Supporting Information

Bicyclic Lactams derived from Serine or Cysteine and 2-Methylpropanal

Halima Bagum,† Bethany R. Shire,† Kirsten E. Christensen,† Alexander Pretsch,‡ Dagmar Pretsch,‡ and Mark G. Moloney*,†,#

†The Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford. OX1 3TA
#Oxford Suzhou Centre for Advanced Research, Building A, 388 Ruo Shui Road, Suzhou Industrial Park, Jiangsu, 215123, P.R. China.

mark.moloney@chem.ox.ac.uk
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Experimental

The required starting materials were obtained by literature methods\(^1\)

**Synthesis of Methyl Ester Hydrochloride: General Method A**

SOCl\(_2\) (1.5 eq) was added dropwise to stirring anhydrous MeOH (2M) at 0°C, followed by L-amino acid (1 eq) portion-wise. The mixture was heated to 40°C and stirred at this temperature for 3 h. The solvent was then evaporated under reduced pressure to give methyl ester hydrogen chlorides.

**Synthesis of Oxazolidine and Thiazolidine Compounds: General Method B\(^2,3\)**

The ester hydrogen chloride of the L-amino acid (1.0 eq) was dissolved in petroleum ether. Triethylamine (1.5 eq) and isobutyraldehyde (1.2 eq) were then added. The mixture was heated at reflux with continuous removal of water using a Dean-Stark apparatus for 18 h. The white precipitate was then filtered and washed with Et\(_2\)O. The combined filtrates were concentrated under reduced pressure to furnish the oxazolidines or thiazolidine 4a,b.

**N-Acylation of Oxazolidine and Thiazolidine Compounds: General Method C\(^3\)**

DMAP (0.05 eq) and DCC (1.05 eq) were added to a solution of oxazolidine or thiazolidine 4a,b (1.0 eq) in anhydrous DCM. The mixture was cooled to 0°C and ethyl hydrogen malonate (1.05 eq) was added. The reaction mixture was then stirred 30 min at 0°C and 5 h at room temperature. A white precipitate was formed, which was filtered and washed with DCM. The combined filtrates were concentrated in vacuo and purified by flash column chromatography to give the required N-acyl oxazolidines or thiazolidine 5a,b.

**Dieckmann Cyclisation: General Method D\(^3\)**

To a solution of N-acyl oxazolidine or thiazolidine 5a,b(1.0 eq) in anhydrous THF was added potassium tert-butoxide (1.05 eq). The mixture was heated at reflux for 3 h. The reaction mixture was separated between Et\(_2\)O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH\(_2\)PO\(_4\) and brine, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure to give the methyl ester tetramic acids 6a-e.

**Synthesis of Tosylate/Mesylate: General Method E\(^4\)**

Tetramic acid 6a-e (1.0 eq) was dissolved in DCM under nitrogen atmosphere. Methanesulfonyl chloride (1 eq) and DIPEA (2 eq) were added to this solution. The resulting mixture was stirred for 2-6 h at room temperature until total consumption of the starting material. The reaction mixture was washed with 5% HCl, 5% NaHCO\(_3\), and brine, dried over MgSO\(_4\), and filtered. The solvent was removed in vacuo, and the residue was chromatographed on silica gel using ethyl acetate:petroleum ether as eluants to give mesylates 7a,c.

**Suzuki Coupling: General Method F\(^5\)**

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A mixture of 1,4-bis(diphenylphosphino)butane (0.06 eq) and bis(benzonitrile)palladium(II) chloride (0.05 eq) in dry toluene was stirred at room temperature under nitrogen atmosphere for 30 minutes to form a creamy orange slurry of [1,4-bis(diphenylphosphino)butane] palladium(II) chloride. Tosylate/mesylate (1.0 eq), boronic acid (1.05-1.8 eq), ethanol (7.0 eq), 1M aqueous sodium carbonate solution (9-18 eq) and dry toluene were added to the catalyst and the mixture was refluxed for 3-30 hours. After cooling, water was added, and the mixture was diluted with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were dried and evaporated in vacuo to find the crude product, which was then purified by flash column chromatography.

**Hydrogenation of C6-C7 double bond: General Method G**

To a solution of α,β-unsaturated lactam (1eq) in EtOAc (0.05 M), platinum(IV) oxide (0.15 eq) was added. The reaction mixture was stirred at room temperature under H₂ atmosphere for 1-48 h, filtered through Celite, evaporated under reduced pressure, and then purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as eluents to give pure pyrrolidinones.

**N,O-Acetal deprotection: General Method I**

Under a nitrogen atmosphere, the pyrrolinone or pyrrolidinone (1 eq) was treated with propane-1,3-dithiol (2.1-4.0 eq) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol. The solution was stirred at room temperature for 24-36 h or at 50°C for 12-17 h. The reaction mixture was concentrated in vacuo, the crude residue was dissolved in MeOH, washed with petroleum ether and concentrated under reduced pressure to give N,O-acetal deprotected amides.

**Single Crystal X-ray Diffraction: General Method**

Low temperature single crystal X-ray diffraction data were collected using a (Rigaku) Oxford Diffraction SuperNova diffractometer. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip' before refinement with CRYSTALS as per the SI (CIF). Full refinement details are given in the Supporting Information (CIF); Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1961419-21) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

**(2R,5R)- and (2S,5R)-2-(Isopropyl)-5-methoxycarbonyl-1,3-thiazolidine, 4b**

According to General Method B, reaction of L-cysteine methyl ester hydrochloride (2.0 g, 11.65 mmol) with 2-methylpropanal (1.27 mL, 14.0 mmol) and Et₃N (2.4 mL, 17.47 mmol) in petrol (60 mL) furnished thiazolidine 4b. Yield 76% (1.68 g); colourless oil; 2:1 mixture of diastereomers; Rᵋ (30% EtOAc in Petrol) 0.40; νₑᵥₑₑcm⁻¹ 3295 (N-H),
According to General Method C, N-acetyl thiazolidine 5b was prepared from thiazolidine 4b (2.19 g, 11.6 mmol), DCC (2.5 g, 12.18 mmol), DMAP (70 mg, 0.6 mmol), and ethyl hydrogen malonate (1.44 mL, 12.18 mmol) in DCM (50 mL). Yield 74% (2.58 g); colourless oil; 1:1.5 mixture of rotamers (major A, minor B); Rf (40% EtOAc in Petrol) 0.28; νmax/cm⁻¹ 2960 (C-H), 2873 (C=O), 1743 (C=O), 1658 (C=O); δH (400 MHz, CDCl₃) major isomer (2R): 1.10 (6H, dd, J 19.7, 6.7, CH(CH₃)₂), 1.99 (1H, h, J 6.7, CH(CH₃)₂), 2.21 (1H, br s, NH), 2.76 (1H, dd, J 10.6, 9.2, C(4)H₄NO), 3.28 (1H, dd, J 10.1, 6.9, C(4)H₄NO), 3.78 (3H, s, CO₂CH₃), 3.82 (1H, dd, J 9.6, 7.1, C(5)H), 4.36 (1H, d, J 7.2, C(2)H); δC (100 MHz, CDCl₃) major isomer (2R): 20.3, 20.7 (CH(CH₃)₂), 33.6 (CH(CH₃)₂), 37.5 (C(4)), 52.5 (CO₂CH₃), 65.4 (C(5)), 78.0 (C(2)), 171.8 (CO₂CH₃); minor isomer (2S): 19.7, 20.5 (CH(CH₃)₂), 35.1 (CH(CH₃)₂), 37.3 (C(4)), 52.5 (CO₂CH₃), 64.4 (C(5)), 76.8 (C(2)), 172.2 (CO₂CH₃); m/z ([ESI]⁺) 190.0 ([M+H]⁺, 100%); HRMS ([ESI]⁺) found 190.0893, C₅H₁₀NO₂S ([M+Na]⁺) requires 190.0896.

