

Synthetic Access to 3-Substituted Pyroglutamic acids from Tetramate Derivatives of Serine, Threonine, *allo*-Threonine and Cysteine

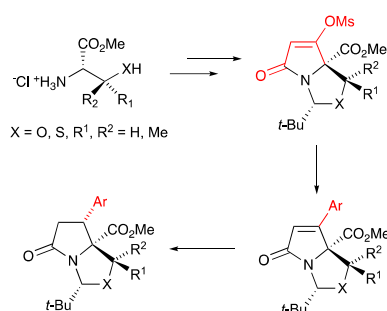
Halima Bagum,[†] Kirsten E. Christensen,[†] Alexander Pretsch,[‡] Dagmar Pretsch,[‡] and Mark G. Moloney^{*,†,‡,‡}

[†]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.

[‡]Oxford Antibiotic Group, The Oxford Science Park, Magdalen Centre, Oxford OX4 4GA, UK.

mark.moloney@chem.ox.ac.uk



Abstract: A general route which provides direct access to pyroglutamates from tetramates, making use of Suzuki coupling on an enol mesylate, followed by reduction, is reported. This work permits direct scaffold hopping from tetramate to substituted pyroglutamates. Some compounds in the library showed modest antibacterial activity against Gram-positive bacteria.

Introduction

Pyroglutamates are of interest particularly for their role as starting materials¹ and in drug discovery;^{2, 3} we have been interested in the application of pyroglutamic acids as a chiral starting material, and have shown that, in a suitably protected form, it may be selectively alkylated, hydroxylated and aminated,^{4, 5} as well as used for conjugate additions by carbon,⁶ oxygen⁷ and nitrogen nucleophiles.⁸ While this does provide access to highly functionalised heterocyclic

derivatives, it can require sequential activation of different positions around the heterocyclic ring and such a multi-step sequence lacks convenience; an approach involving C-H activation for direct ring functionalisation has, however, been recently reported.⁹ Of interest to us was a more efficient entry to pyroglutamates with peripheral ring functionality, and with the potential for generalisation; we envisaged that tetramates,¹⁰⁻¹² readily available from malonyloxazolidines by highly chemoselective Dieckmann ring closures¹³ might find application in that regard.¹⁴ We report work here which demonstrates that such substituted pyroglutamates are accessible from tetramate precursors, providing a general approach for scaffold hopping between these two systems,¹⁵⁻¹⁷ with scope for control of substituents around the ring periphery.

Results and Discussion

The required tetramates **4a-d** were prepared from the methyl ester hydrochlorides of L-serine **1a**, L-threonine **1b**, L-*allo*-threonine **1c** and L-cysteine **1d** respectively via the oxa(thia)zolidines **2a-d** and malonamides **3a-d** according to methodology reported in the literature (Scheme 1 and Table 1);¹⁸ the latter compounds exist predominantly in enolic form. Moreover, a mixture of two different species, even after careful column chromatography, was apparent in the ¹H NMR spectra of malonamides **3a,b,d**, but VT and gradient NOE NMR analysis confirmed that these were due to the presence of rotamers, and that these systems were solely the *cis*-2,4-diastereomer.

Table 1: Key results for the synthesis of tetramate templates **4a-d**.

Tetramate	2a-d		Yield	Yield
	<i>cis:trans</i>	Yield(%)	3a-d (%)	4a-d (%)
4a	1.4:1	86	80	75
4b	1.0:1	88	67	73
4c	2.5:1	71	66	75
4d	1.5:1	95	78	74

The tetramate derivatives **4a,b** could be reacted with tosyl chloride using the literature method¹⁹ to give tosylates **5a,b** in 78 and 57% yield respectively but these were found to show poor reactivity towards Suzuki coupling under a range of conditions,²⁰⁻²² except with PdCl₂(dppb) as ligand (Scheme 1 and Table 2). Suspecting that a more activated system was required for coupling in this extensively resonance delocalised tetramate system, mesylate **5c** was prepared (64% yield), and this was found to couple with 4-methoxyphenylboronic acid using PdCl₂(dppb) catalyst to give the desired product **6ai** with a yield of 80%. On this basis, the mesylates **5d-f** were prepared (Scheme 1 and Table 3), and of immediate interest were the different values of δ_{H4} depending on its location on the *exo*- or *endo* face of the bicyclic system. The structure of these compounds was confirmed by single crystal X-ray diffraction studies (ESI),²³ which for **5d** (derived from threonine) highlighted the steric congestion on the *endo*-face caused by the C-4 methyl group.

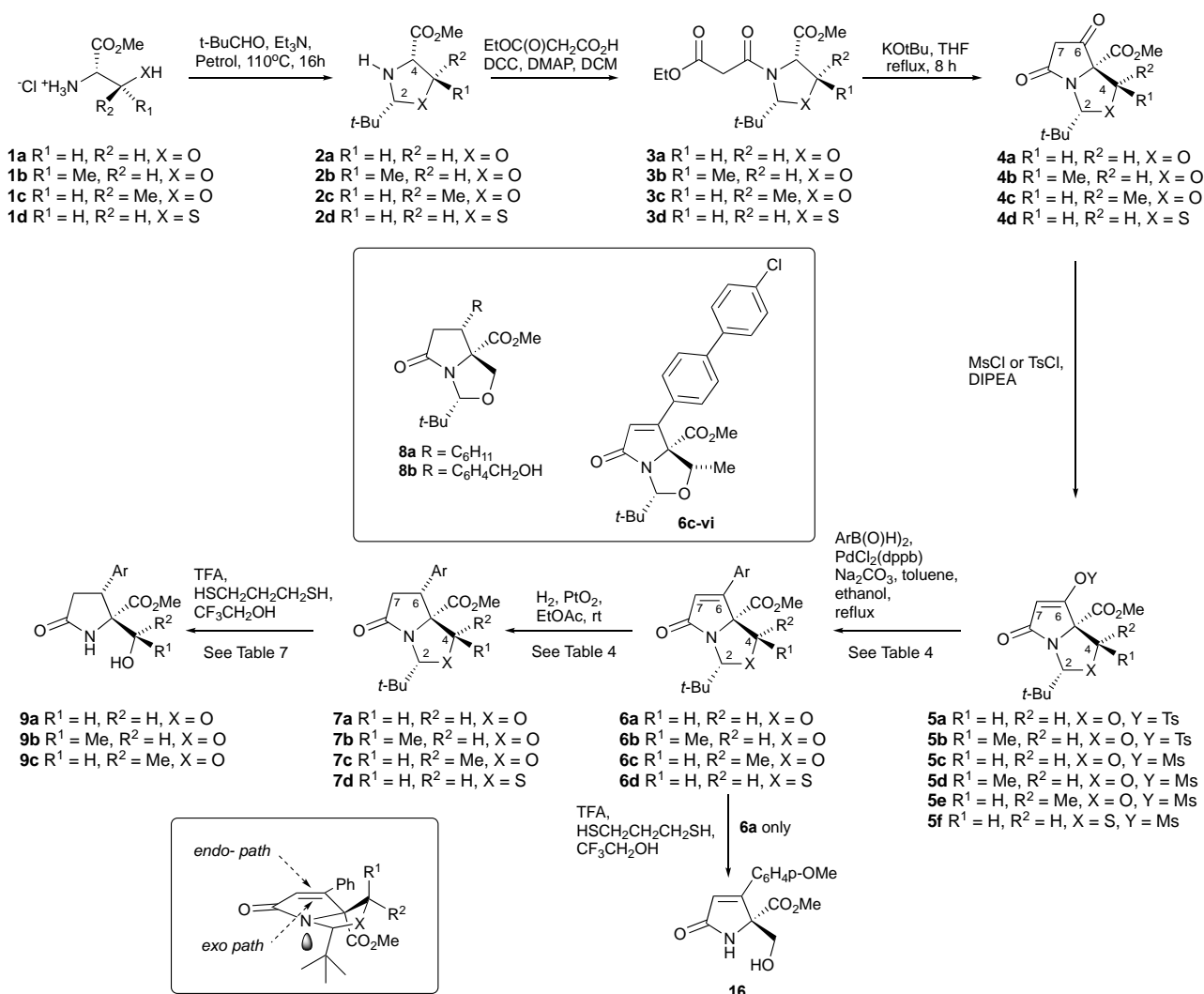


Table 2: Suzuki coupling reactions of tosylates **5a,b** with arylboronic acids ArB(OH)₂.

Compound	Y	Ar	Conditions	Product (Yield)
5a	H	4-MeOC ₆ H ₄	PdCl ₂ (dppf), Cs ₂ CO ₃ , THF/H ₂ O, 65°C, 6h	6ai (18%)
5a	H	4- MeOC ₆ H ₄	NiCl ₂ (PPh ₃) ₂ , THF, rt, 15h	-
5a	H	4- MeOC ₆ H ₄	NiCl ₂ (PPh ₃) ₂ , Cs ₂ CO ₃ , THF, 65°C, 15h	-
5a	H	4- MeOC ₆ H ₄	PdCl ₂ (dppb), Na ₂ CO ₃ , Toluene/EtOH, 110°C, 8h	6ai (56%)
5a	H	Ph	PdCl ₂ (dppf), Cs ₂ CO ₃ , THF/H ₂ O, 65°C, 12h	-
5a	H	4-BrC ₆ H ₄	PdCl ₂ (dppf), Cs ₂ CO ₃ , THF/H ₂ O, 65°C, 12h	-
5a	H	2-Thienyl	PdCl ₂ (dppf), Cs ₂ CO ₃ , THF/H ₂ O, 65°C, 12h	-
5b	Me	4- MeOC ₆ H ₄	PdCl ₂ (dppb), Na ₂ CO ₃ , Toluene/EtOH, 110°C, 20h	6bi (<14%)

Table 3: Mesylation of tetramates **4a-d** and characteristic chemical shifts for H₄ (δ_{H4}).

Entry	X, R ₁ , R ₂	Product	Yield (%)	δ_{H4} (ppm)
4a	O, H, H	5c	64	3.45, 4.74
4b	O, Me, H	5d	25	5.01
4c	O, H, Me	5e	52	3.72
4d	S, H, H	5f	44	2.81, 3.60

The Suzuki-Miyaura cross-coupling reactions of **5c-f** were explored using the optimal conditions established earlier with a range of commercially available arylboronic acids (Table 4). Of interest is that the coupling of serine derivative **5c** proceeded successfully, although less efficiently for electron-poor boronic acids, but by contrast the L-threonine system **5d** gave a poor yield (14%) of **6bi** from a sluggish reaction. Attempts to optimise this outcome using the catalyst tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄) by Zhang's conditions²⁴ or Gauler's conditions²⁵ gave complex mixtures. Suspecting that the root cause of the low reactivity was likely to be the steric effect of the *endo*-methyl substituent, the *allo*-L-threonine system **5e** was examined, and was found to give excellent conversion (Scheme 1 and Table 4), except for electron-poor

boronic acids (using p-chlorophenylboronic acid also gave a low yield of **6cvi**). X-ray crystal structures for the 4-methoxyphenyl adducts obtained from L-serine, L-threonine, and L-*allo*-threonine²³ confirmed their structure but also indicated that the *endo*-Me group of threonine derivative **6bi** leads to greater steric hindrance as compared to *endo*-H for the serine **6ai** and *allo*-threonine **6ci** systems (ESI).²³ With the cysteine-derived mesylate **5f**, coupling was also successful, giving adducts **6di** - **6dvii** in 15-62% yields (Table 4). This methodology provides an alternative coupling approach to the recently reported nickel-catalyzed cross-coupling of β -carbonyl alkenyl pivalates with arylzinc chlorides.²⁶

Table 4: Suzuki coupling and reduction reactions for tetramates **5c-f** and **6a-d**.

Entry	Ar	Reaction Time (h)	Product	Yield (%)	Product	Yield (%)
5c	4-Methoxyphenyl	4	6ai	80	7ai	98
5c	Phenyl	5	6aii	64	7aii	88
5c	2-Furyl	12	6aiii	47	7aiii	28
5c	4-Formylphenyl	11	6aiv	28	8b	76
5c	4-Chlorophenyl	7	6av	49 _a (16)	7av	33
5c	4-Bromophenyl	overnight	-	-	-	-
5c	<i>trans</i> -2-Phenylvinyl	48	6avi	25	-	-
5c	2-Phenyl-1-ethynyl	12	6avii	20	-	-
5d	4-Methoxyphenyl	4	6bi	14	-	-
5e	4-Methoxyphenyl	4	6ci	70	7ci	71
5e	Phenyl	4	6cii	80	7cii	94
5e	2-Furyl	overnight	6ciii	28	7ciii	67
5e	4-Formylphenyl	28	6civ	36	7civ	79
5e	4-Chlorophenyl	4	6cv	71 _a	7cv	84
			6cvi	5		
5f	4-Methoxyphenyl	3	6di	62	-	-
5f	Phenyl	3	6dii	58	-	-
5f	2-Furyl	20	6diii	22	-	-
5f	4-Formylphenyl	overnight	6div	25	-	-
5f	4-Chlorophenyl	6	6dv	43 _a	-	-
5f	4-Bromophenyl	20	-	-	-	-
5f	<i>trans</i> -2-Phenylvinyl	24	6dvi	20	-	-
5f	2-Phenyl-1-ethynyl	24	6dvii	15	-	-

^a 1.05 eq 4-Chlorophenyl boronic acid

Having been able to synthesise a library of pyrrolinones **6a-d**, reduction of the C6-C7 double bond to achieve a library of pyrrolidinones was examined; this could not be achieved using the NaBH₄ in AcOH conditions of Castro^{27, 28} or the NaBH₃CN in AcOH of Pinheiro.²⁹ However, hydrogenation using PtO₂ as a catalyst³⁰ gave more success. Thus, treatment of serine derivatives **6a** with atmospheric hydrogen and PtO₂ catalyst over 1-6h efficiently furnished the desired products **7a** (Scheme 1 and Table 4), and the *allo*-threonine derivatives **6c** under the same reaction conditions similarly provided derivatives **7c**; delivery of hydrogen to the *endo*- face of the bicyclic system was clearly preferred. Over-reduction was observed for aldehyde **6aiv** giving benzyl alcohol **8b** (76%) while a shorter reaction time (1h) gave partially reduced lactam **6a** (Ar = C₆H₄CH₂OH) resulting from preferential reduction of the aldehyde over the alkene system; in the case of chlorophenyl derivative **6av**, in addition to the expected product **7av** (33%), the over-reduced cyclohexyl derivative **8a** (35%) was also obtained. The stereochemistry of pyroglutamates **7a** and **7c** was assigned by NOE analysis (Figure 1) and further confirmed by determination of the X-ray crystal structure of **7aii** and **7cii** (ESI).²³ However, of interest is that for hydrogenation of threonine derivative **6bi** under similar conditions, only unreacted starting material was recovered, further confirming the steric hindrance of the C4-methyl group.

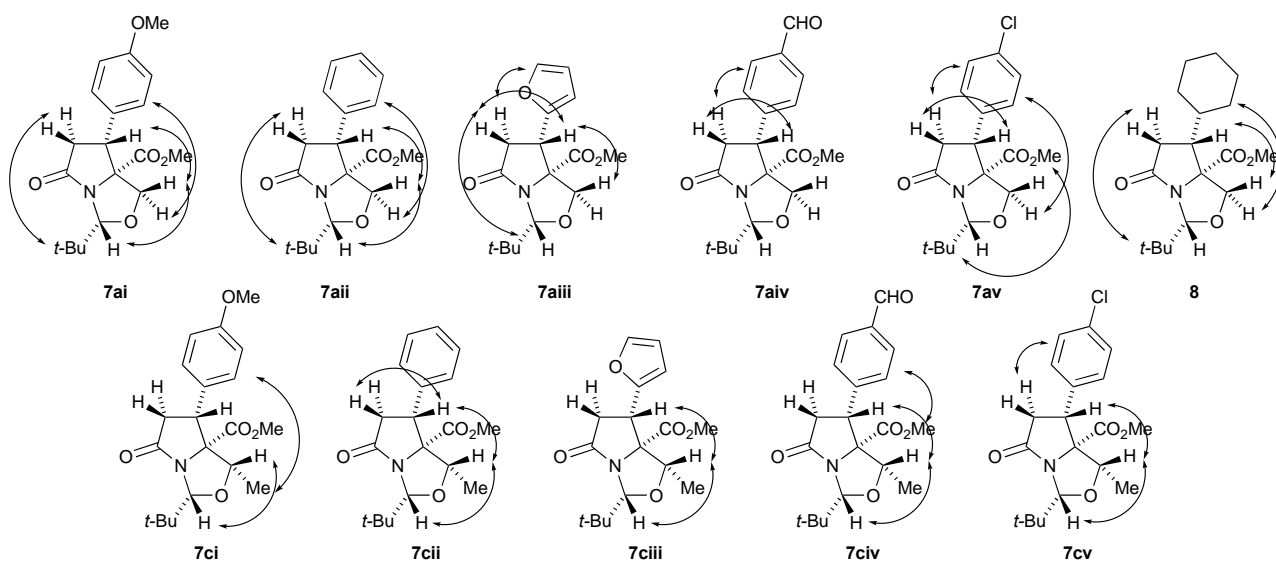


Figure 1. NOE data for selected compounds

By contrast, the cysteine-derived system **6d** was unreactive under these reductive conditions; this is consistent with catalyst poisoning from the heterocyclic sulphur atom.³¹ In order to overcome this problem, sulfone systems were examined;³² Keith *et al.*³³ reported the conversion of the sulfur to sulfone system in lactams by using *m*-chloroperbenzoic acid (*m*-CPBA) and after application of these conditions to tetramate **4d**, the product could not be isolated, possibly due to its high polarity which prevented its isolation on silica. However, *m*-CPBA oxidation of mesylate **5f**

furnished desired product **10** in 77% yield (Scheme 2), and its structure was confirmed by single-crystal X-ray diffraction analysis (ESI).²³

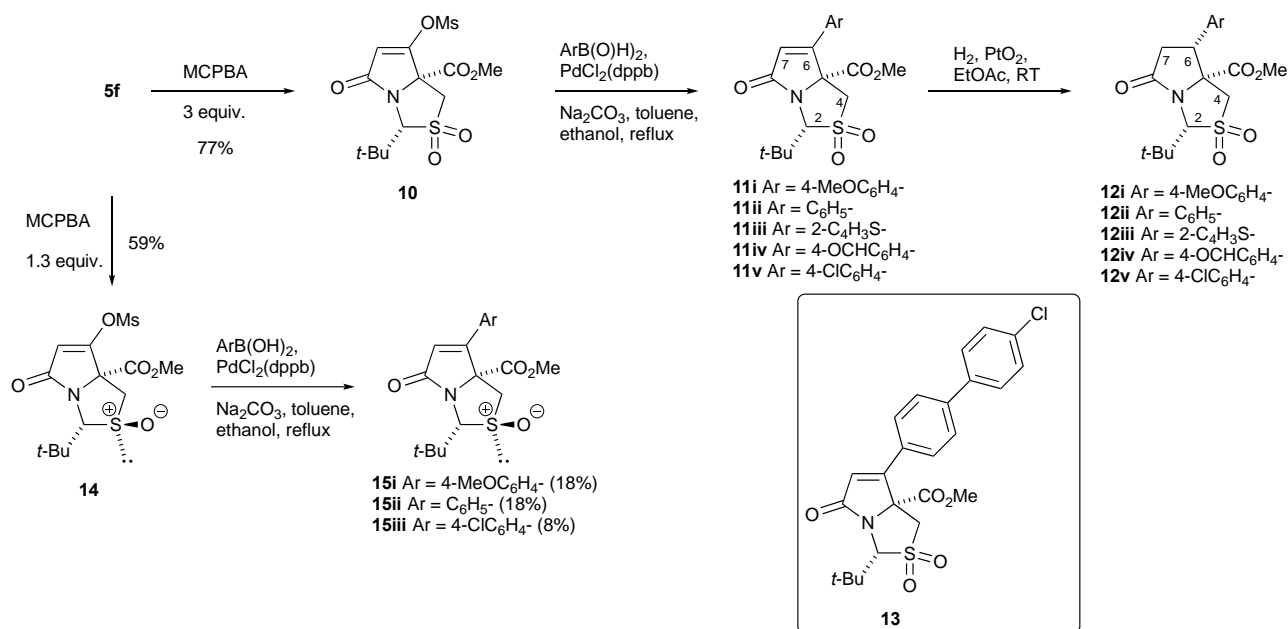
This sulfone was subjected to the optimal conditions for Suzuki coupling, and gave sulfone adducts **11i-v** in good yield (Table 5), consistent with the *S*-analogues **6d**. The formation of by-product **13** was also observed for the Suzuki coupling with 4-chlorophenylboronic acid, giving increased yields of this product for higher equivalents of the boronic acid (Scheme 2 and Table 5). These adducts were subjected to hydrogenation which proceeded in good yield and diastereoselectivity to give pyroglutamates **12i-v** (Table 5); of interest is the conservation of NMR and $[\alpha]_D$ values in each compound series, but in particular the complete inversion of the sign of $[\alpha]_D$ in going from the Suzuki coupled product to the reduced system. The stereochemistry of the newly formed chiral centre C6 was assigned by NOESY analysis which displayed a strong interaction between *endo*-H4-H6-H2 for all synthesised products in this series. The absolute stereochemistry was further confirmed by X-ray crystal structure determination of **12v** (ESI).²³

Table 5: Suzuki coupling and subsequent hydrogenation of sulfone: representative values for **11i-v** and **12i-v**.

Ar	Products, Yield	δ_{H6} (ppm)	δ_{H7} (ppm)	$[\alpha]_{D25}$ (<i>c</i> 1.0 in DCM)
4-MeOC ₆ H ₄	11i , 56%	-	6.52	+129.2
4-MeOC ₆ H ₄	12i , 83%	3.79	2.57, 3.26	-87.6
C ₆ H ₅	11ii , 53%	-	6.65	+132.3
C ₆ H ₅	12ii , 82%	3.84	2.60, 3.32	-89.8
2-Furyl	11iii , 20%	-	6.47	+88.3
2-Furyl	12iii , 37%	3.90	2.62, 3.18	-65.1
4-CHOC ₆ H ₄	11iv , 26%	-	6.80	+103.0
4-HOCH ₂ C ₆ H ₄	12iv , 54%	3.82	2.54, 3.29	-72.7
4-ClC ₆ H ₄	11v , 48%	-	6.65	+105.4

4-ClC ₆ H ₄ C ₆ H ₄	13 , 8%	-	6.70	+70.2
4-ClC ₆ H ₄	12v , 77%	3.81	2.60, 3.26	-65.1

Given the successful hydrogenation of sulfones **11iv**, preparation of the corresponding sulfoxide using a limiting amount of *m*-CPBA was attempted; use of 1.3 equivalents gave a yield of 52% for sulfoxide **14** (Scheme 2) in a reaction which proceeded with complete stereoselectivity, and whose structure was determined by single crystal X-ray diffraction studies (ESI);²³ the sulfoxide oxygen was positioned towards the *endo*-face of the bicyclic ring system, *anti*- to the bulky adjacent *t*-butyl group.



Scheme 2

Of interest was that Suzuki coupling of sulfoxide **14** with boronic acids gave adducts **15i-iii** (Scheme 2) although less efficiently than for the sulfone. In this case, it seems that the *endo*-face suffers from the steric hindrance caused by the *endo*-sulfoxide, and in this sense is similar to the threonine-derived system **5d**. The structure of sulfoxide adduct **15i** was confirmed by single crystal X-ray diffraction studies (ESI).²³ Attempted hydrogenation of **15i** resulted in quantitative recovery of starting material, similar to that observed in the threonine series.

Application of Corey-Reichard protocol³⁴ to representative analogues efficiently removed the *N,O*-protecting group (Table 7), giving the product pyroglutaminol systems but this approach was not successful for the equivalent *N,S*-system **7dv**.

Table 7: *N, O*-acetal deprotection (see Scheme 1).

Starting Compound	Product	Yield (%)
6a	16	94
7ai	9ai	80
7aii	9aii	79
8b	9a , R = C ₆ H ₄ CH ₂ OH	90
7ci	9ci	81
6dv	-	0

Broth assay of these compounds against a small panel of Gram positive (*Methicillin* resistant *Staphylococcus aureus*) and Gram negative (*Escherichia coli* (EC 34), *Klebsiella pneumonia* (KL 18) and *Pseudomonas aeruginosa* (PS 23)) bacteria mostly showed no activity, confirming earlier results that simple lactam systems do not display such activity.³⁵ The exceptions were **6civ**, **6div**, **7ai**, and **15iii** which showed modest activity against *Methicillin* resistant *Staphylococcus aureus* with MIC values of 15.6, 15.6, 62.0, 31.3 μ g/mL respectively (assays conducted using reported methodology³⁶).

