



Cite this: DOI: 10.1039/c6ob00557h

Chemoselectivity and stereoselectivity of cyclisation pathways leading to bicyclic tetramates controlled by ring-chain tautomerisation in thiazolidines†

Tharindi D. Panduwawala, Sarosh Iqbal, Rémi Tirfoin and Mark G. Moloney*

Received 14th March 2016,
Accepted 12th April 2016

DOI: 10.1039/c6ob00557h

www.rsc.org/obc

Chemoselective Dieckmann cyclisation reactions on *N*-malonyl thiazolidine templates derived from cysteine and pivaldehyde or aromatic aldehydes may be used to access bicyclic tetramates, for which different pathways operate as a result of differing ring-chain tautomeric behaviour of the respective intermediate imines.

The tetramate system occurs as a scaffold in natural products which exhibit a wide range of bioactivities,^{1,2} and we have previously established that Dieckmann cyclisation of oxazolidine/thiazolidine templates **2a–c** derived from pivaldehyde and serine **1a**,³ threonine **1b**⁴ or cysteine **1c**⁵ respectively may be used to generate enantiopure tetramates **3a–c** (Scheme 1). Although this key cyclisation is highly chemo-, diastereo- and enantioselective, it has been limited to the use of pivaldehyde as the initial condensing species, since this both gives relatively stable oxazolidine/thiazolidine intermediates **2a–c** and makes for a system in which the bulky *t*-butyl group exerts strong steric influence in a ring-chain tautomeric equilibrium which strongly favours the ring form.⁵ We examined the Dieckmann cyclisation process in detail, and found that ring closure occurred from the predominantly formed *cis*-acyloxazolidines **2a,b**, in which closure from the C-5 enolate onto the ethyl ester giving **3a–c** is preferred (Scheme 1, Route a), placing the C-2 *t*-butyl group on the *exo*-face (that is, less hindered convex face) of the newly generated bicyclic ring system;^{3,6} this is a cyclic example of the Self Regeneration of Stereocentres concept developed extensively by Seebach.⁷ An alternative mode of cyclisation, starting from the *trans*-acyloxazolidines **4a,b** (which arise only as a very minor intermediate by epimerisation at C-5 under the basic conditions of the cyclisation reaction) by closure of the more stabilised malonamide side chain enolate onto the C-5 ester (Scheme 1, Route b), and also placing the C-2 *t*-Bu group on the *exo*-face, generates the alternative tetramates **5a,b** as minor products. Although we

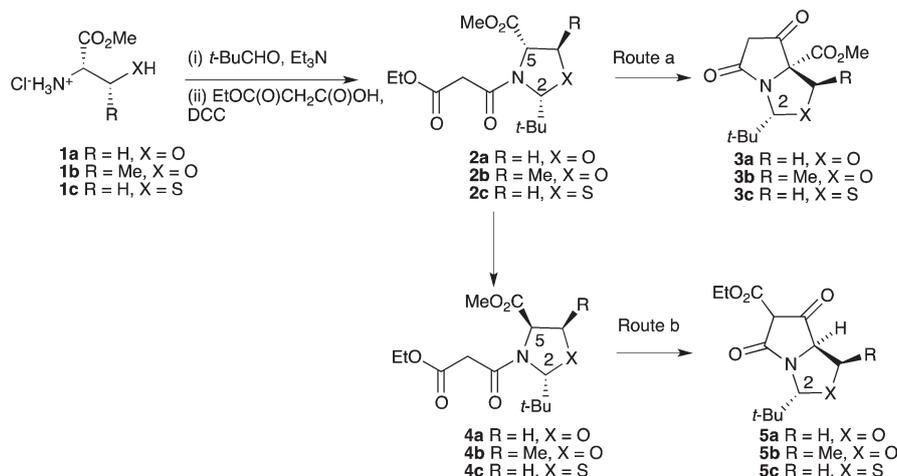
and others have found that other cyclic *N,O*-hemiaminal ethers derived from aldehydes and ketones are highly stable provided that the *N*-heteroatom is acylated,^{8–11} aldehydes other than pivaldehyde were unsuitable in the process shown in Scheme 1; this necessarily results in a highly hydrophobic group at C-2, and limits the synthetic scope of the process. However, thiazolidine substrates derived from cysteine using aromatic aldehydes were found to give hemiaminal thioether systems that were more stable than their oxazolidine counterparts, and Dieckmann cyclisation successfully gave the corresponding tetramate products;¹² of interest is that ring chain tautomerism in such *N,S*-hemiaminal thioethers has been only rarely reported.^{8,13} We had assumed that this would result in a directly analogous chemo- and stereo-selective outcome to that observed for the oxazolidine series, but a detailed investigation has shown that this is not the case, and the results are reported here.

Results and discussion

Condensation of *L*-cysteine methyl ester hydrochloride with the relevant substituted benzaldehyde **6a–g** gave the corresponding stable thiazolidines **7a–g** in good yield (76–94%, Table 1) as a mixture of *cis*- and *trans*-diastereomers (readily assigned by NOE (Fig. 1, ESI†)) in a ratio of between 1:1 and 2:1 (Scheme 2), and which could be readily distinguished by difference in the chemical shift of H-2, with the value of H-2 for the *trans*-isomer invariably being more downfield than that of the *cis*-isomer. These thiazolidines could then be converted by DCC coupling¹⁴ to the corresponding malonamides **8a–g** in good yield (85–99%, Table 2), and in which the *cis*- to *trans*-ratio (readily assigned again by NOE, (Fig. 2, ESI†)) was essentially preserved from the starting thiazolidines **7a–g** in all

Department of Chemistry, Chemistry Research Laboratory, The University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: mark.moloney@chem.ox.ac.uk

† Electronic supplementary information (ESI) available. CCDC 1452987. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob00557h



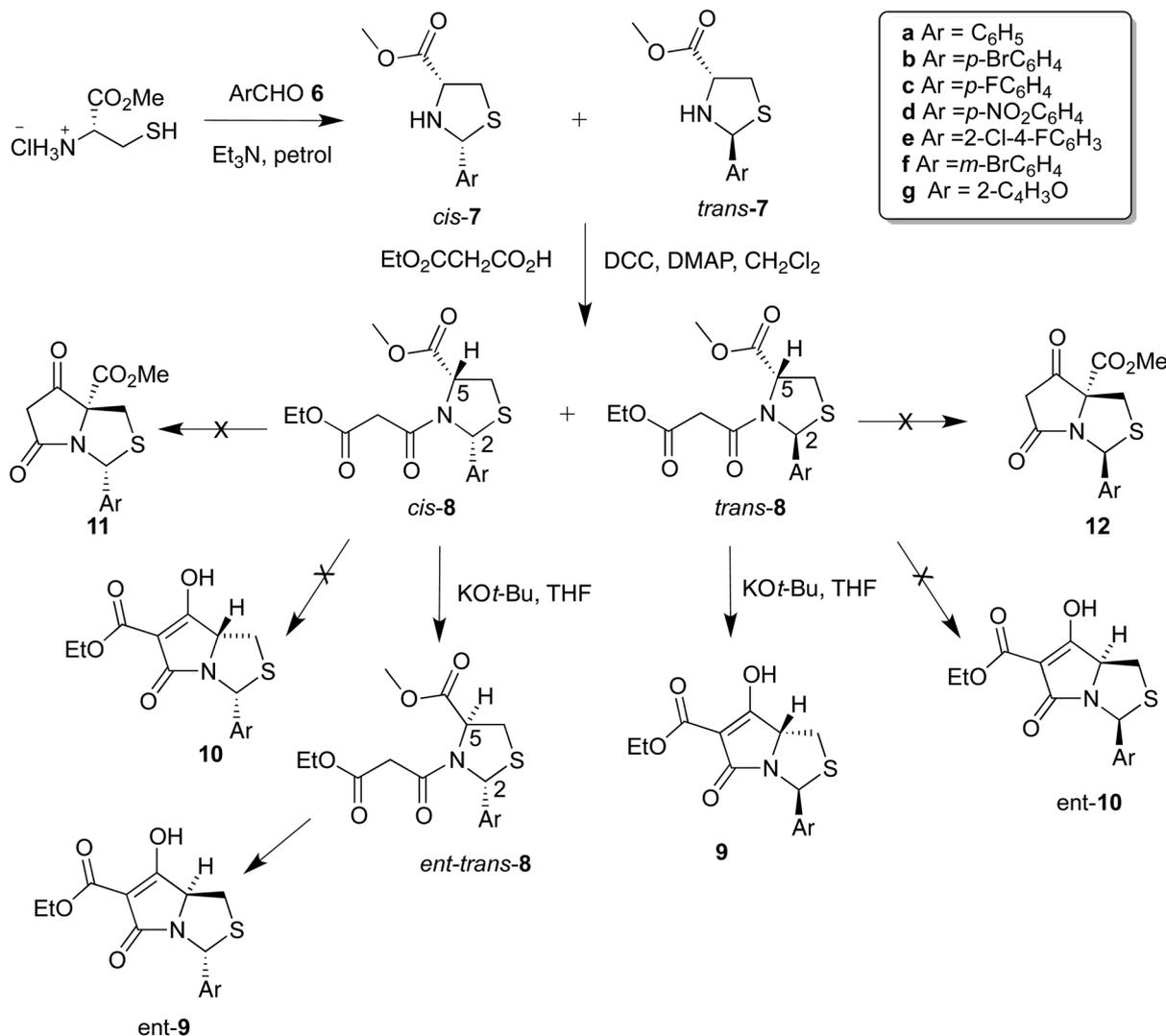
Scheme 1

Table 1 Yields and NMR data for thiazolidines 7a–g

Compound no.		δ_{H} (ppm) for H-2		<i>cis</i> : <i>trans</i> ratio	Yield (%)
		<i>cis</i>	<i>trans</i>		
7a		5.57	5.82	1.7 : 1	91
7b		5.49	5.76	1.3 : 1	94
7c		5.53	5.79	1.7 : 1	90
7d		5.69	5.87	0.8 : 1	94
7e		5.89	6.02	0.8 : 1	76
7f		5.43	5.71	1.2 : 1	78
7g		5.48	5.68	0.9 : 1	85

cases. This is very different behaviour to the corresponding oxazolidine series, in which the free equilibration led to a preferred formation of the *cis*-malonyloxazolidine.^{3,6} Again, characteristic values of the H-2 thiazolidine chemical shifts were seen for each of the diastereomers, which also appeared

as a rotameric pair (Table 2): for the major rotamers, with the exception of furfuryl **8g**, H-2 for the *trans*-isomer was invariably more downfield than that of the *cis*-isomer, but interestingly this was reversed for the minor rotamer. Because the *cis* : *trans*-ratio is essentially unchanged in this reaction, the *cis*-

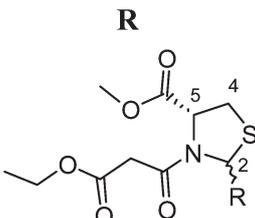


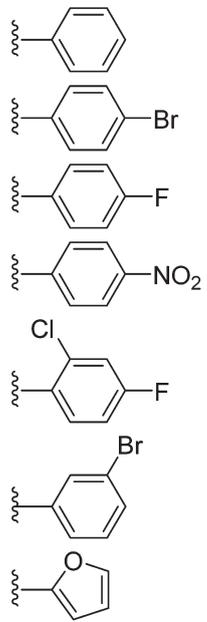
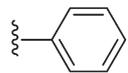
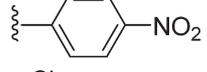
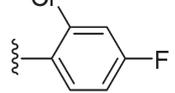
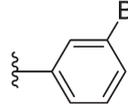
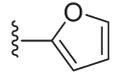
Scheme 2

malonamide **8** derives from *cis*-thiazolidine **7** and *trans*-malonamide **8** from *trans*-thiazolidine **7**; *i.e.* there is no cross-over arising from epimerisation in the course of the acylation reaction. Moreover, the *cis*- and *trans*-diastereomeric ratios of any recovered starting thiazolidines **7b,c,e** from this reaction were the same as that of the corresponding starting thiazolidines **7b,c,e** used for the reaction, which further confirms that there is no inter-conversion between *cis*- and *trans*-thiazolidines, or selective reaction, during the course of the acylation. Unfortunately, the *cis*- and *trans*-diastereomers **8a-g** could not be easily separated, and so the subsequent Dieckmann cyclisation step was performed on this mixture. This behaviour contrasts with the corresponding *t*-butyl system, in which the *cis*-isomer **2a-c** (Scheme 1) was formed predominantly.³

