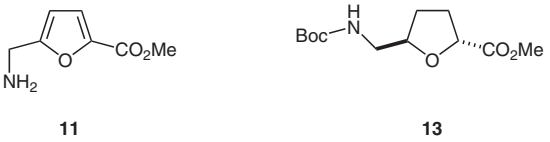
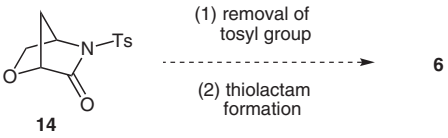


Figure 5 Structure of compounds **11** and **13**

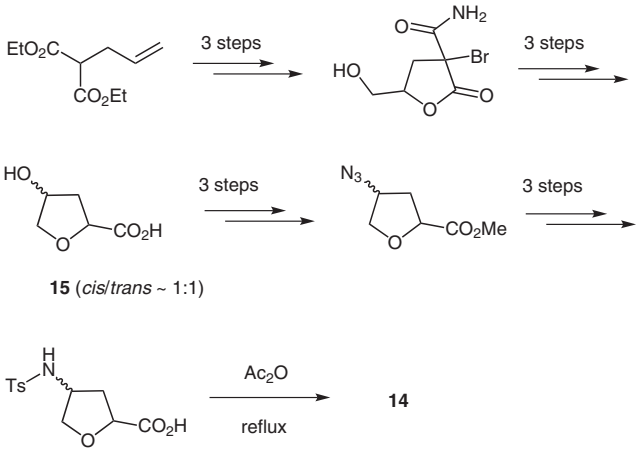
given that 10–15% of the *trans*-product is produced in the hydrogenation of similar 2,5-disubstituted furans.[11]

Bicyclic lactam **10** was realized in 93% yield via cleavage of the Boc group with hydrogen chloride, followed by subsequent heating in the presence of sodium acetate (Scheme 1). Subjection of the lactam in **10** to Lawesson's reagent furnished in 93% yield the desired thiolactam **5**.

Our next synthetic target was thiolactam **6**. Toward this end, we envisioned a synthetic route wherein the known bicyclic lactam **14**[12a] would be transformed into thiolactam **6** via reductive removal of the tosyl moiety followed by thiolactam formation (Scheme 2). However, the published synthesis of **14** is lengthy, requiring 13 linear steps from commercially available material, and it is nonstereoselective (Scheme 3).[12] Hence, we sought to develop a more efficient and stereoselective synthesis of lactam **14**.



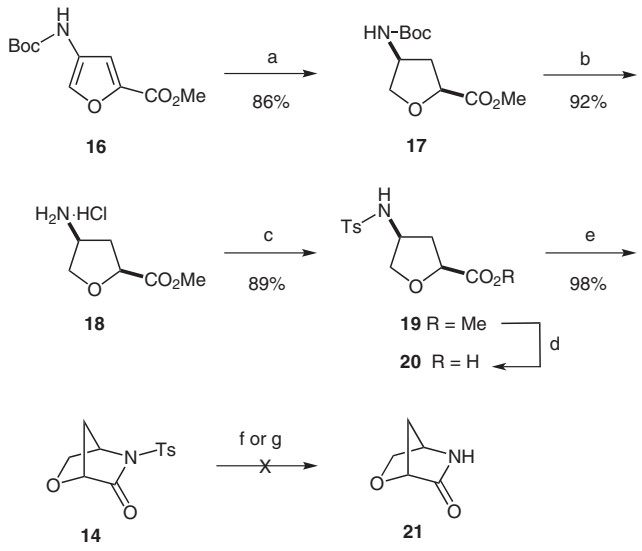
Scheme 2 Original synthetic plan for preparing bicyclic thiolactam **6**



Scheme 3 Allen and Tran's synthesis of bicyclic lactam **14** utilizing Matsumoto's tetrahydrofuran **15**