Conclusion

Diastereocontrol in the reactions of bicyclic lactams³⁷⁻³⁹ is governed by several phenomena including steric,^{40, 41} electronic⁴² and hydrogen bonding⁷ effects. The work described here adds a further aspect of steric control in the facial selectivity of bicyclic lactams, showing that ring substituents may critically influence stereochemical outcome in such functionally dense bicyclic ring systems. It has direct implications for the stereocontrolled synthesis of the recently identified clausenamide group of natural products.⁴³ This work complements other approaches which permit scaffold hopping from tetramate to pyroglutamates, by providing a general route to more highly substituted systems.^{44, 45}

Experimental Section

General methods. All reagents were obtained from commercial sources and used without further purification. Anhydrous solvents were dried by pre-storing them over activated 3 Å molecular sieves before being passed through an activated alumina column on a solvent tower under N₂ pressure. Analytical thin-layer chromatography (TLC) was carried out on Merck aluminum foil backed sheets precoated with 0.2 mm Kielselgel 60 F254. The spots were visualized by UV irradiation (λ 254 nm) and by staining with a KMnO₄ solution followed by heating. *Flash* column chromatography was performed on Kielselgel 60 silica gel (230–400 mesh particle size). Optical rotations were recorded at 25 °C on a polarimeter using the D line of sodium (589 nm) and a path length of 1 dm. Concentrations (c) are given in g/100 mL, and specific rotations ($[\alpha]_D^{25}$) are quoted in 10⁻¹ deg cm² g⁻¹. Melting points were measured with a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an FT-IR spectrometer; absorption maxima (ν_{\max}) are reported in wavenumbers (cm⁻¹) and only selected peaks are reported. ¹H NMR spectra were recorded 400, 500 and 600 MHz, and ¹³C NMR spectra at 100 and 125 MHz. Chemical shifts (δ_{H} and δ_{C}) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are quoted in hertz. Two-dimensional COSY, NOESY, HSQC and HMBC experiments were recorded at 500 MHz. Assignment of the NMR spectra have been made using DEPTQ, COSY and HSQC and confirmation of stereochemistry was made using NOESY and X-ray crystallography. Low-resolution mass spectra (*m/z*) were recorded using electrospray ionization (ESI); selected peaks are reported in daltons and their intensities given as percentages of the base peak. High-resolution mass spectra (HRMS) were recorded using TOF (ESI, EI or CI).

Synthesis of Methyl Ester Hydrochloride: General Method A₄₆

SOCl₂ (1.5 eq) was added dropwise to stirring anhydrous MeOH (2 M) 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 hydrochlorides **1a-d**.

Synthesis of Oxazolidine and Thiazolidine Compounds: General Method B₄₇

The ester hydrochloride of the L-amino acid **1a-d** (1.0 eq) was suspended in petroleum ether. Triethylamine (1.5 eq) and trimethylacetaldehyde (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 Et₂O. The combined filtrates were concentrated under reduced pressure to furnish the oxazolidines or thiazolidine **2a-d**.

***N*-Acylation of Oxazolidine and Thiazolidine Compounds: General Method C₁₃**

DMAP (0.05 eq) and DCC (1.05 eq) were added to a solution of oxazolidine or thiazolidine **2a-d** (1.0 eq) in anhydrous DCM. The mixture was cooled to 0 °C and ethyl 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 **3a-d**.

Dieckmann Cyclisation: General Method D₁₃

To a solution of *N*-acyl oxazolidine or thiazolidine **3a-d** (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 Et₂O 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 NaH₂PO₄ and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the tetramic acids **4a-d**.

Synthesis of Tosylate/Mesylate: General Method E₁₉

Tetramic acid **4a-d** (1.0 eq) was dissolved in DCM under nitrogen atmosphere. *p*-Toluenesulfonyl chloride or 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% NaHCO₃, and brine, dried over MgSO₄, 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 tosylates **5a,b** or mesylates **5c-f**.

Attempted Methods for Suzuki Coupling

Procedure 1:²⁰ Tosylate/mesylate (1.0 eq) and boronic acid (1.2 eq) were dissolved in THF (0.1 M). Pd(dppf)Cl₂ (5 mol%) and a solution of Cs₂CO₃ (3.0 eq) in water (1/10 THF) was added

subsequently to this solution. The reaction mixture was then stirred at room temperature for 40 minutes and refluxed until total consumption of the starting material. After completion, the reaction mixture was filtered through Celite and washed with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crude material, which was purified by flash column chromatography.

Procedure 2:²¹ To a suspension of the boronic acid (227 mg, 1.50 mmol) and the $\text{NiCl}_2(\text{PPh}_3)_2$ (24 mg, 0.04 mmol) in THF (10 mL) was added tosylate (153 mg, 0.37 mmol) in THF (0.1 M). The reaction mixture was stirred at room temperature or refluxed for 15 h and quenched using saturated sodium bicarbonate. The product was extracted with EtOAc, the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crude material, which was purified by flash column chromatography.

Procedure 3: General Method F²²

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), 1 M 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 to give the product by flash column chromatography.

Procedure 4:⁴⁸ To a solution of aryl chloride (1.0 eq) in DMA:water (20/1) was added Pd/C (5 mol%), 4-methoxyphenylboronic acid (1.2 eq), and K_2CO_3 (2.0 eq) under a N_2 atmosphere. The reaction mixture was degassed and allowed to stir at 80 °C. The catalyst was filtered, washed with

acetonitrile, and evaporated to find crude material, which was then purified by flash column chromatography.

Procedure 5:²⁴ A mixture of tosylate (1.0 eq) and tetrakis(triphenylphosphine)palladium(0) (0.05 eq) in DME was degassed and then stirred with gentle heating until it turned into a clear solution. 4-Methoxyphenylboronic acid (1.0 eq) and potassium *tert*-butoxide (2.0 eq) in *tert*-butyl alcohol (2.0 M) were then added. The reaction mixture was degassed again and refluxed at 95 °C for 15 minutes under N₂ atmosphere. The reaction mixture was filtered through Celite and washed with DCM. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography.

Procedure 6:²⁵ The mesylate (1.0 eq) was dissolved in a mixture of dry DMF and toluene. To this solution was added K₂CO₃ (7.6 eq), tetrakis(triphenylphosphine)palladium(0) (10 mol%) and 4-methoxyphenylboronic acid (3.8 eq). The reaction mixture was heated at 95 °C for 18 h under N₂ atmosphere. After being cooled to room temperature, water was added, and the solution was extracted with DCM. The organic layer was washed with water, dried over anhydrous Na₂SO₄, concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography.

Hydrogenation: ³⁰ General Method G

To a solution of α,β -unsaturated lactam (1 eq) 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 column chromatography on silica gel using ethyl acetate/petroleum ether as eluents to give pure pyrrolidinones.

Preparation of sulfone and sulfoxide: General Method H³³

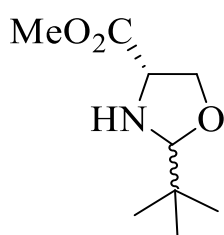
A solution of cysteine-derived mesylate **5f** (1 eq) in CHCl₃ (0.086 M) was cooled to 0°C. A solution of *m*-chloroperbenzoic acid (1.3-3.0 eq) in CHCl₃ (0.15 M) was added dropwise. The reaction

mixture was stirred at room temperature for 12-17 hours. After completion, the mixture was poured into EtOAc (0.01 M) and the resultant solution was washed with sat. aq. solution of NaHCO₃ and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to get crude sulfone or sulfoxide. The sulfone **10** or sulfoxide **14** was purified by flash column chromatography using 35-40% EtOAc in petroleum ether.

***N,O*-Acetal deprotection: 34 General Method I**

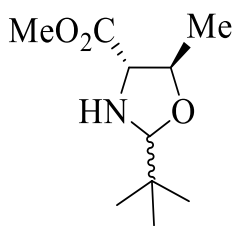
Under a nitrogen atmosphere, the pyrrolinone or pyrrolidinone (1 eq) was treated with propane-1,3-dithiol (2.1-4.0 eq) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol. The solution was stirred at room temperature for 24-36 h or at 50 °C for 12-17 h. The reaction mixture 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.

(2*R*,5*S*)- and (2*S*,5*S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-1,3-oxazolidine, 2a



According to General Method B, L-serine methyl ester hydrochloride **1a** (7.40 g, 47.5 mmol) was reacted with triethylamine (9.9 mL, 71 mmol) and (CH₃)₃CCHO (6.2 mL, 57 mmol). Yield 86% (7.6 g); yellow oil; 1.4:1 mixture of diastereomers; R_f (85% EtOAc in DCM) 0.60; ν_{max} /cm⁻¹ 3316 (N-H), 2957 (C-H), 2871 (C-H), 1740 (C=O); δ_{H} (400 MHz, CDCl₃) major isomer (2*R*): 0.95 (9H, s, C(CH₃)₃), 2.48 (1H, br s, NH), 3.64-3.67 (1H, m, C(4)H_AH_B), 3.72 (3H, s, CO₂CH₃), 3.84-3.88 (2H, m, C(4)H_AH_B) + (C(5)H)), 4.04 (1H, s, C(2)H); minor isomer (2*S*): 0.87 (9H, s, C(CH₃)₃), 2.48 (1H, br s, NH), 3.67-3.69 (1H, m, C(4)H_AH_B), 3.70 (3H, s, CO₂CH₃), 3.89-3.93 (1H, m, C(5)H), 4.07 (1H, dd, *J* 8.0, 7.3, C(4)H_AH_B), 4.28 (1H, s C(2)H); δ_{C} (100 MHz, CDCl₃) major isomer (2*R*): 25.2 (C(CH₃)₃), 33.2 (C(CH₃)₃), 52.5 (CO₂CH₃), 59.6 (C(5)), 68.3 (C(4)), 99.9 (C(2)), 172.9 (CO₂CH₃); minor isomer (2*S*): 24.9 (C(CH₃)₃), 34.6 (C(CH₃)₃), 52.4 (CO₂CH₃), 59.4 (C(5)), 68.9 (C(4)), 99.2 (C(2)), 173.1 (CO₂CH₃); m/z ([ESI]⁺) 188.1 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₉H₁₈NO₃ 188.1281; Found 188.1282.

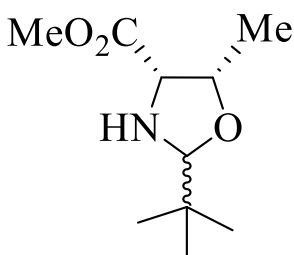
(2*R*,4*R*,5*S*)- and (2*S*,4*R*,5*S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 2b



According to General Method B, L-threonine methyl ester hydrochloride **1b** (9.7 g, 57 mmol) was reacted with triethylamine (11.9 mL, 85.8 mmol) and trimethylacetaldehyde (7.46 mL, 68.6 mmol). Yield 88% (10.1 g); yellow oil; 1:1 mixture of diastereomers; R_f (50% EtOAc in DCM) 0.62; $\nu_{\max}/\text{cm}^{-1}$ 3341

(N-H), 2957 (C-H), 2870 (C-H), 1741 (C=O); δ_H (400 MHz, CDCl_3) isomer (2*R*): 0.96 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (3H, d, J 6.0, C(4)CH₃), 2.67 (1H, br s, NH), 3.34 (1H, d, J 7.2, C(5)H), 3.75 (3H, s, CO_2CH_3), 3.78-3.85 (1H, m, C(4)H), 4.27 (1H, s, C(2)H); isomer (2*S*): 0.88 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.35 (3H, d, J 6.0, C(4)CH₃), 2.67 (1H, br, NH), 3.45 (1H, d, J 7.2, C(5)H), 3.74 (3H, s, CO_2CH_3), 3.78-3.85 (1H, m, C(4)H), 4.36 (1H, s, C(2)H); δ_C (100 MHz, CDCl_3) isomer (2*R*): 19.9 (C(4)CH₃), 25.2 ($\text{C}(\text{CH}_3)_3$), 34.6 ($\text{C}(\text{CH}_3)_3$), 52.4 (OCH₃), 65.7 (C(5)), 76.2 (C(4)), 98.2 (C(2)), 171.9 (CO_2CH_3); isomer (2*S*): 18.9 (C(4)CH₃), 24.8 ($\text{C}(\text{CH}_3)_3$), 33.5 ($\text{C}(\text{CH}_3)_3$), 52.3 (OCH₃), 67.1 (C(5)), 77.3 (C(4)), 98.8 (C(2)), 172.7 (CO_2CH_3); m/z ([ESI]⁺) 202.1 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z : [MH]⁺ Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_3$ 202.1438; Found 202.1438.

(2*R*,4*S*,5*S*)- and (2*S*,4*S*,5*S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 2c

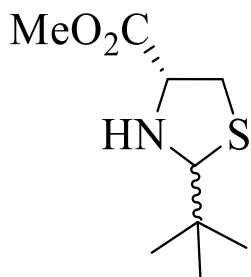


According to General Method B, L-*allo*-threonine methyl ester hydrochloride **1c** (2.96 g, 17.5 mmol) was reacted with triethylamine (3.65 mL, 26.2 mmol) and trimethylacetaldehyde (2.27 mL, 20.9 mmol). Yield 71% (2.5 g); colourless oil; 2.5:1 mixture of diastereomers; R_f (50%

EtOAc in DCM) 0.60; $\nu_{\max}/\text{cm}^{-1}$ 3313 (N-H), 2956 (C-H), 2872 (C-H), 1742 (C=O); δ_H (400 MHz, CDCl_3) major isomer (2*R*): 0.94 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.01 (3H, d, J 6.4, C(4)CH₃), 2.49 (1H, br s, NH), 3.70 (3H, s, CO_2CH_3), 3.88-3.92 (1H, m, C(5)H), 4.02 (1H, s, C(2)H), 4.16 (1H, dq, J 8.2, 6.4, C(4)H); minor isomer (2*S*): 0.82 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.00 (3H, d, J 6.4, C(4)CH₃), 2.49 (1H, br, NH), 3.68 (3H, s, CO_2CH_3), 3.88-3.92 (1H, m, C(5)H), 4.28-4.39 (1H, m, C(4)H), 4.54 (1H, s, C(2)H); δ_C (100 MHz, CDCl_3) major isomer (2*R*): 16.8 (C(4)CH₃), 25.3 ($\text{C}(\text{CH}_3)_3$), 32.8 ($\text{C}(\text{CH}_3)_3$), 52.1 (OCH₃), 63.3 (C(5)), 73.4 (C(4)), 98.5 (C(2)), 171.7 (CO_2CH_3); minor isomer (2*S*): 16.0 (C(4)CH₃), 24.7 ($\text{C}(\text{CH}_3)_3$), 35.7 ($\text{C}(\text{CH}_3)_3$), 52.0 (OCH₃), 63.2 (C(5)), 74.6 (C(4)), 98.1 (C(2)),

171.8 (CO₂CH₃); m/z ([ESI]⁺) 202.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₁₀H₂₀NO₃ 202.1438; Found 202.1438.

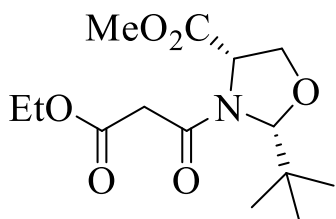
(2*R*,5*S*)- and (2*S*,5*S*)-2-(*tert*-Butyl)-5-methoxycarbonyl-1,3-thiazolidine, 2d



According to General Method B, L-cysteine methyl ester hydrochloride **1d** (5.0 g, 29 mmol) was reacted with triethylamine (6.09 mL, 43.7 mmol) and trimethylacetaldehyde (3.8 mL, 35.0 mmol). Yield 95% (5.62 g); yellow oil; 1.5:1 mixture of diastereomers; R_f (75% EtOAc in DCM) 0.58; ν_{max}/cm⁻¹

3317 (N-H), 2954 (C-H), 2868 (C-H), 1740 (C=O); δ_H (400 MHz, CDCl₃) major isomer (2*R*): 1.01 (9H, s, C(CH₃)₃), 2.19 (1H, br s, NH), 2.62 (1H, t, *J* 10.0, C(4)H_AH_B), 3.20 (1H, dd, *J* 10.2, 6.7, C(4)H_AH_B), 3.72 (3H, s, CO₂CH₃), 4.72-3.78 (1H, m, C(5)H), 4.40 (1H, s, C(2)H); minor isomer (2*S*): 0.92 (9H, s, C(CH₃)₃), 2.19 (1H, br s, NH), 2.96 (1H, dd, *J* 10.6, 5.6, C(4)H_AH_B), 3.05 (1H, dd, *J* 10.2, 6.4, C(4)H_AH_B), 3.69 (3H, s, CO₂CH₃), 4.08 (1H, dd, *J* 6.3, 5.6, C(5)H), 4.47 (1H, s, C(2)H); δ_C (100 MHz, CDCl₃) major isomer (2*R*): 27.0 (C(CH₃)₃), 34.0 (C(CH₃)₃), 37.5 (C(4)), 52.5 (CO₂CH₃), 65.5 (C(5)), 81.9 (C(2)), 171.9 (CO₂CH₃); minor isomer (2*S*): 26.6 (C(CH₃)₃), 35.9 (C(CH₃)₃), 37.1 (C(4)), 52.5 (CO₂CH₃), 65.1 (C(5)), 79.9 (C(2)), 172.5 (CO₂CH₃); m/z ([ESI]⁺) 204.1 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₉H₁₈NO₂S 204.1053; Found 204.1055.

(2*R*,5*S*)-2-(*tert*-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-1,3-oxazolidine, 3a

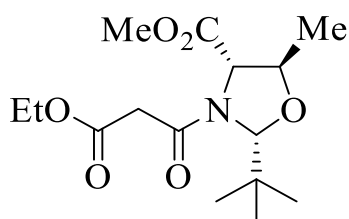


According to General Method C, oxazolidine **2a** (10.6 g, 56.5 mmol), DCC (12.2 g, 59.3 mmol), and DMAP (345 mg, 2.80 mmol) was reacted with ethyl hydrogen malonate (7.0 mL, 59.3 mmol) in DCM.

Yield 80% (13.6 g); colourless oil; R_f (10% EtOAc in DCM) 0.52; $[\alpha]_D^{25}$ -62.4 (*c* 1.0 in DCM); ν_{max}/cm⁻¹ 2958 (C-H), 1741 (C=O), 1672 (C=O); δ_H (400 MHz, CDCl₃): 0.83 (9H, s, C(CH₃)₃), 1.23 (3H, t, *J* 7.1, OCH₂CH₃), 3.46 (1H, d, *J* 15.5, C(7)H_AH_B), 3.65 (1H, d, *J* 15.5, C(7)H_AH_B), 3.74 (3H, s, CO₂CH₃), 3.89-4.06 (1H, m, C(4)H_AH_B), 4.14 (2H, q, *J* 7.1, OCH₂CH₃), 4.42-4.53 (1H, m,

C(4)H_AH_B), 4.60-4.68 (1H, m, C(5)H), 5.22 (1H, s, C(2)H); δ_c (100 MHz, CDCl₃): 13.9 (OCH₂CH₃), 25.4 (C(CH₃)₃), 37.1 (C(CH₃)₃), 42.9 (C(7)), 52.6 (CO₂CH₃), 59.3 (C(5)), 61.4 (OCH₂CH₃), 67.5 (C(4)), 96.4 (C(2)), 167.4 (C(8)), 167.6 (CO₂CH₃), 169.8 (C(6)); m/z ([ESI]⁺) 302.2 ([M+H]⁺, 55%), 324.1 ([M+Na]⁺, 65%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₁₄H₂₄NO₆ 302.1598; Found 302.1594.

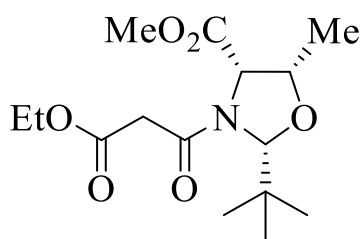
(2*R*,4*R*,5*S*)-2-(*tert*-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 3b



According to General Method C, oxazolidine **2b** (9.95 g, 49.4 mmol), DCC (10.7 g, 51.9 mmol), and DMAP (302 mg, 2.5 mmol) was reacted with ethyl hydrogen malonate (6.12 mL, 51.9 mmol) in DCM.

Yield 67% (10.5 g); yellow oil; R_f (10% EtOAc in DCM) 0.42; $[\alpha]_D^{25}$ -37.5 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2977 (C-H), 2958 (C-H), 1741 (C=O), 1669 (C=O); δ_H (400 MHz, CDCl₃): 0.84 (9H, s, C(CH₃)₃), 1.22 (3H, t, *J* 7.1, OCH₂CH₃), 1.30 (3H, d, *J* 6.0, C(4)CH₃), 3.38 (1H, d, *J* 15.4, C(7)H_AH_B), 3.52 (1H, d, *J* 15.4, C(7)H_AH_B), 3.74 (3H, s, CO₂CH₃), 4.14 (2H, q, *J* 7.1, OCH₂CH₃), 4.23-4.27 (1H, m, C(5)H), 4.68-4.75 (1H, m, C(4)H), 5.37 (1H, s, C(2)H); δ_c (100 MHz, CDCl₃): 14.1 (OCH₂CH₃), 20.1 (C(4)CH₃), 25.8 (C(CH₃)₃), 37.9 (C(CH₃)₃), 42.9 (C(7)), 52.9 (CO₂CH₃), 61.7 (OCH₂CH₃), 65.5 (C(5)), 76.1 (C(4)), 96.2 (C(2)), 167.3, 167.4 (C(6), C(8)), 170.0 (CO₂CH₃); m/z ([ESI]⁺) 316.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₁₅H₂₆NO₆ 204.1053; Found 316.1752.

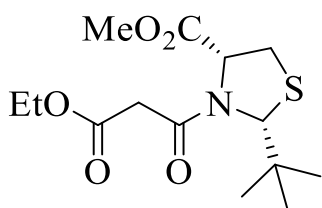
(2*R*,4*S*,5*S*)-2-(*tert*-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 3c



According to General Method C, oxazolidine **2c** (3.50 g, 17.4 mmol), DCC (3.77 g, 18.3 mmol), and DMAP (106 mg, 0.9 mmol) was reacted with ethyl hydrogen malonate (2.15 mL, 18.3 mmol) in DCM. Yield 66% (1.83 g); colourless oil; R_f (40% EtOAc in Petrol) 0.35;

$[\alpha]_D^{25}$ -50.3 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2981 (C-H), 2958 (C-H), 1743 (C=O), 1677 (C=O); δ_H (400 MHz, CDCl_3): 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.21 (3H, t, J 7.2, $\text{C}(10)\text{CH}_3$), 1.35 (3H, d, J 6.4, $\text{C}(4)\text{CH}_3$), 3.33 (1H, d, J 15.3, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.42 (1H, d, J 15.3, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.70 (3H, s, CO_2CH_3), 4.08-4.18 (3H, m, $\text{C}(9)\text{H}_2 + \text{C}(4)\text{H}$), 4.44 (1H, d, J 6.6, $\text{C}(5)\text{H}$), 5.13 (1H, s, $\text{C}(2)\text{H}$); δ_C (100 MHz, CDCl_3): 14.1 ($\text{C}(10)$), 15.4 ($\text{C}(4)\text{CH}_3$), 26.3 ($\text{C}(\text{CH}_3)_3$), 36.9 ($\text{C}(\text{CH}_3)_3$), 43.7 ($\text{C}(7)$), 52.0 (CO_2CH_3), 61.7 ($\text{C}(9)$), 62.8 ($\text{C}(5)$), 74.9 ($\text{C}(4)$), 96.5 ($\text{C}(2)$), 167.4 ($\text{C}(8)$), 167.8 (CO_2CH_3), 168.9 ($\text{C}(6)$); m/z ($[\text{ESI}]^+$) 338.2 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+) m/z : $[\text{MH}]^+$ Calcd for $\text{C}_{15}\text{H}_{26}\text{NO}_6$ 316.1755; Found 316.1746.

(2*R*,5*R*)-2-(*tert*-Butyl)-1-ethoxycarbonylacetyl-5-methoxycarbonyl-1,3-thiazolidine, 3d

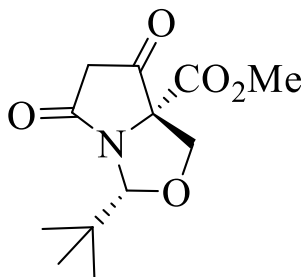


According to General Method C, thiazolidine **2d** (5.54 g, 27.3 mmol), DCC (5.9 g, 28.6 mmol), and DMAP (167 mg, 1.4 mmol) was reacted

with ethyl hydrogen malonate (3.38 mL, 28.6 mmol) in DCM. Yield 78% (5.88 g); colourless oil; R_f (10% EtOAc in DCM) 0.71; $[\alpha]_D^{25}$ -102.5 (c 1.0 in CHCl_3); 1.5:1 mixture of rotamers, major **A** and minor **B**; $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 1740 (C=O), 1664 (C=O); δ_H (400 MHz, CDCl_3): 0.92 (9H, s, $\text{C}(\text{CH}_3)_3$ **A**), 1.01 (9H, s, $\text{C}(\text{CH}_3)_3$ **B**), 1.22 (3H, t, J 7.1, CH_2CH_3), 3.21-3.52 (4H, m, ($\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}} + \text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$)), 3.70 (3H, s, CO_2CH_3 **B**), 3.75 (3H, s, CO_2CH_3 **A**), 4.14 (2H, q, J 7.1, OCH_2CH_3), 4.74 (1H, s, $\text{C}(2)\text{H}$ **B**), 4.83 (1H, t, J 8.0, $\text{C}(5)\text{H}$ **A**), 5.05 (1H, t, J 9.5, $\text{C}(5)\text{H}$ **B**), 5.48 (1H, s, $\text{C}(2)\text{H}$ **A**); δ_C (100 MHz, CDCl_3): 14.1 (OCH_2CH_3), 26.9 ($\text{C}(\text{CH}_3)_3$ **A**), 27.2 ($\text{C}(\text{CH}_3)_3$ **B**), 32.9 ($\text{C}(4)$ **B**), 34.2 ($\text{C}(4)$ **A**), 39.4 ($\text{C}(\text{CH}_3)_3$ **A**), 40.1 ($\text{C}(\text{CH}_3)_3$ **B**), 42.4 ($\text{C}(7)$), 52.5 (CO_2CH_3 **B**), 53.0 (CO_2CH_3 **A**), 61.6 (OCH_2CH_3 **B**), 61.7 (OCH_2CH_3 **A**), 64.2 ($\text{C}(5)$), 73.3 ($\text{C}(2)$ **A**), 74.7 ($\text{C}(2)$ **B**), 166.8, 167.0

(C(8), CO₂CH₃), 170.6 (C(6) **B**), 170.8 (C(6) **A**); m/z (ESI⁺) 318.1 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₁₄H₂₄NO₅S 318.1370; Found 318.1367.