Upon reaction of malonamides **8a-g** with potassium *t*-butoxide, ring closure was found to be very efficient (Scheme 2 and Table 3) giving tetramate products in good yield, and again with characteristic H-2 chemical shift values for the

bicyclic ring system. NOE analysis clearly indicated that the products were either **9a-g** or *ent*-**9a-g** (Fig. 3, ESI†). Neither of the epimers **10** or *ent*-**10** were formed. Mass spectrometric analysis showed the formation of some tetramate **11e**, but this was only isolated from the cyclisation of *cis*-**8e** in <1% yield, indicating that it is not the predominant product of cyclisation of thiazolidine-derived tetramate systems, and neither was **12** formed (which would arise by the alternative cyclisation pathway). This favoured pathway for the thiazolidine system corresponds to Route b (Scheme 1) and is in contrast to the *t*-butyl series,^{3,6,14} and for which this mode of closure of the malonate enolate onto the C-5 methyl ester had only been a minor pathway (Scheme 1, Route b). Thus, in the case of oxazolidines and thiazolidines derived from the pivaldehyde (which therefore possess the bulky *t*-butyl group), ring closure by Route a proceeds preferentially since the bulky group ends up on the less hindered *exo*-bicyclic face, even though reaction is *via* a relatively unfavourable enolate formation. In the case

Table 2 Yields and NMR data for *N*-acylthiazolidines **8a–g**


Compound no.		δ_{H} (ppm) for H-2				<i>cis</i> : <i>trans</i> ratio	Yield (%)
		<i>cis</i>		<i>trans</i>			
		Major rotamer	Minor rotamer	Major rotamer	Minor rotamer		
8a		6.10	6.28	6.14	6.24	1.6 : 1	99
8b		6.11	6.27	6.14	6.24	1.3 : 1	99
8c		6.13	6.30	6.17	6.29	1.5 : 1	87
8d		6.22	6.27	6.23	6.24	0.9 : 1	85
8e		6.34	6.46	6.42	6.45	0.8 : 1	97
8f		6.06	6.16	6.11	6.13	1.4 : 1	81
8g		6.18	6.56	6.16	6.32–6.35 (obscured by H4')	0.8 : 1	89

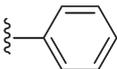
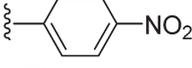
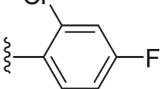
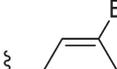
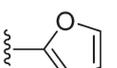
of the aryl-substituted thiazolidines **8**, reaction may proceed readily by cyclisation of the malonamide enolate (Scheme 1, Route b), since the smaller aryl substituent does not invoke the same steric demands as the *t*-butyl system in the bicyclic product.

However, this reduction in steric demand of the C-2 group results in an unforeseen and subtle change of selectivity in the process. Since cyclisation was performed on the *cis*-/*trans*-diastereomeric mixture of **8a–g**, this leads to the additional complication that the Dieckmann ring closure might occur after epimerisation at C-5 of *cis*-malonamides **8a–g** under the basic conditions of the cyclisation reaction, while *trans*-malonamides **8a–g** cyclise directly, leading to formation of either of **9a–g** or *ent*-**9a–g**. This dual pathway does not arise to the same extent in the case of the *t*-butyl system, since such epimerisation would lead to the much less stable *trans*-oxazolidine/thiazolidine.^{3,6} Importantly, if the cyclisation and epimerisation processes were simultaneous, erosion of the ee of the product from the Dieckmann cyclisation reaction would result. Thus, in order to determine the enantiomeric excess of the product

arising from Dieckmann cyclisation, the racemic analogue of **9c** was synthesised and this was compared with product **9c** obtained from the enantiopure series by chiral HPLC, and gave an ee value of 80% (Fig. 1 and 2 in the ESI†). Similarly, the ee values for **9b**, **9e** and **9g** obtained from the corresponding diastereomeric mixture were in the range of 76–83%. In the case of **8f**, the unseparated *cis*-/*trans*-mixture of *N*-malonylthiazolidines was cyclized, and although this successfully gave the tetramate product **9f**, it was clearly of compromised enantiopurity, at the least on the basis of optical rotation values.

In order to study the reason for the observed ee values, the *cis*- and *trans*-malonamide diastereomers of **8e** were successfully separated by careful column chromatography (other malonamides could not be similarly separated). The relative stereochemistry of each isolated malonamide diastereomer was further confirmed by NOE (Fig. 2, ESI†), and for *trans*-**8e**, by single crystal X-ray analysis (Fig. 1).¹⁵ Each of these was then cyclised separately under the standard reaction conditions; *trans*-**8e** gave product **9e** in 58% yield while *cis*-**8e** gave

Table 3 Yields and NMR data for tetramates 9a–f

Compound no.	R	δ_{H} (ppm) for H-2	% Yield
9a		6.25	43
9b		6.43	45
9c		6.34	50
9d		6.43	52
9e		6.45	49
9f		6.22	78 ^a
9g		6.30	40

^a Isolation without acidification and extraction.

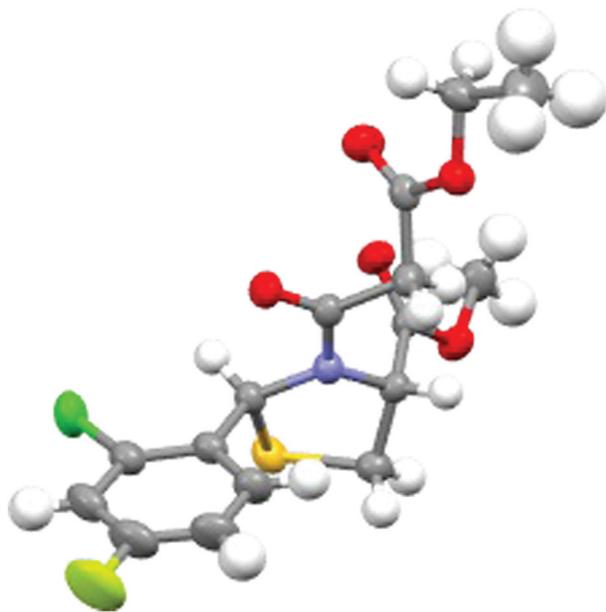


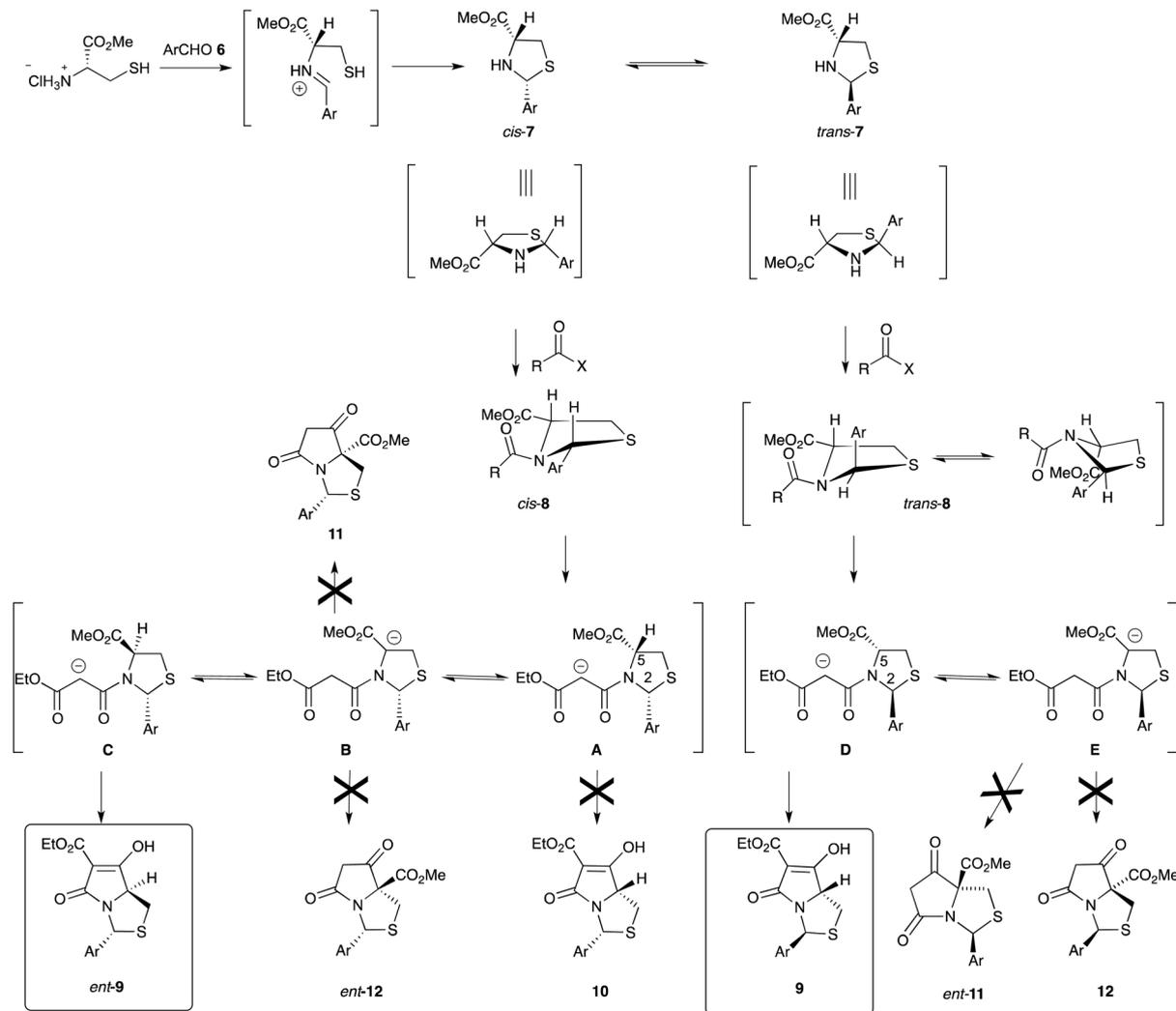
Fig. 1 Single crystal X-ray structure for *trans*-8e.

product *ent*-9e but only in 6% yield. This latter process was presumably less efficient as a result of the unfavourable initial epimerization of *cis*-8e to *ent*-*trans*-8e before closure to *ent*-9e is possible. NOE data clearly indicated that both products 9e and *ent*-9e have the same relative stereochemistry (Fig. 3, ESI[†]). They showed different retention times on chiral HPLC

indicating that they are enantiomers (Fig. 3 and 4, ESI[†]) and the $[\alpha]_{\text{D}}$ values were nearly equal in magnitude but opposite in sign (*ent*-9e = +309.5 and 9e = −331.8). Thus, it is clear that under the standard experimental conditions, *trans*-diastereomer 8e cyclises efficiently while *cis*-8e does not, with the yield ratio being close to 10 : 1. Since an ee of 83% corresponds to an enantiomeric ratio of 10.7 : 1 and because the cyclisation of *trans*-diastereomer gives approximately 10 times more yield than *cis*-, the observed ee attrition could be accounted for. To further support the difference in yields obtained for the cyclisation of *cis*- and *trans*-malonamides, unreacted malonamides from the Dieckmann cyclisation step for compounds 8b, 8c and 8e were recovered from the reaction mixture, but these showed the presence of *cis*-, but no *trans*-, diastereomer. This further confirms that *trans*-malonamides cyclise in preference to the *cis*-malonamide 8, and this is in stark contrast to the observed reactivity in the *t*-butyl series, in which the *cis*-2 preferentially closes (Scheme 1, Route a).