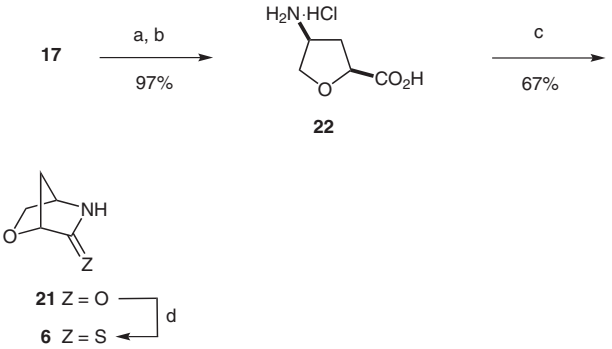
Our synthetic route to prepare lactam **14** is outlined in Scheme 4. The route is similar to the preparation of tetrahydrofuran **12** (vide supra) in that hydrogenation of an appropriately substituted furan ring was utilized to stereoselectively generate a *cis*-disubstituted tetrahydrofuran. Toward this end, hydrogenation of the known furan **16**,[13] prepared in three steps from commercial 3-furaldehyde

via remote functionalization,[14] gave rise (86%) to tetrahydrofuran **17**. Inspection of the crude ^{1}H NMR spectrum (500 MHz) showed a single stereoisomer. Subsequent 2D NMR studies confirmed that the amine and carboxylic acid groups were *cis* to one another (data not shown). Cleavage of the Boc group in **17** generated amino ester **18**, which upon exposure to tosyl chloride afforded sulfonamide **19**. Saponification of the ester led to carboxylic acid **20**, which set the stage for the lactamization reaction. Subjection of **20** to acetic anhydride in the presence of sodium acetate[15] gave rise to lactam **14**. The use of sodium acetate to facilitate the lactamization is noteworthy as it reduced the reaction time by 46 hours and improved the yield from 42% to 98% compared to acetic anhydride alone.[12a] Unfortunately, attempts to convert *N*-tosyl lactam **14** into lactam **21** met with no success. For instance, treatment of **14** with either sodium naphthalide in dimethoxyethane[16] or sodium in liquid ammonia[17] did result in efficient removal of the tosyl moiety; however, the product subsequently underwent significant decomposition under the reaction conditions. As a result, only trace amounts of the desired lactam could be detected in the crude ^{1}H NMR spectrum.



Scheme 4 *Reagents and conditions*: (a) 5% Rh/C, MeOH, 50 psi, r.t., 36 h; (b) aq 4 M HCl in 1,4-dioxane (4.0 equiv), CH_2Cl_2, r.t., 1 h; (c) TsCl (1.0 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 24 h; (d) LiOH·H_2O (7.0 equiv), THF–MeOH–H_2O (6:3:1), r.t., 1 h; (e) Ac_2O, NaOAc (10 equiv), reflux, 2 h; (f) Na, naphthalene, DME, –78 °C, 30 min; (g) Li, NH_3, –78 °C, 30 min.

To circumvent the issues associated with removing the tosyl moiety, we next attempted an intramolecular cyclization on the unprotected amino acid **22**, which was prepared in two steps from Boc-protected amino ester **17** (Scheme 5). However, heating a slurry of amino acid **22** in Dowtherm® A (bp 257 °C/760 Torr)[18] led to significant decomposition. Several reports on related carbocyclic systems have shown that thermal cyclization on the corresponding amino ester can be effected at lower temperatures than the parent amino acid.[19] Unfortunately, in our case, refluxing amino ester **18** (prepared according to Scheme 4) in mesitylene (bp 163–165 °C/760 Torr) was also unsuccessful. For both amino acid **22** and amino ester **18** no lactamization occurred at temperatures up to 150 °C. At temperatures >150 °C, significant decomposition ensued. Fortunately, cyclization of amino acid **22** was effected in refluxing acetonitrile in the presence of DCC,[20] affording a 67% yield of the previously unknown bicyclic lactam **21**. With lactam **21** finally in hand, treatment with Lawesson's reagent furnished the desired thiolactam **6** in good yield.