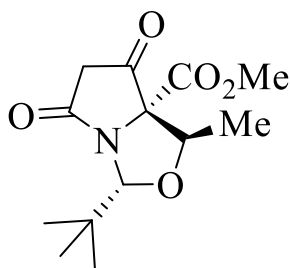
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-6,8-dioxobicyclo[3.3.0]-octane, 4a



According to General Method D, malonamide **3a** (7.06 g, 23.4 mmol) was refluxed with potassium *tert*-butoxide (2.76 g, 24.6 mmol) in THF (0.2 M). Yield 75% (4.49 g); yellow solid, m. p. 118-120°C (lit.¹⁶ m. p. 131-133°C); R_f (25% MeOH in EtOAc) 0.30; $[\alpha]_D^{25} +111.3$ (c 1.2 in

DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 1747 (C=O), 1724 (C=O), 1621 (C=O); δ_{H} (400 MHz, CDCl₃): 0.84 (9H, s, C(CH₃)₃), 3.11 (1H, d, *J* 21.2, C(7)H_AH_B), 3.56 (1H, d, *J* 9.0, C(4)H_AH_B), 3.68 (1H, d, *J* 21.2, C(7)H_AH_B), 3.76 (3H, s, CO₂CH₃), 4.73 (1H, d, *J* 9.0, C(4)H_AH_B), 5.01 (1H, s, C(2)H); δ_{C} (100 MHz, CDCl₃): 24.7 (C(CH₃)₃), 35.6 (C(CH₃)₃), 44.8 (C(7)), 53.7 (CO₂CH₃), 67.9 (C(4)), 80.5 (C(5)), 98.3 (C(2)), 166.9 (CO₂CH₃), 172.3 (C(8)), 198.3 (C(6)); m/z ([ESI]⁻) 254.1 ([M-H]⁻, 100%); HRMS (ESI⁻) m/z: ([M-H]⁻) Calcd for C₁₂H₁₆NO₅ 254.1034; Found 254.1032.

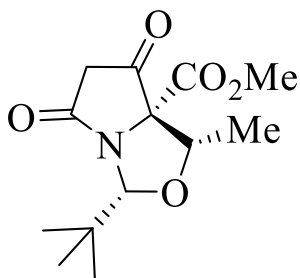
(2*R*,4*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-6,8 dioxobicyclo [3.3.0]-octane, 4b



According to General Method D, malonamide **3b** (5.23 g, 16.6 mmol) was refluxed with potassium *tert*-butoxide (1.95 g, 17.4 mmol) in THF (0.2 M). Yield 73% (3.25 g); yellow solid, m. p. 134-136°C (lit.¹⁶ m. p. 132-134°C); R_f (20% MeOH in EtOAc) 0.38; $[\alpha]_D^{25} +41.3$ (c 1.1 in DCM);

$\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 2874 (C-H), 1782 (C=O), 1749 (C=O), 1617 (C=O); δ_{H} (400 MHz, CDCl₃): 0.83 (9H, s, C(CH₃)₃), 0.98 (3H, d, *J* 6.7, C(4)CH₃), 3.08 (1H, d, *J* 21.7, C(7)H_AH_B), 3.58 (1H, d, *J* 21.7, C(7)H_AH_B), 3.74 (3H, s, CO₂CH₃), 5.02 (1H, q, *J* 6.7, C(4)H), 5.05 (1H, s, C(2)H); δ_{C} (100 MHz, CDCl₃): 15.1 (C(4)CH₃), 24.7 (C(CH₃)₃), 35.5 (C(CH₃)₃), 45.1 (C(7)), 53.6 (CO₂CH₃), 75.0 (C(4)), 83.6 (C(5)), 95.9 (C(2)), 167.1 (CO₂CH₃), 172.9 (C(8)), 199.4 (C(6)); m/z ([ESI]⁺) 270.1 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₁₃H₂₀NO₅ 270.1336; Found 270.1336.

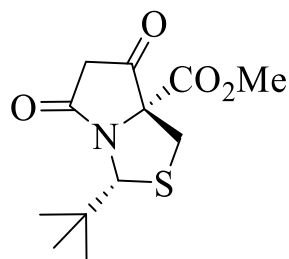
(2*R*,4*S*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-6,8-dioxobicyclo [3.3.0]-octane, 4c



According to General Method D, malonamide **3c** (1.84 g, 5.80 mmol) was refluxed with potassium *tert*-butoxide (685 mg, 6.1 mmol) in THF (0.2 M). Yield 75% (1.17 g); yellow solid, m. p. 118-120; *R_f* (20% MeOH in EtOAc) 0.38; $[\alpha]_D^{25} +76.9$ (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 2872

(C-H), 1755 (C=O), 1723 (C=O), 1623 (C=O); δ_{H} (400 MHz, CDCl₃): 0.87 (9H, s, C(CH₃)₃), 1.60 (3H, d, *J* 6.5, C(4)CH₃), 3.07 (1H, d, *J* 21.2, C(7)H_AH_B), 3.65 (1H, d, *J* 21.2, C(7)H_AH_B), 3.71 (3H, s, CO₂CH₃), 3.75 (1H, q, *J* 6.5, C(4)H), 4.90 (1H, s, C(2)H); δ_{C} (100 MHz, CDCl₃): 14.6 (C(4)CH₃), 25.0 (C(CH₃)₃), 35.3 (C(CH₃)₃), 45.1 (C(7)), 52.9 (CO₂CH₃), 76.6 (C(4)), 80.1 (C(5)), 96.8 (C(2)), 165.7 (CO₂CH₃), 172.6 (C(8)), 198.3 (C(6)); *m/z* ([ESI]⁺) 270.2 ([M+H]⁺, 80%), 292.1 ([M+Na]⁺, 100%); HRMS (ESI⁺) *m/z*: [MH]⁺ Calcd for C₁₃H₂₀NO₅ 270.1336; Found 270.1336.

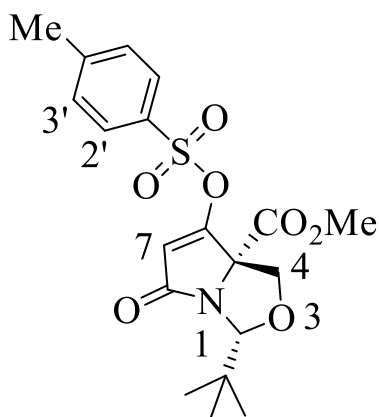
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6,8-dioxo-3-thiabicyclo[3.3.0]-octane, 4d



According to General Method D, malonamide **3d** (5.81 g, 18.3 mmol) was refluxed with potassium *tert*-butoxide (2.16 g, 19.2 mmol) in THF (0.2 M). Yield 74% (3.7 g); yellow solid, m. p. 114-116 (lit.¹⁶ m. p. 114-116°C); *R_f* (25% MeOH in EtOAc) 0.38; $[\alpha]_D^{25} +150.1$ (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$

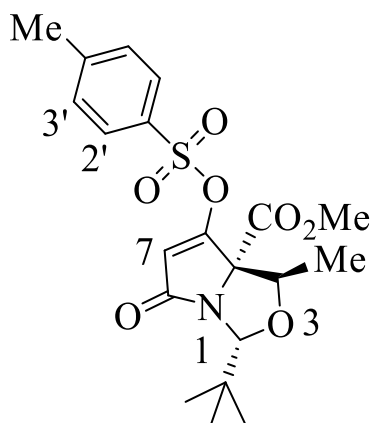
2957 (C-H), 1748 (C=O), 1714 (C=O), 1626 (C=O); δ_{H} (400 MHz, CDCl₃): 0.89 (9H, s, C(CH₃)₃), 2.95 (1H, d, *J* 11.6, C(4)H_AH_B), 3.07 (1H, d, *J* 21.5, C(7)H_AH_B), 3.56 (1H, d, *J* 21.5, C(7)H_AH_B), 3.72 (1H, d, *J* 11.6, C(4)H_AH_B), 3.76 (3H, s, CO₂CH₃), 5.26 (1H, s, C(2)H); δ_{C} (100 MHz, CDCl₃): 26.4 (C(CH₃)₃), 33.8 (C(4)), 37.2 (C(CH₃)₃), 42.9 (C(7)), 53.9 (CO₂CH₃), 73.7 (C(2)), 84.9 (C(5)), 167.1 (CO₂CH₃), 170.6 (C(8)), 199.5 (C(6)); *m/z* ([ESI]⁻) 270.1 ([M-H]⁻, 100%); HRMS (ESI⁺) *m/z*: [MH]⁺ Calcd for C₁₂H₁₈NO₄S 272.0951; Found 272.0951.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-tosyloxybicyclo[3.3.0]-oct-6-ene, 5s



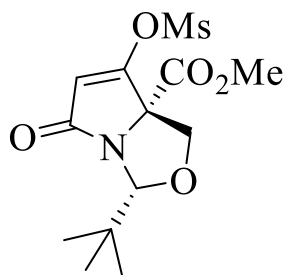
According to General Method E, tetramic acid **4a** (2.37 g, 9.30 mmol) was reacted with TsCl (1.77 g, 9.30 mmol) and DIPEA (3.20 mL, 18.6 mmol) in DCM (0.1 M). Yield 78% (2.97 g); white solid, m. p. 144-148°C; R_f (20% EA in PE) 0.26; $[\alpha]_D^{25} +72.9$ (c 1.3 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 2873 (C-H), 1723 (C=O), 1629 (C=O); δ_H (400 MHz, CDCl_3): 0.78 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.43 (3H, s, Ar-CH₃), 3.21 (1H, d, J 8.6, C(4) H_AH_B), 3.50 (3H, s, CO_2CH_3), 4.58 (1H, s, C(2)H), 4.63 (1H, d, J 8.6, C(4) H_AH_B), 5.77 (1H, s, C(7)H), 7.35 (2H, d, J 8.6, C(3')H), 7.74 (2H, d, J 8.6, C(2')H); δ_C (100 MHz, CDCl_3): 21.9 (Ar-CH₃), 24.6 ($\text{C}(\text{CH}_3)_3$), 35.1 ($\text{C}(\text{CH}_3)_3$), 53.3 (CO_2CH_3), 69.4 (C(4)), 75.0 (C(5)), 96.9 (C(2)), 107.5 (C(7)), 128.7 (C(2')), 130.3 (C(3')), 130.8 (C(4')), 147.2 (C(1')), 163.6 (CO_2CH_3), 166.8 (C(8)), 175.6 (C(6)); m/z ($[\text{ESI}]^+$) 410.2 ($[\text{M}+\text{H}]^+$, 100%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{MH}]^+$ Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_7\text{S}$ 410.1268; Found 410.1277.

(2R,4R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-6-tosyloxy bicyclo[3.3.0]oct-6-ene, **5b**



According to General Method E, tetramic acid **4b** (56.0 mg, 0.2 mmol) was reacted with TsCl (40.0 mg, 0.20 mmol) and DIPEA (0.07 mL, 0.4 mmol) in DCM (0.1 M). Yield 57% (50 mg); Colourless oil; R_f (20% EA in PE) 0.35; $[\alpha]_D^{25} +79.4$ (c 1.1 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 2874 (C-H), 1720 (C=O), 1627 (C=O); δ_H (400 MHz, CDCl_3): 0.76 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.85 (3H, d, J 6.8, C(4)CH₃), 2.43 (3H, s, ArCH₃), 3.45 (3H, s, CO_2CH_3), 4.66 (1H, s, C(2)H), 4.94 (1H, q, J 6.8, C(4)H), 5.84 (1H, s, C(7)H), 7.35 (2H, d, J 8.2, C(3')H), 7.75 (2H, d, J 8.4, C(2')H); δ_C (100 MHz, CDCl_3): 14.3 (C(4)CH₃), 21.9 (Ar-CH₃), 24.6 ($\text{C}(\text{CH}_3)_3$), 35.1 ($\text{C}(\text{CH}_3)_3$), 53.2 (CO_2CH_3), 73.5 (C(4)), 78.1 (C(5)), 94.0 (C(2)), 107.7 (C(7)), 128.7 (C(2')), 130.3 (C(3')), 130.8 (C(4')), 147.2 (C(1')), 161.9 (CO_2CH_3), 167.3 (C(8)), 175.4 (C(6)); m/z ($[\text{ESI}]^+$) 424.2 ($[\text{M}+\text{H}]^+$, 60%), 446.0 ($[\text{M}+\text{Na}]^+$, 100%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{MH}]^+$ Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_7\text{NS}$ 424.1425; Found 424.1419.

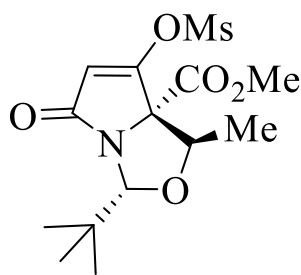
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 5c



According to General Method E, tetramic acid **4a** (6.83 g, 26.8 mmol) was reacted with MsCl (2.10 mL, 26.8 mmol) and DIPEA (9.30 mL, 53.6 mmol) in DCM (0.1 M). Yield 64% (5.7 g); white solid, m. p. 186-188°C; R_f (50% EA in PE) 0.50; $[\alpha]_D^{25} +144.3$ (c 1.1 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-

H), 2885 (C-H), 1721 (C=O), 1632 (C=O); δ_H (400 MHz, CDCl_3): 0.85 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.17 (3H, s, OSO_2CH_3), 3.45 (1H, d, J 8.6, C(4) $\text{H}_\text{A}\text{H}_\text{B}$), 3.76 (3H, s, CO_2CH_3), 3.67 (1H, s, C(2)H), 4.75 (1H, d, J 8.6, C(4) $\text{H}_\text{A}\text{H}_\text{B}$), 5.86 (1H, s, C(7)H); δ_C (100 MHz, CDCl_3): 23.6 ($\text{C}(\text{CH}_3)_3$), 34.2 ($\text{C}(\text{CH}_3)_3$), 37.2 (OSO_2CH_3), 52.5 (CO_2CH_3), 68.5 (C(4)), 74.0 (C(5)), 96.0 (C(2)), 107.0 (C(7)), 161.9 (CO_2CH_3), 166.3 (C(8)), 174.2 (C(6)); m/z ($[\text{ESI}]^+$) 356.0 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{13}\text{H}_{19}\text{NNaO}_7\text{S}$ 356.0774; Found 356.0774.

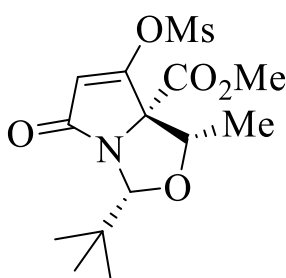
(2*R*,4*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 5d



According to General Method E, tetramic acid **4b** (3.45 g, 12.8 mmol) was reacted with MsCl (0.99 mL, 12.8 mmol) and DIPEA (4.45 mL, 25.6 mmol) in DCM (0.1 M). Yield 25% (1.1 g); white solid, m. p. 138-140°C; R_f (40% EA in PE) 0.38; $[\alpha]_D^{25} +150.0$ (c 1.1 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2961

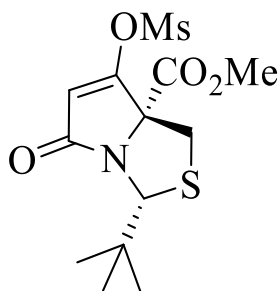
(C-H), 2875 (C-H), 1720 (C=O), 1629 (C=O); δ_H (400 MHz, CDCl_3): 0.82 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.01 (3H, d, J 6.7, C(4) CH_3), 3.17 (3H, s, OSO_2CH_3), 3.75 (3H, s, CO_2CH_3), 4.73 (1H, s, C(2)H), 5.01 (1H, q, J 6.7, C(4)H), 5.90 (1H, s, C(7)H); δ_C (100 MHz, CDCl_3): 14.6 (C(4) CH_3), 24.6 ($\text{C}(\text{CH}_3)_3$), 35.2 ($\text{C}(\text{CH}_3)_3$), 38.2 (OSO_2CH_3), 53.5 (CO_2CH_3), 73.6 (C(4)), 78.1 (C(5)), 94.1 (C(2)), 108.6 (C(7)), 161.4 (CO_2CH_3), 167.7 (C(8)), 175.0 (C(6)); m/z ($[\text{ESI}]^+$) 348.2 ($[\text{M}+\text{H}]^+$), 370.0 ($[\text{M}+\text{Na}]^+$, 90%); HRMS (ESI^+) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{14}\text{H}_{21}\text{NNaO}_7\text{S}$ 370.0931; Found 370.0918.

(2*R*,4*S*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 5e



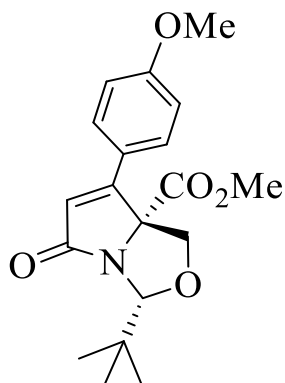
According to General Method E, tetramic acid **4c** (478 mg, 1.80 mmol) was reacted with MsCl (0.14 mL, 1.8 mmol) and DIPEA (0.62 mL, 3.6 mmol) in DCM (0.1 M). Yield 52% (320 mg); white solid, m. p. 88-90°C; R_f (40% EA in PE) 0.35; $[\alpha]_D^{25} +71.5$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-H), 2884 (C-H), 1719 (C=O), 1630 (C=O); δ_H (400 MHz, CDCl_3): 0.87 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.58 (3H, d, J 6.5, C(4)CH₃), 3.19 (3H, s, OSO_2CH_3), 3.71 (3H, s, CO_2CH_3), 3.72 (1H, q, J 6.5, C(4)H), 4.61 (1H, s, C(2)H), 5.83 (1H, s, C(7)H); δ_C (100 MHz, CDCl_3): 14.7 (C(4)CH₃), 25.1 (C(CH₃)₃), 35.0 (C(CH₃)₃), 38.0 (OSO_2CH_3), 52.7 (CO_2CH_3), 75.1 (C(5)), 79.5 (C(4)), 96.8 (C(2)), 107.3 (C(7)), 163.9 (CO_2CH_3), 166.1 (C(8)), 175.8 (C(6)); m/z ($[\text{ESI}]^+$) 348.2 ($[\text{M}+\text{H}]^+$, 100%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{MH}]^+$ Calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_7\text{S}$ 348.1112; Found 348.1110.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-((methylsulfonyl)oxy)-5-methoxycarbonyl-8-oxa-3-thiabicyclo[3.3.0]-oct-6-ene, 5f



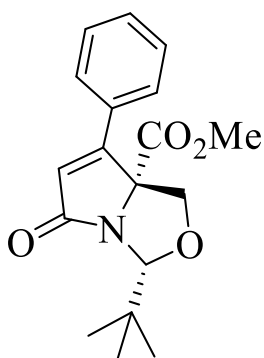
According to General Method E, tetramic acid **4d** (5.54 g, 20.4 mmol) was reacted with MsCl (1.58 mL, 20.4 mmol) and DIPEA (7.11 mL, 40.8 mmol) in DCM (0.1 M). Yield 44% (3.16 g); white solid, m. p. 140-142°C; R_f (50% EA in PE) 0.48; $[\alpha]_D^{25} +232.3$ (c 1.2 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 3010 (C-H), 2960 (C-H), 1714 (C=O), 1639 (C=O); δ_H (400 MHz, CDCl_3): 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.81 (1H, d, J 11.2, C(4)H_AH_B), 3.20 (3H, s, OSO_2CH_3), 3.60 (1H, d, J 11.2, C(4)H_AH_B), 3.78 (3H, s, CO_2CH_3), 4.91 (1H, s, C(2)H), 5.79 (1H, s, C(7)H); δ_C (100 MHz, CDCl_3): 26.4 (C(CH₃)₃), 33.0 (C(4)), 36.8 (C(CH₃)₃), 38.2 (OSO_2CH_3), 53.6 (CO_2CH_3), 71.5 (C(2)), 79.6 (C(5)), 105.5 (C(7)), 162.7 (CO_2CH_3), 167.3 (C(8)), 173.1 (C(6)); m/z ($[\text{ESI}]^+$) 372.0 ($[\text{M}+\text{Na}]^+$, 100%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{MH}]^+$ Calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_6\text{S}_2$ 350.0727; Found 350.0724.

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



According to General Method F, mesylate **5c** (623 mg, 1.90 mmol) was reacted with 4-methoxyphenylboronic acid (369 mg, 2.40 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.8 mL, 16.6 mmol) in ethanol (0.8 mL, 13.1 mmol) and toluene (15 mL) for 4 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (48 mg, 0.1 mmol) and (C₆H₅CN)₂PdCl₂ (35 mg, 0.1 mmol) in toluene (3 mL). Yield 80% (513 mg); white solid, m. p. 136-138°C; R_f (50% EA in PE) 0.58; $[\alpha]_D^{25} +155.1$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 2870 (C-H), 1742 (C=O), 1707 (C=O); δ_{H} (400 MHz, CDCl₃): 0.89 (9H, s, C(CH₃)₃), 3.41 (1H, d, *J* 8.4, C(4)*H*_A*H*_B), 3.57 (3H, s, CO₂CH₃), 3.77 (3H, s, OCH₃), 4.68 (1H, s, C(2)H), 5.05 (1H, d, *J* 8.4, C(4)*H*_A*H*_B), 6.19 (1H, s, C(7)H), 6.86 (2H, d, *J* 9.0, C(3')H), 7.31 (2H, d, *J* 9.0, C(2')H); δ_{C} (100 MHz, CDCl₃): 24.8 (C(CH₃)₃), 35.3 (C(CH₃)₃), 53.2 (CO₂CH₃), 55.5 (OCH₃), 70.4 (C(4)), 77.4 (C(5)), 96.3 (C(2)), 114.7 (C(3')), 119.1 (C(7)), 122.5 (C(1')), 128.7 (C(2')), 159.2 (C(6)), 161.9 (C(4')), 170.0 (CO₂CH₃), 177.8 (C(8)); m/z ([ESI]⁺) 346.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₁₉H₂₄NO₅ 346.1649; Found 346.1642.

(2*R*,5*S*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo[3.3.0]-oct-6-ene, 6aii

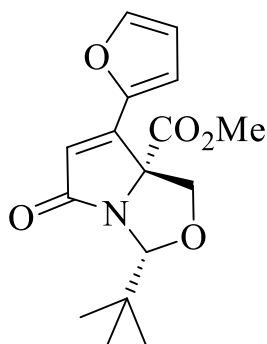


According to General Method F, mesylate **5c** (741 mg, 2.20 mmol) was reacted with phenylboronic acid (351 mg, 2.90 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (2.1 mL, 20.0 mmol) in ethanol (0.9 mL, 15.5 mmol) and toluene (15 mL) for 5 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (57 mg, 0.13 mmol) and (C₆H₅CN)₂PdCl₂ (43 mg,

0.1 mmol) in toluene (3 mL). Yield 64% (300 mg); white solid, m. p. 162-164°C; R_f (20% EA in PE) 0.25; $[\alpha]_D^{25} +153.8$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 2866 (C-H), 1742 (C=O), 1699

(C=O); δ_{H} (400 MHz, CDCl_3): 0.89 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.44 (1H, d, J 8.4, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.57 (3H, s, CO_2CH_3), 4.70 (1H, s, $\text{C}(2)\text{H}$), 5.08 (1H, d, J 8.4, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 6.33 (1H, s, $\text{C}(7)\text{H}$), 7.36 (5H, s, ArH); δ_{C} (100 MHz, CDCl_3): 24.8 ($\text{C}(\text{CH}_3)_3$), 35.3 ($\text{C}(\text{CH}_3)_3$), 53.2 (CO_2CH_3), 70.4 ($\text{C}(4)$), 77.4 ($\text{C}(5)$), 96.3 ($\text{C}(2)$), 121.6 ($\text{C}(7)$), 126.9-131.2 (ArC), 159.5 ($\text{C}(6)$), 169.7 (CO_2CH_3), 177.4 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$) 316.2 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) m/z : $[\text{MH}]^+$ Calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_4$ 316.1543; Found 316.1543.

