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Synthetic access to 3,4-disubstituted pyroglutamates from tetramate derivatives from serine, *allo*-threonine and cysteine

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ABSTRACT

A route allowing the conversion of substituted tetramates to 3,4-disubstituted pyroglutamates, making use of Suzuki coupling on an enol mesylate, followed by reduction, is both general and fully stereoselective.

We recently reported that tetramates could be converted to monosubstituted pyroglutamates by application of Suzuki coupling on a highly electron deficient enol triflate [1]; since 3,4-disubstituted pyrrolinones and pyrrolidinones [2] are known for their broad diversity of biological activities [3,4], of interest was whether this approach might be extended to more highly substituted systems. Such an approach would complement alternative literature methodologies [5,6] including the direct elaboration of a pyroglutamate core [7–9], providing improved access to this important system [10–12], and we report the results of this work here.

Oxa(thia)zolidines derived from L-serine **1a**, L-*allo*-threonine **1b** and L-cysteine **1c** respectively are readily available via literature methodology [1,13] and were converted to malonamides **2a-c** by coupling to the respective ethyl methylmalonyl chloride **3**, which was itself prepared by partial hydrolysis of the corresponding diethyl malonate (Scheme 1, Fig. 1 and Table 1) [14]. However, cyclisation of **2a**, under basic conditions using potassium *tert*-butoxide in THF, did not give the expected tetramate **4a** but exclusively hydroxy derivative **5a** instead; this was evident by LRMS and HRMS analysis and was later confirmed by single-crystal X-ray diffraction studies of both **5a** and its derived mesylate **5b** (Fig. S1, SI) [15]. The phenomenon of auto-oxidation in C7-methyl tetramates had been earlier observed by Andrews and co-workers [16], although interestingly in that case had been slower, and led to the equivalent oxidation product only as a minor species over extended time. The attempted Suzuki coupling of the mesylate **5b** with 4-methoxyphenylboronic acid supported this structural assignment, resulting in quantitative recovery of starting material which was consistent with the known lower reactivity of sp3 centres in Suzuki processes.

Tetramates **4b,c** derived from threonine and cysteine were also prepared applying the same conditions and were found to exist as the enolic tautomers by NMR analysis [17]. The parent malonamides **2b,c** were obtained as the *cis*-2,5 diastereomer with the 7*R* epimer as the major one, as assigned by NOE analysis (Fig. 1), and for which the cysteine-derived malonamides were separable C2 epimers. Cyclisation of **2b,c** gave pure **4b,c** (Scheme 1 and Table 1).

The analogous phenyl derivatives were obtained from diethyl phenylmalonate using an equivalent approach (Scheme 1); however, partial ester hydrolysis of diethylphenylmalonate using Danieli's [14] or Niwayama's protocol [18,19] needed optimisation, so that excess 0.25 M aqueous Na_2CO_3 solution furnished mono-acid **6** in 92% yield. The respective malonamides **7a-b** were obtained predominantly as their *cis*-2,5 diastereomers (Table 1). The ring but not the side-chain stereochemistry for malonamides **7a-c** was assigned by NOE analysis and this was confirmed by single crystal X-ray diffraction studies (Fig. S1, SD and Fig. 2) [15]; moreover, clear evidence from peak broadening for the presence of rotameric species was observed. Dieckmann cyclisation under basic conditions provided the desired tetramic acids **8a-c** (Scheme 1 and Table 1) [16]. For L-serine and L-*allo*-threonine systems, the tetramic acids **8a-b** were obtained as the sole product, but the L-cysteine system gave in addition to the desired tetramate **8c**, the decarboxylated material **9a**. Their stereochemistry was assigned by NOE

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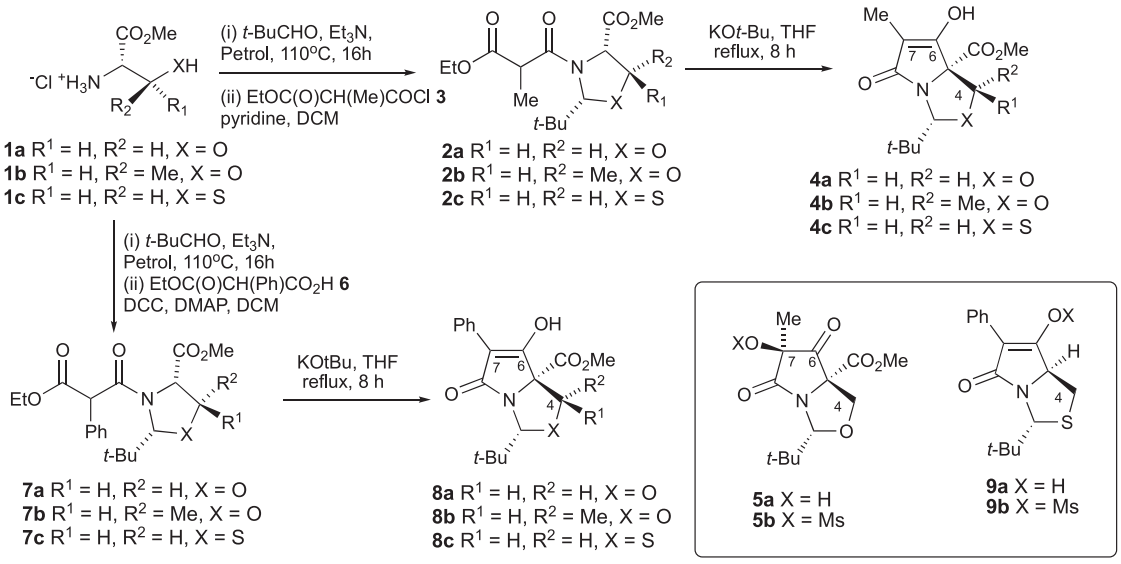


Scheme 1. Synthesis of tetramates.

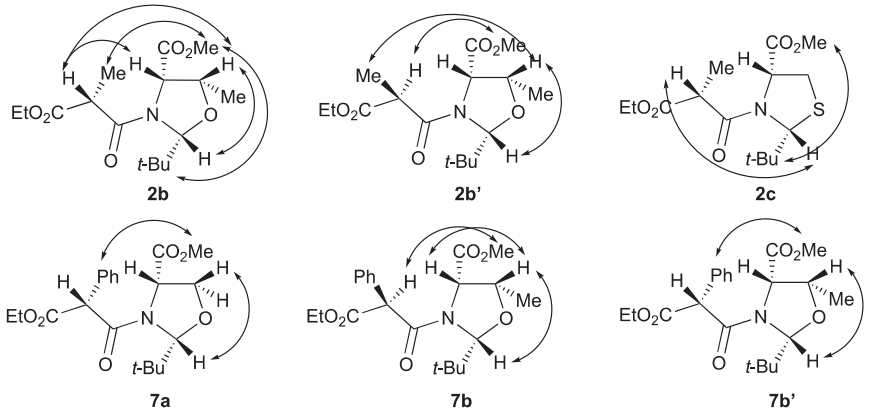


Fig. 1. NOESY correlations of oxazolidines.

Table 1
The preparation of malonamides **2a-c and 7a-c** and tetramates **4a-c** and **8a-c.**

Parent amino acid	Solvent	Malonamides 2a-c, 7a-c, Yield (%), Ratio		Tetramates (Yield %)
		Cis-2,5	*trans*-2,5	
L-Serine, **1a**	^{t}BuOH	**2a,** 74 (7*R*:7*S*, 2.2:1.0)	–	**4a** (82)
L-*allo*-Threonine, **1b**	^{t}BuOH	**2b,** 86 (7*R*:7*S*, 2.1:1.0)	–	**4b** (67)
L-Cysteine, **1c**	THF	**2c,** 71 (7*R*), 2.5	27 (7*S*), 1.0	**4c** (84)
L-Serine, **1a**	^{t}BuOH	**7a,** 88 (7*R*:7*S*, 1.0:2.0)	–	**8a** (82)
L-*allo*-Threonine, **1b**	^{t}BuOH	**7a,** 95 (7*R*:7*S*,2.6:2.0)	–	**8b** (70)
L-Cysteine, **1c**	^{t}BuOH	**7a,** 85 (7*R*:7*S*, 1.0:1.8)	–	**8c** (73)

analysis (Fig. 2).

Tetramic acids **4a-c** and **8a-c** were reacted with methanesulfonyl chloride and *N,N*-diisopropylethylamine (DIPEA) to furnish mesylates **10a-f** in good to excellent yields (Scheme 2). Cyclisation of **2a** and mesylation of the crude product **4a** in quick succession could avoid aerial oxidation alluded to earlier, giving the desired mesylate **10a**. The mesylate **10f** and decarboxylated mesylate **9b** which were produced from reaction of the inseparable mixture of tetramates **8c** and **9a** were separable by *flash* column chromatography. Of interest is that these C7−Me/Ph derivatives were prepared with improved yields compared to the unsubstituted mesylates [1], and this might arise from the preferred enolic structure for the more substituted systems. The structure of mesylate **10a** was confirmed by single crystal X-ray diffraction studies (Fig. S1, SD) [15]. Careful product analysis also indicated the presence of C-mesylated products **11a-c**, at least in some cases; of interest for these is that the chemical shift of their H-2 signal was deshielded by 0.39−0.43 ppm compared to their analogous *O*-mesyl analogues **10a,b** and **f** (Table 2). Single crystal X-ray analysis for by-product **11a** confirmed this structural assignment (Fig. S1,

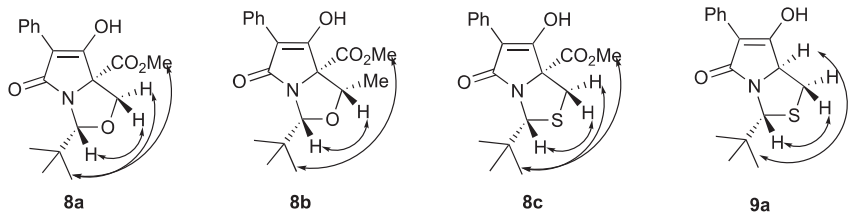
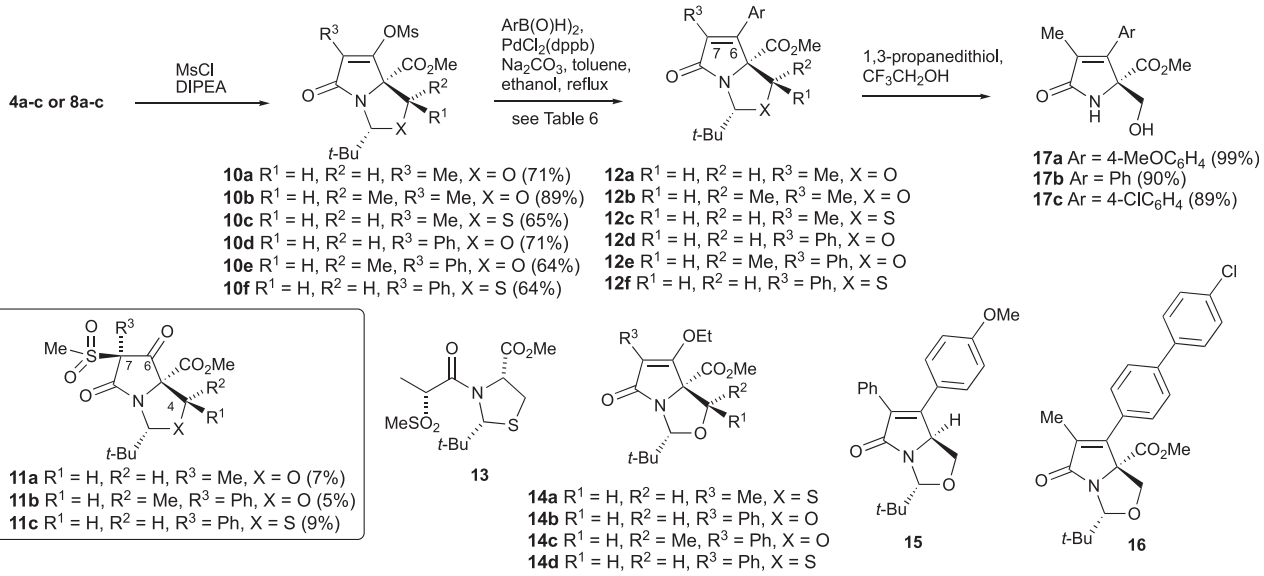


Fig. 2. NOESY correlations of tetramates.



Scheme 2. Elaboration of tetramates.

Table 2
NMR data for mesyl derivatives.

Products	Chemical shifts δ (ppm)				
	H2	H4		ArH	C7
		H_A, H_B	Δ_{HB-HA}		
10a	4.65	3.45, 4.74	1.29	–	125.6
11a	5.05	3.91, 4.73	0.82	–	79.1
10e	4.71	3.87, -	–	7.32–7.38, 7.57	126.8
11b	5.10	4.19, -	–	7.36–7.42, 7.71–7.79	80.1
10f	5.00	2.98, 3.73	0.75	7.31–7.41, 7.60–7.67	124.9
11c	5.43	3.25, 3.67	0.42	7.36–7.45, 7.80–7.85	82.8

SD). Whether these products arose by direct C-mesylation, or by rearrangement of the *O*-mesyl systems, was not investigated.

Treatment of mesylates **10a-f** with boronic acids in the presence of $PdCl_2$(dppb) catalyst furnished the coupling adducts **12a-f** (Scheme 2 and Table 3) in a reaction which was much slower than that of the unsubstituted system [1]. In these reactions, by-products **13**–**16** were also obtained in some cases; the structure of **13** was confirmed by single crystal X-ray diffraction studies (Fig. S2, SD) [15].

The steric bulk at C7 appears to be important for coupling efficiency in this system; thus, the yields were comparatively poorer for 7-phenyl derivatives **12d-f** than for the 7-methyl derivatives **12a-c** (Table 3). Prolonged reaction time during the formation of **12di** also resulted in decarboxylated adduct **15**. The L-*allo*-threonine system, which experiences an additional steric effect from the

Table 3
Suzuki Coupling of mesylates **10a-f** according to Scheme 2.

Substrate	Ar–B(OH)$_2$	Products, %
10a	4-MeOC$_6$H$_4$B(OH)$_2$	**12ai**, 32
	C$_6$H$_5$B(OH)$_2$	**12aii**, 33
	4-ClC$_6$H$_4$B(OH)$_2$[a]	**12aiii**, 38; **16**, 5
10b	4-MeOC$_6$H$_4$B(OH)$_2$	**12b**, 9
10c	4-MeOC$_6$H$_4$B(OH)$_2$	**12ci**, 23; **13**, 2; **14a**, 3
	C$_6$H$_5$B(OH)$_2$	**2cii**, 23
	4-ClC$_6$H$_4$B(OH)$_2$[a]	**12ciii**, 21
10d	4-MeOC$_6$H$_4$B(OH)$_2$	**12di**, 9; **14b**, 4-5
	C$_6$H$_5$B(OH)$_2$	**12dii**, 9
	4-ClC$_6$H$_4$B(OH)$_2$[a]	**12diii**, 5
10e	4-MeOC$_6$H$_4$B(OH)$_2$	**12ei**, 2; **14c**, 7
10f	4-MeOC$_6$H$_4$B(OH)$_2$	**12fi**, 23; **14d**, 5
	C$_6$H$_5$B(OH)$_2$	**12fii**, 17
	4-ClC$_6$H$_4$B(OH)$_2$[a]	**12fiii**, 9

[a] 1.05 eq (4)-ClC$_6$H$_4$B(OH)$_2$.

C4-methyl group, gave even poorer yields of coupling adducts **12b** and **12e**. However, the results for **12ci-ciii** and **12fi-12fiii** were better and it appears in this case that the larger sulfur atom opens the bicyclic core and improves reactivity. The structures of coupling products were confirmed by single crystal X-ray diffraction studies of representative adducts **12ai**, **12di**, and **12fi** (Fig. S2, SD) [15]. The formation of **13** might arise by ring opening and decarboxylation of the sulfone **11c**. The formation of enol ethers **14a-d** was studied further; when **10d** was treated with Na_2CO_3 and EtOH, quantitative recovery of starting material was obtained; this outcome was not consistent with the formation of **14d** by direct addition-elimination

on the mesylate, or by a sulfonyl transfer process [20]. However, reaction with Na_2CO_3 and EtOH in the presence of Pd(dppb)Cl_2 gave 4% of ether **14b** along with unreacted starting material **10d,** and when the coupling reaction was conducted with less than 1 equivalent of p-methoxyphenylboronic acid, the expected coupling adduct **12di** was obtained along with enol ether **14b** and unreacted starting material **10d**. This suggested that the enol ethers arise by Pd-catalysed reaction of the mesylate with the ethanol co-solvent, a process which is faster than the slow Suzuki coupling caused by the C7 substituent. Since rate of coupling relative to reaction with solvent was clearly important, of interest was further study of the effect of base on the Suzuki coupling. The coupling of the representative mesylates **9d**, **9a**, **9e**, **9f**, and **9c** was examined with 4-methoxyphenylboronic acid or phenylboronic acid using different amounts of base (Table 4). In most cases, the reaction proceeded in a shorter time with improved yields using larger amounts of base, and 18 equivalents of base gave best results.

However, for the *S*-system, the use of larger equivalents of base gave poorer yields and the optimal number of equivalents of base was 15.5 for coupling of **10f** with phenylboronic acid permitting a maximum yield of 56% (entry 15, Table 4).

Dieckmann ring closure of malonamide **18**, the *7R* epimer of *trans*-2,5 diastereomer which was isolated as a minor product in the sequence from L-cysteine, and whose structure was determined by single crystal X-ray diffraction studies (Fig. S1, SD) [15], was attempted separately and resulted in decarboxylated tetramate **19a** in quantitative yield, and whose relative stereochemistry was established by NOE analysis (Scheme 3 and Fig. 3); this product presumably arises by cyclisation followed by immediate decarboxylation, as observed for the formation of **9a** earlier (Scheme 1). Mesylation of **19a** provided a complex mixture of products among which the expected mesylate **19b** and by-product **20** were isolated in 18% and 9% yield respectively, by careful *flash* column chromatography (Scheme 3). The stereochemistry of by-product **20** was again confirmed by NOE analysis (Fig. 3). However, attempted coupling of **19b** with 4-methoxyphenylboronic acid only gave a significant amount of unreacted starting material (40%) and no desired product could be isolated; this outcome serves to emphasise the sterically hindered nature of these bicyclic tetramates, and the consequent effects on reactivity.