Scheme 5 *Reagents and conditions*: (a) LiOH·H_2O (7.0 equiv), THF–MeOH–H_2O (6:3:1), r.t., 1 h; (b) aq 3 M HCl, 70 °C, 1 h; (c) DCC (1.0 equiv), pyridine (3.0 equiv), MeCN, reflux, 1 h; (d) Lawesson's reagent, toluene, 90 °C, 1 h, 74%.

In summary, we have prepared in racemic form two different, conformationally restricted morpholinethiones **5** and **6**, which should serve as useful synthons for the preparation of heteroaryl-annulated bicyclic morpholine analogues. Both bicyclic compounds **5** and **6** were derived from a respective key *cis*-disubstituted tetrahydrofuran, which, in turn, was prepared with high stereoselectivity via hydrogenation of an appropriately substituted furan. In addition, our novel synthesis of (±)-2-oxa-5-azabicyclo[2.2.1]heptan-6-one (**21**) represents a significant improvement over the previously reported route to prepare the 2-oxa-5-azabicyclo[2.2.1]heptan-6-one ring system.

^{1}H and ^{13}C NMR spectra were collected on either a Varian Inova 500 with a 5 mm 4NG probe at 25 °C or a Varian Inova 400 with a 5 mm DBG probe at 25 °C. Chemical shifts are reported in parts per million (δ) relative to TMS (0.0). IR spectra were recorded on a Thermo-Nicolet Avatar 370 IR spectrometer. High-resolution mass spectra (HRMS) were acquired on an Agilent 1200 LCMS TOF spectrometer with UV detection. Combustion analyses were performed by QTI Intertek, Whitehouse, N.J. Melting points were recorded on a Thomas Hoover melting point apparatus and are uncorrected. Reactions were monitored by TLC using Analtech silica gel GF 250 micron plates. The plates were visualized either by UV inspection or by staining with an ammonium molybdate/ceric sulfate mixture. Flash chromatography was performed on a Biotage unit or glass column using EMD silica gel (230–400 mesh). All reagents were purchased from the Aldrich Chemical Co. and used without further purification. All solvents were HPLC grade unless otherwise stated. Anhyd solvents were purchased from EMD Chemical Co. and used as supplied.

Methyl 5-(Azidomethyl)-2-furoate (9)

The title compound was prepared according to the established procedure[10] with slight modification:

To a stirred solution of chloride **8** (10.0 g, 57.3 mmol) in 2-methyltetrahydrofuran (230 mL) in a 500 mL one-necked round-bottomed flask at r.t. was added Bu_4NN_3 (17.6 g, 60.1 mmol) in a single portion. The mixture was stirred for 1.5 h at r.t. and then washed with a 1:1 mixture of brine and 1 M aq HCl (2 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 10.4 g of a pale yellow oil. The crude product was purified by silica gel column chromatography (Biotage, 100 g SNAP cartridge). Elution with a heptane–EtOAc gradient (98:2 → 80:20) afforded azide **9** as a colorless oil; yield: 10.3 g (98%); R_f = 0.48 (hexanes–EtOAc, 80:20).

IR (film): 2097, 1724, 1523, 1437, 1300, 1206, 1134, 1020, 761 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 3.5 Hz, 1 H), 6.46 (d, *J* = 3.5 Hz, 1 H), 4.38 (s, 2 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 153.2, 144.8, 118.6, 110.9, 52.0, 46.9.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_7H_7N_3O_3$: 182.1; found: 182.0.