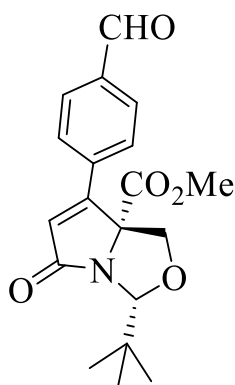
(2*R*,5*S*)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 6a_{iii}



According to General Method F, mesylate **5c** (513 mg, 1.5 mmol) was reacted with 2-furylboronic acid (206 mg, 1.80 mmol), $\text{PdCl}_2(\text{dppb})$, 1 M aqueous Na_2CO_3 solution (1.47 mL, 13.8 mmol) in ethanol (0.62 mL, 10.8 mmol) and toluene (15 mL) for 12 h. $\text{PdCl}_2(\text{dppb})$ was prepared from $(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_4\text{P}(\text{C}_6\text{H}_5)_2$ (39 mg, 0.09 mmol) and $(\text{C}_6\text{H}_5\text{CN})_2\text{PdCl}_2$ (29 mg,

0.08 mmol) in toluene (3 mL). Yield 47% (219 mg); yellow solid, m. p. 98-102°C; R_f (30% EA in PE) 0.43; $[\alpha]_D^{25} +47.3$ (c 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2959 (C-H), 2871 (C-H), 1711 (C=O), 1627 (C=O); δ_{H} (400 MHz, CDCl_3): 0.88 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.33 (1H, d, J 8.5, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.64 (3H, s, CO_2CH_3), 4.67 (1H, s, $\text{C}(2)\text{H}$), 4.92 (1H, d, J 8.5, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 6.15 (1H, s, $\text{C}(7)\text{H}$), 6.43 (1H, dd, J 3.6, 1.8, $\text{C}(3')\text{H}$), 6.59 (1H, d, J 3.6, $\text{C}(4')\text{H}$), 7.49 (1H, d, J 1.8, $\text{C}(5')\text{H}$); δ_{C} (100 MHz, CDCl_3): 24.7 ($\text{C}(\text{CH}_3)_3$), 35.3 ($\text{C}(\text{CH}_3)_3$), 53.3 (CO_2CH_3), 70.3 ($\text{C}(4)$), 75.9 ($\text{C}(5)$), 96.7 ($\text{C}(2)$), 112.7 ($\text{C}(3')$), 113.8 ($\text{C}(4')$), 118.1 ($\text{C}(7)$), 145.9 ($\text{C}(5')$), 146.1 ($\text{C}(2')$), 147.8 ($\text{C}(6)$), 169.6 (CO_2CH_3), 177.6 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$) 328.0 ($[\text{M}+\text{Na}]^+$, 20%); HRMS (ESI^+) m/z : $[\text{MH}]^+$ Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_5\text{N}$ 306.1336; Found 306.1336.

(2*R*,5*S*)-1-Aza-2-(*tert*-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene, 6a_{iv}

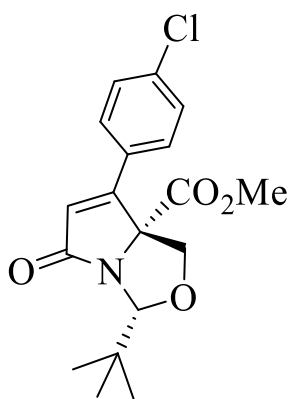


According to General Method F, mesylate **5c** (676 mg, 2.0 mmol) was reacted with 4-formylphenylboronic acid (396 mg, 2.60 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.9 mL, 18.3 mmol) in ethanol (0.82 mL, 14.2 mmol) and toluene (15 mL) for 11 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (39.0 mg, 0.09 mmol) and (C₆H₅CN)₂PdCl₂ (29 mg, 0.08 mmol) in toluene (3 mL). Yield 28% (194 mg); white solid, m. p. 154-

158°C; R_f (10% EA in DCM) 0.46; $[\alpha]_D^{25} +119.5$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 2871 (C-H), 1743 (C=O), 1702 (C=O); δ_{H} (400 MHz, CDCl₃): 0.90 (9H, s, C(CH₃)₃), 3.47 (1H, d, *J* 8.4, C(4)H_AH_B), 3.58 (3H, s, CO₂CH₃), 4.72 (1H, s, C(2)H), 5.10 (1H, d, *J* 8.4, C(4)H_AH_B), 6.47 (1H, s, C(7)H), 7.53 (2H, d, *J* 8.6, C(2')H), 7.88 (2H, d, *J* 8.6, C(3')H). 9.98 (1H, s, CHO); δ_{C} (100 MHz, CDCl₃): 24.7 (C(CH₃)₃), 35.4 (C(CH₃)₃), 53.4 (CO₂CH₃), 70.4 (C(4)), 77.4 (C(5)), 96.5 (C(2)), 124.4 (C(7)), 127.5 (C(2')), 130.4 (C(3')), 135.1 (C(4')), 137.6 (C(1')), 157.8 (C(6)), 169.4 (CO₂CH₃), 176.6 (C(8)), 191.1 (CHO); m/z ([ESI]⁺) 344.2 ([M+H]⁺, 30%), 366.2 ([M+Na]⁺, 50%); HRMS (ESI⁺) m/z: [M+Na]⁺ Calcd for C₁₉H₂₁O₅NNa 366.1312; Found 366.1309.

(2R,5S)-1-Aza-2-(tert-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo

[3.3.0]-oct-6-ene, 6av

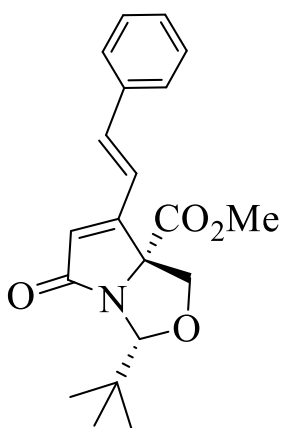


According to General Method F, mesylate **5c** (676 mg, 2.00 mmol) was reacted with 4-chlorophenylboronic acid (201 mg, 0.60 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.60 mL, 5.4 mmol) in ethanol (0.24 mL, 4.2 mmol) and toluene (15 mL) for 7 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (15 mg, 0.04 mmol) and (C₆H₅CN)₂PdCl₂ (11.5 mg, 0.03 mmol) in toluene (2 mL). Yield 49% (103

mg); white solid, m. p. 168-172°C; R_f (20% EA in PE) 0.32; $[\alpha]_D^{25} +133.2$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 2870 (C-H), 1743 (C=O), 1709 (C=O); δ_{H} (400 MHz, CDCl₃): 0.88 (9H, s, C(CH₃)₃), 3.42 (1H, d, *J* 8.4, C(4)H_AH_B), 3.57 (3H, s, CO₂CH₃), 4.69 (1H, s, C(2)H), 5.05 (1H, d, *J*

8.4, C(4)H_AH_B), 6.32 (1H, s, C(7)H), 7.29 (2H, d, *J* 8.9, C(2')H), 7.33 (2H, d, *J* 8.9, C(3')H); δ_c (100 MHz, CDCl₃): 24.7 (C(CH₃)₃), 35.3 (C(CH₃)₃), 53.3 (CO₂CH₃), 70.3 (C(4)), 77.4 (C(5)), 96.4 (C(2)), 122.1 (C(7)), 128.2 (C(2')), 128.3 (C(4')), 129.7 (C(3')), 137.4 (C(1')), 158.1 (C(6)), 169.6 (CO₂CH₃), 177.0 (C(8)); *m/z* ([ESI]⁺) 372.0 ([M+Na]⁺, ³⁵Cl, 100%), 374.0 ([M+Na]⁺, ³⁷Cl, 25%); HRMS (ESI⁺) *m/z*: [M+Na], ³⁵Cl]⁺ Calcd for C₁₈H₂₀O₄NCINa 372.0973; Found 372.0970.

(2*R*,5*S*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-((*E*)-styryl)bicyclo[3.3.0]-oct-6-ene, 6avi

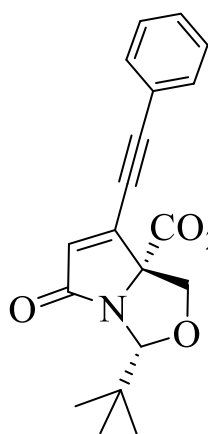


According to General Method F, mesylate **5c** (101 mg, 0.30 mmol) was reacted with *trans*-2-phenylvinylboronic acid (67 mg, 0.45 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.3 mL, 2.7 mmol) in ethanol (0.12 mL, 2.1 mmol) and toluene (10 mL) for 48 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (7.7 mg, 0.018 mmol) and (C₆H₅CN)₂PdCl₂ (5.8 mg, 0.015 mmol) in toluene (1 mL). Yield 25% (26

mg); yellow solid, m. p. 218-220°C; *R_f* (30% EA in PE) 0.45; $[\alpha]_D^{25} +6.4$ (*c* 0.9 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 1742 (C=O), 1707 (C=O); δ_H (500 MHz, CDCl₃): 0.98 (9H, s, C(CH₃)₃), 3.44 (1H, d, *J* 8.5, C(4)H_AH_B), 3.77 (3H, s, CO₂CH₃), 4.76 (1H, s, C(2)H), 5.08 (1H, d, *J* 8.5, C(4)H_AH_B), 6.09 (1H, s, C(7)H), 6.84 (1H, d, *J* 16.7, C(10)H), 6.94 (1H, d, *J* 16.7, C(9)H), 7.36-7.53 (5H, m, ArH); δ_c (125 MHz, CDCl₃): 24.7 (C(CH₃)₃), 35.3 (C(CH₃)₃), 53.3 (CO₂CH₃), 70.1 (C(4)), 76.7 (C(5)), 96.3 (C(2)), 119.2 (C(10)), 123.8 (C(7)), 127.5-135.1 (ArC), 137.4 (C(9)), 157.3 (C(6)), 170.1 (CO₂CH₃), 177.6 (C(8)); *m/z* ([ESI]⁺) 342.2 ([M+H]⁺, 100%); HRMS (ESI⁺) *m/z*: [MH]⁺ Calcd for C₂₀H₂₄NO₄ 342.1700; Found 342.1699.

(2*R*,5*S*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-(phenylethynyl)bicyclo [3.3.0]-oct-6-ene, 6avii

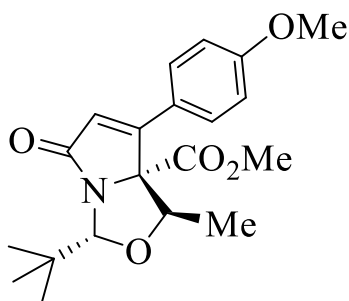
According to General Method F, mesylate **5c** (276 mg, 0.830 mmol) was reacted with 2-phenyl-1-ethynylboronic acid (303 mg, 1.33 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.8 mL, 7.5



mmol) in ethanol (0.34 mL, 5.8 mmol) and toluene (13 mL) for 12 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (21 mg, 0.05 mmol) and (C₆H₅CN)₂PdCl₂ (16 mg, 0.04 mmol) in toluene (1 mL). Yield 20% (55.0 mg); yellow sticky material; R_f (20% EA in PE) 0.32; $[\alpha]_D^{25} +11.5$ (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 2871 (C-H), 1748 (C=O), 1716 (C=O); δ_{H} (400 MHz, CDCl₃): 0.88 (9H, s, C(CH₃)₃), 3.36 (1H, d, *J* 8.5, C(4)H_AH_B), 3.73 (3H, s, CO₂CH₃), 4.68 (1H, s, C(2)H), 4.85 (1H, d, *J*

8.5, C(4)H_AH_B), 6.16 (1H, s, C(7)H), 7.25-7.45 (5H, m, ArH); δ_{C} (100 MHz, CDCl₃): 24.7 (C(CH₃)₃), 35.4 (C(CH₃)₃), 53.3 (CO₂CH₃), 70.4 (C(4)), 78.9 (C(5)), 79.5 (C(9)), 97.4 (C(2)), 105.2 (C(10)), 120.9, 128.6, 130.3, 132.2 (ArC), 129.4 (C(7)), 141.9 (C(6)), 168.3 (CO₂CH₃), 177.3 (C(8)); *m/z* ([ESI]⁺) 362.2 ([M+Na]⁺, 20%); HRMS (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₀H₂₁NNaO₄ 362.1363; Found 362.1362.

(2R,4R,5S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 6bi

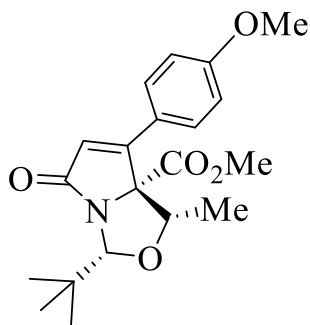


According to General Method F, mesylate **5d** (106.0 mg, 0.30 mmol) was reacted with 4-methoxyphenylboronic acid (60 mg, 0.40 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.3 mL, 2.8 mmol) in ethanol (0.13 mL, 2.2 mmol) and toluene (10 mL) for 50 h.

PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (8.0 mg, 0.018 mmol) and (C₆H₅CN)₂PdCl₂ (6.0 mg, 0.015 mmol) in toluene (1 mL). Yield 14% (15 mg); white solid, m. p. 150-152°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25} +193.5$ (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 2872 (C-H), 1743 (C=O), 1707 (C=O); δ_{H} (500 MHz, CDCl₃): 0.95 (9H, s, C(CH₃)₃), 0.96 (3H, d, *J* 6.6, C(4)CH₃), 3.65 (3H, s, CO₂CH₃), 3.86 (3H, s, OCH₃), 4.83 (1H, s, C(2)H), 5.40 (1H, q, *J* 6.6, C(4)H), 6.35 (1H, s, C(7)H), 6.95 (2H, d, *J* 8.9, C(3')H), 7.41 (2H, d, *J* 8.9, C(2')H); δ_{C} (125 MHz, CDCl₃): 14.0 (C(4)CH₃), 24.8 (C(CH₃)₃), 35.3 (C(CH₃)₃), 53.1 (CO₂CH₃), 55.5 (OCH₃), 74.3 (C(4)), 80.3 (C(5)), 93.3 (C(2)), 114.7 (C(3')), 120.2 (C(7)), 122.3 (C(1')), 128.7 (C(2')), 157.3

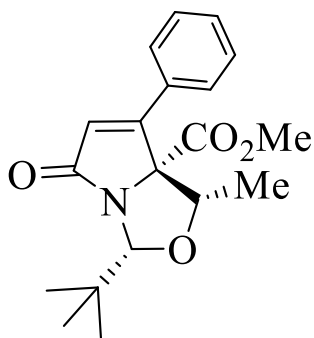
(C(6)), 161.8 (C(4')), 170.4 (CO₂CH₃), 177.3 (C(8)); m/z ([ESI]⁺) 360.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₂₀H₂₆NO₅ 360.1806; Found 360.1808.

(2*R*,4*S*,5*S*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 6c-i



According to General Method F, mesylate **5e** (264.0 mg, 0.730 mmol) was reacted with 4-methoxyphenylboronic acid (166 mg, 1.10 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.7 mL, 6.6 mmol) in ethanol (0.3 mL, 5.1 mmol) and toluene (13 mL) for 4 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (18.7 mg, 0.043 mmol) and (C₆H₅CN)₂PdCl₂ (14.0 mg, 0.037 mmol) in toluene (2 mL). Yield 70% (183 mg); white solid, m. p. 174-176°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25}$ -86.8 (*c* 1.0 in DCM); ν_{max} /cm⁻¹ 2956 (C-H), 2870 (C-H), 1710 (C=O), 1607 (C=O); δ_{H} (400 MHz, CDCl₃): 0.90 (9H, s, C(CH₃)₃), 1.71 (3H, d, *J* 6.6, C(4)CH₃), 3.51 (1H, q, *J* 6.6, C(4)H), 3.61 (3H, s, CO₂CH₃), 3.78 (3H, s, OCH₃), 4.67 (1H, s, C(2)H), 6.23 (1H, s, C(7)H), 6.86 (2H, d, *J* 9.0, C(3')H), 7.37 (2H, d, *J* 9.0, C(2')H); δ_{C} (100 MHz, CDCl₃): 14.7 (C(4)CH₃), 25.1 (C(CH₃)₃), 35.1 (C(CH₃)₃), 52.5 (CO₂CH₃), 55.5 (OCH₃), 76.7 (C(5)), 80.3 (C(4)), 95.9 (C(2)), 114.5 (C(3')), 119.9 (C(7)), 122.9 (C(1')), 128.5 (C(2')), 159.0 (C(4')), 161.6 (C(6)), 169.4 (CO₂CH₃), 178.0 (C(8)); m/z ([ESI]⁺) 360.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [MH]⁺ Calcd for C₂₀H₂₆NO₅ 360.1806; Found 360.1803.

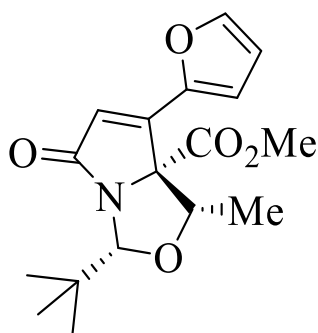
(2*R*,4*S*,5*S*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0]-oct-6-ene, 6c-ii



According to General Method F, mesylate **5e** (92.0 mg, 0.26 mmol) was reacted with phenylboronic acid (48 mg, 0.39 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.25 mL, 2.34 mmol) in ethanol (0.1 mL, 1.82 mmol) and toluene (10 mL) for 4 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (7 mg, 0.0156 mmol) and

(C₆H₅CN)₂PdCl₂ (5 mg, 0.013 mmol) in toluene (1 mL). Yield 80% (70.0 mg); white solid, m. p. 110-112°C; R_f (20% EA in PE) 0.33; $[\alpha]_D^{25}$ -25.4 (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2956 (C-H), 2869 (C-H), 1748 (C=O), 1710 (C=O); δ_{H} (500 MHz, CDCl₃): 1.00 (9H, s, C(CH₃)₃), 1.78 (3H, d, *J* 6.5, C(4)CH₃), 3.63 (1H, q, *J* 6.5, C(4)H), 3.71 (3H, s, CO₂CH₃), 4.77 (1H, s, C(2)H), 6.44 (1H, s, C(7)H), 7.38-7.53 (5H, m, ArH); δ_{C} (125 MHz, CDCl₃): 14.7 (C(4)CH₃), 25.1 (C(CH₃)₃), 35.1 (C(CH₃)₃), 52.6 (CO₂CH₃), 76.8 (C(5)), 80.2 (C(4)), 96.0 (C(2)), 122.6 (C(7)), 126.8-130.8 (ArC), 159.5 (C(6)), 169.0 (CO₂CH₃), 177.6 (C(8)); *m/z* ([ESI]⁺) 352.2 ([M+Na]⁺, 100%); HRMS (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₉H₂₃NNaO₄ 352.1519; Found 352.1513.

(2R,4S,5S)-1-Aza-2-(tert-butyl)-6-(2-furyl)-5-methoxycarbonyl-4-methyl-8-oxa-3-oxobicyclo[3.3.0]-oct-6-ene, 6ciii

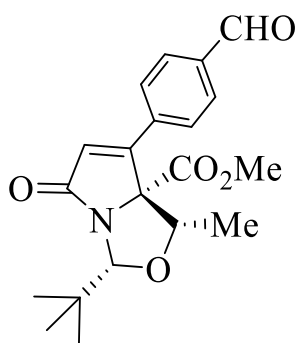


According to General Method F, mesylate **5e** (116.0 mg, 0.330 mmol) was reacted with 2-furylboronic acid (56.0 mg, 0.50 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.31 mL, 3.0 mmol) in ethanol (0.14 mL, 2.3 mmol) and toluene (10 mL) for overnight. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (8.5 mg, 0.02

mmol) and (C₆H₅CN)₂PdCl₂ (6.4 mg, 0.017 mmol) in toluene (1 mL). Yield 28% (30.0 mg); yellow solid, m. p. 38-40°C; R_f (20% EA in PE) 0.27; $[\alpha]_D^{25}$ -10.3 (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2957 (C-H), 2871 (C-H), 1749 (C=O), 1711 (C=O); δ_{H} (400 MHz, CDCl₃): 0.90 (9H, s, C(CH₃)₃), 1.73 (3H, d, *J* 6.6, C(4)CH₃), 3.52 (1H, q, *J* 6.6, C(4)H), 3.59 (3H, s, CO₂CH₃), 4.68 (1H, s, C(2)H), 6.18 (1H, s, C(7)H), 6.44 (1H, dd, *J* 3.6, 1.8, C(3')H), 6.67 (1H, d, *J* 3.6, C(4')H), 7.49 (1H, d, *J* 1.8, C(5')H); δ_{C}

(100 MHz, CDCl₃): 14.4 (C(4)CH₃), 25.0 (C(CH₃)₃), 35.2 (C(CH₃)₃), 52.5 (CO₂CH₃), 75.7 (C(5)), 80.6 (C(4)), 96.2 (C(2)), 112.6 (C(3')), 113.7 (C(4')), 118.7 (C(7)), 145.5 (C(5')), 146.3 (C(2')), 148.1 (C(6)), 168.6 (CO₂CH₃), 177.8 (C(8)); m/z ([ESI]⁺) 320.2 ([M+H]⁺, 60%), 342.2 ([M+Na]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₇H₂₂O₅N 320.1493; Found 320.1483.

(2*R*,4*S*,5*S*)-1-Aza-2-(*tert*-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-4-methyl-8-oxa-3-oxobicyclo [3.3.0]-oct-6-ene, 6civ

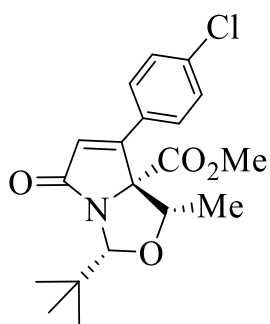


According to General Method F, mesylate **5e** (118 mg, 0.340 mmol) was reacted with 4-formylphenylboronic acid (76.5 mg, 0.510 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.32 mL, 3.06 mmol) in ethanol (0.14 mL, 2.38 mmol) and toluene (10 mL) for 28 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (8.7 mg, 0.02 mmol) and

(C₆H₅CN)₂PdCl₂ (6.5 mg, 0.017 mmol) in toluene (1 mL). Yield 36% (44 mg); white solid, m. p. 82-84°C; R_f (40% EA in PE) 0.44; $[\alpha]_D^{25}$ -71.0 (c 1.0 DCM); $\nu_{\max}/\text{cm}^{-1}$ 2980 (C-H), 2870 (C-H), 1748 (C=O), 1713 (C=O); δ_{H} (400 MHz, CDCl₃): 0.91 (9H, s, C(CH₃)₃), 1.69 (3H, d, *J*, 6.5, C(4)CH₃), 3.56 (1H, q, *J*, 6.5, C(4)H), 3.64 (3H, s, CO₂CH₃), 4.69 (1H, s, C(2)H), 6.48 (1H, s, C(7)H), 7.56 (2H, d, *J* 8.4, C(2')H), 7.87 (2H, d, *J* 8.4, C(3')H). 9.98 (1H, s, CHO); δ_{C} (100 MHz, CDCl₃): 14.8 (C(4)CH₃), 25.0 (C(CH₃)₃), 35.2 (C(CH₃)₃), 52.7 (CO₂CH₃), 76.9 (C(5)), 80.1 (C(4)), 96.1 (C(2)), 125.4 (C(7)), 127.3 (C(2')), 130.2 (C(3')), 135.8 (C(4')), 137.3 (C(1')), 157.8 (C(6)), 168.7 (CO₂CH₃), 176.7 (C(8)), 191.1 (CHO); m/z ([ESI]⁺) 358.2 ([M+H]⁺, 90%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₂₀H₂₄O₅N 358.1649; Found 358.1650.

(2*R*,4*S*,5*S*)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 6cv

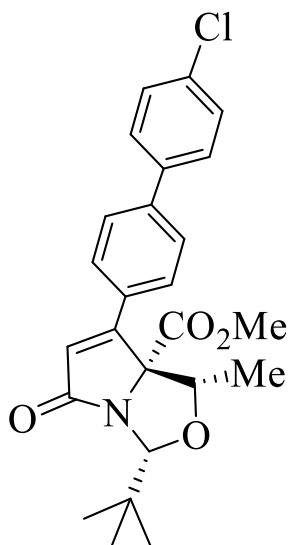
According to General Method F, mesylate **5e** (122 mg, 0.350 mmol) was reacted with 4-chlorophenylboronic acid (58 mg, 0.37 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.33 mL, 3.15 mmol) in ethanol (0.14 mL, 2.45 mmol) and toluene (10 mL) for 4 h. PdCl₂(dppb) was



prepared from $(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_4\text{P}(\text{C}_6\text{H}_5)_2$ (9.0 mg, 0.021 mmol) and $(\text{C}_6\text{H}_5\text{CN})_2\text{PdCl}_2$ (6.7 mg, 0.018 mmol) in toluene (1 mL). Yield 71% (90.0 mg); white solid, m. p. 128-130°C; R_f (20% EA in PE) 0.40; $[\alpha]_D^{25}$ -51.0 (c 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2977 (C-H), 2870 (C-H), 1748 (C=O), 1711 (C=O); δ_{H} (400 MHz, CDCl_3): 0.90 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.68 (3H, d, J 6.5, $\text{C}(4)\text{CH}_3$),

3.52 (1H, q, J 6.5, $\text{C}(4)\text{H}$), 3.62 (3H, s, CO_2CH_3), 4.67 (1H, s, $\text{C}(2)\text{H}$), 6.34 (1H, s, $\text{C}(7)\text{H}$), 7.33 (4H, s, ArH); δ_{C} (100 MHz, CDCl_3): 14.7 ($\text{C}(4)\text{CH}_3$), 25.0 ($\text{C}(\text{CH}_3)_3$), 35.1 ($\text{C}(\text{CH}_3)_3$), 52.7 (CO_2CH_3), 76.7 ($\text{C}(5)$), 80.2 ($\text{C}(4)$), 96.0 ($\text{C}(2)$), 123.0 ($\text{C}(7)$), 128.0-137.0 (ArC), 158.0 ($\text{C}(6)$), 168.9 (CO_2CH_3), 177.2 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$) 364.2 ($[\text{M}+\text{H}]^+$, ^{35}Cl , 50%), 366.2 ($[\text{M}+\text{H}]^+$, ^{37}Cl , 15%); HRMS (ESI^+) m/z : $[\text{M}+\text{H}, ^{35}\text{Cl}]^+$ Calcd for $\text{C}_{19}\text{H}_{23}\text{ClNO}_4$ 364.1310; Found 364.1307.