Attempted reduction of **12ai** and **12di** using $NaBH_4$/AcOH or hydrogenation in the presence of PtO_2 catalyst delivered quantitative recovery of the starting material, further highlighting the steric hindrance operating in these bicyclic systems. However, sulfone **21**, obtained by the reaction of **12fii** with *m*-CPBA, after catalytic hydrogenation furnished pyrrolidinone **22** in 41% yield with the recovery of 51% of unreacted starting material **21** in a reaction which was very slow when compared to less substituted systems (Scheme 4) [1]. This outcome again suggests that the larger sulfur atom flattens the bicyclic core structure which gives better access to the catalyst surface and that the metal binding behaviour of sulfones might assist the hydrogenation reaction [21]. The stereochemistry of the newly formed chiral centres C6 and C7 was assigned by NOE analysis (Scheme 4). This hydrogenation result was consistent with the hydrogenation of similar analogues reported earlier [1].

N,O-Acetal deprotection of methyl-substituted systems **12ai-aiii** by applying the Corey-Reichard protocol proceeded efficiently but slowly giving products **17a-c** (Scheme 1) [22], but was not successful for phenyl substituted **12di**.

A possible alternative route for the synthesis of 3,4-disubstituted pyrrolinones which would expand the scope of this process would be to use the recently reported ethoxycarbonyltetramic acid **23a** (Scheme 5) [23]. This was readily prepared from tetramate **24** using ethyl chloroformate in 44% yield, but of interest is that attempted mesylation of **23a** using MsCl and DIPEA gave less than 2% yield of the expected product **25a**. This could not be improved using the Gilfillan (MsCl and Et_3N [24]) or the Kobayashi (MsCl and NaH [25]) protocols. Similarly, attempted mesylation with MsCl and DIPEA of Weinreb amide **23b**, available by treatment of *N*-methoxy-*N*-methylcarbamoyl derivative **26** with DBU, showed no detectable conversion (Scheme 5) [23]. This outcome serves to illustrate the highly electron deficient and therefore unreactive nature of this tetramate system.

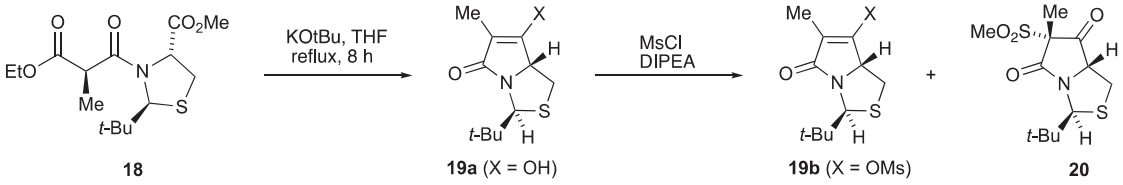
Some of the pyrrolinone and pyroglutaminol derivatives were tested for antibacterial activity against Gram-negative and Gram-positive bacteria and all of them with the exception of **17b** and **17c** showed very little or no activity (Table 5). Such sharp contrast between the antibacterial behaviour of generally inactive pyroglutamates and generally active tetramates has been previously noted [1,26]

1. Conclusion

We have established a route which allows scaffold hopping from pyroglutamates from tetramates, making use of Suzuki coupling on an enol mesylate, followed by reduction. While this route is both general and stereoselective, providing access to 3,4-disubstituted pyroglutamates, these systems appear to exhibit very limited antibacterial activity.

Table 4
Effect of the base on the Suzuki coupling of representative mesylates **10a-f.**

Systems		Na_2CO_3 (1M aq solution)	Entry	Reaction time	Yield	
					Product	By-product
*O*_System	1	9 eq	**10d**	24 h	**12di**, 9%	**14b**, 7%
	2	13 eq		24 h	**12di**, 25%	**14b**, 9%
	3	16 eq		20 h	**12di**, 19%	**14b**, 7%
	4	18 eq		24 h	**12di**, 30%	**14b**, 4%
	5	21 eq		15 h	**12di**, 26%	**14b**, 11%
	6	25 eq		19 h	**12di**, 12%	**14b**, 6%
	7	30 eq		15 h	**12di**, 8%	**14b**, 17%
	8	9 eq	**10a**	30 h	**12ai**, 32%	–
	9	18 eq		15 h	**12ai**, 54%	-
	10	9 eq	**10e**	43 h	**12ei**, <2%	**14c**, 7%
	11	18 eq		17 h	**12ei**, 7%	**14c**, 1%
S_System	12	9 eq	**10f**	24 h	**12fi**, 23%	**14d**, 5%
	13	18 eq		13 h	**12fi**, 8%	**14d**, 3%
	14	9 eq		24 h	**12fii**, 17%	**14d**, 5%
	15	15.5 eq		12 h	**12fii**, 56%	-
	16	9 eq	**10c**	24 h	**12ci**, 23%	**14a**, 3%
	17	18 eq		13 h	**12ci**, 2%	**14a**, 3%



Scheme 3. Synthesis of tetramates.

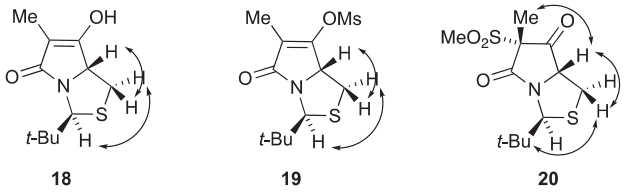


Fig. 3. NOESY correlations of tetramates.

2. Experimental [33–35]

2.1. Synthesis of methyl ester hydrochloride: General Method A [1,27]

$SOCl_2$ (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**.

2.2. Synthesis of oxazolidine and thiazolidine compounds: General Method B [1,16,28]

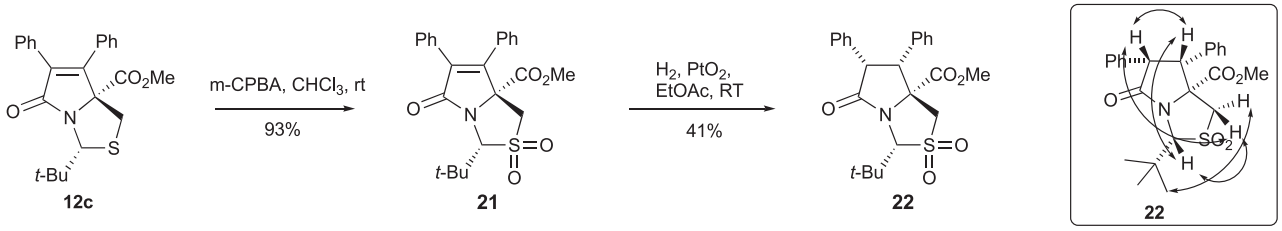
The ester hydrochloride of the L-amino acid **1a-c** (1.0 eq) was suspended in petroleum ether. Triethylamine (1.5 eq) and trimethylacetaldehyde (1.2 eq) were then added. The mixture was heated at reflux with continuous removal of water using a Dean-Stark apparatus for 18 h. The white precipitate was then filtered and washed with Et_2O. The combined filtrates were concentrated under reduced pressure to furnish the oxazolidines or thiazolidine.

2.3. Preparation of oxazolidine and thiazolidines 180a-c/2a-c: General Method C [1,16]

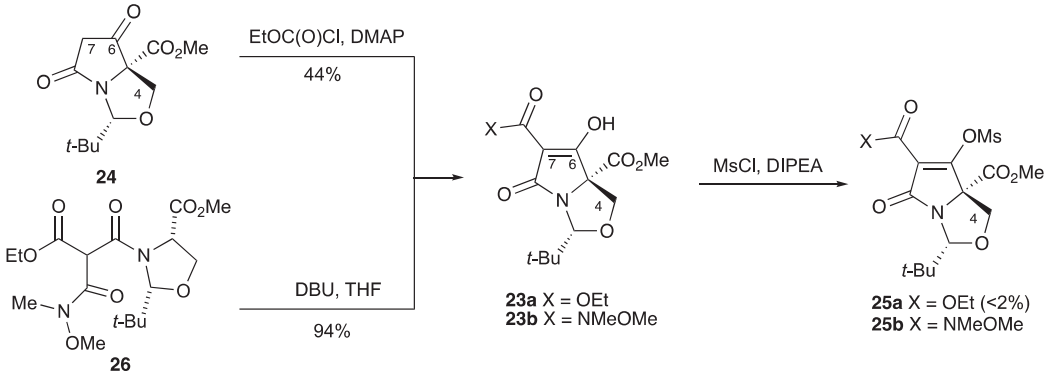
To a solution of oxazolidine/thiazolidines (0.5 eq) prepared above and dry pyridine (1.04 eq) in anhydrous DCM, a solution of the malonyl chloride **3** (1 eq) in anhydrous DCM was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and at room temperature for 6 h. It was then washed with sat. aq. NH_4Cl and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude *N*-acyl oxazolidine/thiazolidine was purified by flash column chromatography (20%–35% EtOAc in petroleum ether) to yield **180a-c/2a-c** as a mixture of diastereomers 7*R* (major) and 7*S* (minor).

2.4. Preparation of oxazolidine and thiazolidine compounds 185a-c/7a-c: General Method C [16]

DMAP (0.07 eq) and DCC (1.1 eq) were added to a solution of oxazolidine or thiazolidines (1.0 eq) in anhydrous DCM. The mixture was cooled to 0 °C and ethyl α-phenyl malonic acid (1.1 eq) was added. Then the reaction mixture was stirred 30 min at 0 °C and 6 h at room temperature. A white precipitate was formed, which was



Scheme 4. Elaboration of tetramates.



Scheme 5. Reactivity of substituted tetramates.

Table 5
Screening of compounds against bacteria.

Compound	Gram-negative bacteria			Gram-positive bacteria	
	EC 34	KL 18	PS 23	MRSA 1	MRSA 2
12ai	n.a.	n.a.	n.a.	n.a.	n.a.
12aii	n.a.	n.a.	n.a.	n.a.	n.a.
12aiii	n.a.	n.a.	n.a.	n.a.	n.a.
12bi	n.a.	n.a.	n.a.	n.a.	n.a.
12ci	n.a.	n.t.	n.t.	n.a.	n.t.
12cii	n.a.	n.t.	n.t.	n.a.	n.t.
12ciii	n.a.	n.t.	n.t.	n.a.	n.t.
17a	n.a.	n.a.	n.a.	n.a.	n.a.
17b	n.a.	n.a.	n.a.	n.a.	125 μg/mL
17c	n.a.	n.a.	n.a.	n.a.	125 μg/mL

n. a. = not active; n. t. = not tested.

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 **7a-c**.

2.5. Dieckmann cyclisation: General Method D [16]

To a solution of *N*-acyl oxazolidine or thiazolidine **2a-c** or **7a-c** (1.0 eq) in anhydrous ^{t}BuOH or THF (0.1 M) was added potassium *tert*-butoxide (1.09–1.10 eq). The mixture was heated at reflux for 3–6 h. Then the reaction mixture was separated between Et_2O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the tetramic acids **4a-c** and **8a-c**.

2.6. Synthesis of mesylate: General Method E [29]

Tetramic acid **4a-c** or **8a-c** (1.0 eq) was dissolved in DCM under nitrogen atmosphere. *M*ethanesulfonyl chloride (1 eq) and DIPEA (2 eq) were added to this solution. The resulting mixture was stirred for 2–6 h at room temperature until total consumption of the starting material. The reaction mixture was washed with 5% HCl, 5% $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel using ethyl acetate:petroleum ether as eluants to give mesylates **10a-f**.

2.7. Suzuki coupling: General Method F [29,30]

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 min to form a creamy orange slurry of [1,4-bis(diphenylphosphino) butane] palladium(II) chloride. 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 h. 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.

2.8. Hydrogenation: General Method G [31]

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 H_2 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.

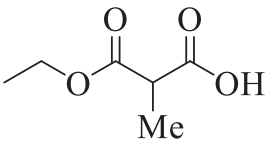
2.9. Preparation of sulfone and sulfoxide: General Method H [32]

A solution of cysteine-derived **12fii** (1 eq) in $CHCl_3$ (0.086 M) was cooled to 0 °C. A solution of *m*-chloroperbenzoic acid (1.3–3.0 eq) in $CHCl_3$ (0.15 M) was added dropwise. The reaction mixture was stirred at room temperature for 12–17 h. After completion, the mixture was poured into EtOAc (0.01 M) and the resultant solution was washed with sat. aq. solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 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.

2.10. N,O-acetal deprotection: General Method I [22]

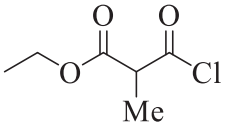
Under a nitrogen atmosphere, the pyrrolinone or pyrrolidinone (1 eq) was treated with propane-1,3-dithiol (2.1–4.0 eq) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol. The solution was stirred at room temperature for 24–36 h or at 50 °C for 12–17 h. The reaction mixture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

2.11. Ethyl α-methylmalonic acid



Diethyl methylmalonate (9.0 mL, 53 mmol) was added to a solution of KOH (2.99 g, 53.3 mmol) in EtOH (55 mL) at 0 °C and stirred at room temperature for 24 h or refluxed for 90 min. The resulting mixture was filtered and concentrated to give white solid. Water was then added, acidified the solution with HCl (pH 3.0) and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired mono-acid. Yield 68% (5.28 g); colorless oil; ν_{max}/cm^{-1} 3183 (O–H), 2989 (C–H), 2947 (C–H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$): 1.21 (3H, t, *J* 7.1, C(5)H_3), 1.38 (3H, d, *J* 7.3, C(2)CH_3), 3.42 (1H, q, *J* 7.3, C(2)H), 4.15 (2H, q, *J* 7.1, C(4)H_2), 11.35 (1H, s, COOH); δ_C (100 MHz, $CDCl_3$): 13.4 (C(2)$\underline{C}H_3$), 13.9 (C(5)), 46.0 (C(2)), 61.7 (C(4)), 169.9 (C(3)), 176.0 (C(1)); *m/z* ([ESI]$^+$) 147.0 ([M+H]$^+$, 90%), 169.0 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 147.0653, $C_6H_{11}O_4$ ([M+H]$^+$) requires 147.0652.

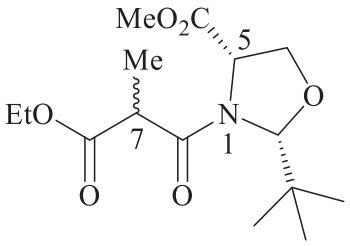
2.12. Ethyl α-methylmalonyl chloride 3



Thionyl chloride (4.76 mL, 65.2 mmol) was added dropwise to

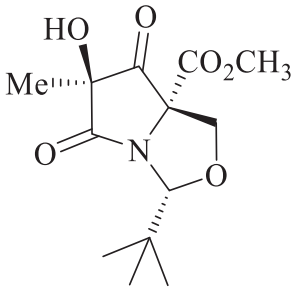
the mono-acid (4.767 g, 32.6 mmol) at 0 °C and the reaction mixture was stirred at 40 °C for overnight. The excess thionyl chloride was removed *in vacuo* to give acid chloride **3**, which was used directly in the next step. Yield 96% (5.15 g); orange oil; ν_{max}/cm^{-1} 2988 (C–H), 2945 (C–H), 1789 (C=O), 1736 (C=O); δ_H (400 MHz, $CDCl_3$): 1.24 (3H, t, *J* 7.1, C(5)H_3), 1.46 (3H, d, *J* 7.2, C(2)CH_3), 3.78 (1H, q, *J* 7.2, C(2)H), 4.19 (2H, q, *J* 7.1, C(4)H_2); δ_C (100 MHz, $CDCl_3$): 13.9 (C(5)), 14.0 (C(2)$\underline{C}H_3$), 57.0 (C(2)), 62.3 (C(4)), 167.5 (C(3)), 170.7 (C(1)).

2.12.1. (2R,5S)-2-(tert-Butyl)-1-((R)-1-ethoxycarbonyl-1-methylacetyl)- and (2R, 5S)-2-(tert-Butyl)-1-((S)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-1,3-oxazolidine, 2a and 2a'



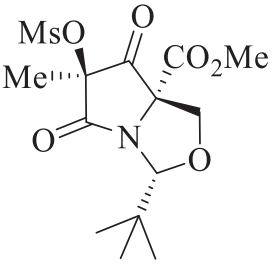
According to General Method C, oxazolidine (2.32 g, 12.4 mmol) was reacted with dry pyridine (2.02 mL, 25.77 mmol) and malonyl chloride **3** (4.08 g, 24.8 mmol) in anhydrous DCM (66 mL). The crude product was purified by *flash* column chromatography (20%–35% EtOAc in petroleum ether) to give *N*-acyl oxazolidine as a 2.2:1 mixture of diastereomers **2a and 2a'**. Yield 74% (5.01 g); yellow oil; 2.2:1 mixture of diastereomers. R_f (40% EtOAc in Petrol) 0.65 + 0.51; ν_{max}/cm^{-1} 2959 (C–H), 1745 (C=O), 1672 (C=O); δ_H (400 MHz, $CDCl_3$) Major isomer (**2a**): 0.86 (9H, s, C$(CH_3)_3$), 1.22–1.24 (3H, m, $CO_2CH_2C\underline{H}_3$), 1.38 (3H, d, *J* 7.2, CHC$\underline{H}_3$), 3.63 (1H, q, *J* 7.0, C$\underline{H}$CH$_3$), 3.71 (3H, s, CO_2CH_3), 3.92 (1H, dd, *J* 7.3, 5.8, C(4)$\underline{H}_A$H$_B$), 4.13–4.18 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.43–4.51 (1H, m, C(4)H$_A\underline{H}_B$ + C(5)H), 5.29 (1H, s, C(2)H); Minor isomer (**2a'**): 0.81 (9H, s, C$(CH_3)_3$), 1.18 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 1.40 (3H, d, *J* 6.9, CHC$\underline{H}_3$), 3.40 (1H, q, *J* 6.9, C$\underline{H}$CH$_3$), 3.74 (3H, s, CO_2CH_3), 3.90 (1H, dd, *J* 8.8, 6.8, C(4)$\underline{H}_A$H$_B$), 4.10 (2H, q, *J* 7.1 $CO_2C\underline{H}_2CH_3$), 4.51 (1H, dd, *J* 8.8, 2.0, C(4)H$_A\underline{H}_B$), 4.86 (1H, dd, *J* 6.8, 2.0, C(5)H), 5.28 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) Major isomer (**2a**): 13.7 ($CO_2CH_2\underline{C}H_3$), 14.1 (CH$\underline{C}H_3$), 25.6 (C$(\underline{C}H_3)_3$), 37.6 ($\underline{C}(CH_3)_3$), 45.7 ($\underline{C}$HCH$_3$), 52.7 ($CO_2\underline{C}H_3$), 59.4 (C(5)), 61.7 ($CO_2\underline{C}H_2CH_3$), 68.1 (C(4)), 96.7 (C(2)), 169.1, 170.3, 171.6 (N$\underline{C}$O, $\underline{C}O_2CH_3$, CO_2Et); Minor isomer (**2a'**): 14.0 ($CO_2CH_2\underline{C}H_3$), 14.4 (CH$\underline{C}H_3$), 25.5 (C$(\underline{C}H_3)_3$), 37.2 ($\underline{C}(CH_3)_3$), 45.8 ($\underline{C}$HCH$_3$), 52.9 ($CO_2\underline{C}H_3$), 59.4 (C(5)), 61.7 ($CO_2\underline{C}H_2CH_3$), 67.5 (C(4)), 96.4 (C(2)), 170.1, 170.2 (N$\underline{C}$O, $\underline{C}O_2CH_3$), 171.9 (CO_2Et); *m/z* (ESI$^+$) 338.2 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 316.1750, $C_{15}H_{26}NO_6$ ([M+H]$^+$) requires 316.1755.