Methyl (±)-*cis*-5-[(*tert*-Butoxycarbonylamino)methyl]tetrahydrofuran-2-carboxylate (12)

A mixture of azide **9** (5.0 g, 27.6 mmol), di-*tert*-butyl dicarbonate (9.04 g, 41.4 mmol) and 5% Rh/C (Aldrich, 570 mg) in MeOH (190 mL) was placed in a 500 mL PARR shaker flask and hydrogenated at 50 psi overnight. The catalyst was removed by filtration through Celite. The filtrate was concentrated in vacuo to afford a pale oil. The crude product was purified by silica gel column chromatography (Biotage, 100 g SNAP cartridge). Elution with a heptane–EtOAc gradient (88:12 → 25:75) afforded **12** as a colorless oil; yield: 6.10 g (85%); R_f = 0.21 (hexanes–EtOAc, 80:20).

IR (film): 1738, 1709, 1512, 1365, 1250, 1213, 1166, 1093 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.52 (br s, 1 H), 4.49 (dd, *J* = 8.8, 4.1 Hz, 1 H), 4.24–4.15 (m, 1 H), 3.76 (s, 3 H), 3.43 (dt, *J* = 13.9, 4.2 Hz, 1 H), 3.31–3.22 (m, 1 H), 2.34–2.23 (m, 1 H), 2.14–2.06 (m, 1 H), 1.94 (dddd, *J* = 12.4, 8.1, 6.2, 4.1 Hz, 1 H), 1.79–1.67 (m, 1 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 156.3, 80.2, 78.9, 76.8, 52.1, 43.4, 30.7, 28.3, 27.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ $C_{12}H_{21}NO_5$ + Na: 282.1318; found: 282.1304.

(±)-8-Oxa-3-azabicyclo[3.2.1]octan-2-one (10)

To a stirred solution of carbamate **12** (6.1 g, 23.5 mmol) in CH_2Cl_2 (20 mL) was added HCl (4.0 M soln in 1,4-dioxane; 24 mL, 96 mmol). The reaction mixture was stirred at r.t. for 4 h. The volatiles were removed in vacuo to afford methyl (±)-*cis*-5-(aminomethyl)tetrahydrofuran-2-carboxylate hydrochloride as a viscous oil; yield: 4.5 g (99%).

^1H NMR (400 MHz, CD_3OD): δ = 4.61 (dd, 1 H, *J* = 8.8, 4.3 Hz), 4.37–4.30 (m, 1 H), 3.76 (s, 3 H), 3.21–3.15 (m, 1 H), 3.09–3.02 (m, 1 H), 2.45–2.34 (m, 1 H), 2.20–2.08 (m, 2 H), 1.80–1.70 (m, 1 H).

A mixture of the above oil and anhyd NaOAc (2.89 g, 35 mmol) in butan-2-ol (200 mL) was heated to 100 °C for 3 h. The mixture was concentrated in vacuo to dryness. The remaining residue was triturated with CH_2Cl_2 (50 mL) to afford a precipitate. The precipitate was filtered through Celite and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated in vacuo to a yellow oil. The crude product was purified by silica gel column chromatography (Biotage, 50 g SNAP cartridge). Elution with a CH_2Cl_2–EtOAc–MeOH gradient (70:10:20 → 40:40:20) afforded **10** as a white solid; yield: 2.74 g (92%); mp 70–72 °C (Lit.[10] mp 70–71 °C); R_f = 0.33 (EtOAc–MeOH, 90:10).

IR (film): 1660, 1491, 1345, 1024, 886 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (br s, 1 H), 4.58 (m, 1 H), 4.38 (d, *J* = 6.84 Hz, 1 H), 3.65 (dd, *J* = 11.3, 4.10 Hz, 1 H), 2.97 (dd, *J* = 11.52, 3.12 Hz, 1 H), 2.22–2.00 (m, 3 H), 1.85 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 76.91, 71.86, 47.83, 31.67, 27.75.

Anal. Calcd for $C_6H_9NO_2$ (127.1): C, 56.49; H, 7.15; N, 10.98. Found: C, 56.49; H, 7.17; N, 10.98.