(2R,5R)-2-Isopropyl-1-ethoxycaranylacetyl-5-methoxy carbonyl-1,3-thiazolidine, 5b

According to general method K, thiazolidine 4b (1.35 g, 7.1 mmol) was reacted with dry pyridine (0.6 mL, 7.4 mmol) and malonyl chloride (2.3 mL, 14.2 mmol) in DCM (50 mL). Purification of crude product by flash column chromatography (20% EtOAc in petroleum ether) yielded N-acetyl thiazolidine 5c as a mixture of diastereomers and their rotamers. Only 7R (major) was isolated. Yield 81% (1.82 g); colourless oil; mixture of rotamers; Rf (40% EtOAc in Petrol) 0.43; [α]D²⁵²⁰ -114.3 (c 1.0 in DCM); νmax/cm⁻¹ 2960 (C-H), 2874 (C=O), 1742 (C=O); δH (400 MHz, CDCl₃): 0.89 (6H, dd, J 15.7, 6.4, CH(CH₃)₂), 1.01-1.04 (6H, only one peak was observed at 1.01-1.04).
According to general method D, 6b was synthesised via Dieckman cyclisation of 5b (2.39 g, 7.87 mmol) under basic condition (KOH, 928 mg, 8.27 mmol) in THF (0.2 M). The decarboxylated tetramic acid 6c was found as a nearly inseparable minor compound. 6b: Yield 47% (1.24 g); yellow solid, m. p. 82-84°C; \([\text{C} 12\text{H}18\text{O}_5\text{Na}]^+ + 134.8 (c 1.0 \text{in DCM})\); \(\nu_{\text{max}}/\text{cm}^{-1} 2962 (\text{C-H}), 2872 (\text{C-H}), 1782 (\text{C=O}), 1746 (\text{C=O}), 1713 (\text{C=O}); \delta_{\text{H}} (400 \text{MHz, CDCl}_3): 0.89 (3H, d, J 6.6, \text{CH(CH}_3\text{)}_3), 1.02 (3H, d, J 6.6, \text{CH(CH}_3\text{)}_3), 1.62 (1H, dq, J 10.0, 6.6, \text{CH(CH}_3\text{)}_3), 2.97 (1H, d, J 11.2, \text{C(4)H}_2\text{H}_3, 3.12 (1H, d, J 21.6, \text{C(7)H}_2\text{H}_3), 3.47 (1H, d, J 21.6, \text{C(7)H}_2\text{H}_3, 3.75 (1H, d, J 11.2, \text{C(4)H}_2\text{H}_3), 3.78 (3H, s, \text{CO}_2\text{CH}_3), 5.04 (1H, d, J 10.0, \text{C(2)H}); \delta_{\text{C}} (100 \text{MHz, CDCl}_3): 19.3, 20.0 (\text{CH(3)H}_3), 34.8 (\text{C(4)}), 36.6 (\text{CH(CH}_3\text{)}_3), 42.6 (\text{C(7)}), 54.0 (\text{CO}_2\text{CH}_3), 68.5 (\text{C(2)}), 83.3 (\text{C(5)}), 166.9 (\text{CO}_2\text{CH}_3), 168.8 (\text{C(8)}), 198.4 (\text{C(6)}); m/z ([ESI]−) 258.0 ([M+H]+, 100%), 280.0 ([M+Na]+, 70%); HRMS ([ESI]−) found 258.0795, C_{11}H_{16}NO_3S ([M+H]⁺) requires 258.0795.

(2R,5R)-1-Aza-2-isopropyl-5-methoxycarbonyl-6,8-dioxo-3-thiabicyclo[3.3.0]octane, 6b

According to general method D, reaction of N-acyl thiazolidine 5c (4.2 g, 13.2 mmol) with KO'Bu (1.6 g, 14.5 mmol) in THF (0.2 M) gave inseparable mixture of tetramic acids 6d and 6e. Yield 76% (2.7 g); white solid; inseparable mixture of A and B (2.3:1); \(\nu_{\text{max}}/\text{cm}^{-1} 3377 (\text{O-H}), 2960 (\text{C-H}), 2930 (\text{C-H}), 2872 (\text{C-H}), 1750 (\text{C=O}), 1647 (\text{C=O}); \delta_{\text{H}} (400 \text{MHz, MeOD}): 0.81-0.95 (6H, m, \text{CH(3)H}_3), (A+B)), 1.51 (3H, s, \text{C(7)CH}_3, \text{B}), 1.55 (3H, s, \text{C(7)CH}_3, \text{A}), 1.62-1.72 (1H, m, \text{CH(CH}_3\text{)}_2, \text{A}), 1.77-1.84 (1H, m, \text{CH(CH}_3\text{)}_2, \text{B}), 2.52-2.60 (1H, m, \text{C(4)H}_2\text{H}_3, \text{B}), 2.77 (1H, d, J 11.9, \text{C(4)H}_2\text{H}_3, \text{A}), 3.06 (1H, dd, J 10.8, 6.8, \text{C(4)H}_2\text{H}_3, \text{B}), 3.63 (1H, d, J 11.9, \text{C(4)H}_2\text{H}_3, \text{A}), 3.68 (3H, s, \text{CO}_2\text{CH}_3), 4.35 (1H, t, J 7.7, \text{C(5)H}), 4.57 (1H, d, J 9.4, \text{C(2)H}), 4.69 (1H, d, J 7.3, \text{C(2)H}), \delta_{\text{C}} (100 \text{MHz, MeOD}): 4.5 (\text{C(7)CH}_3, \text{B}), 4.8 (\text{C(7)CH}_3, \text{A}), 18.0, 18.5 (\text{CH(CH}_3\text{)}_2, \text{B}), 18.4, 19.0 (\text{CH(CH}_3\text{)}_2, \text{A}), 31.6 (\text{C(4)}, \text{B}), 33.2 (\text{C(4)}, \text{A}), 35.7 (\text{CH(CH}_3\text{)}_2, \text{B}), 36.1 (\text{CH(CH}_3\text{)}_2, \text{A}), 52.3 (\text{CO}_2\text{CH}_3, \text{A}), 65.7 (\text{C(2)}, \text{B}), 66.0 (\text{C(5)}, \text{B}), 67.2 (\text{C(2)}, \text{A}), 77.9 (\text{C(5)}, \text{A}), 100.1 (\text{C(7)}, \text{B}), 100.7 (\text{C(7)}, \text{A}), 167.8 (\text{CO}_2\text{CH}_3, \text{A}), 169.2 (\text{C(8)}, \text{A}), 169.5 (\text{C(8)}, \text{B}), 178.1 (\text{C(6)}, \text{A}); m/z ([ESI]−) 214.0 ([M+H]+, \text{B}, 100%), 272.0 ([M+H]+, \text{A}, 30%), 294.0 ([M+Na]+, \text{A}, 75%); HRMS ([ESI]−)A found 272.0951, C_{12}H_{18}NO_3S ([M+H]⁺) requires 272.0951; HRMS ([ESI]−)B found 214.0896, C_{10}H_{16}NO_3S ([M+H]⁺) requires 214.0896.
(2R,5R)-1-Aza-2-isopropyl-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-3-oxo-8-oxobicyclo[3.3.0] oct-6-ene, 7a