2.12.2. (2R,5R,7S)-1-Aza-2-(tert-butyl)-7-hydroxy-5-methoxycarbonyl-7-methyl-3-oxa-6,8-dioxobicyclo[3.3.0]-octane 5a



According to General Method D, malonamide **2a** (2.45 g, 7.78 mmol) was refluxed with potassium *tert*-butoxide (961 mg, 8.56 mmol) in anhydrous THF (0.2 M). Yield 68% (1.42 g); white solid, m. p. 158–160 °C (lit [2]. m. p. 188–191 °C); R_f (40% EtOAc in Petrol) 0.25; $[\alpha]_D^{25}$ +65.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3424 (O–H), 2964 (C–H), 1784 (C=O), 1742 (C=O), 1694 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, C$(CH_3)_3$), 1.67 (C(7)CH_3), 3.56 (1H, d, *J* 8.9, C(4)$\underline{H}_A$H$_B$), 3.77 (3H, s, CO_2CH_3), 4.78 (1H, d, *J* 8.9, C(4)H$_A\underline{H}_B$), 5.00 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 23.8C(7)$\underline{C}H_3$, 24.7 (C$(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.8 ($CO_2\underline{C}H_3$), 69.6 (C(4)), 77.3 (C(5)), 77.5 (C(7)), 99.0 (C(2)), 166.4 ($\underline{C}O_2CH_3$), 177.8 (C(8)), 200.7 (C(6)); *m/z* ([ESI]$^+$) 286.1 ([M+H]$^+$, 75%), 308.0 ([M+Na]$^+$); HRMS ([ESI]$^+$) found 286.1286, $C_{13}H_{20}NO_6$ ([M+H]$^+$) requires 286.1285.

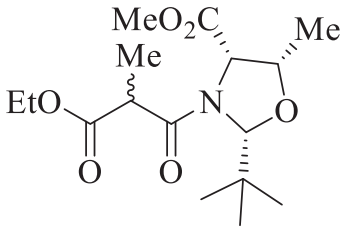
2.12.3. (2R,5R,7S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-7-methyl-7-((methylsulfonyl)oxy)-3-oxa-6, 8-dioxobicyclo [3.3.0]-octane, 5b



According to General Method E, tetramate **5a** (132 mg, 0.49 mmol) was reacted with MsCl (0.04 mL, 0.49 mmol) and DIPEA (0.17 mL, 0.98 mmol) in DCM (0.1 M). Yield 56% (100 mg); white solid, m. p. 115–117 °C; R_f (40% EA in PE) 0.40; $[\alpha]_D^{25}$ +53.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C–H), 2908 (C–H), 1795 (C=O), 1733 (C=O); δ_H (400 MHz, $CDCl_3$): 0.87 (9H, s, C$(CH_3)_3$), 1.80 (3H, s, C(7)CH_3), 3.18 (3H, s, $OSO_2C\underline{H}_3$), 3.78 (3H, s, CO_2CH_3), 3.89 (1H, d, *J* 8.5, C(4)$\underline{H}_A$H$_B$), 4.78 (1H, d, *J* 8.5, C(4)H$_A\underline{H}_B$), 5.02 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 21.3 (C(7)$\underline{C}H_3$), 24.8 (C$(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 41.0 (SO_2CH_3), 54.0 ($CO_2\underline{C}H_3$), 70.3 (C(4)), 77.6 (C(5)), 84.7 (C(7)), 99.6

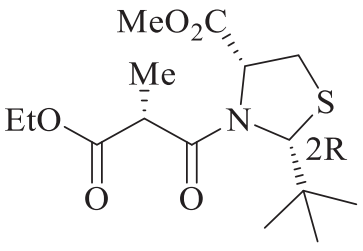
(C(2)), 166.4 ($\underline{C}O_2CH_3$), 172.7 (C(8)), 197.1 (C(6)); *m/z* ([ESI]$^+$) 386.0 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 364.1066, $C_{14}H_{22}NO_8S$ ([M+H]$^+$) requires 364.1067.

2.12.4. (2R,4S,5S)-2-(tert-Butyl)-1-((R)-1-ethoxycarbonyl-1-methylacetyl)- and (2R, 4S, 5S)-2-(tert-Butyl)-1-((S)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine, 2b and 2b'

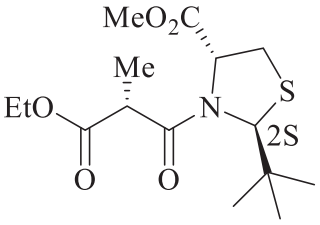


According to General Method C, oxazolidine (690 mg, 3.43 mmol) was reacted with dry pyridine (0.57 mL, 7.1 mmol) and malonyl chloride **3** (1.1 g, 6.85 mmol) in anhydrous DCM (12 mL). The crude product was purified by *flash* column chromatography (20%–35% EtOAc in petroleum ether) to give *N*-acyl oxazolidine as a 2.1:1 mixture of diastereomers **2b** and **2b'**. Yield 86% (968 mg). Major isomer (**2b**): Colorless oil; R_f (30% EtOAc in Petrol) 0.38; $[\alpha]_D^{25}$ – 76.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2986 (C–H), 2873 (C–H), 1755 (C=O), 1676 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 1.36 (3H, d, *J* 6.9, C(7)CH_3), 1.37 (3H, d, *J* 6.4, C(4)$C\underline{H}_3$), 3.44 (1H, q, *J* 6.9, C(7)H), 3.71 (3H, s, CO_2CH_3), 4.07–4.19 (3H, m, C(9)H_2 + C(4)H), 4.64 (1H, d, *J* 6.4, C(5)H), 5.17 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 14.1 (C(10)), 14.6, 15.5 (C(7)$\underline{C}H_3$ + C(4)$\underline{C}H_3$), 26.3 ($C(\underline{C}H_3)_3$), 36.8 ($\underline{C}(CH_3)_3$), 46.4 (C(7)), 52.1 ($CO_2\underline{C}H_3$), 61.6 (C(9)), 62.7 (C(5)), 74.9 (C(4)), 96.2 (C(2)), 169.3, 170.0, 172.3 (C(6)), $\underline{C}O_2CH_3$, C(8)); *m/z* (ESI$^+$) 352.0 ([M+Na]$^+$, 25%); HRMS ([ESI]$^+$) found 330.1910, $C_{16}H_{28}NO_6$ ([M+H]$^+$) requires 330.1911. Minor isomer (**2b'**): Colourless oil; R_f (30% EtOAc in Petrol) 0.25; ν_{max}/cm^{-1} 2986 (C–H), 2874 (C–H), 1755 (C=O), 1678 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.2, $CO_2CH_2C\underline{H}_3$), 1.31 (6H, t, *J* 7.2, C(7)CH_3 + C(4)CH_3), 3.35–3.46 (1H, m, C(7)H), 3.69 (3H, s, CO_2CH_3), 4.01–4.19 (3H, m, C(9)H_2 + C(4)H), 4.28–4.37 (1H, m, C(5)H), 5.15 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 13.4 (C(7)$\underline{C}H_3$), 14.0 (C(10)), 15.4 (C(4)$\underline{C}H_3$), 26.4 ($C(\underline{C}H_3)_3$), 37.1 ($\underline{C}(CH_3)_3$), 46.8 (C(7)), 51.9 ($CO_2\underline{C}H_3$), 61.6, 63.4 (C(4), C(9)), 75.0 (C(5)), 96.7 (C(2)), 168.7, 170.0, 171.7 (C(6)), $\underline{C}O_2CH_3$, C(8)); *m/z* (ESI$^+$) 352.0 ([M+Na]$^+$, 20%); HRMS ([ESI]$^+$) found 330.1909, $C_{16}H_{28}NO_6$ ([M+H]$^+$) requires 330.1911.

2.12.5. (2R,5R)-2-(tert-Butyl)-1-((R)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-1,3-oxazolidine, 2c and (2S, 5R)-2-(tert-Butyl)-1-((S)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-1,3-oxazolidine, 2c'

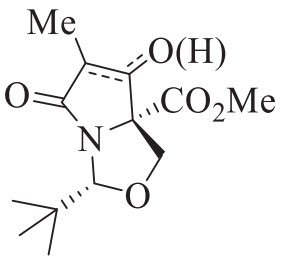


According to General Method C, thiazolidine (700 mg, 3.5 mmol) was reacted with dry pyridine (0.6 mL, 7.35 mmol) and malonyl chloride **3** (1.15 g, 7 mmol) in anhydrous DCM (20 mL). The crude *N*-acyl thiazolidine was purified by flash column chromatography (20%–35% EtOAc in petroleum ether) to yield **2c and 2c'** as a 2.5:1 mixture of diastereomers. Major isomer (**2c**): Yield 71% (808 mg); colorless oil; mixture of rotamers; R_f (30% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ -105.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2981 (C–H), 1746 (C=O), 1664 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95, 1.02 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 1.37 (3H, d, *J* 6.9, C(7)$C\underline{H}_3$), 3.15–3.30 (2H, m, C(4)H_AH_B), 3.70, 3.73 (3H, s, CO_2CH_3), 3.87 (1H, q, *J* 6.9, C(7)$\underline{H}$), 4.10 (2H, q, *J* 7.1 $CO_2C\underline{H}_2CH_3$), 4.69, 4.96 (1H, td, *J* 9.5, C(5)H), 5.02, 5.52 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 12.8, 13.5 (C(7)$\underline{C}H_3$), 14.0, 14.1 ($CO_2CH_2\underline{C}H_3$), 26.9, 27.0 ($C(\underline{C}H_3)_3$), 32.9, 33.8 (C(4)), 39.6, 39.9 ($\underline{C}(CH_3)_3$), 44.3, 44.9 (C(7)), 52.5, 52.9 ($CO_2\underline{C}H_3$), 61.5, 61.7 ($CO_2\underline{C}H_2CH_3$), 63.9, 64.6 (C(5)), 73.2, 73.8 (C(2)), 169.6–170.0 (N$\underline{C}$O, $\underline{C}O_2CH_3$, CO_2Et); *m/z* (ESI$^+$) 332.2 ([M+H]$^+$, 10%), 354.2 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 354.1349, $C_{15}H_{25}NO_5SNa$ ([M+Na]$^+$) requires 354.1346.



Minor isomer (**2c'**): Yield 27% (307 mg); white solid, m. p. 82–84 °C; mixture of rotamers; R_f (30% EtOAc in Petrol) 0.30; $[\alpha]_D^{25}$ -22.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 1744 (C=O), 1678 (C=O), 1652 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02 (9H, s, $C(CH_3)_3$), 1.24–1.28 (3H, m, $CO_2CH_2C\underline{H}_3$), 1.38 (3H, d, *J* 7.1, C(7)$C\underline{H}_3$), 2.90 (1H, d, *J* 12.2, C(4)$\underline{H}_AH_B$), 3.48 (1H, d, *J* 11.2, C(4)$H_A\underline{H}_B$), 3.65 (3H, s, CO_2CH_3), 3.90–3.98 (1H, m, C(7)$\underline{H}$), 4.09–4.26 (2H, q, *J* 7.1 $CO_2C\underline{H}_2CH_3$), 4.65–4.73 (1H, m, C(5)H), 4.76 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$) 13.6 (C(7)$\underline{C}H_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 27.2 ($C(\underline{C}H_3)_3$), 34.1 (C(4)), 35.5 ($\underline{C}(CH_3)_3$), 45.3 (C(7)), 52.3 ($CO_2\underline{C}H_3$), 61.8 ($CO_2\underline{C}H_2CH_3$), 65.4 (C(5)), 73.9 (C(2)), 169.8, 170.4, 171.2 (N$\underline{C}$O, $\underline{C}O_2CH_3$, CO_2Et); *m/z* ([ESI]$^+$) 354.2 ([M+Na]$^+$, 100%); HRMS ([ESI]$^+$) found 354.1341, $C_{15}H_{25}NO_5SNa$ ([M+Na]$^+$) requires 354.1346.

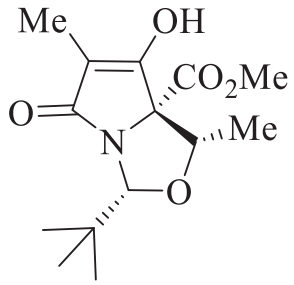
2.12.6. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-7-methyl-3-oxa-6,8-dioxobicyclo [3.3.0]octane 4a



According to General Method D, KOBu^t (555 mg, 4.9 mmol) was added to a solution of oxazolidine **2a** (1.42 g, 4.5 mmol) in Bu^{t}OH (0.2 M). The mixture was refluxed for 3 h and successive workup furnished the desired tetramate **4a**. Yield 82% (1.0 g); white solid,

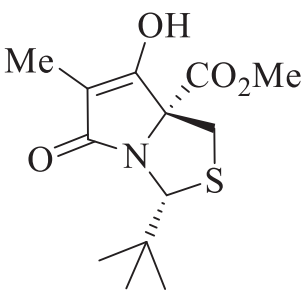
m. p. 135–137 °C (lit [2]. m.p. 94–100 °C); 1:2 mixture of keto-enol tautomers. R_f (10% MeOH in EtOAc) 0.30; $[\alpha]_D^{25}$ +80.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3298 (O–H), 2963 (C–H), 2876 (C–H), 1790 (C=O), 1733 (C=O); δ_H (400 MHz, $CDCl_3$): 0.84 (9H, s, $C(CH_3)_3$ (keto + enol)), 1.22 (3H, d, *J* 7.2, C(7)CH_3 (keto)), 1.63 (3H, s, C(7)CH_3 (enol)), 3.35 (1H, d, *J* 8.5, C(4)H_AH_B (enol)), 3.49 (1H, d, *J* 9.4, C(4)H_AH_B (keto)), 3.65 (1H, q, J 7.2, C(7)H (keto)), 3.71 (3H, s, CO_2CH_3 (enol)), 3.76 (3H, s, CO_2CH_3 (keto)), 4.59 (1H, s, C(2)H (enol)), 4.71–4.82 (2H, m, C(4) H_AH_B (keto + enol)), 4.99 (1H, s, C(2)H (keto)); δ_C (100 MHz, $CDCl_3$): 6.3 (C(7)CH_3)(keto), 7.6 (C(7)CH_3 (enol)), 24.6 ($C(CH_3)_3$ (enol)), 24.7 ($C(CH_3)_3$ (keto)), 35.1 ($C(CH_3)_3$ (enol)), 35.6 ($C(CH_3)_3$ (keto)), 49.4 (C(7) keto), 53.1 (CO_2CH_3 (keto)), 53.8 (CO_2CH_3 (enol)), 68.3 (C(4) enol), 69.9 (C(4) keto), 74.2 (C(5) (enol)), 79.1 (C(5) (keto)), 96.6 (C(2) keto), 98.0 (C(2) enol), 103.9 (C(7) enol), 166.9 (CO_2CH_3 (enol)), 168.0 (CO_2CH_3 (keto)), 169.2 (C(8) keto), 175.4 (C(8) enol), 181.5 (C(6) enol), 201.1 (C(6) keto); *m/z* ($[ESI]^+$) 270.2 ($[M+H]^+$, 60%), 292.0 ($[M+Na]^+$); HRMS ($[ESI]^+$) found 270.1333, $C_{13}H_{20}NO_5$ ($[M+H]^+$) requires 270.1336.

2.12.7. (2R,4S,5R)-1-Aza-2-(tert-butyl)-6-hydroxy-5-methoxycarbonyl-4, 7-dimethyl-3-oxa-8-oxobicyclo[3.3.0] oct-6-ene, 4b



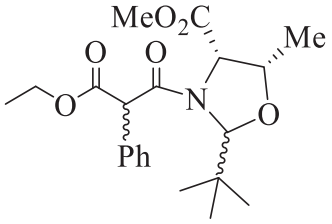
According to General Method D, malonamide **2b** (853 mg, 2.6 mmol) was reacted with KO^{t}Bu (319 mg, 2.85 mmol) in ^{t}BuOH (0.2 M) to furnish tetramic acid **4b**. Yield 67% (494 mg); white solid, m. p. 168–170 °C; R_f (EtOAc) 0.30; $[\alpha]_D^{25}$ +96.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3420 (O–H), 2958 (C–H), 2871 (C–H), 1755 (C=O), 1649 (C=O); δ_H (400 MHz, MeOD): 0.81 (9H, s, $C(CH_3)_3$, 1.55 (6H, d, *J* 6.3, C(7)CH_3 + C(4)CH_3), 3.50 (1H, q, *J* 6.5, C(4)H), 3.60 (3H, s, CO_2CH_3), 4.45 (1H, s, C(2)H); δ_C (100 MHz, MeOD): 4.8 (C(7)CH_3), 13.6 (C(4)CH_3), 24.2 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 51.2 (CO_2CH_3), 73.7 (C(5)), 79.8 (C(4)), 95.8 (C(2)), 102.0 (C(7)), 167.8 (CO_2CH_3), 169.4 (C(8)), 181.7 (C(6)); *m/z* ($[ESI]^+$) 284.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 284.1492, $C_{14}H_{22}NO_5$ ($[M+H]^+$) requires 284.1493.