(±)-8-Oxa-3-azabicyclo[3.2.1]octan-2-thione (5)

To a stirred solution of lactam **10** (508 mg, 4.00 mmol) in toluene (30 mL) was added Lawesson's reagent (1.75 g, 4.20 mmol) and the mixture was heated to 90 °C for 1.5 h. The mixture was cooled to r.t. and the solvent was removed in vacuo to afford a yellow solid. The solid was triturated with CH_2Cl_2 (5 mL) to remove insoluble material. The filtrate containing the product was purified by silica gel column chromatography (Biotage, 50 g SNAP cartridge). Elution with CH_2Cl_2–EtOAc gradient (100:0 → 80:20) afforded **5** as a white solid; yield: 530 mg (93%); mp 117–118 °C; R_f = 0.28 (hexanes–EtOAc, 1:1).

IR (film): 3227, 2945, 1533, 1337, 1160, 1121, 1064, 883 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.4 (br s, 1 H), 4.89 (d, *J* = 7.22 Hz, 1 H), 4.69 (m, 1 H), 3.73 (dd, *J* = 12.9, 4.49 Hz, 1 H), 3.06 (dd, *J* = 12.9, 3.32 Hz, 1 H), 2.35–2.30 (m, 1 H), 2.27–2.15 (m, 2 H), 1.95–1.80 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.9, 82.19, 71.07, 50.48, 33.86, 28.11.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_6H_{10}NOS$: 144.0484; found: 144.0479.

Anal. Calcd for C_6H_9NOS (143.2): C, 50.33; H, 6.34; N, 9.79. Found: C, 50.39; H, 6.36; N, 9.76.

Methyl (±)-*cis*-4-(*tert*-Butoxycarbonylamino)tetrahydrofuran-2-carboxylate (17)

A mixture of furan **16**[13] (800 mg, 3.32 mmol) and 5% Rh/C (Aldrich, 80 mg) in MeOH (40 mL) was placed in a Parr bottle and hydrogenated at 50 psi for 24 h at r.t. The mixture was filtered through Celite and washed with MeOH (30 mL). Concentration of the filtrate in vacuo afforded an oil. The crude product was passed through a silica gel plug, eluting with hexanes–EtOAc (1:1) to afford **17** as white solid; yield: 700 mg (86%); mp 53–54 °C; R_f = 0.51 (hexanes–EtOAc, 1:1).

IR (film): 3342, 2977, 1740, 1709, 1512, 1165, 1082 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H), 4.48 (dd, *J* = 9.52, 4.15 Hz, 1 H), 4.33 (m, 1 H), 3.97 (dd, *J* = 9.27, 5.37 Hz, 1 H), 3.87 (br d, *J* = 8.06 Hz, 1 H), 3.76 (s, 3 H), 2.51 (ddd, *J* = 13.7, 9.51, 7.32 Hz, 1 H), 1.99 (dt, *J* = 13.1, 3.42 Hz, 1 H), 1.40 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 155.2, 79.56, 75.93, 74.89, 52.32, 50.90, 36.95, 28.36.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{19}NO_5$ + Na: 268.1161; found: 268.1149.

Anal. Calcd for $C_{11}H_{19}NO_5$ (245.3): C, 53.86; H, 7.81; N, 5.71. Found: C, 53.89; H, 8.15; N, 5.72.

Methyl (±)-*cis*-4-Aminotetrahydrofuran-2-carboxylate Hydrochloride (18)

To a stirred solution of **17** (2.50 g, 10.2 mmol) in CH_2Cl_2 (15 mL) was added HCl (4.0 M solution in 1,4-dioxane; 15 mL). The solution was stirred for 1 h. The solvent was removed in vacuo [Note:

heating the reaction mixture to greater than 30 °C during concentration caused partial (ca. 10%) hydrolysis of the methyl ester]. The crude product was triturated with EtOAc (20 mL) to give a precipitate. The precipitate was filtered and dried in vacuo to afford **18** as a white solid; yield: 1.86 g (92%); mp 150–152 °C.