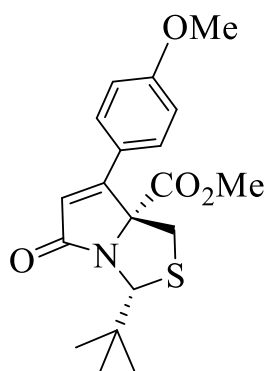
(2R,4S,5S)-1-Aza-2-(tert-butyl)-6-(4'-chloro-[1,1'-biphenyl]-4-yl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-oct-6-ene, 6cvi



By-product from **6cv**; Yield 5% (15 mg); white solid, m. p. 148-150°C; R_f (20% EA in PE) 0.35; $[\alpha]_D^{25}$ -56.7 (c 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2957 (C-H), 1748 (C=O), 1709 (C=O); δ_{H} (400 MHz, CDCl_3): 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.73 (3H, d, J 6.5, $\text{C}(4)\text{CH}_3$), 3.55 (1H, q, J 6.5, $\text{C}(4)\text{H}$), 3.64 (3H, s, CO_2CH_3), 4.69 (1H, s, $\text{C}(2)\text{H}$), 6.40 (1H, s, $\text{C}(7)\text{H}$), 7.34-7.57 (8H, m, ArH); δ_{C} (100 MHz, CDCl_3): 14.8 ($\text{C}(4)\text{CH}_3$), 25.1 ($\text{C}(\text{CH}_3)_3$), 35.2 ($\text{C}(\text{CH}_3)_3$), 52.7 (CO_2CH_3), 80.3 ($\text{C}(4)$), 96.0 ($\text{C}(2)$), 122.5 ($\text{C}(7)$), 127.4-142.3 (ArC), 158.7 ($\text{C}(6)$), 169.1 (CO_2CH_3), 177.5 ($\text{C}(8)$); m/z ($[\text{ESI}]^-$)

338.8 ($[\text{M}-\text{H}]^-$, ^{35}Cl , 40%), 340.8 ($[\text{M}-\text{H}]^-$, ^{37}Cl , 30%); HRMS (ESI^+) m/z : $[\text{M}+\text{H}, ^{35}\text{Cl}]^+$ Calcd for $\text{C}_{25}\text{H}_{27}\text{ClNO}_4$ 440.1623; Found 440.1610.

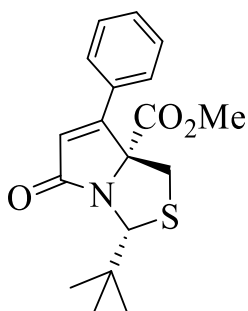
(2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene, 6d-i



According to General Method F, mesylate **5f** (117 mg, 0.330 mmol) was reacted with 4-methoxyphenylboronic acid (75 mg, 0.490 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.30 mL, 2.97 mmol) in ethanol (0.13 mL, 2.31 mmol) and toluene (13 mL) for 3 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (8.4 mg, 0.02 mmol) and (C₆H₅CN)₂PdCl₂ (6.4 mg, 0.02 mmol) in toluene (1 mL). Yield 62% (75

mg); yellow solid, m. p. 50-52°C; R_f (30% EA in PE) 0.38; $[\alpha]_D^{25} +276.8$ (*c* 1.0 in DCM); ν_{max}/cm⁻¹ 3040 (C-H), 2954 (C-H), 2906 (C-H), 1703 (C=O), 1644 (C=O); δ_H (400 MHz, CDCl₃): 0.93 (9H, s, C(CH₃)₃), 2.78 (1H, d, *J* 11.0, C(4)*H*_A*H*_B), 3.58 (3H, s, CO₂CH₃), 3.77 (3H, s, OCH₃), 3.89 (1H, d, *J* 11.0, C(4)*H*_A*H*_B), 4.92 (1H, s, C(2)H), 6.14 (1H, s, C(7)H), 6.85 (2H, d, *J* 8.9, C(3')H), 7.39 (2H, d, *J* 8.9, C(2')H); δ_C (100 MHz, CDCl₃): 26.6 (C(CH₃)₃), 34.6 (C(4)), 37.0 (C(CH₃)₃), 53.2 (CO₂CH₃), 55.5 (OCH₃), 70.6 (C(2)), 81.9 (C(5)), 114.7 (C(3')), 117.6 (C(7)), 122.4 (C(1')), 128.5 (C(2')), 158.8 (C(4')), 161.7 (C(6)), 170.1 (CO₂CH₃), 175.3 (C(8)); *m/z* ([ESI]⁺) 362.2 ([M+H]⁺, 100%), 384.2 ([M+Na]⁺, 60%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₉H₂₄O₄NS 362.1421; Found 362.1417.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0]-oct-6-ene, **6dii**

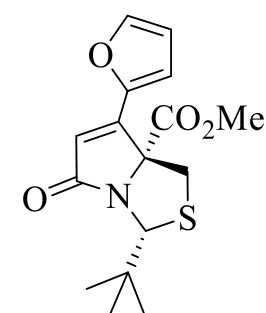


According to General Method F, mesylate **5f** (361 mg, 1.03 mmol) was reacted with phenylboronic acid (188 mg, 1.55 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.98 mL, 9.27 mmol) in ethanol (0.42 mL, 7.21 mmol) and toluene (13 mL) for 3 h. PdCl₂(dppb) was prepared from

(C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (31.5 mg, 0.074 mmol) and (C₆H₅CN)₂PdCl₂ (19.7 mg, 0.052 mmol) in toluene (2 mL). Yield 58% (200 mg); white solid, m. p. 128-130°C; R_f (40% EA in PE) 0.60; $[\alpha]_D^{25} +266.2$ (*c* 1.0 in DCM); ν_{max}/cm⁻¹ 2980 (C-H), 2904 (C-H), 1745 (C=O), 1704 (C=O); δ_H (400 MHz, CDCl₃): 0.93 (9H, s, C(CH₃)₃), 2.81 (1H, d, *J* 11.0, C(4)*H*_A*H*_B), 3.58 (3H, s, CO₂CH₃), 3.90

(1H, d, *J* 11.0, C(4)H_AH_B), 4.93 (1H, s, C(2)H), 6.28 (1H, s, C(7)H), 7.32-7.45 (5H, s, ArH); δ_c (100 MHz, CDCl₃): 26.6 (C(CH₃)₃), 34.6 (C(4)), 37.0 (C(CH₃)₃), 53.3 (CO₂CH₃), 70.6 (C(2)), 82.0 (C(5)), 120.1 (C(7)), 126.8-130.9 (ArC), 159.1 (C(6)), 169.8 (CO₂CH₃), 174.9 (C(8)); *m/z* ([ESI]⁺) 332.2 ([M+H]⁺, 100%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₈H₂₂NO₃S 332.1315; Found 332.1311.

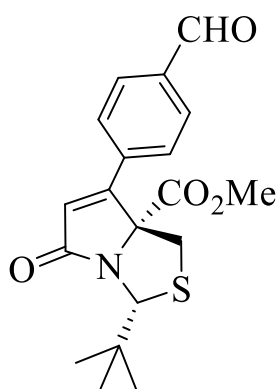
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene, 6diii



According to General Method F, mesylate **5f** (240 mg, 0.690 mmol) was reacted with 2-furylboronic acid (116 mg, 1.04 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.66 mL, 6.21 mmol) in ethanol (0.3 mL, 4.83 mmol) and toluene (12 mL) for 20 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (17.7 mg, 0.04 mmol) and (C₆H₅CN)₂PdCl₂ (13.2 mg, 0.03 mmol) in toluene (2 mL). Yield 22% (35 mg); white solid, m. p. 118-120°C; *R_f* (40% EA in PE) 0.49; $[\alpha]_D^{25} +179.4$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2955 (C-H), 2869 (C-H), 1745 (C=O), 1705 (C=O); δ_H (400 MHz, CDCl₃): 0.92 (9H, s, C(CH₃)₃), 2.69 (1H, d, *J* 11.2, C(4)H_AH_B), 3.64 (3H, s, CO₂CH₃), 3.77 (1H, d, *J* 11.1, C(4)H_AH_B), 4.90 (1H, s, C(2)H), 6.10 (1H, s, C(7)H), 6.43 (1H, dd, *J* 3.6, 1.8, C(3')H), 6.60 (1H, d, *J* 3.6, C(4')H), 7.49 (1H, d, *J* 1.8, C(5')H); δ_c (100 MHz, CDCl₃): 26.6 (C(CH₃)₃), 34.5 (C(4)), 37.0 (C(CH₃)₃), 53.3 (CO₂CH₃), 71.1 (C(2)), 80.4 (C(5)), 112.6 (C(3')), 113.3 (C(4')), 116.4 (C(7)), 145.7 (C(5')), 145.8 (C(2')), 148.1 (C(6)), 169.6 (CO₂CH₃), 175.0 (C(8)); *m/z* ([ESI]⁺) 322.2 ([M+H]⁺, 90%), 344.0 ([M+Na]⁺, 100%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₆H₂₀O₄NS 322.1108; Found 322.1102.

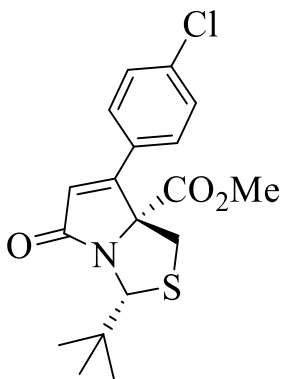
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene, 6div

According to General Method F, mesylate **5f** (617 mg, 1.77 mmol) was reacted with 4-formylphenylboronic acid (398 mg, 2.66 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.69



mL, 15.93 mmol) in ethanol (0.72 mL, 12.4 mmol) and toluene (15 mL) for overnight. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (45 mg, 0.106 mmol) and (C₆H₅CN)₂PdCl₂ (34 mg, 0.088 mmol) in toluene (3 mL). Yield 25% (135 mg); yellow solid, m. p. 148-150°C; R_f (40% EA in PE) 0.40; $[\alpha]_D^{25} +203.1$ (c 1.0 DCM); $\nu_{\max}/\text{cm}^{-1}$ 2956 (C-H), 2842 (C-H), 1745 (C=O), 1702 (C=O); δ_{H} (400 MHz, CDCl₃): 0.94 (9H, s, C(CH₃)₃), 2.83 (1H, d, *J* 11.0, C(4)H_AH_B), 3.60 (3H, s, CO₂CH₃), 3.92 (1H, d, *J* 11.0, C(4)H_AH_B), 4.95 (1H, s, C(2)H), 6.41 (1H, s, C(7)H), 7.60 (2H, d, *J* 8.4, C(2')H), 7.87 (2H, d, *J* 8.4, C(3')H), 9.98 (1H, s, CHO); δ_{C} (100 MHz, CDCl₃): 26.6 (C(CH₃)₃), 34.4 (C(4)), 37.1 (C(CH₃)₃), 53.4 (CO₂CH₃), 70.8 (C(2)), 81.9 (C(5)), 122.9 (C(7)), 127.4 (C(2')), 130.4 (C(3')), 135.1 (C(4')), 137.4 (C(1')), 157.4 (C(6)), 169.5 (CO₂CH₃), 174.1 (C(8)), 191.1 (CHO); m/z ([ESI]⁺) 360.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₉H₂₁O₄NS 360.1264; Found 360.1263.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene, 6dv

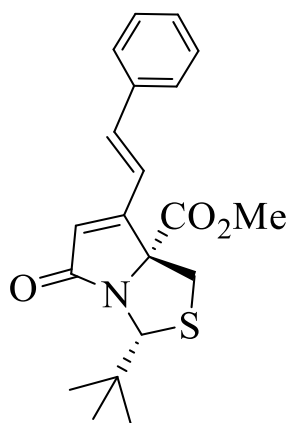


According to General Method F, mesylate **5f** (584 mg, 1.67 mmol) was reacted with 4-chlorophenylboronic acid (274 mg, 1.75 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.6 mL, 15.0 mmol) in ethanol (0.68 mL, 11.7 mmol) and toluene (15 mL) for 6 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (42 mg, 0.1 mmol) and (C₆H₅CN)₂PdCl₂ (32 mg, 0.08 mmol) in toluene (3 mL). Yield 43% (265

mg); white solid, m. p. 165-167°C; R_f (20% EA in PE) 0.33; $[\alpha]_D^{25} +276.2$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 3091 (C-H), 2954 (C-H), 2868 (C-H), 1743 (C=O), 1712 (C=O); δ_{H} (400 MHz, CDCl₃): 0.92 (9H, s, C(CH₃)₃), 2.79 (1H, d, *J* 11.0, C(4)H_AH_B), 3.59 (3H, s, CO₂CH₃), 3.87 (1H, d, *J* 11.0, C(4)H_AH_B), 4.92 (1H, s, C(2)H), 6.26 (1H, s, C(7)H), 7.32 (2H, d, *J* 8.8, C(2')H), 7.38 (2H, d, *J* 8.8, C(3')H); δ_{C} (100 MHz, CDCl₃): 26.6 (C(CH₃)₃), 34.5 (C(4)), 37.0 (C(CH₃)₃), 53.3 (CO₂CH₃),

70.7 (C(2)), 81.9 (C(5)), 120.5 (C(7)), 128.1 (C(3')), 128.3 (C(4')), 129.6 (C(2')), 137.1 (C(1')), 157.7 (C(6)), 169.7 (CO₂CH₃), 174.5 (C(8)); m/z ([ESI]⁺) 366.0 ([M+H]⁺, ³⁵Cl, 20%), 368.2 ([M+H]⁺, ³⁷Cl, 15%), 388.0 ([M+Na]⁺, 100%); HRMS (ESI⁺) m/z: [M+Na, ³⁵Cl]⁺ Calcd for C₁₈H₂₀O₃NCISNa 388.0750; Found 388.0739.

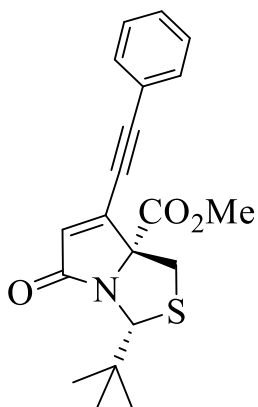
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-((*E*)-styryl)-3-thiabicyclo [3.3.0]-oct-6-ene, 6dvi



According to General Method F, mesylate **5f** (463 mg, 1.33 mmol) was reacted with *trans*-2-phenylvinylboronic acid (294 mg, 2.0 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.26 mL, 12.0 mmol) in ethanol (0.54 mL, 9.3 mmol) and toluene (15 mL) for 24 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (34 mg, 0.08 mmol) and (C₆H₅CN)₂PdCl₂ (25.4 mg, 0.07 mmol) in toluene (2 mL). Yield 20% (95 mg); yellow sticky material; R_f (30% EA in PE) 0.40; $[\alpha]_D^{25} +126.7$ (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2954 (C-H), 1744 (C=O), 1703 (C=O); δ_{H} (400 MHz, CDCl₃): 0.92 (9H, s, C(CH₃)₃), 2.70 (1H, d, *J* 11.2, C(4)*H*_A*H*_B), 3.67 (3H, s, CO₂CH₃), 3.83 (1H, d, *J* 11.1, C(4)*H*_A*H*_B), 4.89 (1H, s, C(2)H), 5.94 (1H, s, C(7)H), 6.76 (1H, d, *J* 16.7, C(10)H), 6.86 (1H, d, *J* 16.7, C(9)H), 7.27-7.43 (5H, m, ArH); δ_{C} (100 MHz, CDCl₃): 26.6 (C(CH₃)₃), 34.2 (C(4)), 37.0 (C(CH₃)₃), 53.3 (CO₂CH₃), 70.9 (C(2)), 81.4 (C(5)), 118.6 (C(10)), 121.8 (C(7)), 127.4-135.2 (ArC), 136.9 (C(9)), 157.1 (C(6)), 170.0 (CO₂CH₃), 175.1 (C(8)); m/z ([ESI]⁺) 358.2 ([M+H]⁺, 20%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₂₀H₂₄NO₃S 358.1471; Found 358.1471.

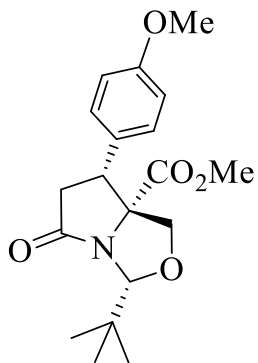
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-(phenylethynyl)-3-thiabicyclo [3.3.0]-oct-6-ene, 6dvii

According to General Method F, mesylate **5f** (203 mg, 0.580 mmol) was reacted with 2-phenyl-1-ethynylboronic acid (198 mg, 0.870 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.55 mL, 5.22 mmol) in ethanol (0.24 mL, 4.06 mmol) and toluene (13 mL) for 24 h. PdCl₂(dppb) was



prepared from $(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_4\text{P}(\text{C}_6\text{H}_5)_2$ (15 mg, 0.035 mmol) and $(\text{C}_6\text{H}_5\text{CN})_2\text{PdCl}_2$ (11 mg, 0.03 mmol) in toluene (1 mL). Yield 15% (30 mg); yellow sticky material. R_f (30% EA in PE) 0.50; $[\alpha]_D^{25} +84.4$ (c 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2955 (C-H), 1749 (C=O), 1709 (C=O); δ_{H} (400 MHz, CDCl_3): 0.93 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.72 (1H, d, J 11.2, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.73 (3H, s, CO_2CH_3), 3.73 (1H, d, J 11.2, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 4.90 (1H, s, $\text{C}(2)\text{H}$), 6.09 (1H, s, $\text{C}(7)\text{H}$), 7.27-7.46 (5H, m, ArH); δ_{C} (100 MHz, CDCl_3): 26.6 ($\text{C}(\text{CH}_3)_3$), 34.0 ($\text{C}(4)$), 37.1 ($\text{C}(\text{CH}_3)_3$), 53.4 (CO_2CH_3), 72.1 ($\text{C}(2)$), 79.3 ($\text{C}(5)$), 83.5 ($\text{C}(9)$), 104.7 ($\text{C}(10)$), 127.4 ($\text{C}(7)$), 120.9, 128.6-132.2 (ArC), 142.4 ($\text{C}(6)$), 168.3 (CO_2CH_3), 174.8 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$) 356.0 ($[\text{M}+\text{H}]^+$, 10%), 378.2 ($[\text{M}+\text{Na}]^+$, 15%); HRMS (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{S}$ 356.1315; Found 356.1312.

(2*R*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxobicyclo[3.3.0]-octane, 7ai

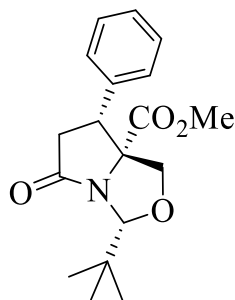


According to General Method G, pyrrolinone **6ai** (51 mg, 0.15 mmol) was hydrogenated for 8 h using platinum(IV) oxide (5.0 mg, 0.02 mmol) in EtOAc (7 mL) to afford pyrrolidinone **7ai**. Yield 98% (50 mg); white solid, m. p. 118-120°C; R_f (40% EA in PE) 0.46; $[\alpha]_D^{25} -40.5$ (c 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2958 (C-H), 2907 (C-H), 2872 (C-H), 1742 (C=O), 1715 (C=O); δ_{H}

(400 MHz, CDCl_3): 0.81 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.63 (1H, dd, J 15.2, 7.5, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.31 (3H, s, CO_2CH_3), 3.53 (1H, dd, J 15.2, 13.8, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.69 (1H, d, J 8.5, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.72 (3H, s, OCH_3), 3.73-3.77 (1H, m, $\text{C}(6)\text{H}$), 4.86 (1H, d, J 8.5, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 4.91 (1H, s, $\text{C}(2)\text{H}$), 6.78 (2H, d, J 8.8, $\text{C}(3')\text{H}$), 6.97 (2H, d, J 8.8, $\text{C}(2')\text{H}$); δ_{C} (100 MHz, CDCl_3): 24.8 ($\text{C}(\text{CH}_3)_3$), 36.2 ($\text{C}(\text{CH}_3)_3$), 39.3 ($\text{C}(7)$), 49.9 ($\text{C}(6)$), 52.1 (CO_2CH_3), 55.3 (OCH_3), 74.7 ($\text{C}(4)$), 77.3 ($\text{C}(5)$), 96.1 ($\text{C}(2)$), 114.0 ($\text{C}(3')$), 126.8 ($\text{C}(1')$), 128.6 ($\text{C}(2')$), 159.3 ($\text{C}(4')$), 170.3 (CO_2CH_3), 176.2 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$)

348.2 ([M+H]⁺, 15%), 370.2 ([M+Na]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₉H₂₆NO₅ 348.1806; Found 348.1801.

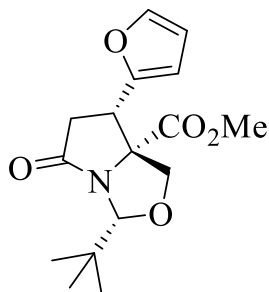
(2*R*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0]-octane, **7a_{ii}**



According to General Method G, pyrrolinone **6a_{ii}** (105 mg, 0.330 mmol) was hydrogenated for 7 h using platinum(IV) oxide (11 mg, 0.050 mmol) in EtOAc (10 mL) to afford pyrrolidinone **7a_{ii}**. Yield 88% (93 mg); white solid, m. p. 180-186°C; R_f (20% EA in PE) 0.33; $[\alpha]_D^{25}$ -42.0 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$

2957 (C-H), 2872 (C-H), 1743 (C=O), 1716 (C=O); δ_{H} (400 MHz, CDCl₃): 0.82 (9H, s, C(CH₃)₃), 2.66 (1H, dd, *J* 15.2, 7.5, C(7)H_AH_B), 3.27 (3H, s, CO₂CH₃), 3.58 (1H, dd, *J* 15.2, 13.6, C(7)H_AH_B), 3.73 (1H, d, *J* 8.5, C(4)H_AH_B), 3.80 (1H, dd, *J* 13.6, 7.5, C(6)H), 4.88 (1H, d, *J* 8.5, C(4)H_AH_B), 4.92 (1H, s, C(2)H), 7.03-7.28 (5H, m, ArH); δ_{C} (100 MHz, CDCl₃): 24.9 (C(CH₃)₃), 36.2 (C(CH₃)₃), 38.9 (C(7)), 50.5 (C(6)), 52.0 (CO₂CH₃), 74.7 (C(4)), 77.2 (C(5)), 96.1 (C(2)), 127.5-135.0 (ArC), 170.2 (CO₂CH₃), 176.1 (C(8)); m/z ([ESI]⁺) 318.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₈H₂₄NO₄ 318.1700; Found 318.1701.

(2*R*,5*S*,6*S*)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0] -octane, **7a_{iii}**

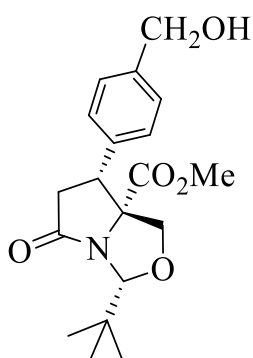


According to General Method G, pyrrolinone **6a_{iii}** (43 mg, 0.14 mmol) was hydrogenated for 18 h using platinum(IV) oxide (4.8 mg, 0.021 mmol) in EtOAc (7 mL) to afford pyrrolidinone **7a_{iii}**. Yield 28% (12 mg); white solid, m. p. 140-146°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25}$ -6.4 (c 1.0 in

DCM); $\nu_{\max}/\text{cm}^{-1}$ 2958 (C-H), 2872 (C-H), 1744 (C=O), 1719 (C=O); δ_{H} (500 MHz, CDCl₃): 0.82 (9H, s, C(CH₃)₃), 2.68 (1H, dd, *J* 15.5, 7.8, C(7)H_AH_B), 3.42 (1H, dd, *J* 15.5, 13.6, C(7)H_AH_B), 3.45 (3H, s, CO₂CH₃), 3.70 (1H, d, *J* 8.8, C(4)H_AH_B), 3.75 (1H, dd, *J* 13.6, 7.8, C(6)H), 4.84 (1H, d, *J* 8.8, C(4)H_AH_B), 4.89 (1H, s, C(2)H), 6.09 (1H, d, *J* 3.3, C(3')H), 6.25 (1H, dd, *J* 3.3, 1.8, C(4')H).

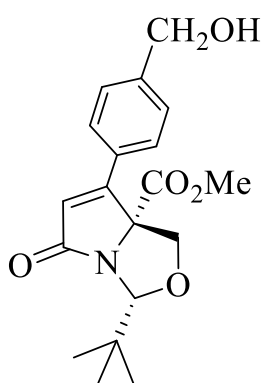
7.28 (1H, d, *J* 1.8, C(5')H); δ_c (125 MHz, CDCl₃): 23.8 (C(CH₃)₃), 35.2 (C(CH₃)₃), 37.7 (C(7)), 43.4 (C(6)), 51.4 (CO₂CH₃), 73.4 (C(4)), 75.0 (C(5)), 95.3 (C(2)), 106.6 (C(3')), 109.4 (C(4')), 141.8 (C(5')), 148.9 (C(2')), 169.2 (CO₂CH₃), 174.5 (C(8)); *m/z* ([ESI]⁺) 308.2 ([M+H]⁺, 25%), 330.2 ([M+Na]⁺, 85%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₆H₂₂NO₅ 308.1493; Found 308.1493.