The mesylate 7a was prepared following General Methods A, B, D and E successively without purification of products in each step of the reactions, due to the instability of the intermediates. Yield: 14%; yellow semi-solid; Rf (40% EtOAc in Petrol) 0.25; [a]D 25 +55.8 (c 1.0 in DCM); νmax/cm⁻¹ 2956 (C-H), 2932 (C-H), 1745 (C=O), 1702 (C=O); δH (400 MHz, CDCl₃): 0.89 (6H, dd, J 8.2, 6.8 (CH(CH₃)₂), 1.78 (1H, dq, J 13.4, 6.8, CH(CH₃)), 3.19 (3H, s, OSO₂CH₃), 3.58 (1H, d, J 8.8, C(4)H₃), 3.77 (3H, s, CO₂CH₃), 4.63 (1H, d, J 8.8, C(4)H₃), 4.81 (1H, d, J 6.3, C(2)H), 5.86 (1H, s, C(7)H); δC (100 MHz, CDCl₃): 17.2 (CH(CH₃)), 32.7 (CH(CH₃)), 32.8 (OSO₂CH₃), 53.7 (CO₂CH₃), 69.3 (C(4)), 74.6 (C(5)), 94.8 (C(2)), 108.2 (C(7)), 163.2 (CO₂CH₃), 167.4 (C(8)), 175.1 (C(6)); m/z ([ESI]⁺) 320.0 ([M+H⁺], 40%); HRMS ([ESI]⁺) found 320.0799, C₁₂H₁₆NO₃S ([M+H⁺]) requires 320.0799.

(2R,5R)-1-Aza-2-isopropyl-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 7b and (2R,5S)-1-Aza-2-isopropyl-6-((methylsulfonyl)-oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 7c

According to General Method E, treatment of tetracarboxylic acids (6b + 6c) (1.19 g, 4.64 mmol) with MsCl (0.36 mL, 4.64 mmol) and DIPEA (1.6 mL, 9.28) in DCM afforded desired mesylates 7b and 7c. 7b: Yield 64% (990 mg); white solid, m. p. 96-98°C; Rf (40% EtOAc in Petrol) 0.29; [a]D 25 +187.1 (c 1.0 in DCM); νmax/cm⁻¹ 2962 (C-H), 2935 (C-H), 1750 (C=O), 1715 (C=O); δH (400 MHz, CDCl₃): 0.87 (3H, d, J 6.6, CH(CH₃)), 0.97 (3H, d, J 6.6, CH(CH₃)), 1.76 (1H, dq, J 9.4, 6.6, CH(CH₃)), 2.89 (1H, d, J 11.2, C(4)H₃), 3.20 (3H, s, OSO₂CH₃), 3.64 (1H, d, J 11.2, C(4)H₃), 3.78 (3H, s, CO₂CH₃), 4.72 (1H, d, J 9.4, C(2)H), 5.79 (1H, s, C(7)H); δC (100 MHz, CDCl₃): 19.4, 19.9 (CH(CH₃)), 34.0 (C(4)), 36.4 (CH(CH₃)), 38.3 (OSO₂CH₃), 53.9 (CO₂CH₃), 67.3 (C(2)), 78.7 (C(5)), 106.7 (C(7)), 161.6 (CO₂CH₃), 167.4 (C(8)), 171.5 (C(6)); m/z ([ESI]⁺) 336.0 ([M+H⁺], 90%), 358.0 ([M+Na⁺], 100%); HRMS ([ESI]⁺) found 336.0570, C₁₂H₁₆NO₃S ([M+H⁺]) requires 336.0581.

7c: Yield 4% (37 mg); yellow oil; Rf (40% EtOAc in Petrol) 0.22; [a]D 25 +21.1 (c 0.2 in DCM); νmax/cm⁻¹ 2964 (C-H), 2873 (C-H), 1700 (C=O); δH (400 MHz, CDCl₃): 0.91-0.99 (6H, m, CH(CH₃)), 1.89 (1H, h, J 6.7, CH(CH₃)), 2.69 (1H, dd, J 10.7, 9.6, C(4)H₃), 3.05 (1H, dd, J 10.7, 6.3, C(4)H₃), 3.22 (3H, s, OSO₂CH₃), 4.59 (1H, dd, J 9.6, 6.3, C(5)H), 4.87 (1H, d, J 7.1, C(2)H), 5.67 (1H, s, C(7)H); δC (100 MHz, CDCl₃): 18.8, 19.4 (CH(CH₃)), 32.2 (C(4)), 36.0 (CH(CH₃)), 38.5 (OSO₂CH₃), 65.5 (C(2)), 67.0 (C(5)), 106.6 (C(7)), 163.1 (C(8)), 171.0 (C(6)); m/z ([ESI]⁺) 278.1 ([M+H⁺], 40%), 300.0 ([M+Na⁺], 100%); HRMS ([ESI]⁺) found 278.0516, C₁₀H₁₆NO₃S ([M+H⁺]) requires 278.0515.