2.12.8. (2R,5R)-1-Aza-2-(tert-butyl)-6-hydroxy-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo[3.3.0] octane, 4c



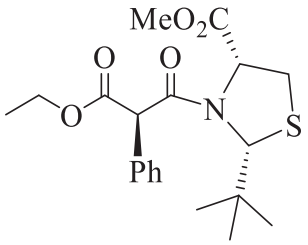
According to General Method D, malonamide **2c** (5.38 g, 16.2 mmol) was reacted with KO^{t}Bu (2.0 g, 17.8 mmol) in THF (0.2 M) to furnish tetramic acid **4c**. Yield 84% (3.9 g); white solid, m. p. 148–150 °C; $[\alpha]_D^{25}$ +291.4 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3366 (O–H), 2956 (C–H), 1751 (C=O), 1650 (C=O); δ_H (400 MHz, MeOD): 0.95 (9H, s, $C(CH_3)_3$), 1.66 (3H, s, C(7)CH_3), 2.80 (1H, d, *J* 11.2, C(4)H_AH_B), 3.68 (1H, d, *J* 11.2, C(4)H_AH_B), 3.78 (3H, s, CO_2CH_3), 4.87 (1H, s, C(2)H); δ_C (100 MHz, MeOD): 4.8 (C(7)CH_3), 25.6 ($C(CH_3)_3$), 32.6 (C(4)), 36.3 ($C(CH_3)_3$), 52.1 (CO_2CH_3), 71.2 (C(2)), 79.1 (C(5)), 100.0 (C(7)), 168.6 (CO_2CH_3), 169.2 (C(8)), 179.4 (C(6)); *m/z* ($[ESI]^+$) 286.0 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 286.1105, $C_{13}H_{20}NO_4S$ ($[M+H]^+$) requires 286.1108.

2.12.9. (2R,4S,5S)-2-(tert-Butyl)-1-((R)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine (7b), (2R,4S,5S)-2-(tert-Butyl)-1-((S)-1-ethoxycarbonyl-1-methylacetyl)-5-methoxycarbonyl-4-methyl-1,3-oxazolidine (7b')

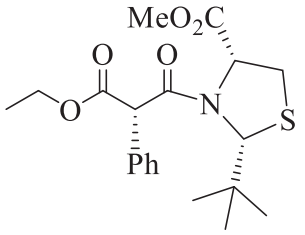


According to General Method C, oxazolidine (870 mg, 4.3 mmol), DCC (969 mg, 4.7 mmol), and DMAP (37 mg, 0.3 mmol) was reacted with ethyl α-phenyl malonic acid **6** (990 mg, 4.7 mmol) in DCM (43 mL). The crude product was purified by *flash* column chromatography (20% EtOAc in petroleum ether) to afford *N*-acyl oxazolidine as a 2:1.6 mixture of diastereomers **7b** and **7b'**. Yield 95% (1.61 g); 2:1.6 mixture of diastereomers; colourless oil; minor isomer **7b'** is solid for which m.p. is 84–86 °C. R_f (20% EtOAc in Petrol) 0.19 + 0.25+0.28. Major isomer **7b**: $[\alpha]_D^{25}$ +25.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2984 (C–H), 2958 (C–H), 2872 (C–H), 1754 (C=O), 1678 (C=O); δ_H (400 MHz, $CDCl_3$) 0.96 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, C(10)H_3), 1.22 (3H, d, *J* 6.4, C(4)CH_3), 3.75 (3H, s, CO_2CH_3), 3.81 (1H, q, *J* 6.4, C(4)H), 4.04–4.22 (3H, m, (C(5)H + C(9)H_2), 4.58 (1H, s, (C(7)H), 5.11 (1H, s, C(2)H), 7.25–7.33 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.0 (C(10)), 15.3 (C(4)CH_3), 26.4 ($C(CH_3)_3$), 37.1 ($C(CH_3)_3$), 52.1 (CO_2CH_3), 59.1 (C(7)), 61.8 (C(9)), 62.2 (C(5)), 74.9 (C(4)), 96.7 (C(2)), 128.5–132.0 (ArC), 168.2 (NC=O), 168.9 (CO_2CH_3), 169.3 (CO_2Et); *m/z* ($[ESI]^+$) 392.2 ($[M+H]^+$, 50%); HRMS ($[ES]I^+$) found 392.2061, $C_{21}H_{30}NO_6$ ($[M+H]^+$) requires 392.2068. Diastereomer **7b'**: $[\alpha]_D^{25}$ – 46.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2985 (C–H), 2957 (C–H), 2873 (C–H), 1751 (C=O), 1672 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, *J* 7.1, C(10)H_3), 1.28 (3H, d, *J* 6.4, C(4)CH_3), 3.50 (3H, s, CO_2CH_3), 4.08–4.21 (3H, m, C(9)H_2 + C(4)H), 4.51 (1H, d, *J* 6.5, C(5)H), 4.68 (1H, s, C(7)H), 5.18 (1H, s, C(2)H), 7.24–7.32 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 14.1 (C(10)), 15.2 (C(4)CH_3), 26.4 ($C(CH_3)_3$), 37.0 ($C(CH_3)_3$), 51.8 (CO_2CH_3), 59.2 (C(7)), 61.9 (C(9)), 63.5 (C(5)), 75.1 (C(4)), 96.9 (C(2)), 128.1–133.1 (ArC), 168.3 (NC=O), 168.6 (CO_2CH_3), 170.5 (CO_2Et); *m/z* ($[ESI]^+$) 392.2 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 392.2069, $C_{21}H_{30}NO_6$ ($[M+H]^+$) requires 392.2068.

2.12.10. (2R,5R)-2-(tert-Butyl)-1-((R)-1-ethoxycarbonyl-1-phenylacetyl)- and (2R,5R)-2-(tert-Butyl)-1-((S)-1-ethoxycarbonyl-1-phenylacetyl)-5-methoxycarbonyl-1,3-thiazolidine, 7c and 7c'

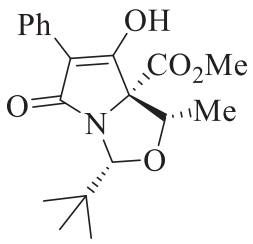


According to General Method C, oxazolidine **1c** (4.0 g, 19.6 mmol), DCC (4.4 g, 21.6 mmol), and DMAP (167 mg, 1.37 mmol) was reacted with ethyl α-phenyl malonic acid **6** (4.5 g, 21.6 mmol) in DCM (196 mL). The crude product was purified by *flash* column chromatography (20% EtOAc in petroleum ether) to afford *N*-acyl oxazolidine as a 1.8:1 mixture of diastereomers **7c** and **7c'** with 85% (6.57 g) yield. Major isomer **7c** (major rotamer A, minor rotamer B): white solid, m. p. 78–80 °C; R_f (20% EtOAc in Petrol) 0.23; $[\alpha]_D^{25}$ -46.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2871 (C–H), 1750 (C=O), 1678 (C=O); δ_H (400 MHz, $CDCl_3$): 0.95 (9H, s, $C(CH_3)_3$ **A**), 1.06 (9H, s, $C(CH_3)_3$ **B**), 1.19 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 3.00 (1H, dd, *J* 11.9, 8.5, C(4)$\underline{H}_AH_B$, **A**), 3.11 (1H, d, *J* 12.1, C(4)$\underline{H}_AH_B$ **B**), 3.23 (1H, dd, *J* 11.8, 6.9, C(4)$H_A\underline{H}_B$ **A**), 3.50 (1H, dd, *J* 12.4, 7.1, C(4)$H_A\underline{H}_B$ **B**), 3.64 (3H, s, CO_2CH_3 **B**), 3.81 (3H, s, CO_2CH_3 **A**), 4.08–4.21 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.60 (1H, t, *J* 7.8, C(5)H **A**), 4.64 (1H, s, C(7)H **A**), 5.10 (1H, s, C(7)H **B**), 5.40 (1H, C(2)H **B**), 5.52 (1H, C(2)H **A**), 7.22–7.32 (5H, s, ArH); δ_C (100 MHz, $CDCl_3$): 14.0 ($CO_2CH_2\underline{C}H_3$), 26.9 ($C(\underline{C}H_3)_3$), 33.9 (C(4)), 39.5 ($\underline{C}(CH_3)_3$), 53.1 ($CO_2\underline{C}H_3$), 57.7 ($\underline{C}$HPh), 61.8 ($CO_2\underline{C}H_2CH_3$), 63.4 (C(5)), 73.2 (C(2)), 128.2–132.7 (ArC), 168.3 (N$\underline{C}$=O), 168.4 (CO_2Et), 171.0 ($\underline{C}O_2CH_3$).



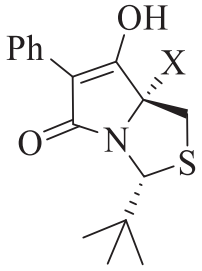
Minor isomer **7c'** (major rotamer C, minor rotamer D): white solid, m. p. 72–74 °C; R_f (20% EtOAc in Petrol) 0.18; $[\alpha]_D^{25}$ – 94.1.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2872 (C–H), 1751 (C=O), 1657 (C=O); δ_H (400 MHz, $CDCl_3$): 0.85 (9H, s, $C(CH_3)_3$ **C**), 1.07 (9H, s, $C(CH_3)_3$ **D**), 1.19 (3H, t, *J* 7.2, $CO_2CH_2C\underline{H}_3$), 2.99–3.38 (2H, m, C(4)H_2), 3.57 (3H, s, CO_2CH_3 **C**), 3.71 (3H, s, CO_2CH_3 **D**), 4.11–4.18 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.59 (1H, s, C(5)H **D**), 4.61 (1H, s, C(2)H **D**), 4.73 (1H, s, C(7)H **C**), 4.96 (1H, s, C(7)H **D**), 5.04 (1H, s, C(5)H **C**), 5.58 (1H, C(2)H **C**), 7.26–7.38 (5H, s, ArH); δ_C (100 MHz, $CDCl_3$): 14.1, 14.1 ($CO_2CH_2\underline{C}H_3$), 26.9, 27.3 ($C(\underline{C}H_3)_3$), 32.8, 34.5 (C(4)), 39.4, 41.2 ($\underline{C}(CH_3)_3$), 52.6, 52.8 ($CO_2\underline{C}H_3$), 56.8, 57.6 ($\underline{C}$HPh), 61.7, 62.1 ($CO_2\underline{C}H_2CH_3$), 64.3, 64.6 (C(5)), 73.6, 73.7 (C(2)), 128.1–133.3 (ArC), 168.3 (N$\underline{C}$=O), 170.6 (CO_2Et), 170.9 ($\underline{C}O_2CH_3$); *m*/*z* ($[ESI]^+$) 394.1 ($[M+H]^+$, 65%), 416.2 ($[M+Na]^+$, 60%); HRMS ($[ESI]^+$) found 394.1691, $C_{20}H_{28}NO_5S$ ($[M+H]^+$) requires 394.1683.

2.12.11. (2R,4S,5R)-1-Aza-2-(tert-butyl)-6-hydroxy-5-methoxycarbonyl-4-methyl-3-oxa-8-oxo-7-phenylbicyclo [3.3.0] oct-6-ene, 8b



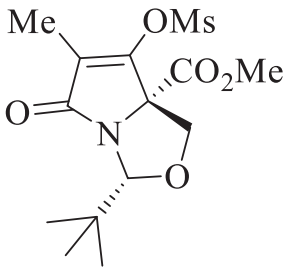
According to General Method D, KO^{t}Bu (452 mg, 4.0 mmol) was reacted with a solution of oxazolidine (1.45 g, 3.7 mmol) in ^{t}BuOH (0.1 M). The crude product was purified by *flash* column chromatography to yield desired tetramic acid **8b**. Yield 70% (899 mg); white solid, m. p. 160–162 °C (lit. m.p. 128–130 °C); R_f (10% MeOH in EtOAc) 0.30; $[\alpha]_D^{25}$ +26.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3329 (O–H), 2958 (C–H), 2871 (C–H), 1757 (C=O), 1685 (C=O); δ_H (400 MHz, MeOD): 0.86 (9H, s, $C(CH_3)_3$), 1.63 (3H, d, *J* 6.5, C(4)CH_3), 3.66 (3H, s, CO_2CH_3), 3.70 (1H, q, *J* 6.5, C(4)H), 4.58 (1H, s, C(2)H), 7.16–7.51 (5H, m, ArH); δ_C (100 MHz, MeOD): 13.7 (C(4)$\underline{C}H_3$), 24.3 ($C(\underline{C}H_3)_3$), 34.6 ($\underline{C}(CH_3)_3$), 51.5 ($CO_2\underline{C}H_3$), 73.7 (C(5)), 79.9 (C(4)), 96.2 (C(2)), 107.4 (C(7)), 127.1–129.7 (ArC), 167.6 ($\underline{C}O_2CH_3$), 169.4 (C(8)), 179.5 (C(6)); *m*/*z* ($[ESI]^+$) 346.1 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 346.1646, $C_{19}H_{24}NO_5$ ($[M+H]^+$) requires 346.1649.

2.12.12. (2R,5R)-1-Aza-2-(tert-butyl)-6-hydroxy-5-methoxycarbonyl-8-oxo-7-phenyl-3-thiabicyclo [3.3.0]oct-6-ene, 8c and (2R,5S)-1-Aza-2-(tert-butyl)-6-hydroxy-8-oxo-7-phenyl-3-thiabicyclo [3.3.0]oct-6-ene, 9a



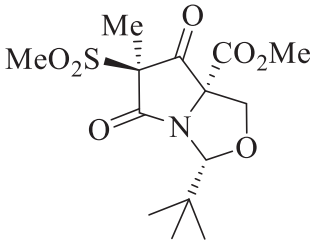
According to General Method D, KO^{t}Bu (1.73 g, 14.17 mmol) was reacted with a solution of oxazolidine (5.12 g, 13.0 mmol) in ^{t}BuOH (87 mL). The crude product was purified by *flash* column chromatography which resulted an inseparable mixture of products. Yield 73% (3.3 g); 8:1 mixture of **8c** and **9a**; white solid; R_f (10% MeOH in EtOAc) 0.20 + 0.23; ν_{max}/cm^{-1} 3284 (O–H), 3057 (C–H), 2955 (C–H), 1750 (C=O), 1649 (C=O), 1600 (C=O); **8c**: δ_H (400 MHz, MeOD): 0.91 (9H, s, $C(CH_3)_3$), 2.71 (1H, d, *J* 11.3, C(4)$\underline{H}_AH_B$), 3.55 (1H, d, *J* 11.3, C(4)$H_A\underline{H}_B$), 3.72 (3H, s, CO_2CH_3), 4.86 (1H, s, C(2)H), 7.19–7.54 (ArH); δ_C (100 MHz, MeOD): 26.7 ($C(\underline{C}H_3)_3$), 33.7 (C(4)), 36.8 ($\underline{C}(CH_3)_3$), 53.4 ($CO_2\underline{C}H_3$), 72.0 (C(2)), 78.5 (C(5)), 106.5 (C(7)), 127.9–130.0 (ArC), 166.1 (C(8)), 169.2 ($\underline{C}O_2CH_3$), 175.7 (C(6)); *m*/*z* ($[ESI]^+$) 348.1 ($[M+H]^+$, 50%), 370.1 ($[M+Na]^+$, 45%); HRMS ($[ESI]^+$) found 346.1117, $C_{18}H_{20}NO_4S$ ($[M-H]^-$) requires 346.1119.

2.12.13. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-7-methyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 10a



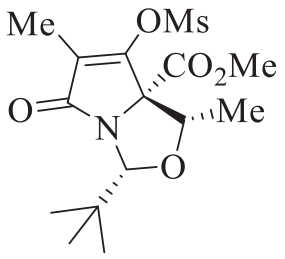
According to General Method E, reaction of tetramic acid **4a** (4.6 g, 17.04 mmol) with MsCl (1.32 mL, 17.04 mmol) and DIPEA (5.9 mL, 34.08 mmol) in DCM (0.1 M) resulted mesylate **10a**. Yield 71% (4.2 g); white solid, m. p. 85–87 °C; R_f (40% EtOAc in Petrol) 0.35; $[\alpha]_D^{25}$ +130.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C–H), 2873 (C–H), 1719 (C=O), 1685 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, $C(CH_3)_3$), 1.84 (3H, s, C(7)CH_3), 3.19 (3H, s, OSO_2CH_3), 3.45 (1H, d, *J* 8.9, C(4)H_AH_B), 3.73 (3H, s, CO_2CH_3), 4.65 (1H, s, C(2)H), 4.74 (1H, d, *J* 8.9, C(4)H_AH_B); δ_C (100 MHz, $CDCl_3$): 8.2 (C(7)CH_3), 24.7 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 39.2 (OSO_2CH_3), 53.4 (CO_2CH_3), 70.8 (C(4)), 74.5 (C(5)), 96.6 (C(2)), 125.6 (C(7)), 155.5 (CO_2CH_3), 168.0 (C(8)), 175.4 (C(6)); *m/z* ($[ESI]^+$) 348.0 ($[M+H]^+$, 100%), 370.0 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 348.1111, $C_{14}H_{22}NO_7S$ ($[M+H]^+$) requires 348.1112.