IR (film): 1740, 1513, 1233, 1105, 1056, 666 cm^{-1}.

^1H NMR (500 MHz, D_2O): δ = 4.62 (dd, *J* = 9.03, 6.83 Hz, 1 H), 4.10–4.00 (m, 3 H), 3.79 (s, 3 H), 2.84 (m, 1 H), 2.19 (m, 1 H).

^{13}C NMR (125 MHz, D_2O): δ = 173.8, 76.31, 71.25, 53.26, 50.67, 33.60.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_6H_{12}NO_3$: 146.0818; found: 146.0813.

Anal. Calcd for $C_6H_{12}ClNO_3$ (181.6): C, 39.68; H, 6.66; N, 7.71. Found: C, 39.49; H, 6.73; N, 7.56.

Methyl (±)-*cis*-4-(4-Methylphenylsulfonamido)tetrahydrofuran-2-carboxylate (19)

To a stirred suspension of **18** (55 mg, 0.30 mmol) in CH_2Cl_2 (2.0 mL) at r.t. were added Et_3N (93 μL, 0.67 mmol) and TsCl (60 mg, 0.32 mmol). The mixture was stirred at r.t. overnight. The mixture was diluted with CH_2Cl_2 (3 mL) and aq 1.0 M HCl (4 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with CH_2Cl_2–EtOAc gradient (0:100 → 100:0) afforded **19** as a white solid; yield: 80 mg (89%); mp 107–109 °C; R_f = 0.35 (hexanes–EtOAc, 1:1).

IR (film): 3250, 1736, 1438, 1218, 1157, 1089, 816, 663 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.30 Hz, 2 H), 7.32 (d, *J* = 8.30 Hz, 2 H), 5.43 (br d, 9.52 Hz, 1 H), 4.44 (dd, *J* = 9.52, 3.17 Hz, 1 H), 4.08 (m, 1 H), 3.83 (dd, *J* = 9.76, 5.12 Hz, 1 H), 3.77 (m, 1 H), 3.76 (s, 3 H), 2.44 (s, 3 H), 2.34 (ddd, *J* = 14.2, 9.52, 7.32 Hz, 1 H), 1.91 (dt, *J* = 13.91, 2.44 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 143.6, 137.7, 129.8, 127.0, 74.45, 53.69, 52.52, 36.61, 21.52.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_5S$: 300.0906; found: 300.0903.

Anal. Calcd for $C_{13}H_{17}NO_5S$ (299.3): C, 52.17; H, 5.73; N, 4.68. Found: C, 52.42; H, 5.66; N, 4.57.

(±)-*cis*-4-(4-Methylphenylsulfonamido)tetrahydrofuran-2-carboxylic Acid (20)

To a stirred solution of ester **19** (375 mg, 1.25 mmol) in THF–MeOH–H_2O (6:3:1; 12 mL) was added LiOH·H_2O (368 mg, 8.77 mmol). The mixture was stirred at r.t. for 30 min and concentrated in vacuo to a volume of ca. 2 mL. The remaining residue was diluted with H_2O (4 mL), and the pH was adjusted to 1 with concd HCl. The mixture was extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine (4 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **20** as a white solid; yield: 358 mg (98%); mp 124–126 °C (Lit.[12a] mp 122–125 °C).

IR (film): 1725, 1327, 1158, 1091, 666 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 12.61 (br s, 1 H), 7.85 (d, *J* = 6.16 Hz, 1 H), 7.69 (d, *J* = 7.69 Hz, 2 H), 7.40 (d, *J* = 8.05 Hz, 2 H), 4.24 (t, *J* = 7.81 Hz, 1 H), 3.70 (dd, *J* = 8.29, 6.84 Hz, 1 H), 3.63 (m, 1 H), 3.44 (dd, *J* = 8.54, 7.08 Hz, 1 H), 2.39 (s, 3 H), 2.24 (dt, *J* = 12.7, 8.05 Hz, 1 H), 1.72 (dt, *J* = 12.7, 7.32 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.0, 143.5, 138.4, 130.4, 127.3, 75.69, 72.20, 53.06, 35.95, 21.64.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{15}NO_5S$ + Na: 308.0569; found: 308.0555.