(2R,5R)-1-Aza-2-(isopropyl)-5-methoxycarbonyl-7-methyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene 7d and (2R,5S)-1-Aza-2-isopropyl-7-methyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene 7e

According to general method E, tetracarbonyl(2) (6d + 6e, 2.32 g, 8.55 mmol) was reacted with MsCl (0.66 mL, 8.55 mmol) and DIPEA (2.9 mL, 17.1 mmol) in DCM (85 mL). Purification by flash column chromatography (20-30% EtOAc in petroleum ether) furnished isolated mesylates 7d and 7e. 7d: Yield 61% (1.82 g); colourless oil; Rf (40% EtOAc in Petrol) 0.37; \([\alpha]_D^{25} +235.0 (c 1.0 \text{ in DCM})\); νmax/cm\(^{-1}\) 2960 (C-H), 2935 (C-H), 1747 (C=O), 1713 (C=O); δH (400 MHz, CDCl\(_3\)): 0.87 (3H, d, J 6.6, CH(CH\(_3\)_3)), 1.02 (3H, d, J 6.6, CH(CH\(_3\)_3)), 1.78-1.84 (1H, m, CH(CH\(_3\)_3)), 1.85 (3H, s, C(7)CH\(_3\)), 2.84 (1H, d, J 11.1, C(4)H\(_3\)H\(_6\)), 3.23 (3H, s, CH\(_3\)), 3.58 (1H, d, J 11.1, C(4)H\(_3\)H\(_6\)), 3.76 (3H, s, CO\(_2\)CH\(_3\)), 4.70 (1H, s, J 9.7, C(2)H); δC (100 MHz, CDCl\(_3\)): 8.6 (C(7)CH\(_3\)), 19.6, 20.2 (CHCH\(_3\)_2), 35.2 (C(4)), 36.9 (CH\(_2\)(CH\(_3\)_2), 39.5 (OSO\(_2\)CH\(_3\)), 53.7 (CO\(_2\)CH\(_3\)), 66.8 (C(2)), 78.2 (C(5)), 124.0 (C(7)), 154.0 (CO\(_2\)CH\(_3\)), 168.4 (C(8)), 171.4 (C(6)); m/z ([ESI\(^+\)]\(^+\)) 372.0 ([M+Na\(^+\)], 100%); HRMS ([ESI\(^+\)]\(^+\)) found 372.0547, C\(_{13}\)H\(_{15}\)N\(_2\)O\(_5\)S \(_2\) ([M+Na\(^+\)]\(^+\)) requires 372.0546.

7e: Yield 13% (180 mg); colourless oil; Rf (40% EtOAc in Petrol) 0.27; \([\alpha]_D^{25} +179.6 (c 1.0 \text{ in DCM})\); νmax/cm\(^{-1}\) 2963 (C-H), 2930 (C-H), 1700 (C=O); δH (400 MHz, CDCl\(_3\)): 0.95 (6H, t, J 6.2, CH(CH\(_3\)_3)), 1.77 (3H, s, C(7)CH\(_3\)), 1.85-1.95 (1H, m, CH(CH\(_3\)_3)), 2.62 (1H, t, J 10.3, C(4)H\(_3\)H\(_6\)), 3.09 (1H, dd, J 10.7, 6.1, C(4)H\(_3\)H\(_6\)), 3.22 (3H, s, OSO\(_2\)CH\(_3\)), 4.66-4.75 (1H, m, C(5)H), 4.86 (1H, d, J 7.1, C(2)H); δC (100 MHz, CDCl\(_3\)): 7.7 (C(7)CH\(_3\)), 18.8, 19.5 (CHCH\(_3\)_2), 32.7 (C(4)), 36.1 (CHCH\(_3\)_2), 39.0 (OSO\(_2\)CH\(_3\)), 65.2 (C(2)), 66.2 (C(5)), 121.5 (C(7)), 156.3 (C(8)), 171.1 (C(6)); m/z ([ESI\(^+\)]\(^+\)) 292.0 ([M+H\(^+\)], 100%), 314.0 ([M+Na\(^+\)], 90%); HRMS ([ESI\(^+\)]\(^+\)) found 292.0671, C\(_{13}\)H\(_{15}\)N\(_2\)O\(_5\)S \(_2\) ([M+H\(^+\)]\(^+\)) requires 292.0672.

(2R,5S)-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 8ai

According to General Method F, mesylate 7a (210 mg, 0.66 mmol) was reacted with 4-methoxyphenylboronic acid (150 mg, 0.98 mmol), PdCl\(_2\)(dpbb), 1 M aqueous Na\(_2\)CO\(_3\) solution (0.62 mL, 5.94 mmol) in ethanol (0.27 mL, 4.62 mmol) and toluene (12 mL) for 6 h. PdCl\(_2\)(dpbb) was prepared from (C\(_6\)H\(_5\))\(_2\)P(CH\(_3\))\(_3\) (16.9 mg, 0.04 mmol) and (C\(_6\)H\(_5\))\(_2\)PdCl\(_2\) (12.6 mg, 0.022 mmol) in toluene (2 mL). Yield 47% (102 mg); yellow solid, m. p. 90-92°C; Rf (30% EtOAc in Petrol) 0.25; \([\alpha]_D^{25} +138.9 (c 1.0 \text{ in DCM})\); νmax/cm\(^{-1}\) 2954 (C-H), 2868 (C-H), 1743 (C=O), 1712 (C=O); δH (400 MHz, CDCl\(_3\)): 0.91 (6H, dd, J 8.9, 6.8, HC(CH\(_3\)_2)), 1.80 (1H, dq, J 6.8, 5.6, (HC\(_2\)CH\(_3\)), 3.48 (1H, d, J 8.3, C(4)H\(_3\)H\(_6\)), 3.59 (3H, s, CO\(_2\)CH\(_3\)), 3.77 (3H, s, OCH\(_3\)), 4.84 (1H, d, J 5.6, C(2)H), 5.02 (1H, d, J 8.3, C(4)H\(_3\)H\(_6\)), 6.19 (1H, s, C(7)H), 6.86 (2H, d, J 8.9, C(3')H), 7.31 (2H, d, J 8.9, C(2')H); δC (100 MHz, CDCl\(_3\)): 17.1, 17.1 (HC\(_2\)CH\(_3\)), 33.2 (HC\(_2\)CH\(_3\)), 53.3 (CO\(_2\)CH\(_3\)), 55.5 (OCH\(_3\)), 70.3 (C(4)), 76.9 (C(5)), 93.5 (C(2)), 114.7 (C(3')), 119.0 (C(7)), 122.5 (C(1')), 128.8 (C(2')), 159.3 (C(6)), 161.9 (C(4')), 170.1 (CO\(_2\)CH\(_3\)), 177.5 (C(8)); m/z ([ESI\(^+\)]\(^+\)) 332.1 ([M+H\(^+\)], 30%); HRMS ([ESI\(^+\)]\(^+\)) found 332.1493, C\(_{18}\)H\(_{22}\)O\(_5\) ([M+H\(^+\)]\(^+\)) requires 332.1493.