(2*R*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-octane, 7aiv



According to General Method G, hydrogenation (reaction time: 20 h) of pyrrolinone **6aiv** (51.0 mg, 0.15 mmol) using platinum(IV) oxide (5 mg, 0.02 mmol) in EtOAc (7 mL) gave 4-(hydroxymethyl)phenyl pyrrolidinone derivative **7aiv**. Yield 76% (39.5 mg); white solid, m. p. 108-112°C; *R_f* (40% EA in PE) 0.18; $[\alpha]_D^{25}$ -30.2 (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 3429 (O-H), 2958 (C-H), 2872 (C-H), 1743 (C=O), 1714 (C=O); δ_H (400 MHz, CDCl₃): 0.81 (9H, s, C(CH₃)₃), 1.97 (1H, s, OH), 2.60 (1H, dd, *J* 15.2, 7.5, C(7)H_AH_B), 3.30 (3H, s, CO₂CH₃), 3.55 (1H, dd, *J* 15.2, 13.5, C(7)H_AH_B), 3.72 (1H, d, *J* 8.5, C(4)H_AH_B), 3.77 (1H, dd, *J* 13.5, 7.5, C(6)H), 4.61 (2H, s, CH₂OH), 4.87 (1H, d, *J* 8.5, C(4)H_AH_B), 4.90 (1H, s, C(2)H), 7.03 (2H, d, *J* 8.0, C(2')H), 7.26 (2H, d, *J* 8.0, C(3')H); δ_c (100 MHz, CDCl₃): 24.8 (C(CH₃)₃), 36.1 (C(CH₃)₃), 39.0 (C(7)), 50.2 (C(6)), 52.1 (CO₂CH₃), 64.6 (CH₂OH), 74.7 (C(4)), 77.1 (C(5)), 96.1 (C(2)), 127.1 (C(3')), 127.6 (C(2')), 134.2 (C(1')), 141.0 (C(4')), 170.2 (CO₂CH₃), 176.2 (C(8)); *m/z* ([ESI]⁺) 348.2 ([M+H]⁺, 100%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₉H₂₆O₅N 348.1806; Found 348.1804.

(2*R*,5*S*)-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]-oct-6-ene

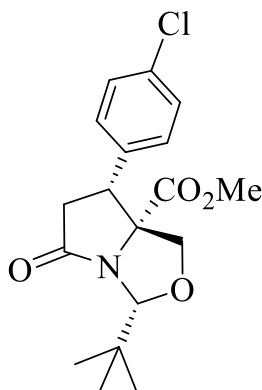


According to General Method G, hydrogenation (reaction time: 1 h) of (4-formylphenyl) pyrrolidinone derivative **6aiv** (51 mg, 0.15 mmol) using PtO₂ (5 mg, 0.02 mmol) in EtOAc (7 mL) afforded 4-(hydroxymethyl)phenyl pyrrolidinone. Yield 49% (25 mg); white solid, m. p. 166-172°C; R_f (40% EA in PE) 0.14; $[\alpha]_D^{25} +122.5$ (*c* 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 3440 (O-H), 2957 (C-H), 2871 (C-H), 1744 (C=O), 1708 (C=O); δ_{H} (400 MHz, CDCl₃): 0.89 (9H,

s, C(CH₃)₃), 3.40 (1H, d, *J* 8.4, C(4)H_AH_B), 3.56 (3H, s, CO₂CH₃), 4.67 (2H, s, CH₂OH), 4.68 (1H, s, C(2)H), 5.06 (1H, d, *J* 8.4, C(4)H_AH_B), 6.28 (1H, s, C(7)H), 7.33 (2H, d, *J* 8.8, C(2')H), 7.35 (2H, d, *J* 8.8, C(3')H); δ_{C} (100 MHz, CDCl₃): 24.7 (C(CH₃)₃), 35.3 (C(CH₃)₃), 53.2 (CO₂CH₃), 64.5 (CH₂OH), 70.4 (C(4)), 77.4 (C(5)), 96.3 (C(2)), 121.4 (C(7)), 127.1 (C(2')), 127.6 (C(3')), 129.0 (C(1')), 144.4 (C(4')), 159.2 (C(6)), 169.7 (CO₂CH₃), 177.5 (C(8)); *m/z* ([ESI]⁺) 346.2 ([M+H]⁺, 100%); HRMS (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₉H₂₃O₅NNa 368.1468; Found 368.1466.

(2*R*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo

[3.3.0]-octane, **7av**

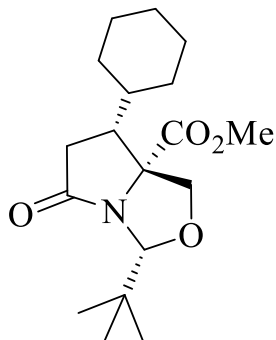


According to General Method G, pyrrolidinone **6av** (60 mg, 0.17 mmol) was hydrogenated for 8 h using platinum(IV) oxide (6.0 mg, 0.03 mmol) in EtOAc (7 mL) to afford pyrrolidinone **7av**. Yield 33% (20 mg); white solid, m. p. 128-130°C; R_f (30% EA in PE) 0.44; $[\alpha]_D^{25} -43.6$ (*c* 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2957 (C-H), 2871 (C-H), 1742 (C=O), 1715 (C=O); δ_{H} (500 MHz,

CDCl₃): 0.81 (9H, s, C(CH₃)₃), 2.66 (1H, dd, *J* 15.2, 7.6, C(7)H_AH_B), 3.32 (3H, s, CO₂CH₃), 3.52 (1H, dd, *J* 15.2, 13.7, C(7)H_AH_B), 3.71 (1H, d, *J* 8.5, C(4)H_AH_B), 3.75 (1H, dd, *J* 13.7, 7.6, C(6)H), 4.87 (1H, d, *J* 8.5, C(4)H_AH_B), 4.91 (1H, s, C(2)H), 6.99 (2H, d, *J* 8.4, C(2')H), 7.24 (2H, d, *J* 8.4, C(3')H); δ_{C} (125 MHz, CDCl₃): 24.8 (C(CH₃)₃), 36.2 (C(CH₃)₃), 39.0 (C(7)), 49.8 (C(6)), 52.2 (CO₂CH₃), 74.6 (C(4)), 77.0 (C(5)), 96.2 (C(2)), 128.9-134.1 (ArC), 170.1 (CO₂CH₃), 175.7 (C(8));

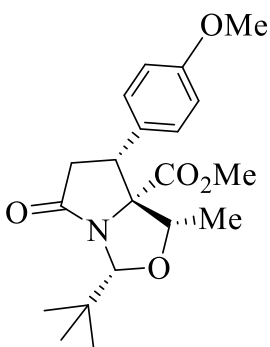
m/z ([ESI]⁺) 352.2 ([M+H]⁺, ³⁵Cl, 15%), 354.2 ([M+H]⁺, ³⁷Cl, 5%); HRMS (ESI⁺) m/z: [M+Na, ³⁵Cl]⁺ Calcd for C₁₈H₂₃ClNO₄ 352.1310; Found 352.1312.

(2*R*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-6-cyclohexyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 8a



Formed from **6av**. Yield 35% (19 mg); white solid, m. p. 72-82°C; R_f (30% EA in PE) 0.58; $[\alpha]_D^{25} +51.0$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2930 (C-H), 2856 (C-H), 1741 (C=O), 1716 (C=O); δ_{H} (500 MHz, CDCl₃): 0.79 (9H, s, C(CH₃)₃), 0.99-1.69 (11H, m, cyclohexyl), 2.06-2.16 (1H, m, C(6)H), 2.42 (1H, dd, *J* 15.2, 7.4, C(7)H_AH_B), 2.79-2.90 (1H, m, C(7)H_AH_B), 3.42 (1H, d, *J* 8.5, C(4)H_AH_B), 3.72 (3H, s, CO₂CH₃), 4.76 (1H, d, *J* 8.5, C(4)H_AH_B), 4.80 (1H, s, C(2)H); δ_{C} (125 MHz, CDCl₃): 24.8 (C(CH₃)₃), 25.6-31.9, 38.5 (cyclohexyl), 36.2 (C(CH₃)₃), 39.9 (C(7)), 52.3 (CO₂CH₃), 53.3 (C(6)), 74.8 (C(4)), 75.7 (C(5)), 95.3 (C(2)), 171.6 (CO₂CH₃), 176.3 (C(8)); m/z ([ESI]⁺) 324.2 ([M+H]⁺, 100%), 346.2 ([M+Na]⁺, 45%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₈H₃₀NO₄ 324.2169; Found 324.2170.

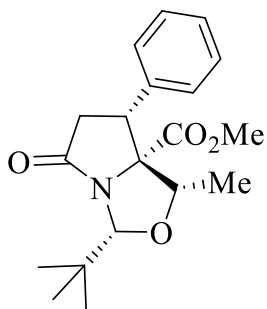
(2*R*,4*S*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 7ci



According to General Method G, pyrrolinone **6ci** (52 mg, 0.14 mmol) was hydrogenated for 4 h with platinum(IV) oxide (5.0 mg, 0.022 mmol) in EtOAc (8 mL) to afford pyrrolidinone **7ci**. Yield 71% (37 mg); white solid, m. p. 92-94°C; R_f (40% EA in PE) 0.50; $[\alpha]_D^{25} -70.6$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2977 (C-H), 2870 (C-H), 1749 (C=O), 1712 (C=O); δ_{H} (400 MHz, CDCl₃): 0.83 (9H, s, C(CH₃)₃), 1.53 (3H, d, *J* 6.6, C(4)CH₃), 2.63 (1H, dd, *J* 15.5, 7.8, C(7)H_AH_B), 3.34 (3H, s, CO₂CH₃), 3.46 (1H, dd, *J* 15.5, 13.5, C(7)H_AH_B), 3.62 (1H, dd, *J* 13.5, 7.8, C(6)H), 3.72 (3H, s, OCH₃), 3.90 (1H, q, *J* 6.6, C(4)H), 4.81 (1H, s, C(2)H), 6.79 (2H, d, *J* 8.8, C(3')H), 7.04 (2H, d, *J* 8.8, C(2')H); δ_{C} (100 MHz, CDCl₃): 15.4 (C(4)CH₃), 25.0 (C(CH₃)₃), 35.8 (C(CH₃)₃),

40.2 (C(7)), 49.4 (C(6)), 51.4 (CO₂CH₃), 55.3 (OCH₃), 77.2 (C(5)), 84.2 (C(4)), 94.3 (C(2)), 114.0 (C(3')), 127.1 (C(1')), 129.0 (C(2')), 159.4 (C(4')), 169.3 (CO₂CH₃), 176.0 (C(8)); m/z ([ESI]⁺) 362.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₂₀H₂₈NO₅ 362.1962; Found 362.1960.

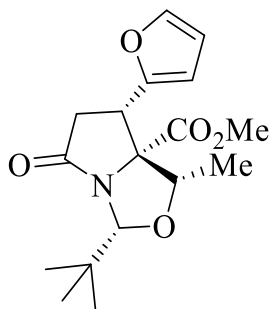
(2*R*,4*S*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-6-phenylbicyclo[3.3.0]-octane, 7cii



According to General Method G, pyrrolinone **6cii** (137 mg, 0.410 mmol) was hydrogenated for 4 h with platinum(IV) oxide (14 mg, 0.060 mmol) in EtOAc (15 mL) to afford pyrrolidinone **7cii**. Yield 94% (129 mg); white solid, m. p. 88-90°C; R_f (20% EA in PE) 0.25; $[\alpha]_D^{25}$ -29.7 (*c* 1.0 in DCM);

$\nu_{\text{max}}/\text{cm}^{-1}$ 2977 (C-H), 2957 (C-H), 2870 (C-H), 1747 (C=O), 1714 (C=O); δ_{H} (400 MHz, CDCl₃): 0.84 (9H, s, C(CH₃)₃), 1.54 (3H, d, *J* 6.5, C(4)CH₃), 2.66 (1H, dd, *J* 15.5, 7.8, C(7)H_AH_B), 3.30 (3H, s, CO₂CH₃), 3.50 (1H, dd, *J* 15.5, 13.4, C(7)H_AH_B), 3.67 (1H, dd, *J* 13.4, 7.8, C(6)H), 3.93 (1H, q, *J* 6.5, C(4)H), 4.82 (1H, s, C(2)H), 7.09-7.29 (5H, m, ArH); δ_{C} (100 MHz, CDCl₃): 15.4 (C(4)CH₃), 25.1 (C(CH₃)₃), 35.8 (C(CH₃)₃), 39.9 (C(7)), 50.1 (C(6)), 51.4 (CO₂CH₃), 77.3 (C(5)), 84.3 (C(4)), 94.4 (C(2)), 127.9-135.3 (ArC), 169.1 (CO₂CH₃), 176.0 (C(8)); m/z ([ESI]⁺) 332.2 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₉H₂₆NO₄ 332.1856; Found 332.1853.

(2*R*,4*S*,5*S*,6*S*)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-4-methyl-8-oxa-3-oxobicyclo[3.3.0]-octane, 7ciii

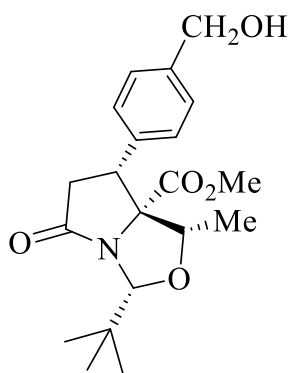


According to General Method G, pyrrolinone **6ciii** (78 mg, 0.24 mmol) was hydrogenated for 8h with platinum(IV) oxide (8.0 mg, 0.037 mmol) in EtOAc (10 mL) to afford pyrrolidinone **7ciii**. Yield 67% (52 mg); white solid, m. p. 83-85°C; R_f (20% EA in PE) 0.21; $[\alpha]_D^{25}$ -14.8 (*c* 1.0 in DCM);

$\nu_{\text{max}}/\text{cm}^{-1}$ 2978 (C-H), 2958 (C-H), 2871 (C-H), 1747 (C=O), 1715 (C=O); δ_{H} (400 MHz, CDCl₃): 0.83 (9H, s, C(CH₃)₃), 1.61 (3H, d, *J* 6.6, C(4)CH₃), 2.68 (1H, dd, *J* 15.5, 7.9, C(7)H_AH_B), 3.32-

3.38 (1H, m, C(7)H_AH_B), 3.41 (3H, s, CO₂CH₃), 3.65 (1H, dd, *J* 13.5, 7.9, C(6)H), 3.86 (1H, q, *J*, 6.6, C(4)H), 4.80 (1H, s, C(2)H), 6.08 (1H, d, *J* 3.3, C(3')H), 6.25 (1H, dd, *J* 3.3, 1.8, C(4')H), 7.30 (1H, d, *J* 1.8, C(5')H); δ_c (100 MHz, CDCl₃): 14.5 (C(4)CH₃), 25.0 (C(CH₃)₃), 35.8 (C(CH₃)₃), 39.2 (C(7)), 43.4 (C(6)), 51.7 (CO₂CH₃), 76.1 (C(5)), 84.1 (C(4)), 94.7 (C(2)), 107.5 (C(3')), 110.4 (C(4')), 142.8 (C(5')), 150.3 (C(2')), 169.1 (CO₂CH₃), 175.1 (C(8)); *m/z* ([ESI]⁺) 322.2 ([M+H]⁺, 100%), 344.2 ([M+Na]⁺, 90%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₇H₂₄O₅N 322.1649; Found 322.1649.

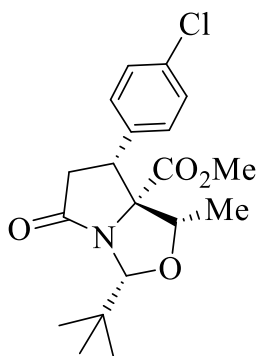
(2*R*,4*S*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 7civ



According to General Method G, pyrrolinone **6civ** (55.6 mg, 0.155 mmol) was hydrogenated for 6 h with platinum(IV) oxide (5.3 mg, 0.02 mmol) in EtOAc (8 mL) to afford pyrrolidinone **7civ**. Yield 79% (44 mg); white solid, m. p. 128-130°C; *R_f* (60% EA in PE) 0.28; $[\alpha]_D^{25}$ -39.5 (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 3409 (O-H), 2957 (C-H), 2871 (C-H), 1709 (C=O); δ_H

(400 MHz, CDCl₃): 0.84 (9H, s, C(CH₃)₃), 1.53 (3H, d, *J* 6.5, C(4)CH₃), 1.75 (1H, br s, OH), 2.61 (1H, dd, *J* 15.4, 7.7, C(7)H_AH_B), 3.33 (3H, s, CO₂CH₃), 3.48 (1H, dd, *J* 15.4, 13.5, C(7)H_AH_B), 3.65 (1H, dd, *J* 13.5, 7.7, C(6)H), 3.92 (1H, q, *J* 6.5, C(4)H), 4.62 (2H, s, CH₂OH), 4.82 (1H, s, C(2)H), 7.11 (2H, d, *J* 7.9, C(2')H), 7.28 (2H, d, *J* 7.9, C(3')H); δ_c (100 MHz, CDCl₃): 15.4 (C(4)CH₃), 25.0 (C(CH₃)₃), 35.8 (C(CH₃)₃), 40.0 (C(7)), 49.9 (C(6)), 51.4 (CO₂CH₃), 64.7 (CH₂OH), 77.1 (C(5)), 84.3 (C(4)), 94.4 (C(2)), 127.1 (C(3')), 128.1 (C(2')), 134.6 (C(1')), 141.1 (C(4')), 169.1 (CO₂CH₃), 175.9 (C(8)); *m/z* ([ESI]⁺) 384.2 ([M+Na]⁺, 60%); HRMS (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₀H₂₇NO₅Na 384.1781; Found 384.1782.

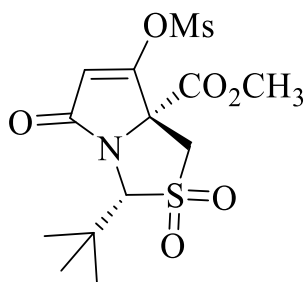
(2*R*,4*S*,5*S*,6*R*)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-4-methyl-3-oxa-8-oxobicyclo [3.3.0]-octane, 7cv



According to General Method G, pyrrolinone **6cv** (79 mg, 0.22 mmol) was hydrogenated for 4 h with platinum(IV) oxide (7.4 mg, 0.03 mmol) in EtOAc (10 mL) to furnish pyrrolidinone **7cv**. Yield 84% (66 mg); white solid, m. p. 132-134°C; R_f (20% EA in PE) 0.23; $[\alpha]_D^{25}$ -32.0 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2956 (C-H), 2870 (C-H), 1712 (C=O); δ_H (400 MHz, CDCl_3): 0.83 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.53 (3H, d, J 6.5, $\text{C}(4)\text{CH}_3$), 2.65 (1H, dd, J 15.5, 7.8, $\text{C}(7)\text{H}_\text{A}\text{H}_\text{B}$),

3.34 (3H, s, CO_2CH_3), 3.44 (1H, dd, J 15.5, 13.4, $\text{C}(7)\text{H}_\text{A}\text{H}_\text{B}$), 3.63 (1H, dd, J 13.4, 7.8, $\text{C}(6)\text{H}$), 3.91 (1H, q, J 6.5, $\text{C}(4)\text{H}$), 4.81 (1H, s, $\text{C}(2)\text{H}$), 7.06 (2H, d, J 8.3, $\text{C}(2')\text{H}$), 7.25 (2H, d, J 8.3, $\text{C}(3')\text{H}$); δ_C (100 MHz, CDCl_3): 15.4 ($\text{C}(4)\text{CH}_3$), 25.0 ($\text{C}(\text{CH}_3)_3$), 35.8 ($\text{C}(\text{CH}_3)_3$), 40.0 ($\text{C}(7)$), 49.3 ($\text{C}(6)$), 51.5 (CO_2CH_3), 84.2 ($\text{C}(4)$), 94.4 ($\text{C}(2)$), 128.9 ($\text{C}(3')$), 129.2 ($\text{C}(2')$), 133.9 ($\text{C}(4')$), 134.2 ($\text{C}(1')$), 169.0 (CO_2CH_3), 175.6 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$) 388.2 ($[\text{M}+\text{Na}]^+$, ^{35}Cl , 20%), 390.2 ($[\text{M}+\text{Na}]^+$, ^{37}Cl , 5%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{M}+\text{Na}, ^{35}\text{Cl}]^+$ Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_4\text{ClNa}$ 388.1286; Found 388.1283.

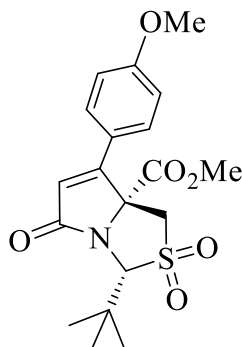
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-((methylsulfonyl)oxy)-5-methoxycarbonyl-8-oxa-3-thiabicyclo [3.3.0]-oct-6-ene 3,3-dioxide, **10**



According to General Method H, of **5f** (203 mg, 0.580 mmol) in CHCl_3 (7 mL) was reacted with *m*-chloroperbenzoic acid (300 mg, 1.74 mmol) in CHCl_3 (4 mL) to prepare **10**. Yield 77% (171 mg); white solid, m. p. 104-106°C; R_f (60% EA in PE) 0.50; $[\alpha]_D^{25}$ +109.1 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$

3022 (C-H), 2965 (C-H), 1730 (C=O), 1638 (C=O); δ_H (400 MHz, CDCl_3): 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.24 (3H, s, OSO_2CH_3), 3.36 (1H, d, J 14.2, $\text{C}(4)\text{H}_\text{A}\text{H}_\text{B}$), 3.81 (3H, s, CO_2CH_3), 3.95 (1H, d, J 14.2, $\text{C}(4)\text{H}_\text{A}\text{H}_\text{B}$), 4.60 (1H, s, $\text{C}(2)\text{H}$), 6.16 (1H, s, $\text{C}(7)\text{H}$); δ_C (100 MHz, CDCl_3): 26.2 ($\text{C}(\text{CH}_3)_3$), 35.1 ($\text{C}(\text{CH}_3)_3$), 38.7 (SO_2CH_3), 50.9 ($\text{C}(4)$), 54.7 (CO_2CH_3), 70.1 ($\text{C}(5)$), 81.9 ($\text{C}(2)$), 107.7 ($\text{C}(7)$), 163.7 (CO_2CH_3), 166.6 ($\text{C}(8)$), 173.5 ($\text{C}(6)$); m/z ($[\text{ESI}]^+$) 382.0 ($[\text{M}+\text{H}]^+$, 100%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_8\text{S}_2$ 382.0625; Found 382.0628.

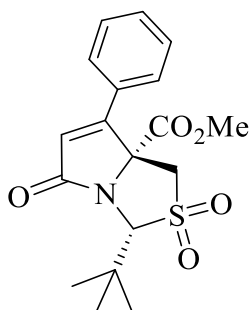
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 11i



According to General Method F, mesylate **10** (105 mg, 0.27 mmol) was reacted with 4-methoxyphenylboronic acid (63 mg, 0.4 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.25 mL, 2.43 mmol) in ethanol (0.11 mL, 1.89 mmol) and toluene (12 mL) for 4 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (7.0 mg, 0.02 mmol) and (C₆H₅CN)₂PdCl₂ (5.0 mg,

0.01 mmol) in toluene (1 mL). Yield 56% (60 mg); colourless oil; R_f (40% EA in PE) 0.30; $[\alpha]_D^{25} +129.2$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2959 (C-H), 1746 (C=O), 1713 (C=O); δ_{H} (400 MHz, CDCl₃): 1.10 (9H, s, C(CH₃)₃), 3.32 (1H, d, *J* 13.5, C(4)*H*_A*H*_B), 3.64 (3H, s, CO₂CH₃), 3.79 (3H, s, OCH₃), 4.44 (1H, d, *J* 13.5, C(4)*H*_A*H*_B), 4.64 (1H, s, C(2)H), 6.52 (1H, s, C(7)H), 6.87 (2H, d, *J* 9.0, C(3')H), 7.37 (2H, d, *J* 9.0, C(2')H); δ_{C} (100 MHz, CDCl₃): 26.3 (C(CH₃)₃), 35.5 (C(CH₃)₃), 54.2, 54.3 (C(4), CO₂CH₃), 55.5 (OCH₃), 71.5 (C(5)), 81.3 (C(2)), 114.9 (C(3')), 118.3 (C(7)), 121.2 (C(1')), 128.8 (C(2')), 160.4 (C(4')), 162.2 (C(6)), 169.4 (CO₂CH₃), 175.1 (C(8)); *m/z* ([ESI]⁺) 394.2 ([M+H]⁺, 100%), 416.2 ([M+Na]⁺, 95%); HRMS (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₉H₂₃O₆NNaS 416.1138; Found 416.1137.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 11ii

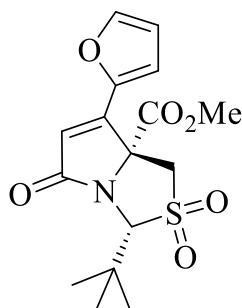


According to General Method F, mesylate **10** (300 mg, 0.780 mmol) was reacted with phenylboronic acid (144 mg, 1.18 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.7 mL, 7.02 mmol) in ethanol (0.32 mL, 5.46 mmol) and toluene (13 mL) for 5 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (20 mg, 0.047 mmol) and (C₆H₅CN)₂PdCl₂ (15 mg,

0.04 mmol) in toluene (2 mL). Yield 53% (150 mg); white solid, m. p. 175-177°C; R_f (40% EA in PE) 0.34; $[\alpha]_D^{25} +132.3$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 1748 (C=O), 1716 (C=O); δ_{H} (400

MHz, CDCl₃): 1.10 (9H, s, C(CH₃)₃), 3.32 (1H, d, *J* 13.5, C(4)H_AH_B), 3.64 (3H, s, CO₂CH₃), 4.45 (1H, d, *J* 13.5, C(4)H_AH_B), 4.64 (1H, s, C(2)H), 6.65 (1H, s, C(7)H), 7.35-7.45 (5H, m, ArH); δ_c (100 MHz, CDCl₃): 26.3 (C(CH₃)₃), 35.6 (C(CH₃)₃), 54.2 (C(4), CO₂CH₃), 71.7 (C(5)), 81.5 (C(2)), 121.0 (C(7)), 127.0-131.7 (ArC), 160.7 (C(6)), 169.0 (CO₂CH₃), 174.7 (C(8)); m/z ([ESI]⁺) 364.2 ([M+H]⁺, 100%), 486.0 ([M+Na]⁺, 95%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₈H₂₂O₅NS 364.1213; Found 364.1218.