(±)-*N*-Tosyl-2-oxa-5-azabicyclo[2.2.1]heptan-6-one (14)

Carboxylic acid **20** (350 mg, 1.23 mmol) and NaOAc (1.01 g, 12.3 mmol), dissolved in Ac_2O (11 mL), were heated to reflux for 30 min. The mixture was cooled to r.t., and the solvent was removed in vacuo. The remaining residue was partitioned between H_2O (10 mL) and EtOAc (40 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organics were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **14** as an off-white solid; yield: 320 mg (98%); mp 125–127 °C (Lit.[12a] mp 127–128 °C); R_f = 0.35 (hexanes–EtOAc, 1:1).

IR (film): 1755, 1361, 1169, 1090, 675 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.54 Hz, 2 H), 7.35 (d, *J* = 8.06 Hz, 2 H), 5.04 (s, 1 H), 4.49 (d, *J* = 1.95 Hz, 1 H), 3.85 (d, *J* = 8.05 Hz, 1 H), 3.62 (d, *J* = 8.05 Hz, 1 H), 2.45 (s, 3 H), 2.10 (dd, *J* = 10.7, 1.22 Hz, 1 H), 1.95 (dt, *J* = 10.9, 1.46 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 145.5, 136.0, 129.9, 127.7, 79.94, 69.73, 61.13, 39.17, 21.68.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{13}NO_4S$ + Na: 290.0464; found: 290.0450.

Anal. Calcd for $C_{12}H_{13}NO_4S$ (267.3): C, 53.93; H, 4.90; N, 5.24. Found: C, 53.98; H, 4.82; N, 5.18.

(±)-*cis*-4-Aminotetrahydrofuran-2-carboxylic Acid Hydrochloride (22)

To a stirred solution of ester **17** (1.60 g, 6.52 mmol) in THF–MeOH–H_2O (6:3:1; 60 mL) was added LiOH·H_2O (1.92 g, 45.7 mmol) The mixture was stirred at r.t. for 2 h and concentrated in vacuo to a volume of ca. 5 mL. The remaining residue was partitioned between H_2O (20 mL) and Et_2O (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL). The combined ethereal layers were discarded. The aqueous layer was acidified with concd HCl to pH 1. The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford (±)-4-*cis*-(*tert*-butoxycarbonylamino)tetrahydrofuran-2-carboxylic acid as a white solid; yield: 1.50 g (99%); mp 112–114 °C; R_f = 0.24 (hexanes–EtOAc–AcOH, 90:9:1).

IR (film): 1724, 1690, 1514, 1164, 1077 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 12.6 (br s, 1 H), 6.95 (br s, 1 H), 4.31 (dd, *J* = 8.19, 7.41 Hz, 1 H), 3.97 (m, 1 H), 3.85 (dd, *J* = 8.20, 6.63 Hz, 1 H), 2.43 (dt, *J* = 12.9, 8.20 Hz, 1 H), 1.81 (dt, *J* = 12.9, 7.03 Hz, 1 H), 1.38 (s, 9 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.7, 155.2, 77.94, 75.20, 71.94, 50.35, 35.18, 28.16.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{17}NO_5$ +Na: 254.1005; found: 254.0995.

Anal. Calcd for $C_{10}H_{17}NO_5$ (231.2): C, 51.93; H, 7.41; N, 6.06. Found: C, 51.94; H, 7.40; N, 5.98.