(2R,5S)-1-Aza-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0] oct-6-ene, 8aii
According to General Method F, mesylate 7a (206 mg, 0.65 mmol) was reacted with phenylboronic acid (119 mg, 0.98 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.62 mL, 5.85 mmol) in ethanol (0.26 mL, 4.55 mmol) and toluene (13 mL) for 6 h. PdCl₂(dppb) was prepared from (C₅H₅)₂P(CH₂)₄P(C₅H₅)₂ (16.6 mg, 0.04 mmol) and (C₅H₅CN)₂PdCl₂ (12.3 mg, 0.033 mmol) in toluene (2 mL). Yield 45% (87 mg); white solid, m. p. 110-112°C; Rf (30% EtOAc in Petrol) 0.35; [α]₀²⁵ +136.5 (c 1.0 in DCM); νmax/cm⁻¹ 2965 (C-H), 2875 (C-H), 1743 (C=O), 1708 (C=O); δHH (400 MHz, CDCl₃): 0.92 (6H, dd, J 9.5, 6.8, HC(CH₃)₂), 1.81 (1H, dq, J 6.8, 5.6, HC(CH₃)₂), 3.50 (1H, d, J 8.4, C(4)H(CH₃)), 3.59 (3H, s, CO₂CH₃), 4.85 (1H, d, J 5.6, C(2)H), 5.04 (1H, d, J 8.4, C(4)H(CH₃)), 6.33 (1H, s, C(7)H), 7.35-7.39 (5H, m, ArH); δC (100 MHz, CDCl₃): 17.1, 17.1 (HC(CH₃)₂), 33.2 (HC(CH₃)), 53.3 (CO₂CH₃), 70.3 (C(4)), 76.9 (C(5)), 93.5 (C(2)), 121.5 (C(7)), 127.0-131.2 (ArC), 159.6 (C(6)), 169.8 (CO₂CH₃), 177.0 (C(8)); m/z ([ESI⁺]⁺ 302.1 (C₆H₅NO₂), 93%); HRMS ([ESI⁺]⁺) found 324.1171, C₁₃H₁₀NO₂Na ([M+Na⁺]⁺ requires 324.1206). Single Crystal Data for 8aii: C₁₃H₁₀NO₂S, Mr =317.41. 150 K – monoclinic, P 2₁, a = 8.07240(10) Å, b = 13.0011(2) Å, c = 8.5311(2) Å, V = 823.23(3) Å, Data/restraints/parameters – 3388/1/200, Flack = 0.001(14) for 1604 Friedel pairs, Rint = 0.017, Final R1 = 0.0270, wR2 = 0.0689 (l>2σ(I)).

(2R,5S)-1-Aza-6-(4-chlorophenyl)-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 8aiii

According to General Method F, mesylate 7a (206 mg, 0.63 mmol) was reacted with 4-chlorophenylboronic acid (104 mg, 0.66 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.6 mL, 5.67 mmol) in ethanol (0.25 mL, 4.41 mmol) and toluene (12 mL) for 3 h. PdCl₂(dppb) was prepared from (C₅H₅)₂P(CH₂)₄P(C₅H₅)₂ (16.0 mg, 0.038 mmol) and (C₅H₅CN)₂PdCl₂ (12.0 mg, 0.032 mmol) in toluene (2 mL). Yield 40% (84 mg); white solid, m. p. 120-122°C; Rf (30% EtOAc in Petrol) 0.42; [α]₀²⁵ +125.9 (c 1.0 in DCM); νmax/cm⁻¹ 2969 (C-H), 2876 (C-H), 1742 (C=O), 1709 (C=O); δHH (400 MHz, CDCl₃): 0.92 (6H, dd, J 9.6, 6.8, HC(CH₃)₂), 1.80 (1H, dq, J 6.8, 5.6, (HC(CH₃)₂), 3.49 (1H, d, J 8.4, C(4)H(CH₃)), 3.60 (3H, s, CO₂CH₃), 4.85 (1H, d, J 5.6, C(2)H), 5.01 (1H, d, J 8.4, C(4)H(CH₃)), 6.32 (1H, s, C(7)H), 7.29 (2H, d, J 8.8, C(2')H), 7.34 (2H, d, J 8.8, C(3')H); δC (100 MHz, CDCl₃): 17.1, 17.1 (HC(CH₃)₂), 33.2 (HC(CH₃)), 53.5 (CO₂CH₃), 70.3 (C(4)), 76.8 (C(5)), 93.6 (C(2)), 122.0 (C(7)), 128.3 (C(2')), 128.3 (C(4')), 129.7 (C(3')), 137.4 (C(1')), 158.2 (C(6)), 169.7 (CO₂CH₃), 176.6 (C(8)); m/z ([ESI⁺]⁺ 336.1 ([M+H⁺], 35Cl, 25%); 338.1 ([M+H⁺], 37Cl, 10%); HRMS ([ESI⁺]⁺) found 358.0812, C₁₇H₁₈ClNO₂Na ([M+Na⁺], 35Cl) requires 358.0817.

(2R,5R)-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 8bi
According to general method F, mesylate 7b (70 mg, 0.21 mmol) was reacted with 4-methoxycarbonylboronic acid (48 mg, 0.315 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.2 mL, 1.89 mmol) in ethanol (0.08 mL, 1.47 mmol) and toluene (10 mL) for 3 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₃P(C₆H₅)₂ (5.3 mg, 0.013 mmol) and (C₆H₅)₂CN·PdCl₂ (4.0 mg, 0.011 mmol) in toluene (1 mL). Yield 72% (52 mg); colourless oil; Rₑ (30% EtOAc in Petrol) 0.28; [α]D 25° +269.8 (c 1.0 in DCM); νmax/cm⁻¹ 2959 (C=H), 2870 (C=H); δH (CDCl₃) 6.6, HC(CH₃), 7.33 (1H, d, J = 1.0); δC (CDCl₃): 0.90 (3H, d, J = 6.6, HC(CH₃)(CH₃)), 1.00 (3H, d, J = 6.6, HC(CH₃)(CH₃)), 1.71 (1H, dq, J = 16.2, 6.6, HC(CH₃)₂), 2.86 (1H, d, J = 10.8, C(4)H₃H₆), 3.62 (3H, s, CO₂CH₃), 3.77 (3H, s, OCH₃), 3.98 (1H, d, J = 10.8, C(4)H₃H₆), 4.74 (1H, d, J = 9.5, C(2)H), 6.15 (1H, s, C(7)H), 6.86 (2H, d, J = 9.0, C(3')H), 7.42 (2H, d, J = 9.0, C(2')H); δₑ (100 MHz, CDCl₃): 19.5, 19.9 (HC(CH₃)₃), 35.3 (C(4)), 37.3 (HC(CH₃)₃), 53.4 (CO₂CH₃), 55.5 (OCH₃), 65.7 (C(2)), 80.6 (C(5)), 114.6 (C(3')), 118.0 (C(7)), 122.3 (C(1')), 128.7 (C(2')), 157.6 (C(6)), 161.7 (C(4')), 170.2 (CO₂CH₃), 173.2 (C(8)); m/z ([ESI⁺]) 348.2 ([M+H]⁺, 40%), 370.0 ([M+Na]⁺, 100%); HRMS ([ESI⁺]) found 348.1264, C₁₈H₂₅NO₂S ([M+H]⁺) requires 348.1264.