2.12.14. (2S,5R,7S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-7-methyl-7-(methylsulfonyl)-3-oxa-6,8-dioxobicyclo [3.3.0] octane, 11a



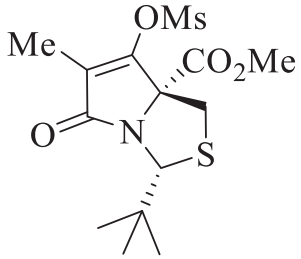
By-product from **11a**: Yield 7% (39 mg); white solid, m. p. 120–122 °C; R_f (40% EtOAc in Petrol) 0.39; $[\alpha]_D^{25}$ +82.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C–H), 2878 (C–H), 1754 (C=O), 1721 (C=O); δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, $C(CH_3)_3$), 1.83 (3H, s, C(7)CH_3), 3.12 (3H, s, SO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.91 (1H, d, *J* 8.6, C(4)H_AH_B), 4.73 (1H, d, *J* 8.6, C(4)H_AH_B), 5.05 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 18.0 (C(7)CH_3), 24.7 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 38.4 (SO_2CH_3), 54.0 (CO_2CH_3), 67.2 (C(4)), 73.7 (C(5)), 79.1 (C(7)), 100.1 (C(2)), 166.7 (CO_2CH_3), 171.5 (C(8)), 195.1 (C(6)); *m/z* ($[ESI]^+$) 370.1 ($[M+Na]^+$, 40%); HRMS ($[ESI]^+$) found 370.0931, $C_{14}H_{21}NO_7SNa$ ($[M+Na]^+$) requires 370.0931.

2.12.15. (2R,4S,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-4, 7-dimethyl-6-((methylsulfonyl)- oxy)-3-oxa-8-oxobicyclo[3.3.0] oct-6-ene, 10b



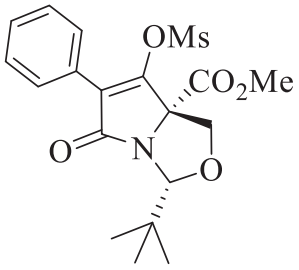
According to General Method E, reaction of tetramic acid **4b** (400 mg, 1.4 mmol) with MsCl (0.11 mL, 1.4 mmol) and DIPEA (0.5 mL, 2.8 mmol) in DCM (0.1 M) resulted in mesylate **10b**. Yield 89% (456 mg); white solid, m. p. 92–94 °C; R_f (20% EtOAc in Petrol) 0.22; $[\alpha]_D^{25}$ +115.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2959 (C–H), 2873 (C–H), 1700 (C=O), 1683 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 1.55 (3H, d, *J* 6.4, C(4)CH_3), 1.86 (3H, s, C(7)CH_3), 3.24 (3H, s, OSO_2CH_3), 3.65–3.69 (4H, m, C(4)H + CO_2CH_3), 4.60 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 8.9 (C(7)$\underline{C}H_3$), 15.3 (C(4)$\underline{C}H_3$),25.2 (C($\underline{C}H_3$)$_3$), 35.1 ($\underline{C}(CH_3)_3$), 39.6 ($OSO_2\underline{C}H_3$), 52.6 ($CO_2\underline{C}H_3$), 74.4 (C(5)), 80.1 (C(4)), 96.4 (C(2)), 124.1 (C(7)), 156.1 ($\underline{C}O_2CH_3$), 166.8 (C(8)), 175.9 (C(6)); *m/z* ($[ESI]^+$) 362.2 ($[M+H]^+$, 50%), 384.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 362.1268, $C_{15}H_{24}NO_7S$ ($[M+H]^+$) requires 362.1268.

2.12.16. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-7-methyl-6-((methylsulfonyl)oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 10c



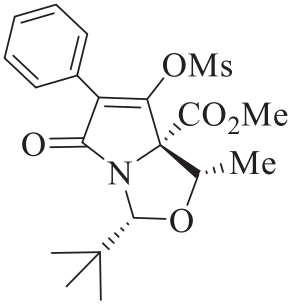
According to General Method E, reaction of tetramic acid **4c** (546 mg, 1.9 mmol) with MsCl (0.15 mL, 1.9 mmol) and DIPEA (0.61 mL, 3.8 mmol) in DCM (0.1 M) resulted in mesylate **10c**. Yield 65% (449 mg); colorless oil; R_f (40% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +198.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3020 (C–H), 2956 (C–H), 1749 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.85 (3H, s, C(7)CH_3), 2.79 (1H, d, *J* 11.3, C(4)$\underline{H}_A\underline{H}_B$), 3.20 (3H, s, OSO_2CH_3), 3.60 (1H, d, *J* 11.3, C(4)$H_A\underline{H}_B$), 3.73 (3H, s, CO_2CH_3), 4.89 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 8.7 (C(7)$\underline{C}H_3$), 26.7 (C($\underline{C}H_3$)$_3$), 33.6 (C(4)), 36.8 ($\underline{C}(CH_3)_3$), 39.5 (OSO_2CH_3), 53.4 ($CO_2\underline{C}H_3$), 71.7 (C(2)), 79.2 (C(5)), 122.7 (C(7)), 155.5 ($\underline{C}O_2CH_3$), 168.1 (C(8)), 173.7 (C(6)); *m/z* ($[ESI]^+$) 386.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 364.0886, $C_{14}H_{22}NO_6S_2$ ($[M+H]^+$) requires 364.0883.

2.12.17. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 10d



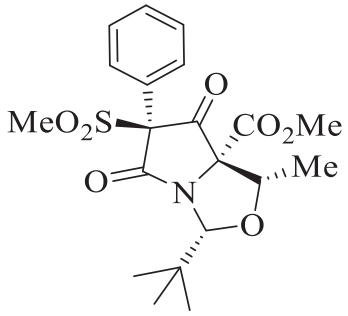
According to General Method E, reaction of tetramic acid **8a** (5.69 g, 17.17 mmol) with MsCl (1.33 mL, 17.17 mmol) and DIPEA (5.98 mL, 34.34 mmol) in DCM (0.1 M) resulted mesylate **10d**. Yield 71% (5.0 g); colorless oil; R_f (30% EtOAc in Petrol) 0.30; $[\alpha]_D^{25}$ +164.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C–H), 2874 (C–H), 1751 (C=O), 1720 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 3.00 (3H, s, OSO_2CH_3), 3.62 (1H, d, *J* 9.1, C(4)H_AH_B), 3.77 (3H, s, CO_2CH_3), 4.77 (1H, s, C(2)H), 4.86 (1H, d, *J* 9.1, C(4)H_AH_B), 7.30–7.40 (3H, m, C(3″)H + C(4″)H)), 7.71 (2H, dd, *J* 8.0, 1.7, C(2″)H); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 39.6 (OSO_2CH_3), 53.6 ($CO_2\underline{C}H_3$), 71.2 (C(4)), 74.3 (C(5)), 96.8 (C(2)), 126.6 (C(7)), 127.0–130.0 (ArC), 155.0($\underline{C}O_2CH_3$), 167.8 (C(8)), 173.4 (C(6)); *m/z* ($[ESI]^+$) 410.1 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 432.1088, $C_{19}H_{23}NO_7SNa$ ($[M+Na]^+$) requires 432.1087.

2.12.18. (2R,4S,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-4-methyl-6-((methylsulfonyl)oxy)- 3-oxa-8-oxo-7-phenylbicyclo [3.3.0] oct-6-ene, 10e



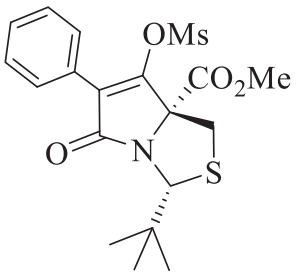
According to General Method E, reaction of tetramic acid **8b** (1.27 g, 3.7 mmol) with MsCl (0.28 mL, 3.7 mmol) and DIPEA (1.29 mL, 7.4 mmol) in DCM (0.1 M) resulted in mesylate **10e**. Yield 64% (1.0 g); colorless oil; R_f (30% EtOAc in Petrol) 0.33; $[\alpha]_D^{25}$ +52.6 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2873 (C–H), 1752 (C=O), 1719 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.67 (3H, d, *J* 6.4, $C(4)CH_3$), 2.87 (3H, s, OSO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.87 (1H, q, *J* 6.4, C(4)H), 4.71 (1H, s, C(2)H), 7.32–7.38 (3H, m, C(3″)H + C(4″)H)), 7.57 (2H, dd, *J* 8.0, 1.5, C(2″)H); δ_C (100 MHz, $CDCl_3$): 15.4 ($C(4)CH_3$), 25.2 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 40.6 (OSO_2CH_3), 52.8 (CO_2CH_3), 74.5 (C(5)), 80.2 (C(4)), 96.5 (C(2)), 126.8 (C(7)), 127.3–129.9 (ArC), 156.8 ($\underline{C}O_2CH_3$), 166.3 (C(8)),173.9 (C(6)); *m/z* ($[ESI]^+$) 424.2 ($[M+H]^+$, 20%), 446.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 424.1419, $C_{20}H_{26}NO_7S$ ($[M+H]^+$) requires 424.1425.

2.12.19. (2S,4S,5R,7S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-4-methyl-7-(methylsulfonyl)-3-oxa-6, 8-dioxo-7-phenylbicyclo[3.3.0] oct-6-ene, 11b



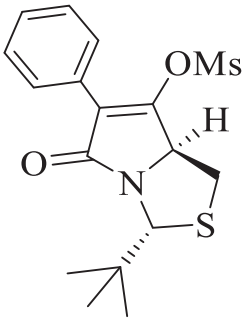
By-product from **11b**: Yield 5% (73 mg); yellow semi-solid; R_f (30% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +27.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C–H), 2875 (C–H), 1758 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$), 1.62 (3H, d, *J* 6.5, $C(4)CH_3$), 2.88 (3H, s, SO_2CH_3), 3.30 (3H, s, CO_2CH_3), 4.19 (1H, q, *J* 6.5, C(4)H), 5.10 (1H, s, C(2)H), 7.36–7.42 (3H, m, C(3″)H + C(4″)H)), 7.71–7.79 (2H, m, C(2″)H); δ_C (100 MHz, $CDCl_3$): 14.3 ($C(4)CH_3$), 25.2 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 38.5 (OSO_2CH_3), 52.7 (CO_2CH_3), 76.3 (C(4)), 78.3 (C(5)), 80.1 (C(7)), 98.5 (C(2)), 127.6–130.4 (ArC), 164.6 (CO_2CH_3), 169.8 (C(8)), 192.1 (C(6)); *m/z* ($[ESI]^+$) 446.2 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 446.1238, $C_{20}H_{25}NO_7SNa$ ($[M+Na]^+$) requires 446.1234.

2.12.20. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-((methylsulfonyl)oxy)-8-oxo-7-phenyl-3-thiabicyclo[3.3.0] oct-6-ene, 10f



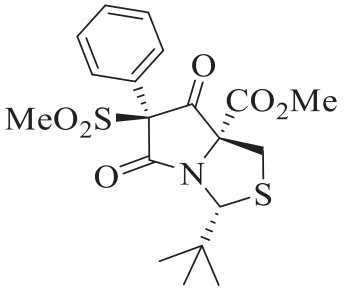
According to General Method E, reaction of tetramic acid **8c** (3.7 g, 10.6 mmol) with MsCl (0.82 mL, 10.6 mmol) and DIPEA (3.7 mL, 21.2 mmol) in DCM (0.1 M) resulted in mesylate **110f**. Yield 64% (2.9 g); white solid, m. p. 110–112 °C; R_f (30% EtOAc in Petrol) 0.31; $[\alpha]_D^{25}$ +229.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C–H), 2935 (C–H), 1750 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$): 0.95 (9H, s, $C(CH_3)_3$), 2.98 (4H, d, *J* 11.9, OSO_2CH_3 + C(4)H_AH_B), 3.73 (1H, d, *J* 11.5, C(4)H_AH_B), 3.78 (3H, s, CO_2CH_3), 5.00 (1H, s, C(2)H), 7.31–7.41 (3H, m, C(3″)H + C(4″)H)), 7.60–7.67 (2H, m, C(2″)H); δ_C (100 MHz, $CDCl_3$): 26.8 ($C(\underline{C}H_3)_3$), 33.9 (C(4)), 37.0 (OSO_2CH_3), 40.1 ($\underline{C}(CH_3)_3$), 53.6 ($CO_2\underline{C}H_3$), 71.7 (C(2)), 79.1 (C(5)), 124.9 (C(7)),127.2–129.9 (ArC), 155.5 ($\underline{C}O_2CH_3$), 167.7(C(8)), 171.6 (C(6)); *m/z* ($[ESI]^+$) 448.1 ($[M+Na]^+$, 75%); HRMS ($[ESI]^+$) found 448.0860, $C_{19}H_{23}NO_6S_2Na$ ($[M+Na]^+$) requires 448.0859.

2.12.21. (2R,5S)-1-Aza-2-(tert-butyl)-6-((methylsulfonyl)oxy)-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 9b



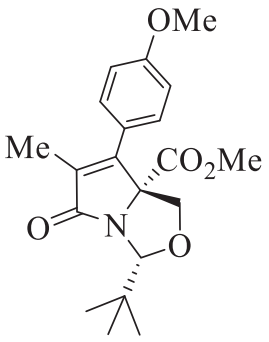
By-product: Yield 6% (23 mg); yellow semi-solid; R_f (30% EtOAc in Petrol) 0.34; $[\alpha]_D^{25}$ +62.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2961 (C–H), 2934 (C–H), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.99 (9H, s, $C(CH_3)_3$), 2.74 (1H, t, *J* 10.3, C(4)$\underline{H}_A H_B$), 2.98 (3H, s, OSO_2CH_3), 3.16–3.24 (1H, m, C(4)$H_A\underline{H}_B$), 4.90 (1H, dd, *J* 10.0, 6.1, C(5)H), 5.01 (1H, s, C(2)H), 7.30–7.39 (3H, m, C(3″)H + C(4″)H)), 7.63–7.69 (2H, m, C(2″)H); δ_C (100 MHz, $CDCl_3$): 26.4 ($C(\underline{C}H_3)_3$), 32.9 (C(4)), 37.5 (OSO_2CH_3), 39.3 ($C(CH_3)_3$), 66.6 (C(5)), 69.1 (C(2)), 121.8 (C(7)), 127.6–129.4 (ArC), 156.5 (C(8)), 169.7 (C(6)); *m/z* ($[ESI]^+$) 368.1 ($[M+H]^+$, 65%); HRMS ($[ESI]^+$) found 368.0985, $C_{17}H_{22}NO_4S_2$ ($[M+H]^+$) requires 368.0985.

2.12.22. (2S,5R,7S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-7-(methylsulfonyl)-6,8-dioxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 11c



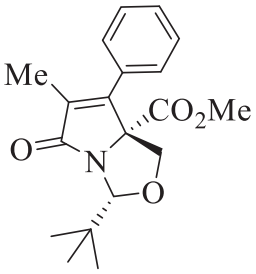
By-product: Yield 9% (400 mg); yellow semi-solid; R_f (30% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +72.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2935 (C–H), 1753 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 2.88 (3H, s, OSO_2CH_3), 3.25 (1H, d, *J* 11.1, C(4)$\underline{H}_A H_B$), 3.40 (3H, s, CO_2CH_3), 3.67 (1H, d, *J* 11.1, C(4)$H_A\underline{H}_B$), 5.43 (1H, s, C(2)H), 7.36–7.45 (3H, m, (C(3″)H + C(4″)H)), 7.80–7.85 (2H, m, C(2″)H); δ_C (100 MHz, $CDCl_3$): 26.6 ($C(\underline{C}H_3)_3$), 33.1 (C(4)), 37.1 ($\underline{C}(CH_3)_3$), 38.4 (OSO_2CH_3), 53.6 ($CO_2\underline{C}H_3$), 74.6 (C(2)), 78.4 (C(5)), 82.8 (C(7)), 127.5–130.3 (ArC), 166.0 ($\underline{C}O_2CH_3$), 168.2 (C(8)), 193.1 (C(6)); *m/z* ($[ESI]^+$) 448.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 426.1034, $C_{19}H_{24}NO_6S_2$ ($[M+H]^+$) requires 426.1040.

2.12.23. (2R,5S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 12ai



According to General Method F, mesylate **10a** (141 mg, 0.41 mmol) was reacted with 4-methoxyphenylboronic acid (93 mg, 0.74 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (0.8 mL, 7.38 mmol) in ethanol (0.17 mL, 2.87 mmol) and toluene (12 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (10.5 mg, 0.025 mmol) and $(C_6H_5CN)_2PdCl_2$ (7.9 mg, 0.021 mmol) in toluene (2 mL). Yield **12ai** 54% (78 mg); white solid, m. p. 148–150 °C; R_f (20% EtOAc in Petrol) 0.32; $[\alpha]_D^{25}$ +270.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2870 (C–H), 1744 (C=O), 1606 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 1.98 (3H, s, C(7)CH_3), 3.43 (1H, d, *J* 8.1, C(4)$\underline{H}_A H_B$), 3.49 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 4.70 (1H, s, C(2)H), 5.04 (1H, d, *J* 8.1, C(4)$H_A\underline{H}_B$), 6.88 (2H, d, *J* 8.5, C(3′)H), 7.16 (2H, d, *J* 8.5, C(2′)H); δ_C (100 MHz, $CDCl_3$): 10.7C(7)$\underline{C}H_3$, 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 55.4 ($O\underline{C}H_3$), 71.0 (C(4)), 77.2 (C(5)), 96.4 (C(2)), 114.4 (C(3′)), 123.5 (C(7)), 129.7 (C(2′)), 129.8 (C(1′)), 151.6 (C(6)), 160.5 (C(4')), 170.0 ($\underline{C}O_2CH_3$), 179.0 (C(8)); *m/z* ($[ESI]^+$) 360.2 ($[M+H]^+$, 40%), 382.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 360.1807, $C_{20}H_{26}NO_5$ ($[M+H]^+$) requires 360.1806.