The above solid (1.50 g, 6.49 mmol), dissolved in aq 3 M HCl (30 mL) was heated to 70 °C for 2 h. The volatiles were removed in vacuo. The remaining residue was triturated with EtOAc (25 mL) to afford a white precipitate. The precipitate was filtered and dried in vacuo to afford **22** as a white solid with a H_2O content of 8.7%, as determined by Karl Fischer titration; yield: 1.05 g (97%); mp 98–100 °C (loss of H_2O).

IR (film): 1728, 1203, 1100, 1051 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 12.90 (br s, 1 H), 8.25 (br s, 3 H), 4.35 (dd, *J* = 8.39, 7.61 Hz, 1 H), 3.90 (td, *J* = 8.20, 2.92 Hz, 1 H), 3.82–3.74 (m, 2 H), 2.59 (dt, *J* = 13.3, 8.20 Hz, 1 H), 1.95 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.7, 75.74, 70.28, 49.45, 33.67.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_5H_{10}NO_3$: 132.0661; found: 132.0656.

Anal. Calcd for $C_5H_{10}ClNO_3 \cdot 8.73\%H_2O$: C, 53.09; H, 6.23; N, 12.39. Found: C, 53.56; H, 6.59; N, 12.37.

(±)-2-Oxa-5-azabicyclo[2.2.1]heptan-6-one (21)

To a stirred suspension of **22** (550 mg, 3.28 mmol) in anhyd MeCN (50 mL) was added pyridine (0.80 mL, 9.9 mmol). The mixture was heated to reflux before DCC (677 mg, 3.28 mmol) was added in a single portion. Heating at reflux was continued for 1 h. The mixture was cooled to r.t. and the resulting precipitate was filtered through a Büchner funnel. The filtrate was concentrated in vacuo to a clear residue. The crude product was purified by flash chromatography on silica gel. Elution with EtOAc–MeOH (95:5) afforded **21** as a clear solid; yield: 250 mg (67%); mp 56–57 °C; R_f = 0.32 (EtOAc–MeOH, 90:10).

IR (film): 3253, 1699, 1253, 1053 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.09 (br s, 1 H), 4.47 (s, 1 H), 4.21 (s, 1 H), 3.94 (dd, *J* = 7.08, 0.98 Hz, 1 H), 3.59 (d, *J* = 7.08 Hz, 1 H), 2.04 (dd, *J* = 9.92, 1.86 Hz, 1 H), 1.87 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 79.31, 70.42, 55.40, 40.83.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_5H_8NO_2$: 114.0555; found: 114.0548.

Anal. Calcd for $C_5H_7NO_2$ (113.1): C, 53.09; H, 6.23; N, 12.39. Found: C, 53.46; H, 6.59; N, 12.37.

(±)-2-Oxa-5-azabicyclo[2.2.1]heptan-6-thione (6)

To a stirred solution of lactam **21** (130 mg, 1.15 mmol) in toluene (12 mL) was added Lawesson's reagent (465 mg, 1.15 mmol). The mixture was heated to 90 °C for 1 h. The mixture was cooled to r.t., and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with CH_2Cl_2–EtOAc (4:1) afforded **6** as a white solid; yield: 110 mg (74%); mp 107–109 °C; R_f = 0.20 (hexanes–EtOAc, 1:1).

IR (film): 3229, 1465, 1239, 1105 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (br s, 1 H), 4.74 (s, 1 H), 4.40 (s, 1 H), 4.00 (d, *J* = 7.32 Hz, 1 H), 3.66 (d, *J* = 7.32 Hz, 1 H), 2.10 (dd, *J* = 10.0, 2.19 Hz, 1 H), 2.00 (d, *J* = 10.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.2, 86.91, 70.13, 60.42, 42.61.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C_5H_8NOS: 130.0327; found: 130.0318.

Anal. Calcd for C_5H_7NOS (129.1): C, 46.50; H, 5.46; N, 10.84. Found: C, 46.47; H, 5.71; N, 10.47.

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