(2R,5R)-1-Aza-2-isopropyl-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0] oct-6-ene, 8bii

According to general method F, mesylate 7b (70 mg, 0.21 mmol) was reacted with phenylboronic acid (38 mg, 0.315 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.2 mL, 1.89 mmol) in ethanol (0.08 mL, 1.47 mmol) and toluene (10 mL) for 3 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₃P(C₆H₅)₂ (5.3 mg, 0.013 mmol) and (C₆H₅)₂CN·PdCl₂ (4.0 mg, 0.011 mmol) in toluene (1 mL). Yield 74% (49 mg); white solid, m. p. 116-118°C; Rₑ (30% EtOAc in Petrol) 0.45; [α]D 25° +250.0 (c 1.0 in DCM); νmax/cm⁻¹ 2960 (C=H), 2871 (C=H); δH (CDCl₃) 6.29 (1H, s, C(7)H), 6.86 (2H, d, J = 9.0, C(3')H), 7.42 (2H, d, J = 9.0, C(2')H); δₑ (100 MHz, CDCl₃): 19.5, 19.9 (HC(CH₃)₃), 35.3 (C(4)), 37.3 (HC(CH₃)₃), 53.4 (CO₂CH₃), 55.5 (OCH₃), 65.7 (C(2)), 80.6 (C(5)), 114.6 (C(3')), 118.0 (C(7)), 122.3 (C(1')), 128.7 (C(2')), 157.6 (C(6)), 161.7 (C(4')), 170.2 (CO₂CH₃), 173.2 (C(8)); m/z ([ESI⁺]) 348.2 ([M+H]⁺, 40%), 370.0 ([M+Na]⁺, 100%); HRMS ([ESI⁺]) found 348.1264, C₁₈H₂₅NO₂S ([M+H]⁺) requires 348.1264.

(2R,5R)-1-Aza-6-(4-chlorophenyl)-2-isopropyl-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 8biii

According to general method F, mesylate 7b (70 mg, 0.21 mmol) was reacted with 4-chlorophenylboronic acid (34.5 mg, 0.22 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.2 mL, 1.89 mmol) in ethanol
(0.08 mL, 1.47 mmol) and toluene (10 mL) for 5 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (5.3 mg, 0.013 mmol) and (C₆H₅CN)₂PdCl₂ (4.0 mg, 0.011 mmol) in toluene (1 mL). Yield 41% (30 mg); colourless oil; Rₜ (30% EtOAc in Petrol) 0.53; [α]D²⁵ +230.9 (c 1.0 in DCM); νmax/cm⁻¹ 2956 (C-H), 2870 (C-H), 1746 (C=O), 1710 (C=O); δH (400 MHz, CDCl₃): 0.90 (3H, d, J 8.9, C(2')H); 9.7 (1H, s, C(7)H), 6.27 (1H, s, C(7)H), 7.33 (2H, d, J 7.7, C(2')H), 6.87 (2H, d, J 10.6, C(7)H); 53.5 (CO₂Me), 65.7 (C(2)), 80.7 (C(5)), 81.1 (C(6)), 114.2 (C(3')) 123.5 (C(7)), 129.6 (C(5)), 135.9 (C(4)), 169.8 (CO₂CH₃), 172.4 (C(8)); m/z ([ESI]⁺) 350.0 ([M+H]⁺, 35Cl, 80%), 354.0 ([M+Na]⁺, 35Cl, 25%), 374.0 ([M+Na]⁺, 35Cl, 40%); HRMS ([ESI]⁺) found 352.0770, C₁₇H₁₆ClNO₃S ([M+H]⁺, 35Cl) requires 352.0769.

(2R,5R)-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene, 8ci

According to general method F, mesylate 7d (295 mg, 0.84 mmol) was reacted with 4-methoxyphenylboronic acid (205 mg, 1.35 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.8 mL, 7.56 mmol) in ethanol (0.34 mL, 5.88 mmol) and toluene (13 mL) for 24 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (21.0 mg, 0.05 mmol) and (C₆H₅CN)₂PdCl₂ (16.0 mg, 0.04 mmol) in toluene (2 mL). Yield 13% (40 mg); yellow oil; Rₜ (40% EtOAc in Petrol) 0.55; [α]D²⁵ +353.6 (c 1.0 in DCM); νmax/cm⁻¹ 2958 (C-H), 2840 (C-H), 1744 (C=O), 1703 (C=O); δH (100 MHz, CDCl₃): 0.89 (3H, d, J 6.6, HC(CH₃)(CH₃)), 1.03 (3H, d, J 10.6, C(4)Ha), 1.17-1.79 (1H, m, HC(CH₃)₂), 1.91 (3H, s, C(7)CH₃), 2.86 (1H, d, J 9.5, C(2)H), 3.56 (3H, s, CO₂CH₃), 3.77 (3H, s, OCH₃), 3.86 (1H, d, J 10.6, C(4)Ha), 4.76 (1H, d, J 8.9, C(2')H); δC (100 MHz, CDCl₃): 10.7 (C(7)CH₃), 19.6, 20.1 (HC(CH₃)₂), 35.9 (C(4)), 37.3 (HC(CH₃)₂), 53.0 (CO₂CH₃), 55.3 (OCH₃), 65.9 (C(2)), 81.1 (C(5)), 114.2 (C(3')) 123.5 (C(7)), 129.4 (C(1')), 129.6 (C(2')), 150.2 (C(6), 160.3 (C(4'))), 170.0 (CO₂CH₃), 174.2 (C(8)); m/z ([ESI]⁺) 362.2 ([M+H]⁺, 100%), 384.2 ([M+Na]⁺, 20%); HRMS ([ESI]⁺) found 362.1417, C₁₉H₂₄NO₄S ([M+H]⁺) requires 362.1421.

(2R,5R)-1-Aza-2-isopropyl-5-methoxycarbonyl-7-methyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0]oct-6-ene, 8cii

According to general method F, mesylate 7d (503 mg, 1.44 mmol) was reacted with phenylboronic acid (280 mg, 2.3 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.37 mL, 12.96 mmol) in ethanol (0.58 mL, 10.08 mmol) and toluene (13 mL) for 20 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (36.8 mg, 0.0864 mmol) and (C₆H₅CN)₂PdCl₂ (27.6 mg, 0.072 mmol) in toluene (3 mL). Yield 12% (55 mg);
colourless oil; R_f (40% EtOAc in Petrol) 0.64; [\text{\text{C}}^{42} \text{S}]^{+} +338.5 (c 1.0 in DCM); \nu_{max}/\text{cm}^{-1} 2958 (C-H), 2927(C-H), 1745 (C=O), 1704 (C=O); \delta_{H} (400 MHz, CDCl_3) 0.89 (3H, d, J 6.6, HC(CH$_3$)$_2$(CH$_3$)), 1.04 (3H, d, J 6.6, HC(CH$_3$)$_2$(CH$_3$)), 1.76 (1H, dq, J 9.4, 6.6, (HC(CH$_3$)$_2$), 1.88 (3H, s, C(7)CH$_3$), 2.89 (1H, d, J 10.6, C(4)H$_4$H$_6$), 3.56 (3H, s, CO$_2$CH$_3$), 3.82 (1H, d, J 10.6, C(4)H$_4$H$_6$), 4.76 (1H, d, J 9.4, C(2)H), 7.19-7.38 (5H, m, ArH); \delta_{C} (100 MHz, CDCl$_3$): 10.5 (C(7)CH$_3$), 19.6, 20.1 (HC(CH$_3$)$_2$), 35.8 (C(4)), 37.3 (HC(CH$_3$)$_2$), 53.0 (CO$_2$CH$_3$), 66.0 (C(2)), 81.3 (C(5)), 128.0-131.2 (ArC+C(7)), 150.6 (C(6)), 169.7 (CO$_2$CH$_3$), 173.9 (C(8)); m/z ([ESI]$^+$) 332.2 ([M+H]$^+$, 20%), 354.0 ([M+Na]$^+$, 25%); HRMS ([ESI]$^+$) found 332.1315, C$_{18}$H$_{20}$NO$_3$S ([M+H]$^+$) requires 332.1315.