An overall scheme of reaction is given in Scheme 3; formation of the intermediate of thiazolidines 7 is favoured by ring-chain tautomerisation^{8,16–18} of the imine derived from cysteine and the starting aldehyde, and the acylation of thiazolidines *cis*-7 and *trans*-7 gave products *cis*-8 and *trans*-8 in approximately equal ratios; that this a mixture of the two possibly reflects the known preference of thiazolidines to exist in the ring-closed rather than the chain form.⁸ The *trans*-8 malonamides close preferentially *via* enolate D over the *cis*-8 malonamides, giving the product 9, but do not react to give the alternative tetramate 11 or 12 (or their enantiomers) *via* enolate B or E. However, epimerisation at C-5 under the basic conditions of the Dieckmann cyclisation of *cis*-8 gives malonamide *ent*-*trans*-8, which can then cyclise to give the bicyclic tetramate *ent*-9 *via* enolate C (that is, the enantiomer of that obtained from the direct cyclisation of *trans*-8), but this is also not a favoured pathway. Closure of enolates A and B to give 10 or *ent*-12 is not observed. In our initial report, we had assigned *ent*-9 as the major product, resulting from the formation of *cis*-8 as the major diastereomer (as mixture of two rotamers), which was assigned by analogy to the similar earlier outcome in the *t*-butyl series, but this is clearly in error.¹²

Another issue of note relates to the purification of tetramates 9a–g. Previously it has been reported that 3-acyltetramic acids form metal chelates during column chromatography on silica gel containing trace amounts of metal impurities such as Mg²⁺, Fe²⁺ and Ca²⁺.^{19–24} Indeed, tetramates 9d and 9e which were purified in this way gave broad signal resonances in the ¹H NMR spectra for compounds, consistent with chelation. Thus, tetramates were routinely purified on silica gel column, run with 1% Et₃N in the eluent, and the purified product was washed with 5% citric acid to remove any Et₃N present to obtain the metal-free form. Moreover, it was observed that tetramates purified by preparative thin layer chromatography with silica also resulted in NMR spectra with peaks slightly broader than their metal-free form and with significant chemical shift differences observed for H-2 and H-5 (Table 4). Further, metal-chelated tetramates had different



Scheme 3

Table 4 Chemical shift values of H-2 and H-5 for metal-chelated tetramates and their metal-free form (in CD₃OD, 400 MHz)

Compound no.		δ_{H} (ppm) Metal-chelated tetramate		δ_{H} (ppm) Metal-free tetramate	
		H-2	H-5	H-2	H-5
9d		6.43 (s)	4.13–4.32 (m)	6.32 (s)	4.95 (dd)
(-)-9e		6.52 (s)	4.42 (app br. t)	6.39 (s)	5.05 (dd)
(+)-9e		6.52 (s)	4.43 (app br. t)	6.39 (s)	5.06 (dd)

physical properties in comparison to their metal free forms, with melting points >250 °C along with different optical rotation data and retention times on chiral HPLC (SI). Mass spectrometric analysis of **9b** showed the presence of peaks that could be attributable to $[M - H] + Ca^{2+}$ and $[M - H] + Mg^{2+}$, confirming the possibility of these tetramates chelating to such divalent metal cations (Figure on last page of ESI†).

In conclusion, the formation of aryl thiazolidines derived from cysteine is readily possible, even though the corresponding oxazolidines derived from serine are unstable, and selective Dieckmann ring cyclisation gives the corresponding tetramate products by a highly chemoselective process, and with good enantioselectivity, but which proceeds in a different direction to that of the *t*-butyl series. These systems are structurally well-defined, and offer interesting opportunities as three dimensional templates for application in drug discovery.

Experimental

Synthesis of tetramic acids were carried out according to published procedures.^{3,7,14}

General procedure 1: esterification of DL-cysteine for racemic tetramates

To a solution of DL-cysteine (1.0 eq.) in MeOH at 0 °C, SOCl₂ (1.2 eq.) was added dropwise and the solution warmed to rt, then refluxed for 3 h. The reaction mixture was concentrated *in vacuo* to obtain DL-cysteine methyl ester hydrochloride.

General procedure 2: synthesis of thiazolidine

Et₃N (1.2 eq.) and aldehyde (1.2 eq.) were added to L-cysteine methyl ester hydrochloride (1.0 eq.) in petrol. The mixture was heated at reflux, with continuous removal of water using Dean Stark apparatus, for 19 h, then filtered and washed with Et₂O. The combined filtrates were concentrated *in vacuo* and residue was purified by flash column chromatography to give the required thiazolidines **7a-g**.

General procedure 3: acylation

A solution of ethyl hydrogen malonate (1.2 eq.) in CH₂Cl₂ was added to a stirred solution of thiazolidine (1.0 eq.), DCC (1.2 eq.) and DMAP (0.1 eq.) in CH₂Cl₂ at 0 °C. The mixture was stirred at 0 °C for 15 min and then at rt for 15 h. The reaction mixture was filtered to remove dicyclohexyl urea and the residue was washed with CH₂Cl₂. The combined filtrates were concentrated *in vacuo* and purified by flash column chromatography to give *N*-acylated thiazolidines **8a-g**.

General procedure 4: Dieckmann cyclisation

KO^tBu (1.2 eq.) was added to a solution of the *N*-acylated thiazolidine in THF and heated at reflux for 3 h. It was then cooled to rt, concentrated *in vacuo* and partitioned between Et₂O and water. The aqueous layer was extracted and acidified with 2 M HCl (to pH 1) and extracted with EtOAc. The combined EtOAc

extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (with 1% Et₃N) to give the desired product. The product was then dissolved in CH₂Cl₂ and washed with 5% citric acid. The organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to yield the desired bicyclic tetramates **9a-g**.

(2*RS*,5*SR*)-5-Methoxycarbonyl-2-phenyl-1,3-thiazolidine **7a**

Yield (2.37 g, 91%); colourless oil; inseparable 1.7 : 1 *cis* and *trans* diastereomers; *R*_f = 0.48 (EtOAc : petrol; 1 : 3); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1736 (s, C=O), 3314 (m, N-H), δ_{H} (400 MHz, CDCl₃) major isomer (*cis*): 2.71 (1H, br. s., NH), 3.12 (1H, dd, *J* = 10.3, 9.1 Hz, H_{4A}), 3.47 (1H, dd, *J* = 10.3, 7.1 Hz, H_{4B}), 3.80 (3H, s, CO₂CH₃), 3.99 (1H, app t, *J* = 7.9 Hz, H₅), 5.57 (1H, s, H₂), 7.27–7.41 (3H, m, H_{3'}, H_{4'}), 7.52–7.56 (2H, m, H_{2'}); minor isomer (*trans*): 2.71 (1H, br. s., NH), 3.20 (1H, dd, *J* = 10.5, 5.9 Hz, H_{4A}), 3.38 (1H, dd, *J* = 10.5, 7.1 Hz, H_{4B}), 3.78 (3H, s, CO₂CH₃), 4.22 (1H, app t, *J* = 6.4 Hz, H₅), 5.82 (1H, s, H₂), 7.27–7.41 (3H, m, H_{3'}, H_{4'}), 7.47–7.51 (2H, m, H_{2'}); δ_{C} (100.6 MHz, CDCl₃) major isomer (*cis*): 39.2 (C₄), 52.6 (CO₂CH₃), 64.3 (C₅), 70.9 (C₂), 127.5 (C_{2'}), 128.5 (C_{3'}), 128.7 (C_{4'}), 138.2 (C₈), 171.6 (CO₂CH₃); minor isomer (*trans*): 38.2 (C₄), 52.6 (CO₂CH₃), 65.6 (C₅), 72.6 (C₂), 127.0 (C_{2'}), 127.9 (C_{3'}), 128.7 (C_{4'}), 141.2 (C_{1'}), 172.2 (CO₂CH₃); *m/z* (ESI⁺) 224 ([M + H]⁺, 100%); HRMS (ESI⁺); C₁₁H₁₃NNaO₂S [M + Na]⁺; found 246.0563, requires 246.0559.

(2*RS*,5*SR*)-2-(4-Bromophenyl)-5-methoxycarbonyl-1,3-thiazolidine **7b**

Yield (5.60 g, 94%); colourless oil; inseparable 1.3 : 1 *cis* and *trans* diastereomers; *R*_f = 0.23 (EtOAc : petrol; 1 : 4); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1737 (s, C=O), 3313 (m, N-H); δ_{H} (400 MHz, CDCl₃) major isomer (*cis*): 2.64 (1H, br. s., NH), 3.10 (1H, dd, *J* = 10.3, 8.8 Hz, H_{4A}), 3.45 (1H, dd, *J* = 10.5, 7.1 Hz, H_{4B}), 3.79 (3H, s, CO₂CH₃), 3.97 (1H, dd, *J* = 9.1, 7.1 Hz, H₅), 5.49 (1H, s, H₂), 7.32–7.51 (4H, m, H_{2'} and H_{3'}); minor isomer (*trans*): 2.64 (1H, br. s., NH), 3.15 (1H, dd, *J* = 10.8, 6.1 Hz, H_{4A}), 3.36 (1H, dd, *J* = 10.5, 7.1 Hz, H_{4B}), 3.78 (3H, s, CO₂CH₃), 4.13 (1H, apparent t, *J* = 6.5 Hz, H₅), 5.76 (1H, s, H₂), 7.32–7.51 (4H, m, H_{2'} and H_{3'}); δ_{C} (100.6 MHz, CDCl₃): major isomer (*cis*): 39.0 (C₄), 52.5 (CO₂CH₃), 65.3 (C₅), 71.6 (C₂), 122.4 (C_{1'}), 129.0 (C_{2'}), 131.6 (C_{3'}), 137.0 (C_{4'}), 171.3 (CO₂CH₃); minor isomer (*trans*): 37.9 (C₄), 52.4 (CO₂CH₃), 64.0 (C₅), 69.8 (C₂), 121.5 (C_{1'}), 128.5 (C_{2'}), 131.0 (C_{3'}), 140.5 (C_{4'}), 171.9 (CO₂CH₃); *m/z* (ESI⁺) 302 ([M + H]⁺, 100%) and 304 ([M + H]⁺, 100%); HRMS (ESI⁺); C₁₁H₁₃O₂NBrS [M + H]⁺; found 301.98412 and 303.98175, requires 301.98449, 303.98244.

(2*RS*,5*SR*)-2-(4-Fluorophenyl)-5-methoxycarbonyl-1,3-thiazolidine **7c**

Yield (2.54 g, 90%); colourless oil; inseparable 1.7 : 1 *cis* and *trans* diastereomers; *R*_f = 0.35 (EtOAc : petrol; 1 : 3); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1225 (s, C-F), 1741 (s, C=O), 3311 (m, N-H); δ_{H} (400 MHz, CDCl₃) major isomer (*cis*): 2.66 (1H, br. s., NH), 3.12 (1H, dd, *J* = 10.3, 8.8 Hz, H_{4A}), 3.47 (1H, dd, *J* = 10.3, 7.1

Hz, H4_B), 3.81 (3H, s, CO₂CH₃), 3.98 (1H, dd, *J* = 8.8, 7.1 Hz, H5), 5.53 (1H, s, H2), 6.98–7.09 (2H, m, H3'), 7.49–7.54 (2H, m, H2'); minor isomer (*trans*): 2.66 (1H, br. s., NH), 3.17–3.23 (1H, m, H4_A), 3.36–3.42 (1H, m, H4_B), 3.80 (3H, s, CO₂CH₃), 4.18 (1H, app t, *J* = 6.5 Hz, H5), 5.79 (1H, s, H2), 6.98–7.09 (2H, m, H3'), 7.44–7.49 (2H, m, H2'); δ_{C} (100.6 MHz, CDCl₃) major isomer (*cis*): 39.2 (C4), 52.6 (CO₂CH₃), 65.4 (C5), 71.8 (C2), 115.5 (d, *J* = 21.5 Hz, C3'), 129.3 (d, *J* = 8.7 Hz, C2'), 133.9 (d, *J* = 3.2 Hz, C1'), 162.8 (d, *J* = 247 Hz, C4'), 171.5 (CO₂CH₃); minor isomer (*trans*): 38.0 (C4), 52.6 (CO₂CH₃), 64.1 (C5), 69.9 (C2), 115.1 (d, *J* = 21.5 Hz, C3'), 128.7 (d, *J* = 8.0 Hz, C2'), 136.9 (d, *J* = 3.2 Hz, C1'), 162.3 (d, *J* = 247 Hz, C4'), 172.1 (CO₂CH₃); *m/z* (ESI⁺) 264 ([M + Na]⁺, 56%); HRMS (ESI⁺); C₁₁H₁₂FNNaO₂S [M + Na]⁺; found 264.0460, requires 264.0465.