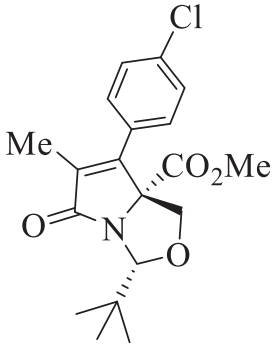
2.12.24. (2R,5S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxo-6-phenylbicyclo [3.3.0] oct-6-ene, 12aii



According to General Method F, mesylate **10a** (600 mg, 1.73 mmol) was reacted with phenylboronic acid (337 mg, 2.76 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (1.65 mL, 15.6 mmol) in ethanol (0.71 mL, 12.11 mmol) and toluene (15 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (44 mg, 0.1 mmol) and $(C_6H_5CN)_2PdCl_2$ (33 mg, 0.086 mmol) in toluene (3 mL). Yield **12aii** 33% (190 mg); white solid, m. p. 134–136 °C; R_f (20% EtOAc in Petrol) 0.42; $[\alpha]_D^{25}$ +250.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2870 (C–H), 1745 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 1.97 (3H, s, C(7)CH_3), 3.46 (1H, d, *J* 8.2, C(4)$\underline{H}_A H_B$), 3.49 (3H, s, CO_2CH_3), 4.72 (1H, s, C(2)H), 5.03 (1H, d, *J* 8.2, C(4)$H_A\underline{H}_B$), 7.13–7.40 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 10.6 (C(7)$\underline{C}H_3$), 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 71.1 (C(4)), 77.3 (C(5)), 96.5 (C(2)), 128.1–131.8 (C(7) + ArC), 151.9 (C(6)), 169.7

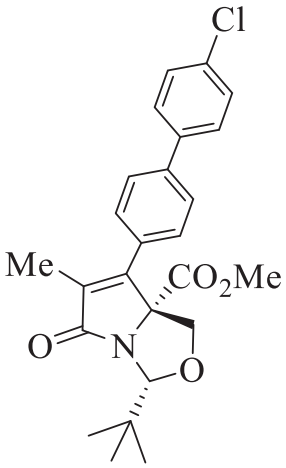
($\underline{C}O_2CH_3$), 178.7 (C(8)); *m/z* ([ESI]$^+$) 352.2 ([M+Na]$^+$, 60%); HRMS ([ESI]$^+$) found 352.1518, $C_{19}H_{23}NO_4Na$ ([M+Na]$^+$) requires 352.1519.

2.12.25. (2R,5S)-1-Aza-2-(tert-butyl)- 6-(4-chloroyphenyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 129aiii/12aiii



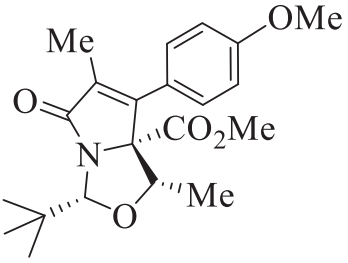
According to General Method F, mesylate **10a** (600 mg, 1.73 mmol) was reacted with 4-chlorophenylboronic acid (283 mg, 1.81 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (1.65 mL, 15.6 mmol) in ethanol (0.71 mL, 12.11 mmol) and toluene (15 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (44 mg, 0.1 mmol) and $(C_6H_5CN)_2PdCl_2$ (33 mg, 0.086 mmol) in toluene (3 mL). Yield **12aiii** 38% (237 mg); white solid, m. p. 120–122 °C; R_f (20% EtOAc in Petrol) 0.50; $[\alpha]_D^{25}$ +225.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2870 (C–H), 1745 (C=O), 1594 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 1.96 (3H, s, C(7)CH_3), 3.44 (1H, d, *J* 8.1, C(4)$\underline{H}_A\underline{H}_B$), 3.51 (3H, s, CO_2CH_3), 4.71 (1H, s, C(2)H), 5.00 (1H, d, *J* 8.1, C(4)$\underline{H}_A\underline{H}_B$), 7.11 (2H, d, *J* 8.3, C(2′)H), 7.34 (2H, d, *J* 8.3, C(3′)H); δ_C (100 MHz, $CDCl_3$): 10.6 (C(7)$\underline{C}H_3$), 24.7 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 70.9 (C(4)), 77.2 (C(5)), 96.5 (C(2)), 129.3 (C(2′)), 129.4 (C(3′)), 129.5 (C(7)), 132.4 (C(4′)), 135.9 (C(1')), 150.5 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 178.3 (C(8)); *m/z* ([ESI]$^+$) 386.2 ([M+Na]$^+$, 10%); HRMS ([ESI]$^+$) found 386.1127, $C_{19}H_{22}ClNO_4Na$ ([M+Na]$^+$) requires 386.1130.

2.12.26. (2R,5S)-1-Aza-2-(tert-butyl)-6-(4′-chloro-[1,1′-biphenyl]-4-yl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo [3.3.0] oct-6-ene, 16



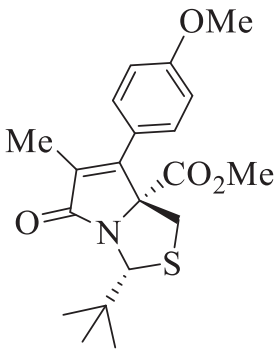
By-product: Yield 5% (36 mg); white solid, m. p. 110–112 °C; R_f (20% EtOAc in Petrol) 0.40; $[\alpha]_D^{25}$ +166.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C–H), 2869 (C–H), 1745 (C=O), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 2.02 (3H, s, C(7)CH_3), 3.48 (1H, d, *J* 8.1, C(4)$\underline{H}_A\underline{H}_B$), 3.52 (3H, s, CO_2CH_3), 4.73 (1H, s, C(2)H), 5.07 (1H, d, *J* 8.1, C(4)$\underline{H}_A\underline{H}_B$), 7.25–7.56 (8H, m ArH); δ_C (100 MHz, $CDCl_3$): 10.8 (C(7)$\underline{C}H_3$), 24.8 ($C(\underline{C}H_3)_3$), 35.3 ($\underline{C}(CH_3)_3$), 52.9 ($CO_2\underline{C}H_3$), 71.0 (C(4)), 77.2 (C(5)), 96.5 (C(2)), 127.4–141.5 (ArC + C(7)), 151.3 (C(6)), 169.8 ($\underline{C}O_2CH_3$), 178.6 (C(8)); *m/z* ([ESI]$^+$) 440.2 ([M+H]$^+$, 90%); HRMS ([ESI]$^+$) found 440.1623, $C_{25}H_{27}ClNO_4$ ([M+H]$^+$) requires 440.1623.

2.12.27. (2R,4S,5S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4,7-dimethyl-8-oxo-3-oxabicyclo [3.3.0] oct-6-ene, 12bi



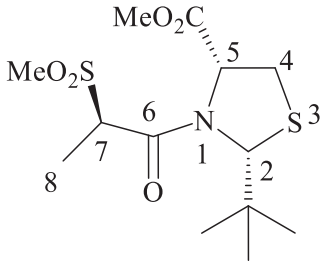
According to General Method F, mesylate **10b** (116 mg, 0.32 mmol) was reacted with 4-methoxyphenylboronic acid (78 mg, 0.51 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (0.3 mL, 2.88 mmol) in ethanol (0.3 mL, 2.88 mmol) and toluene (10 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (8.0 mg, 0.019 mmol) and $(C_6H_5CN)_2PdCl_2$ (6.0 mg, 0.016 mmol) in toluene (1 mL). Yield **12bi** 9% (11 mg); colorless oil; R_f (20% EtOAc in Petrol) 0.35; $[\alpha]_D^{25}$ -13.7 (*c* 0.7 in DCM); ν_{max}/cm^{-1} 2957 (C–H), 2934 (C–H), 1748 (C=O), 1708 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.47 (1H, d, *J* 6.5, C(4)CH_3), 1.83 (3H, s, C(7)CH_3), 3.54 (1H, q, *J* 6.5, C(4)H), 3.62 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 4.64 (1H, s, C(2)H), 6.87 (2H, d, *J* 8.5, C(3′)H), 7.03 (2H, d, *J* 8.5, C(2′)H); δ_C (100 MHz, $CDCl_3$): 10.5 (C(7)$\underline{C}H_3$), 15.1 (C(4)$\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 52.1 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 77.2 (C(5)), 80.2 (C(4)), 95.7 (C(2)), 114.3 (C(3′)), 124.1 (C(7)), 129.1 (C(2′)), 132.3 (C(1′)), 152.9 (C(6)), 160.2 (C(4')), 169.0 ($\underline{C}O_2CH_3$), 178.9 (C(8)); *m/z* ([ESI]$^+$) 374.2 ([M+H]$^+$, 90%), 382.2 ([M+Na]$^+$, 80%); HRMS ([ESI]$^+$) found 374.1964, $C_{21}H_{28}NO_5$ ([M+H]$^+$) requires 374.1962.

2.12.28. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-7-methyl-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 12ci



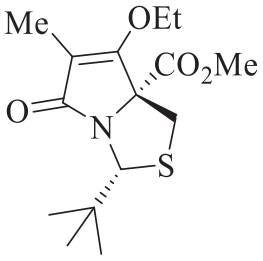
According to General Method F, mesylate **10c** (395 mg, 1.08 mmol) was reacted with 4-methoxyphenylboronic acid (263 mg, 1.73 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (1.03 mL, 9.72 mmol) in ethanol (0.44 mL, 7.56 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (28.0 mg, 0.065 mmol) and $(C_6H_5CN)_2PdCl_2$ (21.0 mg, 0.054 mmol) in toluene (2 mL). Yield **12ci** 23% (95 mg); colorless oil; R_f (20% EtOAc in Petrol) 0.28; $[\alpha]_D^{25}$ +289.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C−H), 2839 (C−H), 1745 (C=O), 1704 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.89 (3H, s, $C(7)CH_3$), 2.80 (1H, d, *J* 10.8, C(4) $\underline{H}_A H_B$), 3.52 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 3.81 (1H, d, *J* 10.8, $C(4)H_A\underline{H}_B$), 4.95 (1H, s, C(2)H), 6.86 (2H, d, *J* 8.5, C(3′)H), 7.17 (2H, d, *J* 8.5, C(2′)H); δ_C (100 MHz, $CDCl_3$): 10.6 ($C(7)\underline{C}H_3$), 26.7 ($C(\underline{C}H_3)_3$), 34.9 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 55.3 ($O\underline{C}H_3$), 71.0 (C(2)), 82.3 (C(5)), 114.3 (C(3′)), 123.5 (C(7)), 128.9 (C(1′)), 129.5 (C(2′)), 151.9 (C(6)), 160.3(C(4')), 169.9 ($\underline{C}O_2CH_3$), 176.5 (C(8)); *m/z* ($[ESI]^+$) 376.2 ($[M+H]^+$, 100%), 398.2 ($[M+Na]^+$, 90%); HRMS ($[ESI]^+$) found 376.1577, $C_{20}H_{26}NO_4S$ ($[M+H]^+$) requires 376.1577.

2.12.29. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-1-((R)-2-(methylsulfonyl)propanoyl)- 1,3-thiazolidine, 13



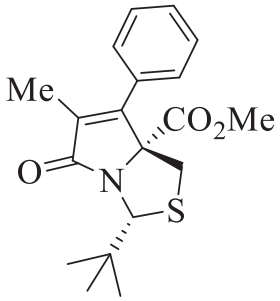
By-product: Yield **13** 2% (9 mg); yellow solid, m. p. 108−110 °C; R_f (40% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +63.4 (*c* 0.7 in DCM); ν_{max}/cm^{-1} 2958 (C−H), 1747 (C=O), 1655 (C=O); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $C(CH_3)_3$), 1.65 (3H, d, *J* 6.9, C(8)H_3), 2.92 (3H, s, SO_2CH_3), 3.34−3.42 (2H, m, $C(4)H_2$), 3.77 (3H, s, CO_2CH_3), 3.95 (1H, q, *J* 6.9, C(7)H), 5.37 (1H, dd, *J* 8.7, 7.1, C(5)H), 5.52 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 14.9 (C(8)), 26.9 ($C(\underline{C}H_3)_3$), 33.3 (C(4)), 36.8 ($SO_2\underline{C}H_3$), 39.5 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 63.3 (C(7)), 63.7 (C(5)), 72.9 (C(2)), 167.5 ($\underline{C}O_2CH_3$), 170.9 (C(6)); *m/z* ($[ESI]^+$) 338.1 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 338.1091, $C_{13}H_{24}NO_5S_2$ ($[M+H]^+$) requires 338.1090.

2.12.30. (2R,5R)-1-Aza-2-(tert-butyl)-6-ethoxy-5-methoxycarbonyl-7-methyl-8-oxo-3-thiabicyclo [3.3.0] oct-6-ene, 14a



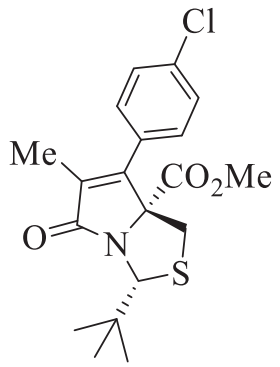
Yield 3% (11 mg); yellow semi-solid; R_f (20% EtOAc in Petrol) 0.25; $[\alpha]_D^{25}$ +124.2 (*c* 0.8 in DCM); ν_{max}/cm^{-1} 2956 (C−H), 2933 (C−H), 1749 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.88 (9H, s, $C(CH_3)_3$), 1.24 (3H, t, *J* 7.0, $OCH_2\underline{C}H_3$), 1.84 (3H, s, $C(7)\underline{C}H_3$), 2.65 (1H, d, *J* 11.1, $C(4)\underline{H}_A H_B$), 3.59 (1H, d, *J* 11.1, $C(4)H_A\underline{H}_B$), 3.70 (3H, s, CO_2CH_3), 4.21−4.30 (2H, m, $OC\underline{H}_2CH_3$), 4.87 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 8.7 ($C(7)\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$), 26.5 ($C(\underline{C}H_3)_3$), 33.9 (C(4)), 36.7 ($\underline{C}(CH_3)_3$), 53.0 ($CO_2\underline{C}H_3$), 67.5 ($O\underline{C}H_2CH_3$), 71.8 (C(2)), 79.0 (C(5)), 101.6 (C(7)), 166.6 ($\underline{C}O_2CH_3$), 169.3 (C(8)), 177.9 (C(6)); *m/z* ($[ESI]^+$) 314.1 ($[M+H]^+$, 45%); HRMS ($[ESI]^+$) found 314.1421, $C_{15}H_{24}NO_4S$ ($[M+H]^+$) requires 314.1421.

2.12.31. (2R,5R)-1-Aza-2-(tert-butyl)- 5-methoxycarbonyl-7-methyl-8-oxo-6-phenyl-3-thiabicyclo[3.3.0] oct-6-ene, 12cii



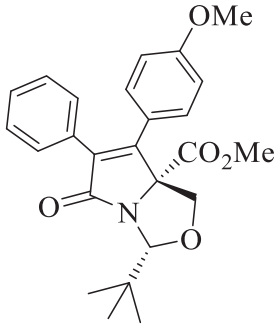
According to General Method F, mesylate **183c/10c** (309 mg, 0.85 mmol) was reacted with phenylboronic acid (166 mg, 1.36 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (0.81 mL, 7.65 mmol) in ethanol (0.34 mL, 5.95 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (21.7 mg, 0.051 mmol) and $(C_6H_5CN)_2PdCl_2$ (16.3 mg, 0.043 mmol) in toluene (2 mL). Yield **12cii** 23% (68 mg); colorless oil; R_f (20% EtOAc in Petrol) 0.50; $[\alpha]_D^{25}$ +325.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C−H), 2869 (C−H), 1746 (C=O), 1707 (C=O); δ_H (400 MHz, $CDCl_3$): 0.94 (9H, s, $C(CH_3)_3$), 1.87 (3H, s, $C(7)CH_3$), 2.83 (1H, d, *J* 10.8, $C(4)\underline{H}_A H_B$), 3.53 (3H, s, CO_2CH_3), 3.77 (1H, d, *J* 10.8, $C(4)H_A\underline{H}_B$), 4.95 (1H, s, C(2)H), 7.15−7.36 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$): 10.4 ($C(7)\underline{C}H_3$), 26.7 ($C(\underline{C}H_3)_3$), 34.7 (C(4)), 37.0 ($\underline{C}(CH_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 71.2 (C(2)), 82.4 (C(5)), 127.9−131.3 (ArC + C(7)), 152.2 (C(6)), 169.6 ($\underline{C}O_2CH_3$), 176.2 (C(8)); *m/z* ($[ESI]^+$) 346.2 ($[M+H]^+$, 100%), 368.2 ($[M+Na]^+$, 80%); HRMS ($[ESI]^+$) found 346.1471, $C_{19}H_{24}NO_3S$ ($[M+H]^+$) requires 346.1471.

*2.12.32. (2R,5R)-1-Aza-2-(tert-butyl)-6-(4-chloroyphenyl)-5-methoxycarbonyl-7-methyl-8-oxo-**3-thiabicyclo [3.3.0] oct-6-ene, 12ciii***



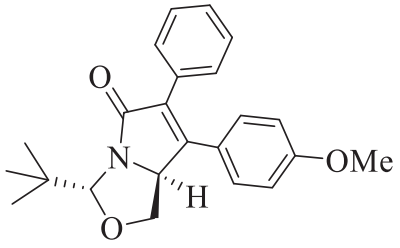
According to General Method F, mesylate **10c** (380 mg, 1.04 mmol) was reacted with 4-chlorophenylboronic acid (172 mg, 1.09 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (0.99 mL, 9.36 mmol) in ethanol (0.43 mL, 7.28 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (26.7 mg, 0.0624 mmol) and $(C_6H_5CN)_2PdCl_2$ (20.0 mg, 0.052 mmol) in toluene (2 mL). Yield **12ciii** 21% (84 mg); colorless oil; R_f (20% EtOAc in Petrol) 0.44; $[\alpha]_D^{25}$ +261.4 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2955 (C−H), 2871 (C−H), 1746 (C=O), 1707 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.86 (3H, s, C(7)CH_3), 2.80 (1H, d, *J* 10.8, C(4)H_AH_B), 3.54 (3H, s, CO_2CH_3), 3.75 (1H, d, *J* 10.8, C(4)H_AH_B), 4.94 (1H, s, C(2)H), 7.12 (2H, d, *J* 8.5, C(2′)H), 7.33 (2H, d, *J* 8.5, C(3′)H); δ_C (100 MHz, $CDCl_3$): 10.4 (C(7)CH_3), 26.7 (C(CH_3)$_3$), 34.7 (C(4)), 37.0 (C(CH_3)$_3$), 52.9 (CO_2CH_3), 71.2 (C(2)), 82.2 (C(5)), 129.3 (C(2′), C(3′)), 129.6 (C(7)), 131.0 (C(4′)), 135.7 (C(1')), 150.8 (C(6)), 169.4 (CO_2CH_3), 175.8 (C(8)); *m*/*z* ($[ESI]^+$) 380.0 ($[M+H]^+$, 100%), 402.0 ($[M+Na]^+$, 40%); HRMS ($[ESI]^+$) found 380.1082, $C_{19}H_{23}ClNO_3S$ ($[M+H]^+$) requires 380.1082.