\textbf{(2R,5R)-1-Aza-6-(4-chlorophenyl)-2-isopropyl-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 8ciii}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

According to general method F, mesylate 7d (570 mg, 1.63 mmol) was reacted with 4-chlorophenylboronic acid (267 mg, 1.71 mmol), PdCl$_2$(dpbb), 1 M aqueous Na$_2$CO$_3$ solution (1.55 mL, 14.67 mmol) in ethanol (0.66 mL, 11.41 mmol) and toluene (13 mL) for 24 h. PdCl$_2$(dpbb) was prepared from (C$_6$H$_5$)$_2$P(CH$_2$)$_2$P(C$_6$H$_5$)$_2$ (42.0 mg, 0.1 mmol) and (C$_6$H$_5$)PdCl$_2$ (31.0 mg, 0.08 mmol) in toluene (3 mL). Yield 11% (67 mg); white solid, m. p. 76-78°C; R_f (40% EtOAc in Petrol) 0.57; [\text{\text{C}}^{42} \text{S}]^{+} +341.8 (c 1.0 in DCM); \nu_{max}/\text{cm}^{-1} 2959 (C-H), 2871 (C-H), 1744 (C=O), 1704 (C=O); \delta_{H} (400 MHz, CDCl$_3$): 0.89 (3H, d, J 6.6, HC(CH$_3$)(CH$_3$)), 1.03 (3H, d, J 6.6, HC(CH$_3$)(CH$_3$)), 1.75 (1H, dq, J 9.7, 6.6, HC(CH$_3$)$_2$), 1.87 (3H, s, C(7)CH$_3$), 2.86 (1H, d, J 10.6, C(4)H$_4$H$_6$), 3.57 (3H, s, CO$_2$CH$_3$), 3.79 (1H, d, J 10.6, C(4)H$_4$H$_6$), 4.75 (1H, d, J 9.7, C(2)H), 7.14 (2H, d, J 8.7, C(2)H), 7.34 (2H, d, J 8.7, C(3)H); \delta_{C} (100 MHz, CDCl$_3$): 10.5 (C(7)CH$_3$), 19.6, 20.1 (HC(CH$_3$)$_2$), 35.8 (C(4)), 37.3 (HC(CH$_3$)$_2$), 53.1 (CO$_2$CH$_3$), 66.0 (C(2)), 81.2 (C(5)), 129.2 (C(3)”), 129.4 (C(2)”), 129.6 (C(7)), 131.8 (C(4”)), 135.6 (C(1”)), 149.1 (C(6)), 169.6 (CO$_2$CH$_3$), 173.5 (C(8)); m/z ([ESI]$^+$) 366.0 ([M+H]$^+$, 35Cl, 100%), 368.0 ([M+H]$^+$, 37Cl, 40%), 388.0 ([M+Na]$^+$, 35Cl, 50%); HRMS ([ESI]$^+$) found 366.0924, C$_{18}$H$_{20}$ClNO$_3$S ([M+H]$^+$, 35Cl) requires 366.0925.

\textbf{(2R,5S,6R)-1-Aza-2-isopropyl-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxobicyclo [3.3.0] octane, 9ai}

According to General Method G, the hydrogenation reaction of 8ai (72 mg, 0.21 mmol) in presence of platinum(IV) oxide (7.4 mg, 0.03 mmol) under a H$_2$ atmosphere for 6 h afforded pyrrolidinone 9ai. Yield 82% (59 mg); white semi-solid; R_f (30% EtOAc in Petrol) 0.22; [\text{\text{C}}^{42} \text{S}]^{+} -52.1 (c 1.0 in DCM); \nu_{max}/\text{cm}^{-1} 2962 (C-H), 2875 (C-H), 1742 (C=O), 1713 (C=O); \delta_{H} (400 MHz, CDCl$_3$): 0.86 (6H, dd, J 15.1, 6.8, HC(CH$_3$)$_2$), 1.69 (1H, dq, J 13.9, 6.8, HC(CH$_3$)$_2$), 2.66 (1H, dd, J 15.8, 7.8, C(7)H$_4$H$_6$), 3.31 (3H, s, CO$_2$CH$_3$), 3.41 (1H, dd, J 15.8, 13.0, C(7)H$_4$H$_6$), 3.68-3.76 (5H, m, C(6)H + OCH$_3$ + C(4)H$_4$H$_6$), 4.69 (1H, d, J 8.6, C(4)H$_4$H$_6$), 5.00 (1H, d, J 6.5, C(2)H), 6.78 (2H, d, J 8.8, C(3)H), 6.99 (2H, d, J 8.8, C(2)H); \delta_{C} (100 MHz, CDCl$_3$): 16.8, 17.5 (HC(CH$_3$)$_2$), 32.4 (HC(CH$_3$)$_2$), 54.8 (OCH$_3$), 70.2 (C(7)H$_4$H$_6$), 125.6 (C(6)H), 129.3 (C(4)H$_4$H$_6$), 135.6 (C(1)”), 149.1 (C(6)), 169.4 (CO$_2$CH$_3$), 173.5 (C(8)).
(2R,5S,6R)-1-Aza-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0] octane, 9aii

According to General Method G, the hydrogenation reaction of 8aii (52 mg, 0.17 mmol) in presence of platinum(IV) oxide (5.9 mg, 0.025 mmol) under a H2 atmosphere for 5 h afforded pyrrolidinone 9aii. Yield 75% (39 mg); white solid, m. p. 76-78°C; Rf (30% EtOAc in Petrol) 0.28; [α]D25 +46.8 (c 1.0 in DCM); νmax/cm⁻¹ 2962 (C-H), 2876 (C-H), 1742 (C=O), 1713 (C=O); δH(400 MHz, CDCl3): 0.86 (6H, dd, J 16.2, 6.8, HC(CH₃)₂), 1.70 (1H, dq, J 13.4, 6.8, HC(CH₃)₂), 2.69 (1H, dd, J 15.8, 7.9, C(7)H₂H₃), 3.27 (3H, s, CO₂CH₃), 3.46 (1H, dd, J 15.8, 12.8, C(7)H₂H₃), 3.70-3.85 (2H, m, C(4)H₂H₃ + C(6)H), 4.71 (1H, d, J 8.7, C(4)H₂H₃), 5.01 (1H, d, J 6.5, C(2)H), 7.05-7.29 (5H, m, ArH); δC (100 MHz, CDCl₃): 16.7, 17.5 (HC(CH₃)₂), 32.4 (HC(CH₃)₂), 39.1 (C(7)), 50.0 (C(6)), 52.1 (CO₂CH₃), 74.0 (C(4)), 76.6 (C(5)), 93.2 (C(2)), 127.5-135.4 (ArC), 170.5 (CO₂CH₃), 175.8 (C(8)); m/z ([ESI]⁺) 304.1 ([M+H]⁺, 50%); HRMS ([ESI]⁺) found 304.1543, C₁₇H₂₄NO₅ ([M+H]⁺) requires 304.1543. Single Crystal Data for 9ii: C₁₇H₂₁NO₄, Mr =303.36. 150 K – monoclinic, P 2₁, a = 11.4888(5) Å, b = 6.2741(3) Å, c = 22.3118(10) Å, V = 1575.18(13) Å, Data/restraints/parameters – 6479/1/399, Flack = -0.11(17) for 2897 Friedel pairs, Rint = 0.046, Final R1 = 0.0514, wR2 = 0.1259 (I>2σ(I)).