(2*RS*,5*SR*)-5-Methoxycarbonyl-2-(4-nitrophenyl)-1,3-thiazolidine 7d

Yield (2.95 g, 94%); yellow oil; 0.8 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.20 (EtOAc : petrol; 1 : 3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1348 (s, ArNO₂), 1516 (s, ArNO₂), 1730 (s, C=O), 3316 (m, N-H); δ_{H} (400 MHz, CDCl₃) major isomer (*trans*): 2.88 (1H, br. s., NH), 3.08–3.16 (1H, m, H4_A), 3.36 (1H, dd, *J* = 10.6, 6.7 Hz, H4_B), 3.78 (3H, s, CO₂CH₃), 4.07 (1H, app t, *J* = 6.7 Hz, H5), 5.87 (1H, s, H2), 7.61 (2H, d, *J* = 8.8 Hz, H2'), 8.12 (2H, d, *J* = 8.8 Hz, H3'); minor isomer (*cis*): 2.88 (1H, br. s., NH), 3.08–3.16 (1H, m, H4_A), 3.46 (1H, dd, *J* = 10.4, 7.0 Hz, H4_B), 3.78 (3H, s, CO₂CH₃), 4.00 (1H, dd, *J* = 8.8, 7.0 Hz, H5), 5.59 (1H, s, H2), 7.67 (2H, d, *J* = 8.8 Hz, H2'), 8.18 (2H, d, *J* = 8.8 Hz, H3'); δ_{C} (100.6 MHz, CDCl₃): major isomer (*trans*): 38.1 (C4), 52.6 (CO₂CH₃), 64.1 (C5), 69.0 (C2), 123.5 (C3'), 127.5 (C2'), 145.5 (C1'), 149.5 (C4'), 171.7 (CO₂CH₃); minor isomer (*cis*): 39.0 (C4), 52.6 (CO₂CH₃), 65.3 (C5), 70.9 (C2), 123.7 (C3'), 128.4 (C2'), 147.1 (C4'), 147.7 (C1'), 171.2 (CO₂CH₃); *m/z* (ESI⁺) 269 ([M + H]⁺, 100%); HRMS (ESI⁺); C₁₁H₁₂N₂NaO₄S [M + Na]⁺; found 291.0405, requires 291.0410.

(2*RS*,5*SR*)-2-(2-Chloro-4-fluorophenyl)-5-methoxycarbonyl-1,3-thiazolidine 7e

Yield (2.45 g, 76%); colourless oil; 0.8 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.58 (EtOAc : petrol; 1 : 3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1226 (s, C-F), 1737 (s, C=O), 3321 (m, N-H); δ_{H} (400 MHz, CDCl₃) major isomer (*trans*): 2.65 (1H, br. s., NH), 3.04–3.14 (1H, m, H4_A), 3.33 (1H, dd, *J* = 10.6, 6.5 Hz, H4_B), 3.81 (3H, s, CO₂CH₃), 4.21 (1H, app t, *J* = 6.6 Hz, H5), 6.02 (1H, s, H2), 6.96 (2H, app td, *J* = 8.3, 2.5 Hz, H5'), 7.08–7.16 (2H, m, H3'), 7.57 (2H, dd, *J* = 8.7, 6.1 Hz, H6'); minor isomer (*cis*): 2.65 (1H, br. s., NH), 3.04–3.14 (1H, m, H4_A), 3.46 (1H, dd, *J* = 10.4, 7.0 Hz, H4_B), 3.80 (3H, s, CO₂CH₃), 4.00 (1H, dd, *J* = 9.1, 6.9 Hz, H5), 5.89 (1H, s, H2), 7.03 (2H, app td, *J* = 8.3, 2.6 Hz, H5'), 7.08–7.16 (2H, m, H3'), 7.74 (2H, dd, *J* = 8.7, 6.1 Hz, H6'); δ_{C} (100.6 MHz, CDCl₃): major isomer (*trans*): 37.3 (C4), 52.6 (CO₂CH₃), 64.7 (C5), 66.5 (C2), 113.8 (d, *J* = 20.7 Hz, C5'), 117.0 (d, *J* = 24.6 Hz, C3'), 127.8 (d, *J* = 8.7 Hz, C6'), 133.5 (d, *J* = 10.3 Hz, C2'), 136.1 (d, *J* = 4.0 Hz, C1'), 161.6 (d, *J* = 250 Hz, C4'), 171.9 (CO₂CH₃); minor isomer (*cis*): 38.8 (C4), 52.6 (CO₂CH₃), 65.3 (C5), 67.6 (C2), 114.5 (d, *J* = 21.5 Hz,

C5'), 117.1 (d, *J* = 24.6 Hz, C3'), 129.7 (d, *J* = 8.7 Hz, C6'), 131.9 (d, *J* = 4.0 Hz, C1'), 134.5 (d, *J* = 10.3 Hz, C2'), 162.1 (d, *J* = 252 Hz, C4'), 171.4 (CO₂CH₃); *m/z* (ESI⁺) 276 ([M + H]⁺, 100%); HRMS (ESI⁺); C₁₁H₁₁ClFNNaO₂S [M + Na]⁺; found 298.0062, requires 298.0075.

(2*RS*,5*SR*)-2-(3-Bromophenyl)-5-methoxycarbonyl-1,3-thiazolidine 7f

Yield (78%); 1.2 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.56 (EtOAc : petrol; 4 : 6); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1235 (C-O), 1737 (C=O), 3313 (NH); δ_{H} (400 MHz, CDCl₃) major isomer (*cis*): 2.55 (1H, br. s., NH), 3.04 (1H, dd, *J* = 10.3, 9.1 Hz, H4_A), 3.39 (1H, dd, *J* = 10.3, 7.1 Hz, H4_B), 3.74 (3H, s, CO₂CH₃), 3.91 (1H, dd, *J* = 9.1, 7.1 Hz, H5), 5.43 (1H, s, H2), 7.15–7.19 (1H, m, H5'), 7.36–7.42 (2H, m, H4',6'), 7.62 (1H, app t, *J* = 1.8 Hz, H2'); minor isomer (*trans*): 2.84 (1H, br. s., NH), 3.09 (1H, dd, *J* = 10.5, 6.1 Hz, H4_A), 3.31 (1H, dd, *J* = 10.5, 7.1 Hz, H4_B), 3.73 (3H, s, CO₂CH₃), 4.07 (1H, app t, *J* = 6.5 Hz, H5), 5.71 (1H, s, H2), 7.09–7.15 (1H, m, H5'), 7.30–7.34 (2H, m, H4',6'), 7.59 (1H, app t, *J* = 1.7 Hz, H2'); δ_{C} (100.6 MHz, CDCl₃) major isomer (*cis*): 39.1 (C4), 52.6 (CO₂CH₃), 65.4 (C5), 71.6 (C2), 122.4 (Ar-C), 126.2, 129.8, 130.5, 131.7 (Ar-CH), 140.5 (Ar-C), 171.3 (CO₂CH₃); minor isomer (*trans*): 38.0 (C4), 52.6 (CO₂CH₃), 64.1 (C5), 69.7 (C2), 122.6 (Ar-C), 125.7, 129.9, 130.1, 130.8 (Ar-CH), 144.0 (Ar-C), 172.0 (CO₂CH₃); *m/z* (ESI⁺) 302 ([M + H]⁺); HRMS (ESI⁺); C₁₁H₁₂BrNNaO₂S [M + Na]⁺; found 323.9651, requires 323.9664.

(2*RS*,5*SR*)-2-(2-Furyl)-5-methoxycarbonyl-1,3-thiazolidine 7g

Yield (3.17 g, 85%); yellow oil; 0.9 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.53 (EtOAc : petrol; 1 : 4); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1736 (s, C=O), 3317 (m, N-H); δ_{H} (400 MHz, CDCl₃) major isomer (*trans*): 2.90 (1H, br. s., NH), 2.91–2.97 (1H, m, H4_A), 3.23–3.29 (1H, m, H4_B), 3.62 (3H, s, CO₂CH₃), 4.09 (1H, app t, *J* = 6.7 Hz, H5), 5.68 (1H, s, H2), 6.15–6.17 (1H, m, H4'), 6.18–6.20 (1H, m, H3'), 7.24–7.26 (1H, m, H5'); minor isomer (*cis*): 2.90 (1H, br. s., NH), 2.91–2.97 (1H, m, H4_A), 3.23–3.29 (1H, m, H4_B), 3.63 (3H, s, CO₂CH₃), 3.81 (1H, dd, *J* = 9.3, 6.9 Hz, H5), 5.48 (1H, s, H2), 6.20–6.22 (1H, m, H4'), 6.28–6.29 (1H, m, H3'), 7.29–7.31 (1H, m, H5'); δ_{C} (100.6 MHz, CDCl₃): major isomer (*trans*): 37.9 (C4), 51.9 (CO₂CH₃), 63.2 (C2), 63.6 (C5), 106.6 (C3'), 109.6 (C4'), 141.9 (C5'), 153.2 (C2'), 171.1 (CO₂CH₃); minor isomer (*cis*): 37.3 (C4), 51.9 (CO₂CH₃), 63.9 (C2), 64.8 (C5), 107.4 (C3'), 109.9 (C4'), 142.2 (C5'), 150.1 (C2'), 170.5 (CO₂CH₃); *m/z* (ESI⁺) 214 ([M + H]⁺, 100%); HRMS (ESI⁺); C₉H₁₁NNaO₃S [M + Na]⁺; found 236.0351, requires 236.0352.

(2*RS*,5*SR*)-1-(3-Ethoxy-3-oxopropanoyl)-5-methoxycarbonyl-2-phenyl-1,3-thiazolidine 8a

Yield (2.54 g, 99%); colourless oil; 1.6 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.61 (EtOAc : petrol; 1 : 1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1658 (s, C=O), 1734 (s, C=O); δ_{H} (400 MHz, CDCl₃) major isomer (*cis*, a mixture of conformers): 1.09–1.21 (3H, m, OCH₂CH₃), 2.98–3.55 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.73 and 3.74 (3H, s, CO₂CH₃), 3.94–4.06 and 4.07–4.14 (2H, m,

OCH₂CH₃), 4.95–5.01 (1H, m, H5), 6.10 and 6.28 (1H, s, H2), 7.13–7.34 (3H, m, H3', H4'), 7.45 (2H, d, *J* = 7.3 Hz, H2', minor conformer), 7.60 (2H, d, *J* = 7.6 Hz, H2', major conformer), 7.57–7.63 (2H, m, H2'); minor isomer (*trans*, a mixture of conformers): 1.09–1.21 (3H, m, OCH₂CH₃), 2.98–3.55 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.69 and 3.70 (3H, s, CO₂CH₃), 3.94–4.06 and 4.07–4.14 (2H, m, OCH₂CH₃), 5.16–5.19 and 5.21–5.25 (1H, m, H5), 6.14 and 6.24 (1H, s, H2), 7.13–7.34 (5H, m, H2', H3' and H4'); δ_C (100.6 MHz, CDCl₃) major isomer (*cis*, a mixture of conformers): 13.5 and 13.6 (OCH₂CH₃), 31.5 and 32.5 (C4), 42.6 and 42.8 (C2''), 52.2 and 52.5 (CO₂CH₃), 60.9 and 61.1 (OCH₂CH₃), 64.2 and 63.3 (C5), 65.7 and 66.5 (C2), 126.0 and 126.5 (C2'), 127.4, 128.0 (C4'), 127.7, 128.5 (C3'), 138.5 and 139.5 (C1'), 164.8 and 165.1 (C1''), 166.2 and 166.6 (C3''), 169.7 and 169.8 (CO₂CH₃); minor isomer (*trans*, a mixture of conformers): 13.5 and 13.7 (OCH₂CH₃), 30.5 and 33.3 (C4), 41.8 and 42.4 (C2''), 52.2 and 52.9 (CO₂CH₃), 60.8 and 61.1 (OCH₂CH₃), 63.5 and 63.83 (C5), 64.5 and 65.1 (C2), 124.3 and 124.5 (C2'), 127.0, 127.9 (C4'), 128.0, 128.7 (C3'), 141.5 and 141.8 (C1'), 164.2 and 164.8 (C1''), 165.8 and 166.7 (C3''), 169.0 and 169.8 (CO₂CH₃); *m/z* (ESI⁺) 338 ([M + H]⁺, 100%), 360.0 ([M + Na]⁺, 55%); HRMS (ESI⁺); C₁₆H₁₉NNaO₅S [M + Na]⁺; found 360.0873, requires 360.0876.