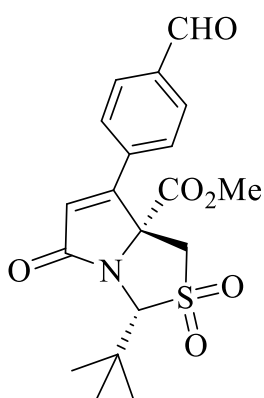
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 11iii



According to General Method F, mesylate **10** (540 mg, 1.42 mmol) was reacted with 2-furylboronic acid (238 mg, 2.13 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.35 mL, 12.8 mmol) in ethanol (0.58 mL, 9.94 mmol) and toluene (15 mL) for 24 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (36 mg, 0.085 mmol) and (C₆H₅CN)₂PdCl₂ (27 mg,

0.07 mmol) in toluene (3 mL). Yield 20% (100 mg); yellow solid, m. p. 130-132°C; R_f (40% EA in PE) 0.37; $[\alpha]_D^{25} +88.3$ (c 1.0 in DCM); ν_{max}/cm⁻¹ 2961 (C-H), 1748 (C=O), 1716 (C=O); δ_H (400 MHz, CDCl₃): 1.10 (9H, s, C(CH₃)₃), 3.30 (1H, d, *J* 13.8, C(4)H_AH_B), 3.69 (3H, s, CO₂CH₃), 4.30 (1H, d, *J* 13.8, C(4)H_AH_B), 4.61 (1H, s, C(2)H), 6.42-6.55 (2H, m, C(7)H + C(3')H), 6.66 (1H, d, *J* 3.6, C(4')H), 7.54 (1H, d, *J* 1.8, C(5')H); δ_c (100 MHz, CDCl₃): 26.3 (C(CH₃)₃), 35.4 (C(CH₃)₃), 53.9 (C(4)), 54.3 (CO₂CH₃), 70.2 (C(5)), 81.6 (C(2)), 112.9 (C(7)), 114.5 (C(4')), 117.5 (C(3')), 145.0 (C(5')), 146.5 (C(2')), 149.6 (C(6)), 168.9 (CO₂CH₃), 175.0 (C(8)); m/z ([ESI]⁺) 354.0 ([M+H]⁺, 45%), 376.0 ([M+Na]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₆H₂₀O₆NS 354.1006; Found 354.1006.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(4-formylphenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 11iv

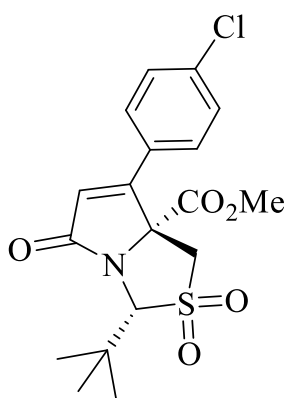


According to General Method F, mesylate **10** (500 mg, 1.31 mmol) was reacted with 4-formylphenylboronic acid (295 mg, 1.97 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (1.25 mL, 11.8 mmol) in ethanol (0.54 mL, 9.17 mmol) and toluene (15 mL) for 8 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (34 mg, 0.08 mmol) and (C₆H₅CN)₂PdCl₂ (25 mg, 0.07 mmol) in toluene (3 mL). Yield 26% (135 mg); white solid, m. p. 138-

140°C; R_f (40% EA in PE) 0.30; $[\alpha]_D^{25} +103.0$ (*c* 1.0 DCM); $\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1747 (C=O), 1717 (C=O); δ_{H} (400 MHz, CDCl₃): 1.11 (9H, s, C(CH₃)₃), 3.34 (1H, d, *J* 13.6 Hz, C(4)H_AH_B), 3.66 (3H, s, CO₂CH₃), 4.47 (1H, d, *J* 13.6, C(4)H_AH_B), 4.66 (1H, s, C(2)H), 6.80 (1H, s, C(7)H), 7.59 (2H, d, *J* 8.4, C(2')H), 7.90 (2H, d, *J* 8.4, C(3')H). 9.99 (1H, s, CHO); δ_{C} (100 MHz, CDCl₃): 26.3 (C(CH₃)₃), 35.6 (C(CH₃)₃), 54.0 (C(4)), 54.4 (CO₂CH₃), 71.7 (C(5)), 81.6 (C(2)), 123.7 (C(7)), 127.6 (C(2')), 130.5 (C(3')), 133.9 (C(4')), 137.9 (C(1')), 159.0 (C(6)), 168.8 (CO₂CH₃), 174.1 (C(8)), 190.9 (CHO); *m/z* ([ESI]⁺) 392.0 ([M+H]⁺, 100%), 414.2 ([M+Na]⁺, 90%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₉H₂₂O₆NS 392.1162; Found 392.1161.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo

[3.3.0]-oct-6-ene 3,3-dioxide, 11v

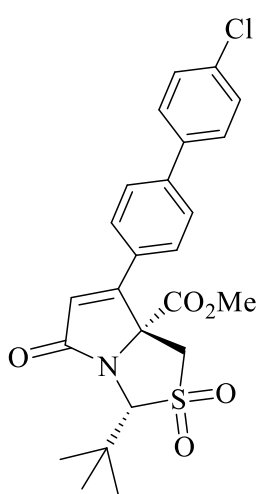


According to General Method F, mesylate **10** (100 mg, 0.260 mmol) was reacted with 4-chlorophenylboronic acid (42.6 mg, 0.270 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.25 mL, 2.34 mmol) in ethanol (0.1 mL, 1.82 mmol) and toluene (10 mL) for 8 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (6.6 mg, 0.016 mmol) and (C₆H₅CN)₂PdCl₂ (5 mg, 0.013 mmol) in toluene (1 mL). Yield 48% (45

mg); white solid, m. p. 50-52°C; R_f (20% EA in PE) 0.20; $[\alpha]_D^{25} +105.4$ (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 1747 (C=O), 1717 (C=O); δ_{H} (400 MHz, CDCl₃): 1.10 (9H, s, C(CH₃)₃), 3.30 (1H, d, *J* 13.4, C(4)H_AH_B), 3.65 (3H, s, CO₂CH₃), 4.43 (1H, d, *J* 13.4, C(4)H_AH_B), 4.65 (1H, s, C(2)H), 6.65

(1H, s, C(7)H), 7.36 (4H, s, ArH); δ_c (100 MHz, CDCl₃): 26.3 (C(CH₃)₃), 35.5 (C(CH₃)₃), 54.0 (C(4)), 54.4 (CO₂CH₃), 71.6 (C(5)), 81.5 (C(2)), 121.4 (C(7)), 127.2-138.0 (ArC), 159.3 (C(6)), 169.0 (CO₂CH₃), 174.5 (C(8)); m/z ([ESI]⁺) 398.0 ([M+H]⁺, ³⁵Cl, 100%), 400.2 ([M+H]⁺, ³⁷Cl, 40%), 420.0 ([M+Na]⁺, 60%); HRMS (ESI⁺) m/z: [M+H, ³⁵Cl]⁺ Calcd for C₁₈H₂₁O₅NCIS 398.0823; Found 398.0822.

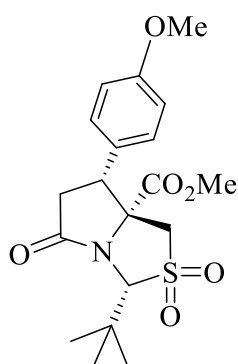
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(4'-chloro-[1,1'-biphenyl]-4-yl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3,3-dioxide, 13



According to General Method F, mesylate **10** (100 mg, 0.26 mmol) was reacted with 4-chlorophenylboronic acid (83 mg, 0.53 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.25 mL, 2.34 mmol) in ethanol (0.1 mL, 1.82 mmol) and toluene (10 mL) for 8 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (6.6 mg, 0.016 mmol) and (C₆H₅CN)₂PdCl₂ (5 mg, 0.013 mmol) in toluene (1 mL). Yield 16% (20 mg); white solid, m.p. 86-88°C; R_f (20% EA in PE) 0.12; $[\alpha]_D^{25} +70.2$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960

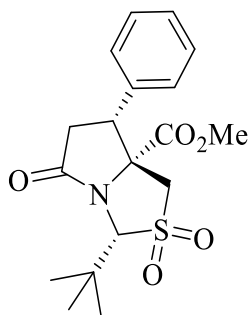
(C-H), 2923 (C-H), 1747 (C=O), 1717 (C=O); δ_H (400 MHz, CDCl₃): 1.12 (9H, s, C(CH₃)₃), 3.35 (1H, d, *J* 13.6, C(4)H_AH_B), 3.67 (3H, s, CO₂CH₃), 4.48 (1H, d, *J* 13.6, C(4)H_AH_B), 4.67 (1H, s, C(2)H), 6.70 (1H, s, C(7)H), 7.35-7.60 (8H, m, ArH); δ_c (100 MHz, CDCl₃): 26.4 (C(CH₃)₃), 35.6 (C(CH₃)₃), 54.2 (C(4)), 54.3 (CO₂CH₃), 71.6 (C(5)), 81.5 (C(2)), 120.8 (C(7)), 127.6-143.1 (ArC), 160.0 (C(6)), 169.2 (CO₂CH₃); m/z ([ESI]⁺) 474.0 ([M+H]⁺, ³⁵Cl, 40%), 476.0 ([M+H]⁺, ³⁷Cl, 15%); HRMS (ESI⁺) m/z: [M+H, ³⁵Cl]⁺ Calcd for C₂₄H₂₅O₅NCIS 474.1137; Found 474.1135.

(2*R*,5*R*,6*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 12i



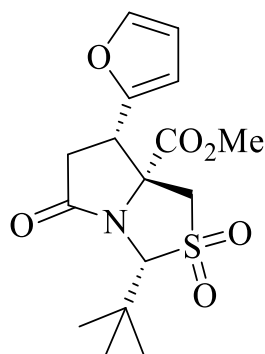
According to General Method G, pyrrolidinone **11i** (24 mg, 0.060 mmol) was hydrogenated for 24 h with platinum(IV) oxide (2.0 mg, 0.0090 mmol) in EtOAc (7 mL) to afford pyrrolidinone **12i**. Yield 83% (20 mg); white solid, m. p. 209-211°C; R_f (40% EA in PE) 0.35; $[\alpha]_D^{25}$ -87.6 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2962 (C-H), 1722 (C=O), 1613 (C=O); δ_H (400 MHz, CDCl_3): 1.04 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.57 (1H, dd, J 16.1, 7.6, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.26 (1H, dd, J 16.1, 13.7, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.38-3.45 (4H, m, (CO_2CH_3 + $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$)), 3.63 (1H, d, J 14.6, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.74 (3H, s, OCH_3), 3.79 (1H, dd, J 13.7, 7.6, $\text{C}(6)\text{H}$), 4.65 (1H, s, $\text{C}(2)\text{H}$), 6.82 (2H, d, J 8.7, $\text{C}(3')\text{H}$), 7.07 (2H, d, J 8.7, $\text{C}(2')\text{H}$); δ_C (100 MHz, CDCl_3): 26.2 ($\text{C}(\text{CH}_3)_3$), 34.4 ($\text{C}(7)$), 35.4 ($\text{C}(\text{CH}_3)_3$), 52.8 ($\text{C}(6)$), 53.1 (CO_2CH_3), 53.9 ($\text{C}(4)$), 55.3 (OCH_3), 71.7 ($\text{C}(5)$), 81.0 ($\text{C}(2)$), 114.5 ($\text{C}(3')$), 125.2 ($\text{C}(1')$), 128.6 ($\text{C}(2')$), 160.1 ($\text{C}(4')$), 169.9 (CO_2CH_3), 176.4 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$) 396.2 ($[\text{M}+\text{H}]^+$, 35%), 418.2 ($[\text{M}+\text{Na}]^+$, 65%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_6\text{S}$ 396.1486; Found 396.1479.

(2R,5R,6R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 12ii



According to General Method G, pyrrolidinone **11ii** (68 mg, 0.19 mmol) was hydrogenated for 7 h with platinum(IV) oxide (6.4 mg, 0.030 mmol) in EtOAc (10 mL) to afford pyrrolidinone **12ii**. Yield 82% (56 mg); white solid, m. p. 218-220°C; R_f (40% EA in PE) 0.43; $[\alpha]_D^{25}$ -89.8 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2967 (C-H), 1725 (C=O); δ_H (400 MHz, CDCl_3): 1.04 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.60 (1H, dd, J 16.1, 7.6, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.32 (1H, dd, J 16.1, 13.6, $\text{C}(7)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.39 (3H, s, CO_2CH_3), 3.47 (1H, d, J 14.6, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.63 (1H, d, J 14.6, $\text{C}(4)\text{H}_{\text{A}}\text{H}_{\text{B}}$), 3.84 (1H, dd, J 13.6, 7.6, $\text{C}(6)\text{H}$), 4.66 (1H, s, $\text{C}(2)\text{H}$), 7.13-7.33 (5H, m, ArH); δ_C (100 MHz, CDCl_3): 26.2 ($\text{C}(\text{CH}_3)_3$), 34.1 ($\text{C}(7)$), 35.4 ($\text{C}(\text{CH}_3)_3$), 53.1 (CO_2CH_3), 53.3 ($\text{C}(6)$), 53.8 ($\text{C}(4)$), 71.7 ($\text{C}(5)$), 80.9 ($\text{C}(2)$), 127.4-133.4 (ArC), 169.8 (CO_2CH_3), 176.4 ($\text{C}(8)$); m/z ($[\text{ESI}]^+$) 366.2 ($[\text{M}+\text{H}]^+$, 60%), 388.2 ($[\text{M}+\text{Na}]^+$, 100%); HRMS ($[\text{ESI}]^+$) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_5\text{S}$ 366.1370; Found 366.1371.

(2*R*,5*R*,6*S*)-1-Aza-2-(*tert*-butyl)-6-(2-furyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 12iii

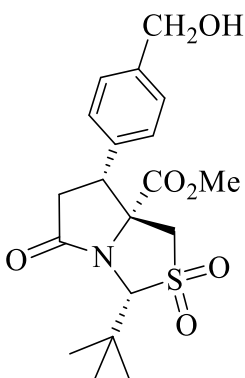


According to General Method G, pyrrolinone **11iii** (41 mg, 0.11 mmol) was hydrogenated with platinum(IV) oxide (3.9 mg, 0.017 mmol) in EtOAc (7 mL) for 8 h to afford pyrrolidinone **12iii**. Yield 37% (15 mg); white solid, m. p. 170-172°C; R_f (30% EA in PE) 0.22; $[\alpha]_D^{25}$ -65.1 (c 1.0 in DCM);

$\nu_{\max}/\text{cm}^{-1}$ 2961 (C-H), 1727 (C=O); δ_H (400 MHz, CDCl_3): 1.04 (9H, s,

$\text{C}(\text{CH}_3)_3$), 2.62 (1H, dd, J 16.1, 7.7, C(7) H_AH_B), 3.18 (1H, dd, J 16.1, 13.6, C(7) H_AH_B), 3.52 (3H, s, CO_2CH_3), 3.57 (1H, d, J 14.7, C(4) H_AH_B), 3.68 (1H, d, J 14.7, C(4) H_AH_B), 3.90 (1H, dd, J 13.6, 7.7, C(6)H), 4.59 (1H, s, C(2)H), 6.18 (1H, d, J 3.3, C(3')H), 6.28 (1H, dd, J 3.3, 1.9, C(4')H), 7.34 (1H, d, J 1.8, C(5')H); δ_C (100 MHz, CDCl_3): 26.2 ($\text{C}(\text{CH}_3)_3$), 33.4 (C(7)), 35.4 ($\text{C}(\text{CH}_3)_3$), 47.0 (C(6)), 53.5 (CO_2CH_3), 53.9 (C(4)), 70.3 (C(5)), 80.9 (C(2)), 108.5 (C(3')), 110.6 (C(4')), 143.5 (C(5')), 148.3 (C(2')), 169.7 (CO_2CH_3), 175.8 (C(8)); m/z ($[\text{ESI}]^+$) 356.0 ($[\text{M}+\text{H}]^+$, 100%), 378.0 ($[\text{M}+\text{Na}]^+$, 50%); HRMS (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6\text{NS}$ 356.1162; Found 356.1162.

(2*R*,5*R*,6*R*)-1-Aza-2-(*tert*-butyl)-6-(4-(hydroxymethyl)phenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 12iv



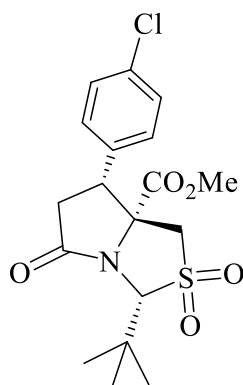
According to General Method G, pyrrolinone **11iv** (65 mg, 0.17 mmol) was hydrogenated with platinum(IV) oxide (5.6 mg, 0.02 mmol) in EtOAc (8 mL) for 18 h to afford pyrrolidinone **12iv**. Yield 54% (35 mg); white solid, m. p.

168-170°C; R_f (60% EA in PE) 0.30; $[\alpha]_D^{25}$ -72.7 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 3464 (O-H), 2980 (C-H), 1723 (C=O); δ_H (400 MHz, CDCl_3): 1.04 (9H, s,

$\text{C}(\text{CH}_3)_3$), 2.54 (1H, dd, J 16.2, 7.6, C(7) H_AH_B), 3.29 (1H, dd, J 16.2, 13.7, C(7) H_AH_B), 3.43 (3H, s, CO_2CH_3), 3.44 (1H, d, J 14.7, C(4) H_AH_B), 3.62 (1H, d, J 14.7, C(4) H_AH_B), 3.82 (1H, dd, J 13.7, 7.6, C(6)H), 4.64-4.66 (3H, m, CH_2OH + C(2)H), 7.14 (2H, d, J 8.2, C(2')H), 7.32 (2H, d, J 8.2, C(3')H); δ_C (100 MHz, CDCl_3): 26.2 ($\text{C}(\text{CH}_3)_3$), 34.3 (C(7)), 35.4 ($\text{C}(\text{CH}_3)_3$), 53.1 (CO_2CH_3), 53.2

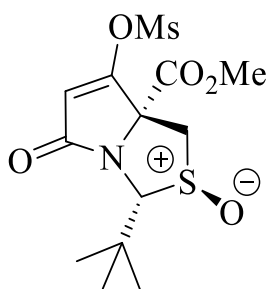
(C(6)), 53.8 (C(4)), 64.6 (C(2)), 71.6 (C(5)), 81.0 (CH₂OH), 127.5 (C(3')), 127.6 (C(2')), 132.6 (C(1')), 142.0 (C(4')), 169.8 (CO₂CH₃), 176.4 (C(8)); m/z ([ESI]⁺) 396.2 ([M+H]⁺, 100%), 418.2 ([M+H]⁺, 45%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₉H₂₆O₆NS 396.1475; Found 396.1475.

(2R,5R,6R)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 12v



According to General Method G, pyrrolinone **11v** (124 mg, 0.30 mmol) was hydrogenated for 6 h with platinum(IV) oxide (10.6 mg, 0.05 mmol) in EtOAc (15 mL) to afford pyrrolidinone **12v**. Yield 77% (96 mg); white solid, m. p. 164-166°C; R_f (20% EA in PE) 0.20; $[\alpha]_D^{25}$ -65.1 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 1723 (C=O); δ_{H} (400 MHz, CDCl₃): 1.04 (9H, s, C(CH₃)₃), 2.60 (1H, dd, *J* 16.1, 7.6, C(7)H_AH_B), 3.26 (1H, dd, *J* 16.1, 13.7, C(7)H_AH_B), 3.40-3.45 (4H, m, CO₂CH₃ + C(4)H_AH_B), 3.64 (1H, d, *J* 14.6, C(4)H_AH_B), 3.77-3.85 (1H, m, C(6)H), 4.65 (1H, s, C(2)H), 7.10 (2H, d, *J* 8.5, C(2')H), 7.27 (2H, d, *J* 8.5, C(3')H); δ_{C} (100 MHz, CDCl₃): 26.2 (C(CH₃)₃), 34.2 (C(7)), 35.4 (C(CH₃)₃), 52.6 (C(6)), 53.2 (CO₂CH₃), 53.7 (C(4)), 71.5 (C(5)), 80.9 (C(2)), 128.8 (C(2')), 129.4 (C(3')), 132.0 (C(4')), 135.1 (C(1')), 169.7 (CO₂CH₃), 176.0 (C(8)); m/z ([ESI]⁺) 422.0 ([M+Na]⁺, ³⁵Cl, 50%), 424.0 ([M+Na]⁺, ³⁷Cl, 10%); HRMS (ESI⁺) m/z: [M+H, ³⁵Cl]⁺ Calcd for C₁₈H₂₃ClNO₅S 400.0980; Found 400.0978.

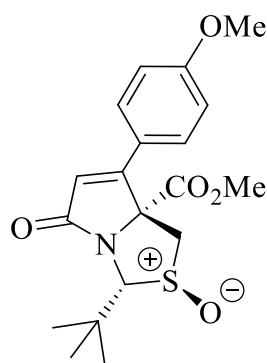
(2R,5R)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo [3.3.0]-oct-6-ene 3-oxide, 14



According to General Method H, **5f** (2.09 g, 5.98 mmol) in CHCl₃ (70 mL) was reacted with *m*-chloroperbenzoic acid (1.34 g, 7.77 mmol) in CHCl₃ (50 mL) to furnish **14**. Yield 52% (1.13 g); white solid, m. p. 160-162°C; R_f (50% EA in PE) 0.15; $[\alpha]_D^{25}$ +138.0 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2965 (C-H), 2935 (C-H), 1723 (C=O), 1637 (C=O); δ_{H} (400 MHz, CDCl₃): 0.99 (9H, s, C(CH₃)₃), 3.13 (1H, d, *J* 14.4, C(4)H_AH_B), 3.23 (3H, s, OSO₂CH₃), 3.78 (3H, s, CO₂CH₃), 3.97 (1H, d, *J* 14.4, C(4)H_AH_B),

4.70 (1H, s, C(2)H), 5.98 (1H, s, C(7)H); δ_c (100 MHz, CDCl₃): 27.2 (C(CH₃)₃), 34.7 (C(CH₃)₃), 38.5 (OSO₂CH₃), 53.4 (C(4)), 54.4 (CO₂CH₃), 78.5 (C(5)), 94.6 (C(2)), 105.8 (C(7)), 164.6 (CO₂CH₃), 167.6 (C(8)), 174.6 (C(6)); m/z ([ESI]⁺) 366.0 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [M+H, ³⁵Cl]⁺ Calcd for C₁₃H₂₀NO₇S₂ 366.0676; Found 366.0678.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-3-thiabicyclo[3.3.0]-oct-6-ene 3-oxide, 15i

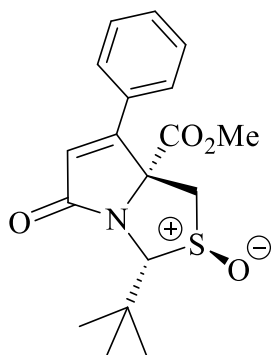


According to General Method F, mesylate **14** (227 mg, 0.620 mmol) was reacted with 4-methoxyphenylboronic acid (142 mg, 0.930 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.6 mL, 5.58 mmol) in ethanol (0.25 mL, 4.34 mmol) and toluene (10 mL) for 24 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (15.8 mg, 0.037 mmol) and

(C₆H₅CN)₂PdCl₂ (12 mg, 0.031 mmol) in toluene (2 mL). Yield 18% (41 mg); white solid, m. p. 154-156°C; R_f (60% EA in PE) 0.20; $[\alpha]_D^{25} +243.4$ (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 1739 (C=O), 1706 (C=O); δ_H (400 MHz, CDCl₃): 1.04 (9H, s, C(CH₃)₃), 2.96 (1H, d, *J* 13.3, C(4)H_AH_B), 3.61 (3H, s, CO₂CH₃), 3.79 (3H, s, OCH₃), 4.50-4.55 (2H, m, C(4)H_AH_B+ C(2)H), 6.36 (1H, s, C(7)H), 6.87 (2H, d, *J* 8.3, C(3')H), 7.37 (2H, d, *J* 8.3, C(2')H); δ_c (100 MHz, CDCl₃): 27.2 (C(CH₃)₃), 35.1 (C(CH₃)₃), 53.9 (CO₂CH₃), 55.5 (OCH₃), 56.5 (C(4)), 79.3 (C(5)), 92.7 (C(2)), 114.8 (C(3')), 117.2 (C(7)), 121.8 (C(1')), 128.6 (C(2')), 159.8 (C(6)), 162.0 (C(4')), 170.5 (CO₂CH₃), 175.8 (C(8)); m/z ([ESI]⁺) 378.2 ([M+H]⁺, 100%), 400.2 ([M+Na]⁺, 60%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₉H₂₄O₅NS 378.1370; Found 378.1365.