(2R,5S,6R)-1-Aza-6-(4-chlorophenyl)-2-isopropyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0] octane, 9aiii

According to General Method G, the hydrogenation reaction of 8aiii (43 mg, 0.12 mmol) in presence of platinum(IV) oxide (4.3 mg, 0.02 mmol) under a H₂ atmosphere for 6 h afforded pyrrolidinone 9aiii. Yield 85% (37 mg); white solid, m. p. 90-92°C; Rf (30% EtOAc in Petrol) 0.27; [α]D25 +49.9 (c 1.0 in DCM); νmax/cm⁻¹ 2962 (C-H), 2876 (C-H), 1742 (C=O), 1714 (C=O); δH(400 MHz, CDCl₃): 0.86 (6H, dd, J 15.2, 6.8 HC(CH₃)₂), 1.69 (1H, dq, J 13.4, 6.8, HC(CH₃)₂), 2.69 (1H, dd, J 15.8, 7.8, C(7)H₂H₃), 3.32 (3H, s, CO₂CH₃), 3.40 (1H, dd, J 15.8, 12.8, C(7)H₂H₃), 3.68-3.79 (2H, m, C(4)H₂H₃ + C(6)H), 4.70 (1H, d, J 8.8, C(4)H₂H₃), 5.00 (1H, d, J 6.5, C(2)H), 7.01 (2H, d, J 8.5, C(2)H), 7.24 (2H, d, J 8.5, C(3)H), 16.8, 17.5 (HC(CH₃)₂), 32.4 (HC(CH₃)₂), 39.2 (C(7)), 49.5 (C(6)), 52.3 (CO₂CH₃), 73.9 (C(4)), 76.4 (C(5)), 93.3 (C(2)), 128.7-134.0 (ArC), 170.4 (CO₂CH₃), 175.4 (C(8)); m/z ([ESI]⁺) 338.1 ([M+H]⁺, 35Cl, 35%), 340.1 ([M+H]⁺, 37Cl, 25%); HRMS ([ESI]⁺) found 338.1154, C₁₇H₂₄NO₅Cl ([M+H]⁺, 35Cl) requires 338.1154.

Methyl (2S,3R)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate, 10
According to General Method I, the bicyclic pyrrolidinone derivative 9ai (22 mg, 0.065 mmol) was treated with propane-1,3-dithiol (0.015 mL, 0.15 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.1 mL) to develop pyroglutaminol derivative 10. Yield 97% (18 mg); colourless oil; $[\text{M}+\text{H}]^+$ 304.1366. HRMS ([ESI]$^+$) found 304.1366.

Methyl(S)-2-(hydroxymethyl)-5-oxo-3-phenyl-2,5-dihydro-1H-pyrole-2-carboxylate, 11

According to General Method I, the bicyclic pyrrolinone derivative 8a(i) (14 mg, 0.046 mmol) was treated with propane-1,3-dithiol (0.01 mL, 0.1 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (0.76 mL) to develop pyroglutaminol derivative 11. Yield 97% (12 mg); colourless oil; $\nu_{\text{max}}$ 3361 (O-H), 2953 (C-H), 1796 (C=O); $\delta_{\text{H}}$ (500 MHz, MeOD): 3.76 (1H, dd, $J_{1,3}$ = 10.4, C(4)); 3.88 (1H, d, $J_{1,8}$ = 9.0, C(4)); 4.17 (1H, s, ArH); 4.25 (1H, s, ArH); 6.49 (1H, s, C(4)); 6.90 (2H, d, $J_{2,6}$ = 9.0, C(3)); 7.42-7.58 (5H, m, ArH); 7.64 (2H, d, $J_{2,6}$ = 9.0, C(3)); 7.70 (2H, d, $J_{2,6}$ = 9.0, C(3)); 123.4 (C(4)); 127.0-131.1 (ArC + C(3)); 158.4 (C(2)); 168.9 (C(5)); $m/z$ ([ESI]$^+$) 248.1 ([M+H]$^+$, 100%); HRMS ([ESI]$^+$) found 324.0998, C$_{15}$H$_{12}$NO$_4$Na ([M+Na]$^+$) requires 324.0998.

(2R,5S)-1-Aza-2-isopropyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene, 12

According to general method F, mesylate 7e (104 mg, 0.36 mmol) was reacted with 4-methoxyphenylboronic acid (87 mg, 0.57 mmol), PdCl$_2$(dpbb), 1 M aqueous Na$_2$CO$_3$ solution (0.34 mL, 3.24 mmol) in ethanol (0.15 mL, 2.52 mmol) and toluene (13 mL) for 24 h. PdCl$_2$(dpbb) was prepared from (C$_6$H$_5$)$_2$P(CH$_2$)$_4$P(C$_6$H$_5$)$_2$ (9.0 mg, 0.021 mmol) and (C$_6$H$_5$CN)$_2$PdCl$_2$ (7.0 mg, 0.018 mmol) in toluene (1 mL). Yield 32% (35 mg); colourless oil; $R_f$ (30% EtOAc in Petrol) 0.45. $[\text{M}+\text{H}]^+$ 304.1366. HRMS ([ESI]$^+$) found 304.1366, C$_{17}$H$_{22}$NO$_2$S ([M+H]$^+$) requires 304.1366.
References


HN
MeO
C

4b
MeO₂C₄
HN
4b

Oct12-2017-10-HB146.2.fid
Instrument AVF400
Chemist HALIMA
Group MGM
Project Account Code DM7300
c13acq csl CDCl3 (C:\NMR) mgmgrp 10
5c
6d (A): X = CO₂Me
6e (B): X = H
6d (A): $X = \text{CO}_2\text{Me}$

6e (B): $X = \text{H}$
7d

Meso.
OMs

CO₂Me
\[
\text{Cl} \quad \text{CO}_2\text{Me}
\]
8aiii
8cii
The image contains a chemical structure with labels indicating peak positions in an NMR spectrum. The chemical structure is labeled as '11' and includes functional groups such as CO₂Me, OH, and a pyrrole ring. The spectrum shows various chemical shifts with corresponding peak assignments and multiplicity labels (s, m, d) and integrals.