(2*RS*,5*R*)-2-Bromophenyl-1-(3-ethoxy-3-oxopropanoyl)-5-methoxycarbonyl-1,3-thiazolidine 8b

Yield (2.06 g, 99%); colourless oil; 1.3 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.17 (EtOAc : petrol; 1 : 3); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1660 (s, C=O), 1738 (s, C=O); δ_H (400 MHz, CDCl₃) major isomer (*cis*, a mixture of conformers): 1.19–1.31 (3H, m, OCH₂CH₃), 3.07–3.55 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.81 and 3.83 (3H, s, CO₂CH₃), 4.03–4.24 (2H, m, OCH₂CH₃), 5.04 (1H, app t, *J* = 7.0 Hz, H5), 6.11 and 6.27 (1H, s, H2), 7.39–7.45 (2H, m, H2'), 7.48–7.59 (2H, m, H3'); minor isomer (*trans*, a mixture of conformers): 1.19–1.31 (3H, m, OCH₂CH₃), 3.07–3.55 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.78 and 3.84 (3H, s, CO₂CH₃), 4.03–4.24 (2H, m, OCH₂CH₃), 5.15–5.21 and 5.26–5.33 (1H, m, H5), 6.14 and 6.24 (1H, s, H2), 7.11 (2H, d, *J* = 8.6 Hz, H2' major conformer) and 7.16 (2H, d, *J* = 8.3 Hz, H2' minor conformer), 7.39–7.45 (2H, m, H3') and 7.48–7.59 (2H, m, H3'); δ_C (100.6 MHz, CDCl₃) major isomer (*cis*, a mixture of conformers): 13.9 and 14.1 (OCH₂CH₃), 32.0 and 33.9 (C4), 42.0 and 42.9 (C2''), 52.7 and 53.1 (CO₂CH₃), 60.3 and 61.6 (OCH₂CH₃), 63.7 and 64.6 (C5), 65.6 and 66.5 (C2), 121.9 and 122.6 (C1'), 128.2 and 128.8 (C2'), 131.3 and 132.0 (C3'), 137.7 and 138.9 (C4'), 165.0 and 165.3 (C1''), 166.5 and 166.9 (C3''), 170.0 and 171.0 (CO₂CH₃); minor isomer (*trans*, a mixture of conformers): 13.9 and 14.0 (OCH₂CH₃), 31.0 and 33.0 (C4), 42.3 and 43.2 (C2''), 52.8 and 53.4 (CO₂CH₃), 61.5 and 61.8 (OCH₂CH₃), 64.0 and 64.2 (C5), 64.4 and 65.1 (C2), 121.3 and 122.4 (C1'), 126.5 and 126.6 (C2'), 131.6 and 132.3 (C3'), 140.9 and 141.1 (C4'), 164.6 and 165.2 (C1''), 166.1 and 167.2 (C3''), 169.2 and 170.0 (CO₂CH₃); *m/z* (ESI⁺) 416 ([M + H]⁺, 100%) and 418 ([M + H]⁺, 100%); HRMS (ESI⁺); C₁₆H₁₉O₅NBrS [M + H]⁺; found 416.01454 and 418.01234, requires 416.01618 and 418.01414.

(2*RS*,5*R*)-1-(3-Ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)-5-methoxycarbonyl-1,3-thiazolidine 8c

Yield (2.32 g, 87%); colourless oil; 1.5 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.61 (EtOAc : petrol; 1 : 1); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1224 (s, C–F), 1662 (s, C=O), 1741 (s, C=O); δ_H (400 MHz, CDCl₃) major isomer (*cis*, a mixture of conformers): 1.19–1.31 (3H, m, OCH₂CH₃), 3.07–3.55 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.81 and 3.83 (3H, s, CO₂CH₃), 4.05–4.24 (2H, m, OCH₂CH₃), 5.03–5.08 (1H, m, H5), 6.13 and 6.30 (1H, s, H2), 6.95–7.01 and 7.04–7.10 (2H, m, H3'), 7.48–7.54 and 7.64–7.69 (2H, m, H2'); minor isomer (*trans*, a mixture of conformers): 1.19–1.31 (3H, m, OCH₂CH₃), 3.07–3.55 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.78 and 3.84 (3H, s, CO₂CH₃), 4.05–4.24 (2H, m, OCH₂CH₃), 5.17–5.21 and 5.28–5.31 (1H, m, H5), 6.17 and 6.29 (1H, s, H2), 6.95–7.01 and 7.04–7.10 (2H, m, H3'), 7.19–7.23 and 7.24–7.29 (2H, m, H2'); δ_C (100.6 MHz, CDCl₃) major isomer (*cis*, a mixture of conformers): 13.9 and 14.0 (OCH₂CH₃), 32.0 and 33.8 (C4), 42.1 and 43.0 (C2''), 52.8 and 53.1 (CO₂CH₃), 61.6 and 61.8 (OCH₂CH₃), 63.7 and 64.6 (C5), 65.7 and 66.4 (C2), 115.0 (d, *J* = 21.5 Hz, C3') and 115.9 (d, *J* = 21.5 Hz, C3''), 128.4 (d, *J* = 8.0 Hz, C2') and 129.0 (d, *J* = 8.7 Hz, C2''), 135.6 (d, *J* = 2.4 Hz, C1'), 162.6 (d, *J* = 249 Hz, C4'), 165.4 (C1''), 166.6 (C3''), 170.2 (CO₂CH₃); minor isomer (*trans*, a mixture of conformers): 13.9 and 14.0 (OCH₂CH₃), 30.9 and 33.0 (C4), 42.3 and 43.3 (C2''), 52.8 and 53.4 (CO₂CH₃), 61.5 and 61.8 (OCH₂CH₃), 64.0 and 64.2 (C5), 64.4 and 65.1 (C2), 115.3 (d, *J* = 22.3 Hz, C3') and 116.2 (d, *J* = 21.5 Hz, C3''), 126.5 (d, *J* = 8.7 Hz, C2') and 126.7 (d, *J* = 8.0 Hz, C2''), 137.9 (d, *J* = 2.4 Hz, C1'), 162.5 (d, *J* = 248 Hz, C4'), 165.3 (C1''), 166.2 (C3''), 169.3 (CO₂CH₃); *m/z* (ESI⁺) 378 ([M + Na]⁺, 100%); HRMS (ESI⁺); C₁₆H₁₈FNNaO₅S [M + Na]⁺; found 378.0779, requires 378.0782.

(2*RS*,5*R*)-1-(3-Ethoxy-3-oxopropanoyl)-5-methoxycarbonyl-2-(4-nitrophenyl)-1,3-thiazolidine 8d

Yield (2.21 g, 85%); orange oil; 0.9 : 1 inseparable *cis* and *trans* diastereomers; *R_f* = 0.48 (EtOAc : petrol; 1 : 1); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1347 (s, ArNO₂), 1520 (s, ArNO₂), 1663 (s, C=O), 1740 (s, C=O); δ_H (400 MHz, CDCl₃): major isomer (*trans*, mixture of conformers): 1.07–1.21 (3H, m, OCH₂CH₃), 2.98–3.54 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.69 and 3.76 (3H, s, CO₂CH₃), 3.93–4.15 (2H, m, OCH₂CH₃), 5.20–5.22 and 5.24–5.28 (1H, m, H5), 6.23 and 6.24 (1H, s, H2), 7.37–7.43 (2H, m, H2'), 8.05 (2H, app d, *J* = 8.8 Hz, H3' major conformer) and 8.14 (2H, app d, *J* = 8.6 Hz, H3' minor conformer); minor isomer (*cis*, mixture of conformers): 1.07–1.21 (3H, m, OCH₂CH₃), 2.98–3.54 (4H, m, H4_A, H4_B, H2''_A, H2''_B), 3.74 and 3.76 (3H, s, CO₂CH₃), 3.93–4.15 (2H, m, OCH₂CH₃), 4.89–4.95 and 5.05–5.09 (1H, m, H5), 6.22 and 6.27 (1H, s, H2), 7.64 (2H, d, *J* = 8.8 Hz, H2' minor conformer) and 7.85 (2H, d, *J* = 8.6 Hz, H2' major conformer), 8.05 (2H, app d, *J* = 8.8 Hz, H3' minor conformer) and 8.14 (2H, app d, *J* = 8.6 Hz, H3' major conformer); δ_C (100.6 MHz, CDCl₃) major isomer (*trans*, a mixture of conformers): 13.6 and 13.7 (OCH₂CH₃), 30.7 and 32.7 (C4), 41.9 and 42.6 (C2''), 53.0 and 53.2 (CO₂CH₃), 61.2 and 61.5

(OCH₂CH₃), 63.7 and 64.0 (C5), 63.7 and 64.3 (C2), 123.5 and 124.1 (C3'), 125.4 and 125.7 (C2'), 146.6 and 147.2 (C4'), 148.7 and 149.3 (C1'), 164.9 (C1''), 165.7 and 166.9 (C3''), 168.8 and 169.6 (CO₂CH₃); minor isomer (*cis*, a mixture of conformers): 13.6 and 13.7 (OCH₂CH₃), 31.9 and 33.9 (C4), 41.6 and 42.4 (C2''), 52.5 and 53.3 (CO₂CH₃), 61.3 and 61.4 (OCH₂CH₃), 63.6 and 64.5 (C5), 64.9 and 66.1 (C2), 123.2 and 123.7 (C3'), 127.2 and 127.5 (C2'), 146.2 and 146.6 (C1'), 147.0 and 147.3 (C4'), 165.1 and 165.2 (C1''), 166.1 and 166.5 (C3''), 169.8 and 170.7 (CO₂CH₃); *m/z* (ESI⁺) 383 ([M + H]⁺, 100%) and 405 ([M + Na]⁺, 63%); HRMS (ESI⁺); C₁₆H₁₈N₂NaO₇S [M + Na]⁺; found 405.0717, requires 405.0727.

(-)-(2*S*,5*R*)- and (+)-(2*R*,5*R*)-2-(2-chloro-4-fluorophenyl)-1-(3-ethoxy-3-oxopropanoyl)-5-methoxycarbonyl-1,3-thiazolidine 8e

Yield (3.06 g, 97%); 0.8 : 1 separable *cis* and *trans* diastereomers; major isomer (*trans*, a mixture of conformers): white crystalline solid, mp 32–34 °C; *R*_f = 0.16 (EtOAc : petrol; 1 : 3); [α]_D²⁵ = -258.0 (*c* = 1.02, CHCl₃); ν_{max}/cm⁻¹ (neat) 1223 (s, C–F), 1662 (s, C=O), 1739 (s, C=O); δ_H (400 MHz, CDCl₃) 1.21 (3H, t, *J* = 7.2 Hz, OCH₂CH₃ major conformer), 1.29 (3H, t, *J* = 7.2 Hz, OCH₂CH₃ minor conformer), 3.04–3.52 (4H, m, H_{4A}, H_{4B}, H_{2''A}, H_{2''B}), 3.79 (3H, s, CO₂CH₃ major conformer), 3.85 (3H, s, OCH₃ minor conformer), 4.08 (2H, q, *J* = 7.2 Hz, OCH₂CH₃ major conformer), 4.16–4.26 (2H, m, OCH₂CH₃ minor conformer), 5.19–5.23 (1H, m, H5 minor conformer), 5.28–5.33 (1H, m, H5 major conformer), 6.42 (1H, s, H2 major conformer), 6.45 (1H, s, H2 minor conformer), 6.92 (1H, app td, *J* = 8.3, 2.4 Hz, H5' minor conformer), 7.02 (1H, app td, *J* = 8.2, 2.4 Hz, H5' major conformer), 7.10–7.18 (2H, m, H3' minor conformer, H6' major conformer), 7.20 (1H, dd, *J* = 8.2, 2.6 Hz, H3' major conformer), 7.32 (1H, dd, *J* = 8.7, 6.0 Hz, H6' minor conformer); δ_C (100.6 MHz, CDCl₃): 13.9 and 14.0 (OCH₂CH₃), 30.5 and 32.4 (C4), 42.0 and 43.0 (C2''), 52.8 and 53.5 (CO₂CH₃), 61.5 and 61.8 (OCH₂CH₃), 62.0 and 62.9 (C2), 64.2 and 64.5 (C5), 113.7 (d, *J* = 21.5 Hz, C5') and 114.5 (d, *J* = 21.5 Hz, C5'), 117.4 (d, *J* = 25.4 Hz, C3') and 118.0 (d, *J* = 24.6 Hz, C3'), 125.7 (d, *J* = 8.7 Hz, C6') and 126.4 (d, *J* = 8.7 Hz, C6'), 132.5 (d, *J* = 10.3 Hz, C2'), 134.6 (d, *J* = 3.2 Hz, C1') and 134.7 (d, *J* = 3.2 Hz, C1'), 161.6 (d, *J* = 249 Hz, C4') and 162.1 (d, *J* = 252 Hz, C4'), 164.5 and 165.0 (C1''), 165.9 and 167.4 (C3''), 169.1 and 170.0 (CO₂CH₃); *m/z* (ESI⁺) 390 ([M + H]⁺, 100%), 412.0 ([M + Na]⁺, 76%); HRMS (ESI⁺); C₁₆H₁₇ClFNNaO₅S [M + Na]⁺; found 412.0390, requires 412.0392.