2.12.33. (2R,5S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 12di



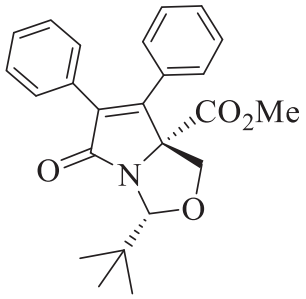
According to General Method F, mesylate **10d** (261 mg, 0.63 mmol) was reacted with 4-methoxyphenylboronic acid (172 mg, 1.13 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (1.2 mL, 11.34 mmol) in ethanol (0.26 mL, 4.41 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (16.1 mg, 0.038 mmol) and $(C_6H_5CN)_2PdCl_2$ (12.2 mg, 0.0315 mmol) in toluene (3 mL). Yield 30% (81 mg); white solid, m. p. 134−136 °C; R_f (30% EtOAc in Petrol) 0.40; $[\alpha]_D^{25}$ +150.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C−H), 2870 (C−H), 1746 (C=O), 1709 (C=O); δ_H (400 MHz, $CDCl_3$): 0.92 (9H, s, $C(CH_3)_3$), 3.51 (3H, s, CO_2CH_3), 3.59 (1H, d, *J* 8.1, C(4)H_AH_B), 3.72 (3H, s, OCH_3), 4.78 (1H, s, C(2)H), 5.12 (1H, d, *J* 8.1, C(4)H_AH_B), 6.72 (2H, d, *J* 8.9, C(3′)H), 7.01 (2H, d, *J* 8.5, C(2')H), 7.22−7.34 (5H, m, C(7)ArH); δ_C (100 MHz, $CDCl_3$): 24.8 (C(CH_3)$_3$), 35.4 (C(CH_3)$_3$), 53.0 (CO_2CH_3), 55.3 (OCH_3), 71.1 (C(4)), 77.1 (C(5)), 96.9 (C(2)), 114.3−152.2 (ArC + C(7)), 160.8 (C(6)), 169.7 (CO_2CH_3), 177.4 (C(8)); *m*/*z* ($[ESI]^+$) 422.2 ($[M+H]^+$, 50%); HRMS ($[ES]I^+$) found 444.1776, $C_{25}H_{27}NO_5Na$ ($[M+Na]^+$) requires 444.1781.

2.12.34. (2R,5S)-1-Aza-2-(tert-butyl)-6-(4-methoxyphenyl)-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] ***oct-6-ene, 15***



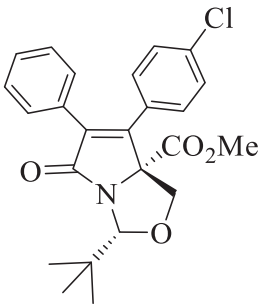
By-product: Colorless oil; R_f (20% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ -21.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2962 (C−H), 2869 (C−H), 1699 (C=O), 1606 (C=O); δ_H (400 MHz, $CDCl_3$): 0.97 (9H, s, $C(CH_3)_3$), 3.30 (1H, dd, *J* 9.6, 8.0, C(4)H_AH_B), 3.73 (3H, s, OCH_3), 4.33 (1H, d, *J* 8.0, 6.2, C(4)H_AH_B), 4.75 (1H, d, *J* 9.6, 6.2, C(5)H), 4.87 (1H, s, C(2)H), 6.73 (2H, d, *J* 8.9, C(3′)H), 7.14 (2H, d, *J* 8.9, C(2')H), 7.23−7.38 (5H, m, C(7)ArH); δ_C (100 MHz, $CDCl_3$): 24.8 (C(CH_3)$_3$), 36.0 (C(CH_3)$_3$), 55.3 (CO_2CH_3), 65.1 (C(5)), 70.0 (C(4)), 94.7 (C(2)), 114.3−151.6 (ArC + C(7)), 160.7 (C(6)), 176.4 (C(8)); *m*/*z* ($[ESI]^+$) 464.2 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 364.1908, $C_{23}H_{26}NO_3$ ($[M+H]^+$) requires 364.1907.

2.12.35. (2R,5S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-3-oxa-8-oxo-6,7-diphenylbicyclo [3.3.0] oct-6-ene, 12dii



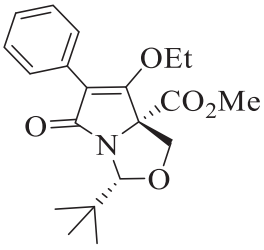
According to General Method F, mesylate **10d** (525 mg, 1.28 mmol) was reacted with phenylboronic acid (250 mg, 2.05 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (1.22 mL, 11.52 mmol) in ethanol (0.52 mL, 8.96 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (32.7 mg, 0.077 mmol) and $(C_6H_5CN)_2PdCl_2$ (24.5 mg, 0.064 mmol) in toluene (3 mL). Yield **12dii** 9% (46 mg); white solid, m. p. 158−160 °C; R_f (30% EtOAc in Petrol) 0.38; $[\alpha]_D^{25}$ +152.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C−H), 2870 (C−H), 1747 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 3.50 (3H, s, CO_2CH_3), 3.62 (1H, d, *J* 8.2, C(4)H_AH_B), 4.80 (1H, s, C(2)H), 5.10 (1H, d, *J* 8.2, C(4)H_AH_B), 7.00−7.34 (10H, m, C(6)Ph + C(7)Ph); δ_C (100 MHz, $CDCl_3$): 24.8 (C(CH_3)$_3$), 35.4 (C(CH_3)$_3$), 52.9 (CO_2CH_3), 71.0 (C(4)), 77.3 (C(5)), 97.1 (C(2)), 128.8 (C(7)), 128.4−133.8 (ArC), 152.4 (C(6)), 169.4 (CO_2CH_3),177.1 (C(8)); *m*/*z* ($[ESI]^+$) 392.2 ($[M+H]^+$, 10%); 414.2 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 392.1856, $C_{24}H_{26}NO_4$ ($[M+H]^+$) requires 392.1856.

2.12.36. (2R,5S)-1-Aza-2-(tert-butyl)-6-(4-chloroyphenyl)-5-methoxycarbonyl-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 12diii



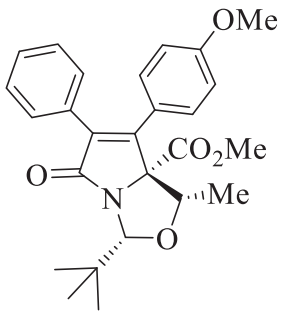
According to General Method F, mesylate **10d** (536 mg, 1.3 mmol) was reacted with 4-chlorophenylboronic acid (215 mg, 1.364 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (1.2 mL, 11.7 mmol) in ethanol (0.5 mL, 9.1 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (33.0 mg, 0.078 mmol) and $(C_6H_5CN)_2PdCl_2$ (25.0 mg, 0.065 mmol) in toluene (3 mL). Yield **12diii** 5% (28 mg); colorless oil; R_f (20% EtOAc in Petrol) 0.53; $[\alpha]_D^{25}$ +124.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C−H), 2870 (C−H), 1747 (C═O), 1711 (C═O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 3.52 (3H, s, CO_2CH_3), 3.60 (1H, d, *J* 8.1, C(4)H_AH_B), 4.79 (1H, s, C(2)H), 5.08 (1H, d, *J* 8.1, C(4)H_AH_B), 6.99 (2H, d, *J* 8.6, C(2′)H), 7.20 (2H, d, *J* 8.6, C(3')H), 7.24−7.30 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 24.8 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 53.1 (CO_2CH_3), 71.0 (C(4)), 77.1 (C(5)), 97.1 (C(2)), 128.5 (C(7)), 129.1−136.1 (ArC), 150.9 (C(6)), 169.3 (CO_2CH_3),176.7 (C(8)); *m/z* ($[ESI]^+$) 426.2 ($[M+H]^+$, 70%), 448.1 ($[M+Na]^+$, 60%); HRMS ($[ESI]^+$) found 426.1465, $C_{24}H_{25}ClNO_4$ ($[M+H]^+$) requires 426.1467.

2.12.37. (2R,5R)-1-Aza-2-(tert-butyl)-6-ethoxy-5-methoxycarbonyl-3-oxa-8-oxo-7-phenylbicyclo [3.3.0] oct-6-ene, 14b



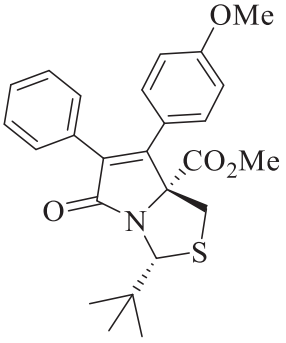
By-product: Yield 4−5% (23 mg); colorless oil; R_f (20% EtOAc in Petrol) 0.45; $[\alpha]_D^{25}$ +142.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C−H), 2870 (C−H), 1747 (C═O), 1708 (C═O); δ_H (400 MHz, $CDCl_3$): 0.87 (9H, s, $C(CH_3)_3$), 1.13 (3H, t, *J* 7.0, OCH_2CH_3), 3.48 (1H, d, *J* 8.4, C(4)H_AH_B), 3.75 (3H, s, CO_2CH_3), 3.78 (1H, dd, *J* 9.8, 7.0, $OCH_AH_BCH_3$), 3.99 (1H, dd, *J* 9.8, 7.0, $OCH_AH_BCH_3$), 4.71 (1H, s, C(2)H), 4.85 (1H, d, *J* 8.4, C(4)H_AH_B), 7.23−7.50 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 15.0 (OCH_2CH_3), 24.7 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 53.0 (CO_2CH_3), 69.1 (OCH_2CH_3), 70.0 (C(4)), 74.0 (C(5)), 97.0 (C(2)), 111.0 (C(7)), 128.1−129.9 (ArC), 167.6 (CO_2CH_3), 169.2 (C(8)), 177.7 (C(6)); *m/z* ($[ESI]^+$) 360.2 ($[M+H]^+$, 40%); HRMS ($[ESI]^+$) found 360.1806, $C_{20}H_{26}NO_5$ ($[M+H]^+$) requires 360.1806.

2.12.38. (2R,4S,5S)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-4-methyl-3-oxa-8-oxo-7-phenylbicyclo[3.3.0] oct-6-ene, 12ei



According to General Method F, mesylate **10e** (230 mg, 0.54 mmol) was reacted with 4-methoxyphenylboronic acid (89 mg, 0.58 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (1.0 mL, 9.32 mmol) in ethanol (0.22 mL, 3.78 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (13.8 mg, 0.032 mmol) and $(C_6H_5CN)_2PdCl_2$ (10.3 mg, 0.027 mmol) in toluene (1 mL). Yield **12ei** 7% (17 mg); yellow semi-solid; R_f (20% EtOAc in Petrol) 0.42; $[\alpha]_D^{25}$ +4.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2958 (C−H), 2870 (C−H), 1749 (C═O), 1705 (C═O); δ_H (400 MHz, $CDCl_3$): 0.93 (9H, s, $C(CH_3)_3$), 1.53 (3H, d, *J* 6.5, $C(4)CH_3$), 3.66 (3H, s, CO_2CH_3), 3.67−3.71 (1H, m, C(4)H), 3.73 (3H, s, OCH_3), 4.76 (1H, s, C(2)H), 6.75 (2H, d, *J* 8.8, C(3′)H), 6.96 (2H, d, *J* 8.8, C(2')H), 7.18−7.37 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 15.2 ($C(4)CH_3$), 25.1 ($C(CH_3)_3$), 35.3 ($C(CH_3)_3$), 52.3 (CO_2CH_3), 55.3 (OCH_3), 80.3 (C(4)), 92.1 (C(5)), 96.0 (C(2)), 114.3−130.8 (ArC), 160.3 (C(6)), 168.8 (CO_2CH_3), 176.9(C(8)); *m/z* ($[ESI]^+$) 458.2 ($[M+Na]^+$, 70%); HRMS ($[ESI]^+$) found 458.1941, $C_{26}H_{29}NO_5Na$ ($[M+Na]^+$) requires 458.1938.

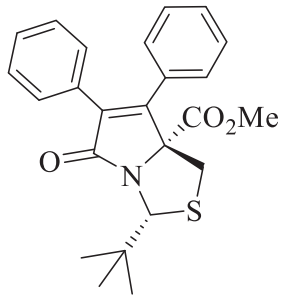
2.12.39. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-6-(4-methoxyphenyl)-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 12fi



According to General Method F, mesylate **10f** (303 mg, 0.71 mmol) was reacted with 4-methoxyphenylboronic acid (195 mg, 1.28 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (0.67 mL, 6.4 mmol) in ethanol (0.3 mL, 4.97 mmol) and toluene (13 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (18.1 mg, 0.043 mmol) and $(C_6H_5CN)_2PdCl_2$ (13.6 mg, 0.035 mmol) in toluene (2 mL). Yield **12fi** 23% (72 mg); white solid, m. p. 152−154 °C; R_f (20% EtOAc in Petrol) 0.36; $[\alpha]_D^{25}$ +313.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C−H), 2906 (C−H), 1745 (C═O), 1702 (C═

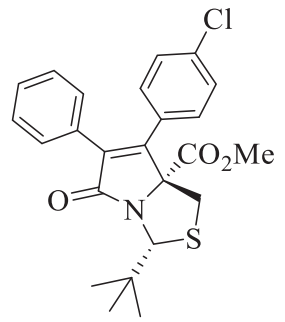
O); δ_H (400 MHz, $CDCl_3$): 0.97 (9H, s, $C(CH_3)_3$), 2.94 (1H, d, *J* 10.8, C(4)H_AH_B), 3.54 (3H, s, CO_2CH_3), 3.72 (3H, s, OCH_3), 3.87 (1H, d, *J* 10.8, C(4)H_AH_B), 5.03 (1H, s, C(2)H), 6.72 (2H, d, *J* 8.8, C(3′)H), 7.05 (2H, d, *J* 8.8, C(2')H), 7.19–7.32 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 26.7 ($C(CH_3)_3$), 34.9 (C(4)), 37.0 ($C(CH_3)_3$), 52.9 (CO_2CH_3), 55.3 (OCH_3), 71.6 (C(2)), 82.0 (C(5)), 123.4 (C(7)), 114.3, 128.3–152.5 (ArC), 160.5 (C(6)), 169.6 (CO_2CH_3), 174.8(C(8)); *m/z* ($[ESI]^+$) 438.2 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 438.1725, $C_{25}H_{28}NO_4S$ ($[M+H]^+$) requires 438.1734.

2.12.40. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-8-oxo-6,7-diphenyl-3-thiabicyclo [3.3.0] oct-6-ene, 12fii



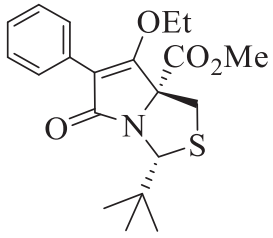
According to General Method F, mesylate **10f** (624 mg, 1.46 mmol) was reacted with phenylboronic acid (462 mg, 3.8 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (2.4 mL, 22.63 mmol) in ethanol (0.59 mL, 10.2 mmol) and toluene (15 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (37.5 mg, 0.088 mmol) and $(C_6H_5CN)_2PdCl_2$ (28.1 mg, 0.073 mmol) in toluene (2 mL). Yield **12fii** 56% (222 mg); white solid, m. p. 180–182 °C; R_f (20% EtOAc in Petrol) 0.46; $[\alpha]_D^{25}$ +321.8 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C–H), 2906 (C–H), 1747 (C=O), 1707 (C=O); δ_H (400 MHz, $CDCl_3$): 0.98 (9H, s, $C(CH_3)_3$), 2.96 (1H, d, *J* 10.8, C(4)H_AH_B), 3.55 (3H, s, CO_2CH_3), 3.83 (1H, d, *J* 10.8, C(4)H_AH_B), 5.04 (1H, s, C(2)H), 7.04–7.33 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.8 ($C(CH_3)_3$), 34.8 (C(4)), 37.1 ($C(CH_3)_3$), 52.9 (CO_2CH_3), 71.7 (C(2)), 82.2 (C(5)), 128.7 (C(7)), 128.2, 128.3, 129.6–132.1 (ArC), 152.7 (C(6)), 169.3 (CO_2CH_3),174.5 (C(8)); *m/z* ($[ESI]^+$) 408.2 ($[M+H]^+$, 50%); HRMS ($[ESI]^+$) found 408.1626, $C_{24}H_{26}NO_3S$ ($[M+H]^+$) requires 408.1628.

2.12.41. (2R,5R)-1-Aza-2-(tert-butyl)-6-(4-chloroyphenyl)-5-methoxycarbonyl-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 12fiii



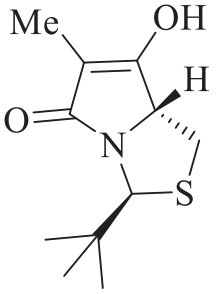
According to General Method F, mesylate **187c/10f** (624 mg, 1.46 mmol) was reacted with 4-chlorophenylboronic acid (240 mg, 1.53 mmol), $PdCl_2$(dppb), 1M aqueous Na_2CO_3 solution (2.4 mL, 22.63 mmol) in ethanol (0.59 mL, 10.2 mmol) and toluene (15 mL). $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (37.5 mg, 0.088 mmol) and $(C_6H_5CN)_2PdCl_2$ (28.1 mg, 0.073 mmol) in toluene (2 mL). Yield **12cfiii** 9% (59 mg); white solid, m. p. 128–130 °C; R_f (20% EtOAc in Petrol) 0.60; $[\alpha]_D^{25}$ +262.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2954 (C–H), 2829 (C–H), 1747 (C=O), 1706 (C=O); δ_H (400 MHz, $CDCl_3$): 0.97 (9H, s, $C(CH_3)_3$), 2.94 (1H, d, *J* 10.8, C(4)H_AH_B), 3.56 (3H, s, CO_2CH_3), 3.82 (1H, d, *J* 10.8, C(4)H_AH_B), 5.03 (1H, s, C(2)H), 7.03 (2H, d, *J* 8.6, C(2′)H), 7.18–7.29 (7H, m, C(3')H) + C(7)Ph); δ_C (100 MHz, $CDCl_3$): 26.7 ($C(CH_3)_3$), 34.8 (C(4)), 37.1 ($C(CH_3)_3$), 53.0 (CO_2CH_3), 71.7 (C(2)), 82.0 (C(5)), 128.4–132.7 (ArC), 135.8 (C(7)), 151.1 (C(6)), 169.2 (CO_2CH_3), 174.2 (C(8)); *m/z* ($[ESI]^+$) 442.2 ($[M+H]^+$, 45%), 464.0 ($[M+Na]^+$, 100%); HRMS ($[ESI]^+$) found 442.1239, $C_{24}H_{25}ClNO_3S$ ($[M+H]^+$) requires 442.1238.