(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-5-methoxycarbonyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0]-oct-6-ene 3-oxide, 15ii

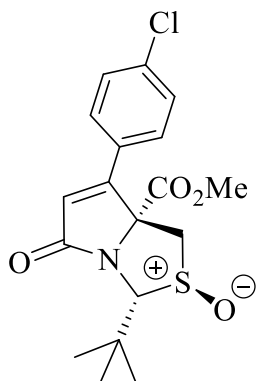
According to General Method F, mesylate **14** (360 mg, 0.98 mmol) was reacted with phenylboronic acid (180 mg, 1.48 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.93 mL, 8.82 mmol) in ethanol (0.4 mL, 6.89 mmol) and toluene (12 mL) for 18 h. PdCl₂(dppb) was prepared from



(C_6H_5)₂P(CH₂)₄P(C₆H₅)₂ (25 mg, 0.06 mmol) and (C₆H₅CN)₂PdCl₂ (19 mg, 0.05 mmol) in toluene (3 mL). Yield 18% (61 mg); white solid, m. p. 154-156°C; R_f (60% EA in PE) 0.16; $[\alpha]_D^{25}$ +219.2 (*c* 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2958 (C-H), 1740 (C=O), 1711 (C=O); δ_{H} (400 MHz, CDCl₃): 1.04 (9H, s, C(CH₃)₃), 2.96 (1H, d, *J* 13.2, C(4)H_AH_B), 3.61 (3H, s, CO₂CH₃), 4.52-4.57 (2H, m, C(4)H_AH_B+ C(2)H), 6.50 (1H, s, C(7)H), 7.38-7.41 (5H, m, ArH);

δ_{C} (100 MHz, CDCl₃): 27.2 (C(CH₃)₃), 35.1 (C(CH₃)₃), 54.0 (CO₂CH₃), 56.4 (C(4)), 79.3 (C(5)), 92.8 (C(2)), 119.8 (C(7)), 126.7-131.3 (ArC), 160.0 (C(6)), 170.2 (CO₂CH₃), 175.4 (C(8)); *m/z* ([ESI]⁺) 348.0 ([M+H]⁺, 40%), 370.0 ([M+Na]⁺, 100%); HRMS (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₈H₂₂O₄NS 348.1264; Found 348.1261.

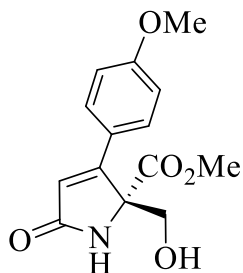
(2*R*,5*R*)-1-Aza-2-(*tert*-butyl)-6-(4-chlorophenyl)-5-methoxycarbonyl-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene 3-oxide, 15iii



According to General Method F, mesylate **14** (360 mg, 0.98 mmol) was reacted with 4-chlorophenylboronic acid (162 mg, 1.48 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.93 mL, 8.82 mmol) in ethanol (0.4 mL, 6.89 mmol) and toluene (12 mL) for 18 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (25 mg, 0.06 mmol) and (C₆H₅CN)₂PdCl₂ (19 mg,

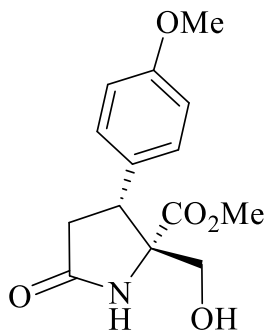
0.05 mmol) in toluene (3 mL). Yield 8% (30 mg); colourless oil; R_f (40% EA in PE) 0.20; $[\alpha]_D^{25}$ +209.0 (*c* 1.0 in DCM); $\nu_{\text{max}}/\text{cm}^{-1}$ 2959 (C-H), 1713 (C=O); δ_{H} (500 MHz, CDCl₃): 1.00 (9H, s, C(CH₃)₃), 2.92 (1H, d, *J* 13.3, C(4)H_AH_B), 3.58 (3H, s, CO₂CH₃), 4.46 (1H, d, *J* 13.3, C(4)H_AH_B), 4.53 (1H, s, C(2)H), 6.44 (1H, s, C(7)H), 7.31 (4H, s, ArH); δ_{C} (125 MHz, CDCl₃): 27.2 (C(CH₃)₃), 35.1 (C(CH₃)₃), 54.1 (CO₂CH₃), 56.2 (C(4)), 79.4 (C(5)), 93.0 (C(2)), 120.3 (C(7)), 128.0-137.6 (ArC), 158.8 (C(6)), 170.1 (CO₂CH₃), 175.2 (C(8)); *m/z* ([ESI]⁺) 404.0 ([M+Na]⁺, ³⁵Cl, 70%), 406.0 ([M+Na]⁺, ³⁷Cl, 25%); HRMS (ESI⁺) *m/z*: [M+H, ³⁵Cl]⁺ Calcd for C₁₈H₂₁O₄NCIS 382.0874; Found 382.0873.

Methyl (S)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxylate, 16



According to General Method I, the bicyclic pyrrolidinone derivative **6ai** (100 mg, 0.29 mmol) was treated with propane-1,3-dithiol (0.06 mL, 0.61 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (4.84 mL) to give pyroglutaminol **16**. Yield 94% (75 mg); yellow solid, m. p. 99-101°C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3245 (O-H), 2955 (C-H), 2840 (C-H), 1731 (C=O), 1691 (C=O); δ_{H} (400 MHz, MeOD): 3.64 (3H, s, CO₂CH₃), 3.73 (3H, s, OCH₃), 3.85 (1H, d, J 11.7, C(6)H_AH_B), 4.16 (1H, d, J 11.7, C(6)H_AH_B), 6.29 (1H, s, C(4)H), 6.87 (2H, d, J 8.9, C(3')H), 7.43 (2H, d, J 8.9, C(2')H); δ_{C} (100 MHz, MeOD): 52.2 (CO₂CH₃), 54.5 (OCH₃), 62.9 (C(6)), 72.4 (C(2)), 114.0 (C(3')), 120.7 (C(1')), 123.3 (C(4)), 128.6 (C(2')), 158.0 (C(4')), 160.4 (C(3)), 161.4 (CO₂CH₃), 170.0 (C(5)); m/z ([ESI]⁺) 300.0 ([M+Na]⁺, 80%); HRMS (ESI⁺) m/z : [M+Na]⁺ Calcd for C₁₄H₁₅NaNO₅ 300.0842; Found 300.0842.

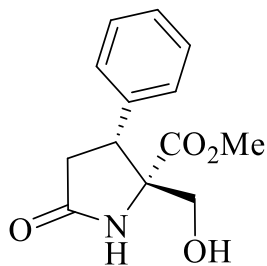
Methyl (2S,3R)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate, 9ai



According to General Method I, the bicyclic pyrrolidinone derivative **7ai** (15 mg, 0.04 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 (0.7 mL) to give pyroglutaminol **9ai**. Yield 80% (12 mg); colourless oil; $[\alpha]_{\text{D}}^{25}$ -74.2 (c 1.0 in MeOH); $\nu_{\text{max}}/\text{cm}^{-1}$ 3273 (O-H), 2952 (C-H), 2839 (C-H), 1736 (C=O), 1687 (C=O); δ_{H} (400 MHz, MeOD): 2.56 (1H, dd, J 17.1, 8.0, C(4)H_AH_B), 2.69 (1H, dd, J 17.1, 9.0, C(4)H_AH_B), 3.22 (3H, s, CO₂CH₃), 3.56 (1H, t, J 8.3, C(3)H), 3.66-3.70 (4H, m, OCH₃ + C(6)H_AH_B), 3.88 (1H, d, J 11.5, C(6)H_AH_B), 6.76 (2H, d, J 8.5, C(3')H), 7.02 (2H, d, J 8.5, C(2')H); δ_{C} (100 MHz, MeOD): 36.8 (C(4)), 44.3 (C(3)), 51.0 (CO₂CH₃), 54.3 (OCH₃), 64.5 (C(6)), 73.2 (C(2)), 113.4 (C(3')), 128.7 (C(2')), 130.1 (C(1')), 159.3 (C(4')), 171.1 (CO₂CH₃),

178.6 (C(5)); m/z ([ESI]⁺) 302.0 ([M+Na]⁺, 100%); HRMS (ESI⁺) m/z : [M+Na]⁺ Calcd for C₁₄H₁₇NO₅Na 302.0999; Found 302.0999.

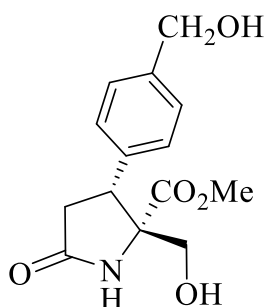
Methyl (2*S*,3*R*)-2-(hydroxymethyl)-5-oxo-3-phenylpyrrolidine-2-carboxylate, 9aii



According to General Method I, the bicyclic pyrrolinone derivative **7aii** (45 mg, 0.14 mmol) was treated with propane-1,3-dithiol (0.03 mL, 0.33 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (2.33 mL) to develop pyroglutaminol derivative **9aii**. Yield 79% (32 mg);

colourless oil; $[\alpha]_D^{25}$ -81.8 (*c* 1.0 in MeOH); $\nu_{\max}/\text{cm}^{-1}$ 3280 (O-H), 2951 (C-H), 1736 (C=O), 1689 (C=O); δ_{H} (400 MHz, MeOD): 2.70 (1H, dd, *J* 17.1, 7.2, C(4)*H_AH_B*), 2.85 (1H, dd, *J* 17.1, 9.1, C(4)*H_AH_B*), 3.28 (3H, s, CO₂CH₃), 3.73 (1H, dd, *J* 9.1, 7.2, C(3)H), 3.82 (1H, d, *J* 11.5, C(6)*H_AH_B*), 4.00 (1H, d, *J* 11.5, C(6)*H_AH_B*), 7.06-7.43 (5H, m, ArH); δ_{C} (100 MHz, MeOD): 36.9 (C(4)), 45.0 (C(3)), 51.0 (CO₂CH₃), 64.7 (C(6)), 73.2 (C(2)), 127.4-138.6 (ArC), 171.0 (CO₂CH₃); m/z ([ESI]⁺) 250.0 ([M+H]⁺, 25%), 272.0 ([M+Na]⁺, 100%); HRMS (ESI⁺) m/z : [M+Na]⁺ Calcd for C₁₃H₁₅NO₄Na 272.0899; Found 272.0894.

Methyl (2*S*,3*R*)-2-(hydroxymethyl)-3-(4-(hydroxymethyl)phenyl)-5-oxopyrrolidine-2-carboxylate, 9a (R = C₆H₄CH₂OH)

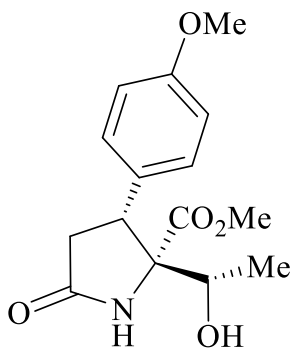


According to General Method I, the bicyclic pyrrolinone derivative **8b** (12 mg, 0.03 mmol) was treated with propane-1,3-dithiol (0.01 mL, 0.08 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (0.5 mL) to give pyroglutaminol derivative **9a**. Yield 90% (9.0 mg);

colourless oil; $[\alpha]_D^{25}$ -56.5 (*c* 0.9 in MeOH); $\nu_{\max}/\text{cm}^{-1}$ 3308 (O-H), 2951 (C-H), 2875 (C-H), 1735 (C=O), 1686 (C=O); δ_{H} (400 MHz, MeOD): 2.58 (1H, dd, *J* 17.1, 7.4, C(4)*H_AH_B*), 2.72 (1H, dd, *J* 17.1, 9.0, C(4)*H_AH_B*), 3.19 (3H, s, CO₂CH₃), 3.62 (1H, dd, *J* 9.0, 7.4, C(3)H), 3.70 (1H, d, *J* 11.5, C(6)*H_AH_B*), 3.88 (1H, d, *J* 11.5, C(6)*H_AH_B*), 4.48 (2H, s, CH₂OH), 7.08 (2H, d, *J* 8.2, C(2')H), 7.21 (2H, d, *J* 8.3, C(3')H); δ_{C} (100 MHz, MeOD): 36.9 (C(4)), 44.7 (C(3)), 51.0 (CO₂CH₃), 63.3

(CH₂OH), 64.6 (C(6)), 73.2 (C(2)), 126.7 (C(3')), 127.6 (C(2')), 137.5 (C(1')), 141.0 (C(4')), 171.0 (CO₂CH₃), 178.5 (C(8)); m/z ([ESI]⁺) 302.1 ([M+Na]⁺, 35%); HRMS (ESI⁺) m/z: [M+Na]⁺ Calcd for C₁₄H₁₇NO₅Na 302.0999; Found 302.1000.

Methyl (2*S*,3*R*)-2-((*S*)-1-hydroxyethyl)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate, **9c-i**



According to General Method I, the bicyclic pyrrolinone derivative **7ci** (21 mg, 0.06 mmol) was treated with propane-1,3-dithiol (0.01 mL, 0.13 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.0 mL) to give pyroglutaminol **9ci**. Yield 81% (12 mg); white solid, m. p. 171-173°C; $[\alpha]_D^{25}$ -41.0 (*c* 1.0 in MeOH); $\nu_{\max}/\text{cm}^{-1}$ 3250

(O-H), 2980 (C-H), 2952 (C-H), 1737 (C=O), 1687 (C=O); δ_{H} (400 MHz, MeOD): 0.99 (3H, d, *J* 6.4, C(6)CH₃), 2.26 (1H, dd, *J* 17.0, 4.1, C(4)H_AH_B), 2.91 (1H, dd, *J* 17.0, 9.4, C(4)H_AH_B), 3.12 (3H, s, CO₂CH₃), 3.66 (3H, s, OCH₃), 3.71 (1H, dd, *J* 9.4, 4.1, C(3)H), 4.15 (1H, q, *J* 6.4, C(6)H), 6.73 (2H, d, *J* 8.7, C(3')H), 6.99 (2H, d, *J* 8.7, C(2')H); δ_{C} (100 MHz, MeOD): 17.2 (C(6)CH₃), 38.6 (C(4)), 46.0 (C(3)), 50.8 (CO₂CH₃), 54.2 (OCH₃), 70.1 (C(6)), 76.7 (C(2)), 113.3 (C(3')), 128.6 (C(2')), 133.0 (C(1')), 159.0 (C(4')), 171.0 (CO₂CH₃), 179.6 (C(5)); m/z ([ESI]⁺) 294.0 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₅H₂₀NO₅ 294.1336; Found 294.1337.

Acknowledgements

H.B. gratefully acknowledges the award of a scholarship from the Commonwealth Scholarship Commission.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxx. ¹H and ¹³C NMR spectra; X-ray crystallographic data (PDF).

References

1. Najera, C.; Yus, M., Pyroglutamic acid: a versatile building block in asymmetric synthesis. *Tetrahedron-Asymmetry* **1999**, *10*, 2245-2303.

2. Stefanucci, A.; Costante, R.; Carradori, S.; Novellino, E.; Mollica, A., Synthetic strategies for aspartic and glutamic acid-proline chimeras: A review. *Mini-Reviews in Organic Chemistry* **2015**, *12*, 216.
3. Stefanucci, A.; Novellino, E.; Costante, R.; Mollica, A., Pyroglutamic acid derivatives: Building blocks for drug discovery. *Heterocycles* **2014**, *89*, 1801 - 1825.
4. Cottrell, I. F.; Davis, P. J.; Moloney, M. G., Stereoselective oxygenation of bicyclic lactams. *Tetrahedron: Asymmetry* **2004**, *15*, 1239-1242.
5. Chan, P. W. H.; Cottrell, I. F.; Moloney, M. G., Pyrrolidinones derived from (S)-pyroglutamic acid. Part 3. β -Aminopyrrolidinones. *J. Chem Soc, Perkin Trans. 1* **2001**, 2997-3006.
6. Dyer, J.; Keeling, S.; King, A.; Moloney, M. G., Pyrrolidinones derived from (S)-pyroglutamic acid. Part 2. Conformationally constrained kainoid analogues. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2793-2804.
7. Tan, B. S. W.; Chai, C. L. L.; Moloney, M. G.; Thompson, A. L., Synthesis of mimics of pramanicin from pyroglutamic acid and their antibacterial activity. *J. Org. Chem.* **2015**, *80*, 2661–2675.
8. Chan, P. W. H.; Cottrell, I. F.; Moloney, M. G., Pyrrolidinones derived from (S)-pyroglutamic acid. Part 4. α , β -Diaminopyrrolidinones. *J. Chem Soc, Perkin Trans. 1* **2001**, 3007-3012.
9. Verho, O.; Maetani, M.; Melillo, B.; Zoller, J.; Schreiber, S. L., Stereospecific palladium-catalyzed C–H arylation of pyroglutamic acid derivatives at the C3 position enabled by 8-aminoquinoline as a directing group. *Org. Lett.* **2017**, *19*, 4424 - 4427.
10. Petermichl, M.; Schobert, R., 3-Acyltetramic acids: A decades-long approach to a fascinating natural product family. *Synlett* **2017**, *28*, 654-663.
11. Schobert, R.; Schlenk, A., Tetramic and tetronic acids: An update on new derivatives and biological aspects. *Bioorg. Med. Chem.* **2008**, *16*, 4203–4221.
12. Royles, B. J. L., Naturally-occurring tetramic acids - Structure, isolation, and synthesis. *Chem. Rev.* **1995**, *95*, 1981-2001.
13. Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D., Regioselective Dieckmann cyclisations leading to enantiopure highly functionalised tetramic acid derivatives. *J. Chem. Soc., Perkin Trans. 1* **1998**, 223-235.
14. Matiadis, D., Metal-catalyzed and metal-mediated approaches to the synthesis and functionalization of tetramic acids. *Catalysts* **2019**, *9*.
15. Hu, Y.; Stumpfe, D.; Bajorath, J., Recent advances in scaffold hopping. *J. Med. Chem.* **2017**, *60*, 1238 - 1246.
16. Sun, H.; Tawa, G.; Wallqvist, A., Classification of scaffold hopping approaches. *Drug Discov Today*. **2012**, *17*, 310 - 324.
17. Böhm, H.-J.; Flohr, A.; Stahl, M., Scaffold hopping. *Drug Discovery Today: Technologies* **2004**, *1*, 217-224.
18. Josa-Cullere, L.; Moloney, M. G.; Thompson, A. L., Stereoselectivity in the reduction of bicyclic tetramates. *Synlett* **2016**, *27*, 1677-1681.
19. Li, W.-R.; Lin, S. T.; Hsu, N.-M.; Chern, M.-S., Efficient total synthesis of pulchellalactam, a CD45 protein tyrosine phosphatase Inhibitor. *J. Org. Chem.* **2002**, *67*, 4702–4706.
20. Yoon-Miller, S. J. P.; Opalka, S. M.; Pelkey, E. T., Short synthesis of 4-aryl-3-pyrrolin-2-ones. *Tetrahedron Lett.* **2007**, *48*, 827–830.
21. Kobayashi, Y.; William, A. D.; Mizojiri, R., Scope and limitation of the nickel-catalyzed coupling reaction between lithium borates and mesylates. *J. Organomet. Chem.* **2002**, *653*, 91–97.
22. Jones, K.; Keenan, M.; Hibbert, F. A., Suzuki coupling approach to pyrazines related to coelenterazine. *Synlett* **1996**, 509–510.
23. 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'⁵¹ before refinement with CRYSTALS.^{52, 53}. Crystallographic data (excluding structure factors) have been deposited with the Cambridge

- Crystallographic Data Centre (CCDC 1918433-1918443) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
24. Zhang, H.; Kwong, F. Y.; Tian, Y.; Chan, K. S., Base and cation effects on the Suzuki cross-coupling of bulky arylboronic Acid with halopyridines: Synthesis of pyridylphenols. *J. Org. Chem.* **1998**, *63*, 6886–6890.
 25. Gauler, R.; Keuper, R.; Winter, A.; Risch, N., Facile preparation of novel β -substituted metalloporphyrins via Suzuki cross-coupling reaction. *Arkivoc* **2004**, 48.
 26. Pan, W.-J.; Wang, Z.-X., Nickel-catalyzed cross-coupling of β -carbonyl alkenyl pivalates with arylzinc chlorides *Org. Biomol. Chem.* **2018**, *16*, 1029-1036.
 27. Poncet, J.; Jouin, P.; Castro, B.; Nicola, L.; Boutar, M.; Gaudemer, A., Tetramic acid chemistry. Part 1. Reinvestigation of racemisation during the synthesis of tetramic acids via Dieckmann cyclisation. *J. Chem. Soc., Perkin Trans. 1* **1990**, 611-616.
 28. Jouin, P.; Castro, B.; Nisato, D., Stereospecific synthesis of N-protected statine and its analogues via chiral tetramic acid. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1177.
 29. Pinheiro, S.; Júnior, R. C. d. S.; Souza, A. S. d.; Carneiro, J. W. d. M.; Muri, E. M. F.; Antunes, O. A. C., A general approach for the synthesis of 5-substituted-4-amino-pyrrolidin-2-ones and 5-substituted-4-amino-3-pyrrolin-2-ones. *Tetrahedron Lett.* **2009**, *50*, 2402–2404.
 30. Milne, C.; Powell, A.; Jim, J.; Nakeeb, M. A.; Smith, C. P.; Micklefield, J., Biosynthesis of the (2 S ,3 R)-3-methyl glutamate residue of nonribosomal lipopeptides. *J. Am. Chem. Soc.* **2006**, *128*, 11250–11259.
 31. Wei, L.; Christoph, S.; Constantin, D.; Frank, G., Asymmetric hydrogenation of vinylthioethers: access to optically active 1,5-benzothiazepine derivatives. *Angew. Chem. Int. Ed.* **2016**, *55*, 3300-3303.
 32. Popova, M. V.; Dobrydnev, A. V.; Dyachenko, M. S.; Duhayon, C.; Listunov, D.; Volovenko, Y. M., Synthesis of a series of tetraminic acid sulfone analogs. *Monatsh Chem* **2017**, *148*, 939–946.
 33. Keith, D. D.; Teng, J.; Rossman, P.; Todaro, L.; Weigele, M., A comparison of the antibacterial and β -lactamase inhibiting properties of penam and (2,3)- β -methylenepenam derivatives. *Tetrahedron* **1983**, *39*, 2445-2458.
 34. Corey, E. J.; Reichard, G. A., Total synthesis of lactacystin. *J. Am. Chem. Soc.* **1992**, *114*, 10677-10678.
 35. Jeong, Y.-C.; Moloney, M. G., Tetramic acids as bioactive templates: synthesis, tautomeric and antibacterial behaviour. *Synlett.* **2009**, 2487-2491
 36. Panduwawala, T. D.; Iqbal, S.; Thompson, A. L.; Genov, M.; Pretsch, A.; Pretsch, D.; Liu, S.; Ebright, R. H.; Howells, A.; Maxwell, A.; Moloney, M. G., Functionalised bicyclic tetramates derived from cysteine as antibacterial agents. *Org. Biomol. Chem.* **2019**, *17*, 5615-563.
 37. Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T., Synthesis of optically active 5-substituted-2-pyrrolidinone derivatives having atropisomeric structure and 3,5-cis-selective reaction of their enolates with electrophiles. *J. Org. Chem.* **2000**, *65*, 1108-1114.
 38. Hamada, Y.; Kawai, A.; Kohno, Y.; Hara, O.; Shioiri, T., New methods and reagents in organic synthesis. 83. Stereoselective total synthesis of AI-77-B, a gastroprotective substance from *Bacillus pumilus* AI-77. *J. Am. Chem. Soc.* **1989**, *111*, 1524-1525.
 39. Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G., Stereoselective alkylations in rigid systems. Effect of remote substituents on π -facial additions to lactam enolates. Stereoelectronic and steric effects. *J. Am. Chem. Soc.* **1998**, *120*, 7429-7438.
 40. Lambert, T. H.; Danishefsky, S. J., Total synthesis of UCS1025A. *J. Am. Chem. Soc.* **2006**, *128*, 426-427.
 41. Hughes, G.; Kimura, M.; Buchwald, S. L., Catalytic enantioselective conjugate reduction of lactones and lactams. *J. Am. Chem. Soc.* **2003**, *125*, 11253-11258.
 42. Bailey, J. H.; Byfield, A. T. J.; Davis, P. J.; Foster, A. C.; Leech, M.; Moloney, M. G.; Muller, M.; Prout, C. K., On the diastereoselectivity in the alkylations of bicyclic lactams. *J. Chem. Soc., Perkin Trans 1* **2000**, 1977-1982.

43. Chu, S.-F.; Zhang, J.-T., Recent advances in the study of (–)clausenamide: chemistry, biological activities and mechanism of action. *Acta Pharm. Sin. B* **2014**, *4*, 417-423.
44. Ling, T.; Potts, B. C.; Macherla, V. R., *J. Org. Chem.* **2010**, *75*, 3882–3885.
45. Mollica, A.; Costante, R.; Stefanucci, A.; Novellino, E., New insight on the synthesis of neurotoxins domoic acid and kainic acid. *Protein Pept Lett.* **2015**, *22*, 696-711.
46. Chaudhari, P.; Bari, S., Efficient synthesis of N-sulfonyl β -arylmethylalaninates from serine via ring opening of N-sulfonyl aziridine-2-carboxylate. *Synth. Commun.* **2015**, *45*, 391–402.
47. Seebach, D.; Aebi, J. D., α -Alkylation of serine with self-reproduction of the center of chirality. *Tetrahedron Lett.* **1984**, *25*, 2545-2548.
48. LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Activation of aryl chlorides for Suzuki cross-coupling by ligandless, heterogeneous palladium. *Org. Lett.* **2001**, *3*, 1555–1557.