Minor isomer (*cis*, a mixture of conformers): colourless oil; *R*_f = 0.24 (EtOAc : petrol; 1 : 3); [α]_D²⁵ = +124.4 (*c* = 1.0, CHCl₃); ν_{max}/cm⁻¹ (neat) 1226 (s, C–F), 1666 (s, C=O), 1742 (s, C=O); minor isomer (mixture of conformers): 1.16–1.25 (3H, m, OCH₂CH₃), 3.03–3.51 (4H, m, H_{4A}, H_{4B}, H_{2''A}, H_{2''B}), 3.80 (3H, s, CO₂CH₃ major conformer), 3.84 (3H, s, CO₂CH₃ minor conformer), 4.04–4.17 (2H, m, OCH₂CH₃), 4.86 (1H, dd, *J* = 9.4, 6.2 Hz, H5 major conformer), 5.04 (1H, app t, *J* = 5.1 Hz, H5 minor conformer), 6.34 (1H, s, H2 major conformer), 6.46 (1H, s, H2 minor conformer), 6.91 (1H, app td, *J* = 8.4, 2.6 Hz, H5' minor conformer), 7.03 (1H, app td, *J* = 8.3, 2.6 Hz, H5' major conformer), 7.12 (1H, dd, *J* = 8.2, 2.6 Hz, H3'), 7.79 (1H,

dd, *J* = 8.7, 6.0 Hz, H6' minor conformer), 8.24 (1H, dd, *J* = 8.7, 6.0 Hz, H6' major conformer); δ_C (100.6 MHz, CDCl₃): 13.8 (OCH₂CH₃), 31.0 and 33.6 (C4), 41.6 and 42.6 (C2''), 52.6 and 53.1 (CO₂CH₃), 61.5 (OCH₂CH₃), 62.7 and 64.3 (C2), 64.0 and 65.0 (C5), 114.1 (d, *J* = 21.5 Hz, C5') and 114.5 (d, *J* = 20.7 Hz, C5'), 116.5 (d, *J* = 24.6 Hz, C3') and 117.2 (d, *J* = 25.4 Hz, C3'), 128.2 (d, *J* = 8.7 Hz, C6') and 128.8 (d, *J* = 8.7 Hz, C6'), 132.5 (d, *J* = 11.1 Hz, C2'), 133.6 (d, *J* = 3.2 Hz, C1'), 161.5 (d, *J* = 249 Hz, C4') and 162.0 (d, *J* = 251 Hz, C4'), 165.0 and 165.1 (C1''), 166.1 and 166.6 (C3''), 170.2 and 170.3 (CO₂CH₃); *m/z* (ESI⁺) 390 ([M + H]⁺, 100%), 412.0 ([M + Na]⁺, 75%); HRMS (ESI⁺); C₁₆H₁₇ClFNNaO₅S [M + Na]⁺; found 412.0391, requires 412.0392.

(-)-(2*S*,5*R*)- and (+)-(2*R*,5*R*)-1-(3-ethoxy-3-oxopropanoyl)-2-(3-bromophenyl)-5-methoxycarbonyl-1,3-thiazolidine 8f

Yield (81%); 1.4 : 1 inseparable *cis* and *trans* diastereomers; *R*_f = 0.52 (EtOAc : petrol; 4 : 6), ν_{max}/cm⁻¹ (neat) 1165 (C–O), 1662 (C=O), 1743 (C=O), 2981, 2954 (CH₂); δ_H (400 MHz, CDCl₃) major isomer (*cis*, a mixture of conformers): 1.04–1.21 (3H, m, OCH₂CH₃), 2.98–3.55 (4H, m, H_{4A}, H_{4B}, H_{2''A}, H_{2''B}), 3.66 and 3.71 (3H, s, CO₂CH₃), 3.92–4.15 (2H, m, OCH₂CH₃), 4.91 (1H, app t, *J* = 7.0 Hz, H5, major rotamer), 4.98–5.01 (1H, m, H5, minor rotamer), 6.06 (1H, s, H2, major rotamer), 6.16 (1H, s, H2, minor rotamer), 7.03–7.79 (4H, m, Ar–CH); minor isomer (*trans*, a mixture of conformers): 1.04–1.21 (3H, m, OCH₂CH₃), 2.98–3.55 (4H, m, H_{4A}, H_{4B}, H_{2''A}, H_{2''B}), 3.66 and 3.71 (3H, s, CO₂CH₃), 3.92–4.15 (2H, m, OCH₂CH₃), 5.15 (1H, d, *J* = 5.4 Hz, H5, minor rotamer), 5.18–5.21 (1H, m, H5, major rotamer), 6.11 (1H, s, H2, major rotamer), 6.13 (1H, s, H2, minor rotamer), 7.03–7.79 (4H, m, Ar–CH); δ_C (100.6 MHz, CDCl₃) 14.02, 14.13, 14.18 (OCH₂CH₃ major, minor and rotamers), 31.00, 31.98, 32.99, 33.95 (C4 major, minor and rotamers), 42.04, 42.27, 42.83, 43.23 (C2'' major, minor and rotamers), 52.74, 53.15, 53.43, 53.77 (CO₂CH₃ major, minor and rotamers), 61.41, 61.54, 61.63, 61.70 (OCH₂CH₃ major, minor and rotamers), 63.82, 63.92, 64.23, 64.70 (C5 major, minor and rotamers), 64.23, 64.70, 65.39, 66.28 (C2 major, minor and rotamers), 122.13, 122.51, 122.84, 123.13 (C3', major, minor and rotamers), 123.76, 125.21, 125.86, 127.69, 128.00, 129.52, 129.89, 130.15, 130.49, 130.56, 130.81, 130.87, 131.46, 131.51 (C2', C4', C5', C6' major, minor and rotamers), 141.47, 142.57, 144.36, 144.70 (C1' major, minor and rotamers), 164.91, 165.21, 165.28, 165.47 (C1'' major, minor and rotamers), 166.15, 166.53, 166.93, 167.00 (C3'' major, minor and rotamers), 169.27, 170.06, 170.10 (CO₂CH₃ major, minor and rotamers); *m/z* (ESI⁺) 416 ([M + H]⁺); HRMS (ESI⁺); C₁₆H₁₈BrNNaO₅S [M + Na]⁺; found 437.9972, requires 437.9981.

(-)-(2*S*,5*R*)- and (+)-(2*R*,5*R*)-1-(3-ethoxy-3-oxopropanoyl)-2-(2-furanyl)-5-methoxycarbonyl-1,3-thiazolidine 8g

Yield (4.05 g, 89%); 0.8 : 1 separable *cis* and *trans* diastereomers; major isomer (*trans*, a mixture of conformers): yellow solid, mp 64–66 °C; *R*_f = 0.23 (EtOAc : petrol; 1 : 2); [α]_D²⁵ = -271.7 (*c* = 0.23, CHCl₃); ν_{max}/cm⁻¹ (neat) 1664 (s, C=O), 1735

(s, C=O); δ_{H} (400 MHz, CDCl_3) 1.23–1.29 (3H, m, OCH_2CH_3), 3.23 (1H, app d, $J = 12.5$ Hz, $\text{H}_{4\text{A}}/\text{H}_{4\text{B}}$ major conformer), 3.31 (1H, d, $J = 15.5$ Hz, $\text{H}_{2\text{A}}''/\text{H}_{2\text{B}}''$ major conformer), 3.38–3.40 (2H, m, $\text{H}_{2\text{A}}''$, $\text{H}_{2\text{B}}''$ minor conformer), 3.45–3.49 (2H, m, $\text{H}_{4\text{A}}/\text{H}_{4\text{B}}$ minor conformer, $\text{H}_{2\text{A}}''/\text{H}_{2\text{B}}''$ major conformer), 3.58 (1H, dd, $J = 12.3$, 6.9 Hz, $\text{H}_{4\text{A}}/\text{H}_{4\text{B}}$ major conformer), 3.69 (1H, dd, $J = 12.0$, 6.0 Hz, $\text{H}_{4\text{A}}/\text{H}_{4\text{B}}$ minor conformer), 3.77 (3H, s, CO_2CH_3 major conformer), 3.83 (3H, s, CO_2CH_3 minor conformer), 4.12–4.21 (2H, m, OCH_2CH_3), 5.05 (1H, app d, $J = 5.9$ Hz, H5 minor conformer), 5.18 (1H, app d, $J = 6.8$ Hz, H5 major conformer), 6.16 (1H, s, H2 major conformer), 6.23–6.25 (1H, m, H3' major conformer), 6.26–6.29 (2H, m, H3' and H4' minor conformer), 6.32–6.35 (2H, m, H2 minor conformer, H4' major conformer), 7.29–7.33 (1H, m, H5' minor conformer), 7.38–7.42 (1H, m, H5' major conformer); δ_{C} (100.6 MHz, CDCl_3): 13.2 (OCH_2CH_3), 31.2 and 33.1 (C4), 41.1 and 42.4 (C2''), 51.8 and 52.6 (CO_2CH_3), 58.0 and 58.5 (C2), 60.6 and 60.7 (OCH_2CH_3), 62.1 and 62.5 (C5), 105.2 and 106.4 (C3'), 109.7 and 109.9 (C4'), 141.1 and 142.5 (C5'), 151.8 and 152.0 (C1'), 164.1 (C1''), 165.7 and 166.3 (C3''), 168.8 and 169.5 (CO_2CH_3); m/z (ESI^+) 328 ($[\text{M} + \text{H}]^+$ 100%), 350 ($[\text{M} + \text{Na}]^+$ 26%); HRMS (ESI^+); $\text{C}_{14}\text{H}_{17}\text{NNaO}_6\text{S} [\text{M} + \text{Na}]^+$; found 350.0677, requires 350.0669. Minor isomer (*cis*): yellow oil; $R_f = 0.35$ (EtOAc : petrol; 1 : 2); $[\alpha]_{\text{D}}^{25} = +41.3$ ($c = 0.15$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1665 (s, C=O), 1736 (s, C=O); δ_{H} (500 MHz, CDCl_3) 1.27 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 3.22–3.35 (2H, m, $\text{H}_{4\text{A}}$, $\text{H}_{4\text{B}}$, major conformer), 3.38 (1H, d, $J = 15.4$ Hz, $\text{H}_{2\text{A}}''/\text{H}_{2\text{B}}''$ major conformer), 3.41–3.46 (2H, m, $\text{H}_{4\text{A}}/\text{H}_{4\text{B}}$ and $\text{H}_{2\text{A}}''/\text{H}_{2\text{B}}''$ minor conformer), 3.49–3.54 (1H, m, $\text{H}_{2\text{A}}''/\text{H}_{2\text{B}}''$ minor conformer), 3.56 (2H, d, $J = 15.5$ Hz, $\text{H}_{2\text{A}}''/\text{H}_{2\text{B}}''$ major conformer), 3.64 (1H, dd, $J = 11.4$, 4.8 Hz, $\text{H}_{4\text{A}}/\text{H}_{4\text{B}}$ minor conformer), 3.76 (3H, s, CO_2CH_3), 4.13–4.25 (4H, m, OCH_2CH_3), 4.91 (1H, dd, $J = 9.0$, 6.8 Hz, H5 major conformer), 4.96 (1H, dd, $J = 6.8$, 4.9 Hz, H5 minor conformer), 6.18 (1H, s, H2 major conformer), 6.56 (1H, s, H2 minor conformer), 6.26–6.29 (1H, m, H4' minor conformer), 6.34 (1H, dd, $J = 3.2$, 1.9 Hz, H4' major conformer), 6.44 (1H, d, $J = 3.2$ Hz, H3' minor conformer), 6.76 (1H, d, $J = 3.2$ Hz, H3' major conformer), 7.32–7.34 (1H, m, H5' minor conformer), 7.41 (1H, d, $J = 1.3$ Hz, H5' major conformer); δ_{C} (100.6 MHz, CDCl_3): 14.0 (OCH_2CH_3), 32.0 and 33.6 (C4), 41.8 and 42.4 (C2''), 52.7 and 53.1 (CO_2CH_3), 58.7 and 59.29 (C2), 61.7 (OCH_2CH_3), 62.7 and 63.4 (C5), 108.6 and 109.1 (C3'), 110.3 and 110.7 (C4'), 142.5 and 143.2 (C5'), 151.2 and 152.0 (C1'), 164.6 (C1''), 166.7 and 166.9 (C3''), 169.9 (CO_2CH_3); m/z (ESI^+) 328 ($[\text{M} + \text{H}]^+$ 100%), 350 ($[\text{M} + \text{Na}]^+$ 60%); HRMS (ESI^+); $\text{C}_{14}\text{H}_{17}\text{NNaO}_6\text{S} [\text{M} + \text{Na}]^+$; found 350.06688, requires 350.06688.