2.12.42. (2R,5R)-1-Aza-2-(tert-butyl)-6-ethoxy-5-methoxycarbonyl-8-oxo-7-phenyl-3-thiabicyclo [3.3.0] oct-6-ene, 14d



By-product: Yield 5% (13 mg); yellow oil; R_f (20% EtOAc in Petrol) 0.39; $[\alpha]_D^{25}$ +195.2 (*c* 0.9 in DCM); ν_{max}/cm^{-1} 2956 (C–H), 2931 (C–H), 1749 (C=O), 1708 (C=O); δ_H (400 MHz, $CDCl_3$): 0.91 (9H, s, $C(CH_3)_3$), 1.07 (3H, t, *J* 7.0, OCH_2CH_3), 2.82 (1H, d, *J* 11.1, C(4)H_AH_B), 3.69 (1H, d, *J* 11.1, C(4)H_AH_B), 3.75 (3H, s, CO_2CH_3), 3.80 (1H, dd, *J* 10.1, 7.0, $OCH_AH_BCH_3$), 3.94 (1H, dd, *J* 10.1, 7.0, $OCH_AH_BCH_3$), 4.96 (1H, s, C(2)H), 7.23–7.39 (5H, m, C(7)Ph); δ_C (100 MHz, $CDCl_3$): 13.9 (OCH_2CH_3), 25.5 ($C(CH_3)_3$), 33.0 (C(4)), 35.6 ($C(CH_3)_3$), 52.1 (CO_2CH_3), 68.1 (OCH_2CH_3), 71.1 (C(2)), 77.9 (C(5)), 107.3 (C(7)), 127.0–129.2 (ArC), 166.4 (CO_2CH_3), 168.1 (C(8)),174.9(C(6)); *m/z* ($[ESI]^+$) 376.2 ($[M+H]^+$, 55%); HRMS ($[ESI]^+$) found 376.1580, $C_{20}H_{26}NO_4S$ ($[M+H]^+$) requires 376.1577.

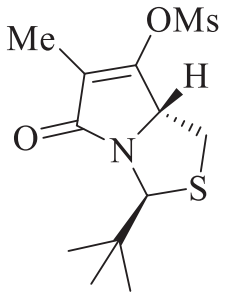
2.12.43. (2S,5R)-1-Aza-2-(tert-butyl)-6-hydroxy-7-methyl-8-oxo-3-thiabicyclo[3.3.0] octane, 19a



According to General Method M, KO^{t}Bu (260 mg, 2.1 mmol) was reacted with a solution of thiazolidine **18** (700 mg, 2.31 mmol) in THF (0.2 M) which gave tetramic acid **19a**. Quantitative yield (543 mg); white solid, m. p. 191–193 °C; $[\alpha]_D^{25}$ -200.7 (*c* 1.0 in

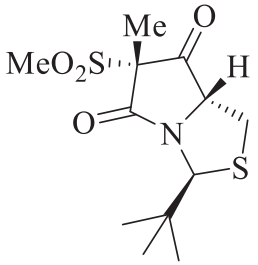
DMSO-d_6); δ_H (400 MHz, DMSO-d_6): 0.92 (9H, s, C$(CH_3)_3$), 1.52 (3H, s, C(7)CH_3), 2.57 (1H, dd, *J* 10.6, 8.9, C(4)$\underline{H}_A H_B$), 3.16 (1H, dd, *J* 10.6, 6.9, C(4)$H_A\underline{H}_B$), 4.40 (1H, t, *J* 7.9, C(5)H), 4.77 (1H, s, C(2)H); δ_C (100 MHz, DMSO-d_6): 6.6 (C(7)$\underline{C}H_3$), 26.6 (C$(\underline{C}H_3)_3$), 32.8 (C(4)), 37.4 ($\underline{C}(CH_3)_3$), 66.9 (C(5)), 69.6 (C(2)), 99.2 (C(7)), 169.2 (C(8)), 176.8 (C(6)); *m*/*z* ($[ESI]^+$) 226.1 ($[M-H]^-$, 100%); HRMS ($[ESI]^+$) found 226.0905, $C_{11}H_{16}NO_2S$ ($[M-H]^-$) requires 226.0907.

2.12.44. (2S,5R)-1-Aza-2-(tert-butyl)-7-methyl-6-((methylsulfonyl) oxy)-8-oxo-3-thiabicyclo[3.3.0] oct-6-ene, 19b



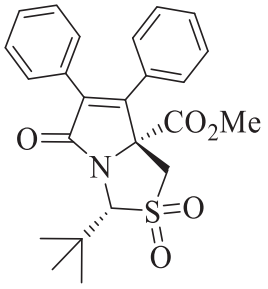
According to General Method E, reaction of tetramic acid **19a** (551 mg, 1.9 mmol) with MsCl (0.15 mL, 1.9 mmol) and DIPEA (0.66 mL, 3.8 mmol) in DCM (0.1 M) gave mesylate **19b.** Yield 18% (104 mg); yellow oil; R_f (40% EtOAc in Petrol) 0.32; $[\alpha]_D^{25}$ -203.9 (*c* 1.0 in DCM); ν_{max}/cm^{-1}2967 (C–H), 1705 (C=O); δ_H (400 MHz, $CDCl_3$): 0.95 (9H, s, C$(CH_3)_3$), 1.77 (3H, s, C(7)CH_3), 2.52–2.64 (1H, m, C(4) $\underline{H}_A H_B$), 3.08 (1H, dd, *J* 10.7, 6.0, C(4)$H_A\underline{H}_B$), 3.21 (3H, s, OSO_2CH_3), 4.65–4.73 (1H, s, C(5)H), 4.91 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 6.7(C(7)$\underline{C}H_3$), 25.3 (C$(\underline{C}H_3)_3$), 31.6 (C(4)), 36.4 ($\underline{C}(CH_3)_3$), 38.0 (OSO_2CH_3), 65.9 (C(5)), 67.8 (C(2)), 120.0 (C(7)), 155.4 (C(8)), 170.4 (C(6)); *m*/*z* ($[ESI]^+$) 306.0 ($[M+H]^+$, 100%); HRMS ($[ESI]^+$) found 306.0828, $C_{12}H_{20}NO_4S_2$ ($[M+H]^+$) requires 306.0828.

2.12.45. (2S,5R,7R)-1-Aza-2-(tert-butyl)-7-methyl-7-(methylsulfonyl)-8-oxo-3-thiabicyclo ***[3.3.0] oct-6-ene, 20***



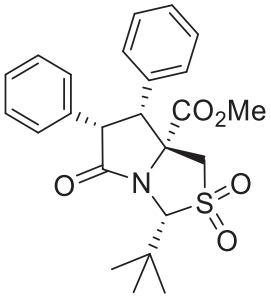
By-product: Yield 9% (52 mg); yellow oil; R_f (40% EtOAc in Petrol) 0.40; δ_H (400 MHz, $CDCl_3$): 1.08 (9H, s, C$(CH_3)_3$), 1.72 (3H, s, C(7)CH_3), 2.88 (1H, t, *J* 10.1, C(4)$\underline{H}_A H_B$), 3.05 (3H, s, SO_2CH_3), 3.28–3.35 (1H, m, C(4)$H_A\underline{H}_B$), 4.83 (1H, dd, *J* 9.5, 7.5, C(5)H), 5.33 (1H, s, C(2)H); δ_C (100 MHz, $CDCl_3$): 14.1 (C(7)$\underline{C}H_3$), 26.2 (C$(\underline{C}H_3)_3$), 32.6 (C(4)), 37.5 ($\underline{C}(CH_3)_3$), 38.7 (SO_2CH_3).

2.12.46. (2R,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-8-oxa-6,7-diphenyl-3-thiabicyclo[3.3.0]-oct-6-ene 3,3-dioxide, 21



A solution of **12fii** (148 mg, 0.36 mmol) in $CHCl_3$ (4.0 mL) was cooled to 0 °C and the solution of *m*-chloroperbenzoic acid (188 mg, 1.08 mmol) in $CHCl_3$ (7 mL) was added dropwise to this solution. The reaction mixture was stirred at room temperature for 30 h. After completion, the mixture was poured into EtOAc (30 mL) and the resultant solution was washed with sat. aq. solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to get crude sulfone. Purification by flash column chromatography using 20% EtOAc in Petroleum ether gave sulfone **201/21**. Yield 93% (149 mg); white solid, m. p. 62–64 °C; R_f (20% EA in PE) 0.30; $[\alpha]_D^{25}$ +163.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2980 (C–H), 2913 (C–H), 1750 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$): 1.15 (9H, s, C$(CH_3)_3$), 3.32 (1H, d, *J* 13.4, C(4)$\underline{H}_A H_B$), 3.65 (3H, s, CO_2CH_3), 4.30 (1H, d, *J* 13.4, C(4)$H_A\underline{H}_B$), 4.77 (1H, s, C(2)H), 7.02–7.35 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$): 26.4 (C$(\underline{C}H_3)_3$), 35.9 ($\underline{C}(CH_3)_3$), 53.9 ($CO_2\underline{C}H_3$), 54.2 (C(4)), 72.1 (C(5)), 82.6 (C(2)), 128.2–130.7 (ArC), 133.6 (C(7)), 154.1 (C(6)), 168.1 ($\underline{C}O_2CH_3$), 174.4 (C(8)); *m*/*z* ($[ESI]^+$) 462.1 ($[M+Na]^+$, 45%); HRMS ($[ESI]^+$) found 462.1342, $C_{24}H_{25}O_5NSNa$ ($[M+Na]^+$) requires 462.1346.

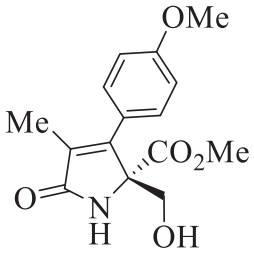
2.12.47. (2R,6R,7S,5R)-1-Aza-2-(tert-butyl)-5-methoxycarbonyl-8-oxo-6,7-diphenyl-3-thiabicyclo [3.3.0]-octane 3,3-dioxide, 22



According to General Method G, a solution of lactam **21** (29 mg, 0.065 mmol) in EtOAc (10 mL), platinum(IV) oxide (2.2 mg, 0.00975 mmol) was added. The reaction mixture was stirred at room temperature under H_2 atmosphere for 43 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 resulted pure product **22**. Yield 41% (12 mg); white solid; m. p. 55 °C. R_f (20% EA in PE) 0.28; $[\alpha]_D^{25}$ +11.7 (*c* 0.5 in DCM); ν_{max}/cm^{-1} 2980 (C–H), 2970 (C–H), 1748 (C=O), 1720 (C=O); δ_H (500 MHz, $CDCl_3$): 1.27 (9H, s, C$(CH_3)_3$), 3.42 (3H, s, CO_2CH_3), 3.44 (1H, d, *J* 14.7, C(4)$\underline{H}_A H_B$), 3.68 (1H, d, *J* 14.7, C(4)$H_A\underline{H}_B$), 4.14 (1H, d, *J* 10.7, C(7)H), 4.36 (1H, d, *J* 10.7, C(6)H), 4.99 (1H, s, C(2) H), 6.51–7.30 (10H, m, ArH); δ_C (125 MHz, $CDCl_3$): 26.4 (C$(\underline{C}H_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 52.6, 52.7 (C(6), $CO_2\underline{C}H_3$), 55.3 (C(4)), 58.1 (C(7)),

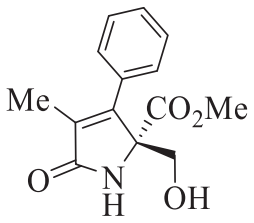
71.9 (C(5)), 82.0 (C(2)), 127.6–134.6 (ArC), 170.6 ($\underline{C}O_2CH_3$), 178.7 (C(8)); *m/z* ($[ESI]^+$) 442.2 ($[M+H]^+$, 10%); HRMS (ESI^+) found 442.1682, $C_{24}H_{28}O_5NS$ $[M+H]^+$) requires 442.1683.

2.12.48. Methyl(S)-2-(hydroxymethyl)-3-(4-methoxyphenyl)-4-methyl-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxylate, 17a



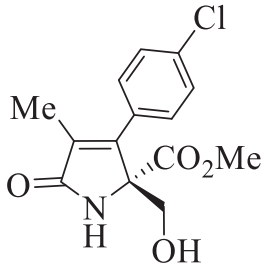
According to General Method I, pyrrolinone **12ai** (34 mg, 0.0946 mmol) was treated with propane-1,3-dithiol (0.04 mL, 0.38 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.58 mL). Successive workup gave *N,O*-acetal deprotected amide **17a**. Yield 99% (27 mg); colorless oil; $[\alpha]_D^{25}$ +20.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3349 (O–H), 2954 (C–H), 2840 (C–H), 1737 (C=O), 1691 (C=O); δ_H (500 MHz, MeOD): 1.80 (3H, s, C(4)CH_3, 3.72 (3H, s, $CO_2C\underline{H}_3$), 3.77 (1H, d, *J* 11.4, C(6)$\underline{H}_AH_B$), 3.84 (3H, s, OCH_3), 4.10 (1H, d, *J* 11.4, C(6)$H_A\underline{H}_B$), 7.00 (2H, d, *J* 8.8, C(3′)H), 7.13 (2H, d, *J* 8.8, C(2′)H); δ_C (125 MHz, MeOD): 8.5 (C(4)$\underline{C}H_3$), 51.9 ($CO_2\underline{C}H_3$), 54.4 ($O\underline{C}H_3$), 62.4 (C(6)), 72.4 (C(2)), 113.7 (C(3′)), 124.1 (C(4)), 129.4 (C(2′)), 132.2 (C(1′)), 151.1 (C(3)), 160.2 (C(4′)), 169.7 ($\underline{C}O_2CH_3$), 175.6 (C(5)); *m/z* ($[ESI]^+$) 292.0 ($[M+H]^+$, 100%), 314.0 ($[M+Na]^+$, 80%); HRMS (ESI^+) found 292.1180, $C_{15}H_{18}NO_5$ ($[M+H]^+$) requires 292.1180.

2.12.49. Methyl(S)-2-(hydroxymethyl)-4-methyl-5-oxo-3-phenyl-2,5-dihydro-1H-pyrrole-2-carboxylate, 17b



According to General Method I, pyrrolinone **12aii** (44 mg, 0.13 mmol) was treated with propane-1,3-dithiol (0.05 mL, 0.52 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (2.17 mL). Successive workup gave *N,O*-acetal deprotected amide **17b**. Yield 90% (31 mg); yellow oil; $[\alpha]_D^{25}$ +32.5 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3306 (O–H), 2953 (C–H), 2925 (C–H), 1738 (C=O), 1695 (C=O); δ_H (500 MHz, MeOD): 1.78 (3H, s, C(4)CH_3, 3.71 (3H, s, $CO_2C\underline{H}_3$), 3.78 (1H, d, *J* 11.4, C(6)$\underline{H}_AH_B$), 4.09 (1H, d, *J* 11.4, C(6)$H_A\underline{H}_B$), 7.18–7.46 (5H, m, ArH); δ_C (125 MHz, MeOD): 8.3 (C(4)$\underline{C}H_3$), 51.9 ($CO_2\underline{C}H_3$), 62.4 (C(6)), 72.6 (C(2)), 128.0–133.0 (ArC + C(4)), 151.2 (C(3)), 169.4 ($\underline{C}O_2CH_3$), 175.3 (C(5)); *m/z* ($[ESI]^+$) 262.0 ($[M+H]^+$, 100%), 284.0 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 262.1074, $C_{14}H_{16}NO_4$ ($[M+H]^+$) requires 262.1074.

2.12.50. Methyl(S)-3-(4-chlorophenyl)-2-(hydroxymethyl)-4-methyl-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxylate, 17c



According to General Method I, pyrrolinone **12aiii** (41 mg, 0.11 mmol) was treated with propane-1,3-dithiol (0.04 mL, 0.44 mmol) followed by a freshly prepared 1.5% solution of HCl in 2,2,2-trifluoroethanol (1.8 mL). Successive workup gave *N,O*-acetal deprotected amide **17c**. Yield 89% (29.8 mg); colorless oil; $[\alpha]_D^{25}$ +36.0 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3343 (O–H), 2953 (C–H), 2855 (C–H), 1738 (C=O), 1695 (C=O); δ_H (500 MHz, MeOD): 1.78 (3H, s, C(4)CH_3, 3.71 (3H, s, $CO_2C\underline{H}_3$), 3.80 (1H, d, *J* 11.4, C(6)$\underline{H}_AH_B$), 4.07 (1H, d, *J* 11.4, C(6)$H_A\underline{H}_B$), 7.19 (2H, d, *J* 8.5, C(2′)H), 7.47 (2H, d, *J* 8.5, C(3′)H); δ_C (125 MHz, MeOD): 8.3 (C(4)$\underline{C}H_3$), 51.9 ($CO_2\underline{C}H_3$), 62.2 (C(6)), 72.6 (C(2)), 128.5 (C(3′)), 128.9 (C(4)), 129.7 (C(2′)), 130.9 (C(4′)), 134.6 (C(1')), 149.8 (C(3)), 169.3 ($\underline{C}O_2CH_3$), 175.0 (C(5)); *m/z* ($[ESI]^+$) 296.0 ($[M+H]^+$, 100%), 318.0 ($[M+Na]^+$, 20%); HRMS ($[ESI]^+$) found 296.0684, $C_{14}H_{15}ClNO_4$ ($[M+H]^+$) requires 296.0684.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.130561.

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[15] 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'[33] before refinement with CRYSTALS[34,35] as per the SI (CIF). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1939246–1939258) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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