(–)-(2*S*,5*R*)-1-Aza-7-ethoxycarbonyl-6-hydroxy-8-oxo-2-phenyl-3-thiabicyclo[3.3.0]oct-6-ene 9a

Yield (1.02 g, 43%); yellow solid, mp 88–90 °C; $R_f = 0.55$ (EtOAc : MeOH; 6 : 1); $[\alpha]_{\text{D}}^{25} = -220.8$ ($c = 1.0$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1617 (s, C=C), 1656 (s, C=O), 1712 (s, C=O); δ_{H} (400 MHz, CDCl_3): 1.30 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 2.90 (1H, dd, $J = 11.0$, 8.1 Hz, $\text{H}_{4\text{A}}$), 3.19 (1H, dd, $J = 11.0$, 7.1 Hz, $\text{H}_{4\text{B}}$), 4.30 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 4.67 (1H, app t, $J = 7.6$

Hz, H5), 6.25 (1H, s, H2), 7.17–7.22 (1H, m, $\text{H}_{4'}$), 7.23–7.28 (2H, m, H3'), 7.35–7.41 (2H, m, H2'); δ_{C} (100.6 MHz, CDCl_3): 14.1 (OCH_2CH_3), 32.5 (C4), 61.6 (OCH_2CH_3), 62.2 (C2), 65.2 (C5), 98.8 (C7), 126.4 (C2'), 128.0 (C4'), 128.5 (C3'), 139.9 (C1'), 166.9 (C9), 168.8 (C8), 185.8 (C6); m/z (ESI^-) 304 ($[\text{M} - \text{H}]^-$, 100%); HRMS (ESI^-); $\text{C}_{15}\text{H}_{14}\text{NO}_4\text{S} [\text{M} - \text{H}]^-$; found 304.0639, requires 304.0649.

(–)-(2*S*,5*R*)-1-Aza-2-bromophenyl-7-ethoxycarbonyl-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene 9b

Yield (0.50 g, 45%); yellow solid, mp 134–136 °C; $R_f = 0.26$ (EtOAc : MeOH; 9 : 1); $[\alpha]_{\text{D}}^{25} = -190.5$ ($c = 1.0$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1656 (s, C=O), 1711 (s, C=O); δ_{H} (400 MHz, CD_2Cl_2): 1.36 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 3.02 (1H, dd, $J = 11.3$, 8.3 Hz, $\text{H}_{4\text{A}}$), 3.29 (1H, dd, $J = 11.3$, 7.1 Hz, $\text{H}_{4\text{B}}$), 4.37 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 4.76 (1H, app t, $J = 7.6$ Hz, H5), 6.22 (1H, s, H2), 7.35 (1H, d, $J = 8.1$ Hz, H2'), 7.49 (2H, d, $J = 8.6$ Hz, H3'); δ_{C} (100.6 MHz, CD_2Cl_2): 14.5 (OCH_2CH_3), 33.3 (C4), 62.3 (OCH_2CH_3), 62.3 (C2), 65.9 (C5), 99.5 (C7), 122.4 (C1'), 128.8 (C2'), 132.2 (C3'), 140.2 (C4'), 167.4 (C9), 186.5 (C6); m/z (ESI^-) 382 ($[\text{M} - \text{H}]^-$ 100%) and 384 ($[\text{M} - \text{H}]^-$ 100%); HRMS (ESI^-); $\text{C}_{15}\text{H}_{13}\text{O}_4\text{NBrS} [\text{M} - \text{H}]^-$; found 381.97563 and 383.97343, requires 381.97541, 383.97337.

(–)-(2*S*,5*R*)-1-Aza-7-ethoxycarbonyl-2-(4-fluorophenyl)-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene 9c

Yield (0.46 g; 50%); yellow solid; $R_f = 0.55$ (EtOAc : MeOH; 6 : 1); $[\alpha]_{\text{D}}^{25} = -192.4$, ($c = 0.47$, MeOH); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1224 (s, C–F), 1658 (s, C=O), 1710 (s, C=O); for **9c** purified by preparative TLC, δ_{H} (400 MHz, methanol- d_4): 1.28 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 2.95 (1H, dd, $J = 11.0$, 7.3 Hz, $\text{H}_{4\text{A}}$), 3.20 (1H, dd, $J = 11.0$, 7.6 Hz, $\text{H}_{4\text{B}}$), 4.15–4.24 (2H, m, OCH_2CH_3 and H5), 6.34 (1H, s, H2), 7.04 (2H, app t, $J = 8.8$ Hz, H3'), 7.47 (2H, dd, $J = 8.6$, 5.4 Hz, H2'); δ_{C} (125.8 MHz, methanol- d_4): 15.2 (OCH_2CH_3), 34.9 (C4), 59.7 (OCH_2CH_3), 64.6 (C2), 70.6 (C5), 91.9 (C7), 116.0 (d, $J = 21.9$ Hz, C3'), 129.6 (d, $J = 8.6$ Hz, C2'), 139.8 (C1'), 163.7 (d, $J = 244$ Hz, C4'), 167.3 (C9), 180.2 (C8), 195.1 (C6); m/z (ESI^-) 322 ($[\text{M} - \text{H}]^-$, 100%); HRMS (ESI^-); $\text{C}_{15}\text{H}_{13}\text{FNO}_4\text{S} [\text{M} - \text{H}]^-$; found 322.0552, requires 322.0555.

(–)-(2*S*,5*R*)-1-Aza-7-ethoxycarbonyl-6-hydroxy-2-(4-nitrophenyl)-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene 9d

Yield (0.32 g; 52%); yellow solid, mp 92 °C; $R_f = 0.52$ (EtOAc : MeOH; 6 : 1); $[\alpha]_{\text{D}}^{25} = -222.2$ ($c = 0.35$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1344 (s, ArNO_2), 1517 (s, ArNO_2), 1660 (s, C=O), 1711 (s, C=O); δ_{H} (400 MHz, CD_2Cl_2): 1.36 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.05 (1H, dd, $J = 10.9$, 8.5 Hz, $\text{H}_{4\text{A}}$), 3.31 (1H, dd, $J = 11.1$, 7.2 Hz, $\text{H}_{4\text{B}}$), 4.38 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 4.79 (1H, app t, $J = 7.6$ Hz, H5), 6.32 (1H, s, H2), 7.63 (2H, d, $J = 8.4$ Hz, H2'), 8.19 (2H, d, $J = 8.4$ Hz H3'); δ_{C} (125.8 MHz, CD_2Cl_2): 14.5 (OCH_2CH_3), 33.5 (C4), 62.2 (C2), 62.4 (OCH_2CH_3), 65.9 (C5), 99.7 (C7), 124.4 (C3'), 127.9 (C2'), 148.3 (C1'), 148.3 (C4'), 167.4 (C9), 169.2 (C8), 186.6 (C6); m/z (ESI^-) 349 ($[\text{M} - \text{H}]^-$, 100%); HRMS (ESI^-); $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_6\text{S} [\text{M} - \text{H}]^-$; found 349.0500, requires 349.0510.

(-)-(2*S*,5*R*)-1-Aza-2-(2-Chloro-4-fluorophenyl)-7-ethoxycarbonyl-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene **9e**

Yield (0.48 g, 49%); yellow solid, mp 128 °C; $R_f = 0.57$ (EtOAc : MeOH; 6 : 1); $[\alpha]_D^{25} = -264.0$ ($c = 0.20$, CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1233 (s, C-F), 1621 (s, C=C), 1658 (s, C=O), 1715 (s, C=O); δ_{H} (400 MHz, CDCl₃): 1.38 (3H, t, $J = 7.1$ Hz, OCH₂CH₃), 2.99 (1H, dd, $J = 11.0$, 8.8 Hz, H_{4A}), 3.28 (1H, dd, $J = 11.0$, 7.0 Hz, H_{4B}), 4.39 (2H, q, $J = 7.1$ Hz, OCH₂CH₃), 4.91 (1H, dd, $J = 8.8$, 7.0 Hz, H₅), 6.45 (1H, s, H₂), 6.97 (1H, app td, $J = 8.3$, 2.5 Hz, H_{5'}), 7.13 (1H, dd, $J = 8.3$, 2.6 Hz, H_{3'}), 7.38 (1H, dd, $J = 8.6$, 5.9 Hz, H_{6'}); δ_{C} (100.6 MHz, CDCl₃): 14.1 (OCH₂CH₃), 32.4 (C₄), 59.4 (C₂), 61.8 (OCH₂CH₃), 66.0 (C₅), 98.8 (C₇), 114.2 (d, $J = 21.5$ Hz, C_{5'}), 117.4 (d, $J = 25.4$ Hz, C_{3'}), 127.3 (d, $J = 9.5$ Hz, C_{6'}), 133.2 (d, $J = 10.3$ Hz, C_{2'}), 134.3 (d, $J = 3.2$ Hz, C_{1'}), 161.9 (d, $J = 250$ Hz, C_{4'}), 167.0 (C₉), 167.9 (C₈), 185.8 (C₆); m/z (ESI⁻) 356 ([M - H]⁻, 100%); HRMS (ESI⁻); C₁₅H₁₂ClFNO₄S [M - H]⁻; found 356.0172, requires 356.0165.

(-)-(2*S*,5*R*)-1-Aza-2-(2-chloro-4-fluorophenyl)-7-ethoxycarbonyl-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene **9e**

Yield (0.03 g, 58%); yellow solid, mp 176–178 °C; $R_f = 0.57$ (EtOAc : MeOH; 6 : 1); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1236 (s, C-F), 1650 (s, C=O), 1712 (s, C=O); for **9e** purified by preparative TLC: $[\alpha]_D^{25} = -240.4$ ($c = 0.27$, MeOH); δ_{H} (400 MHz, methanol-*d*₄): 1.28 (3H, t, $J = 7.0$ Hz, OCH₂CH₃), 2.95 (1H, dd, $J = 11.0$, 7.8 Hz, H_{4A}), 3.20 (1H, dd, $J = 11.0$, 7.3 Hz, H_{4B}), 4.14–4.23 (2H, m, OCH₂CH₃), 4.42 (1H, app t, $J = 7.6$ Hz, H₅), 6.52 (1H, s, H₂), 7.07 (1H, app td, $J = 8.5$, 2.3 Hz, H_{5'}), 7.21 (1H, dd, $J = 8.6$, 2.7 Hz, H_{3'}), 7.52 (1H, dd, $J = 8.7$, 6.0 Hz, H_{6'}); δ_{C} (125.8 MHz, methanol-*d*₄): 15.2 (OCH₂CH₃), 34.2 (C₄), 59.7 (OCH₂CH₃), 62.3 (C₂), 71.8 (C₅), 91.5 (C₇), 115.3 (d, $J = 21.0$ Hz, C_{5'}), 117.9 (d, $J = 25.8$ Hz, C_{3'}), 129.2 (d, $J = 8.6$ Hz, C_{6'}), 134.1 (d, $J = 10.5$ Hz, C_{2'}), 138.3 (d, $J = 2.9$ Hz, C_{1'}), 163.2 (d, $J = 248$ Hz, C_{4'}), 167.2 (C₉), 179.7 (C₈), 195.0 (C₆); m/z (ESI⁻) 356 ([M - H]⁻, 100%); HRMS (ESI⁻); C₁₅H₁₂ClFNO₄S [M - H]⁻; found 356.0170, requires 356.0165. For **9e** purified by flash column chromatography followed by acid wash: $[\alpha]_D^{25} = -331.8$ ($c = 0.27$, CHCl₃); δ_{H} (400 MHz, methanol-*d*₄): 1.32 (3H, t, $J = 7.1$ Hz, OCH₂CH₃), 3.04 (1H, dd, $J = 11.0$, 8.9 Hz, H_{4A}), 3.29–3.40 (1H, m, H_{4B}), 4.31 (2H, q, $J = 7.0$ Hz, OCH₂CH₃), 5.05 (1H, dd, $J = 8.8$, 6.9 Hz, H₅), 6.39 (1H, s, H₂), 7.10 (1H, app td, $J = 8.5$, 2.6 Hz, H_{5'}), 7.25 (1H, dd, $J = 8.5$, 2.6 Hz, H_{3'}), 7.58 (1H, dd, $J = 8.7$, 6.0 Hz, H_{6'}).

(+)-(2*R*,5*S*)-1-Aza-2-(2-chloro-4-fluorophenyl)-7-ethoxycarbonyl-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene *ent*-**9e**

Yield (0.033 g, 6%); yellow solid; $R_f = 0.57$ (EtOAc : MeOH; 6 : 1); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1232 (s, C-F), 1656 (s, C=O), 1709 (s, C=O); for *ent*-**9e** purified by preparative TLC: $[\alpha]_D^{25} = +230.3$ ($c = 0.38$, MeOH); δ_{H} (400 MHz, methanol-*d*₄): 1.28 (3H, t, $J = 7.0$ Hz, OCH₂CH₃), 2.95 (1H, dd, $J = 10.7$, 8.0 Hz, H_{4A}), 3.20 (1H, $J = 10.7$, 7.5 Hz, H_{4B}), 4.19 (2H, q, $J = 7.0$ Hz, OCH₂CH₃), 4.43 (1H, app t, $J = 7.21$ Hz, H₅), 6.52 (1H, s, H₂), 7.07 (1H, app td, $J = 8.5$, 2.6 Hz, H_{5'}), 7.21 (1H, dd, $J = 8.5$, 2.6 Hz, H_{3'}), 7.51 (1H, dd, $J = 8.7$, 6.0 Hz, H_{6'}); δ_{C} (125.8 MHz, methanol-*d*₄):

15.2 (OCH₂CH₃), 34.2 (C₄), 59.7 (OCH₂CH₃), 62.3 (C₂), 71.8 (C₅), 91.5 (C₇), 115.3 (d, $J = 21.9$ Hz, C_{5'}), 117.9 (d, $J = 25.8$ Hz, C_{3'}), 129.2 (d, $J = 8.6$ Hz, C_{6'}), 134.1 (d, $J = 10.5$ Hz, C_{2'}), 138.3 (d, $J = 2.9$ Hz, C_{1'}), 163.2 (d, $J = 248$ Hz, C_{4'}), 167.3 (C₉), 179.7 (C₈), 195.0 (C₆); m/z (ESI⁻) 356 ([M - H]⁻, 100%); HRMS (ESI⁻); C₁₅H₁₂ClFNO₄S [M - H]⁻; found 356.0172, requires 356.0165. For *ent*-**9e** purified by flash column chromatography followed by acid wash: $[\alpha]_D^{25} = +309.5$ ($c = 0.20$, CHCl₃); δ_{H} (400 MHz, methanol-*d*₄): 1.32 (3H, t, $J = 7.1$ Hz, OCH₂CH₃), 3.03 (1H, dd, $J = 10.9$, 8.9 Hz, H_{4A}), 3.29–3.40 (1H, m, H_{4B}), 4.31 (2H, q, $J = 7.0$ Hz, OCH₂CH₃), 5.06 (1H, dd, $J = 8.7$, 7.0 Hz, H₅), 6.39 (1H, s, H₂), 7.10 (1H, app td, $J = 8.4$, 2.6 Hz, H_{5'}), 7.25 (1H, dd, $J = 8.5$, 2.6 Hz, H_{3'}), 7.57 (1H, dd, $J = 8.8$, 6.0 Hz, H_{6'}).

(+)-(2*S*,5*R*)-1-Aza-2-(3-bromophenyl)-7-ethoxycarbonyl-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene **9f**

Yield (78%); $R_f = 0.48$ (EtOAc : MeOH; 4 : 1); $[\alpha]_D^{25} = +55.0$ ($c = 1.6 \times 10^{-3}$, MeOH); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1696 (C=O), 1622 (C=C); δ_{H} (500 MHz, methanol-*d*₄): 1.28 (3H, t, $J = 7.1$ Hz, OCH₂CH₃), 2.97 (1H, dd, $J = 11.0$, 7.3 Hz, H_{4A}), 3.20 (1H, dd, $J = 11.0$, 7.6 Hz, H_{4B}), 4.14–4.23 (3H, m, OCH₂CH₃ and H₅), 6.32 (1H, s, H₂), 7.24 (1H, app t, $J = 7.9$ Hz, H_{5'}), 7.37–7.45 (2H, m, H_{4'} and H_{6'}), 7.58–7.63 (1H, m, H_{2'}); δ_{C} (125 MHz, methanol-*d*₄) 15.2 (OCH₂CH₃), 34.9 (C₄), 59.6 (OCH₂CH₃), 64.6 (C₂), 70.7 (C₅), 91.9 (C₇), 123.4 (C_{3'}), 126.5 (C_{4'/C6'}), 130.6 (C_{2'}), 131.3 (C_{5'}), 131.6 (C_{4'/C6'}), 146.5 (C_{1'}), 167.0 (C₉), 180.2 (C₈), 194.9 (C₆); m/z (ESI⁻) 382 ([M - H]⁻); HRMS (ESI⁻); C₁₅H₁₃BrNO₄S [M - H]⁻; found 381.9744, requires 381.9754.

(-)-(2*S*,5*R*)-1-Aza-7-ethoxycarbonyl-2-(2-furanyl)-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene **9g**

Yield (1.53 g, 40%); brown oil; $R_f = 0.30$ (EtOAc : MeOH; 9 : 1); $[\alpha]_D^{25} = -153.3$ ($c = 0.06$, CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1614 (s, C=C), 1663 (s, C=O), 1709 (s, C=O); δ_{H} (400 MHz, CD₂Cl₂): 1.36 (3H, t, $J = 7.1$ Hz, OCH₂CH₃), 3.08 (1H, dd, $J = 11.0$, 6.9 Hz, H_{4A}), 3.47 (1H, dd, $J = 11.0$, 8.1 Hz, H_{4B}), 4.37 (2H, q, $J = 7.1$ Hz, OCH₂CH₃), 4.83 (1H, app t, $J = 7.5$ Hz, H₅), 6.30 (1H, s, H₂), 6.33–6.35 (2H, m, H_{3'} and H_{4'}), 7.40–7.43 (1H, m, H_{5'}); δ_{C} (125.8 MHz, CD₂Cl₂): 14.5 (OCH₂CH₃), 32.9 (C₄), 56.3 (C₂), 62.3 (OCH₂CH₃), 65.2 (C₅), 99.2 (C₇), 107.5 (C_{3'}), 110.9 (C_{4'}), 143.5 (C_{5'}), 153.4 (C_{1'}), 167.4 (C₉), 168.8 (C₈), 187.2 (C₆); m/z (ESI⁻) 294 ([M - H]⁻, 50%); HRMS (ESI⁻); C₁₃H₁₂NO₅S [M - H]⁻; found 294.0446, requires 294.0442.

(±)-(2*RS*,5*R*)-2-(4-Fluorophenyl)-5-methoxycarbonyl-1,3-thiazolidine (±)-**7c**

Yield (0.42 g, 43%); colourless oil; 1.7 : 1 *cis* and *trans* diastereomers; $R_f = 0.35$ (EtOAc : petrol; 1 : 3); $\nu_{\max}/\text{cm}^{-1}$ (neat) 1223 (s, C-F), 1741 (s, C=O), 3315 (m, N-H); δ_{H} (200 MHz, CDCl₃) major isomer (*cis*): 2.57 (1H, br. s., NH), 3.05–3.26 (1H, m, H_{4A}), 3.33–3.53 (1H, m, H_{4B}), 3.81 (3H, s, CO₂CH₃), 3.99 (1H, dd, $J = 8.8$, 7.1 Hz, H₅), 5.53 (1H, s, H₂), 6.96–7.12 (2H, m, H_{3'}), 7.43–7.56 (2H, m, H_{2'}); minor isomer (*trans*): 2.57 (1H, br. s., NH), 3.05–3.26 (1H, m, H_{4A}), 3.33–3.53 (1H, m, H_{4B}), 3.80 (3H, s, CO₂CH₃), 4.14–4.23 (1H, m, H₅), 5.79 (1H, s, H₂), 6.96–7.12 (2H, m, H_{3'}), 7.43–7.56 (2H, m, H_{2'});

δ_{C} (100.6 MHz, CDCl_3) major isomer (*cis*): 39.2 (C4), 52.6 (CO_2CH_3), 65.4 (C5), 71.8 (C2), 115.5 (d, $J = 21.5$ Hz, C3'), 129.3 (d, $J = 8.7$ Hz, C2'), 133.9 (d, $J = 3.2$ Hz, C1'), 162.8 (d, $J = 247$ Hz, C4'), 171.5 (CO_2CH_3); minor isomer (*trans*): 38.0 (C4), 52.6 (CO_2CH_3), 64.1 (C5), 69.9 (C2), 115.1 (d, $J = 21.5$ Hz, C3'), 128.7 (d, $J = 8.0$ Hz, C2'), 136.9 (d, $J = 3.2$ Hz, C1'), 162.3 (d, $J = 247$ Hz, C4'), 172.1 (CO_2CH_3); m/z (ESI^+) 242 ($[\text{M} + \text{H}]^+$, 100%); HRMS (ESI^+); $\text{C}_{11}\text{H}_{13}\text{FNO}_2\text{S}$ $[\text{M} + \text{H}]^+$; found 242.0642, requires 242.0646.

(±)-(2*RS*,5*R*)-(3-Ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)-5-methoxycarbonyl-1,3-thiazolidine (±)-8c

Yield (0.43 g, 81%); colourless oil; 1.3 : 1 *cis* and *trans* diastereomers; $R_{\text{f}} = 0.61$ (EtOAc : petrol; 1 : 1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1224 (s, C–F), 1662 (s, C=O), 1740 (s, C=O); δ_{H} (400 MHz, CDCl_3) major isomer (*cis*, a mixture of conformers): 1.19–1.31 (3H, m, OCH_2CH_3), 3.07–3.55 (4H, m, H_{4A}, H_{4B}, H_{2''A}, H_{2''B}), 3.81 and 3.83 (3H, s, CO_2CH_3), 4.05–4.24 (2H, m, OCH_2CH_3), 5.03–5.08 (1H, m, H5), 6.13 and 6.30 (1H, s, H2), 6.95–7.01 and 7.04–7.10 (2H, m, H3'), 7.48–7.54 and 7.64–7.69 (2H, m, H2'); minor isomer (*trans*, a mixture of conformers): 1.19–1.31 (3H, m, OCH_2CH_3), 3.07–3.55 (4H, m, H_{4A}, H_{4B}, H_{2''A}, H_{2''B}), 3.78 and 3.84 (3H, s, CO_2CH_3), 4.05–4.24 (2H, m, OCH_2CH_3), 5.17–5.21 and 5.28–5.31 (1H, m, H5), 6.17 and 6.29 (1H, s, H2), 6.95–7.01 and 7.04–7.10 (2H, m, H3'), 7.19–7.23 and 7.24–7.29 (2H, m, H2'); δ_{C} (100.6 MHz, CDCl_3) major isomer (*cis*, a mixture of conformers): 13.9 and 14.0 (OCH_2CH_3), 32.0 and 33.8 (C4), 42.1 and 43.0 (C2''), 52.8 and 53.1 (CO_2CH_3), 61.5, 61.6 and 61.8 (OCH_2CH_3), 63.7 and 64.6 (C5), 65.7 and 66.4 (C2), 115.0 (d, $J = 21.5$ Hz, C3') and 115.9 (d, $J = 21.5$ Hz, C3'), 128.4 (d, $J = 8.0$ Hz, C2') and 129.0 (d, $J = 8.7$ Hz, C2'), 135.6 (d, $J = 2.4$ Hz, C1'), 162.6 (d, $J = 249$ Hz, C4'), 165.4 (C1''), 166.6 (C3''), 170.2 (CO_2CH_3); minor isomer (*trans*, a mixture of conformers): 13.9 and 14.0 (OCH_2CH_3), 30.9 and 33.0 (C4), 42.3 and 43.3 (C2''), 52.8 and 53.4 (CO_2CH_3), 61.5, 61.6 and 61.8 (OCH_2CH_3), 64.0 and 64.2 (C5), 64.4 and 65.1 (C2), 115.3 (d, $J = 22.3$ Hz, C3') and 116.2 (d, $J = 21.5$ Hz, C3'), 126.5 (d, $J = 8.7$ Hz, C2') and 126.7 (d, $J = 8.0$ Hz, C2'), 137.9 (d, $J = 2.4$ Hz, C1'), 162.5 (d, $J = 248$ Hz, C4'), 165.3 (C1''), 166.2 (C3''), 169.3 (CO_2CH_3); m/z (ESI^+) 356 ($[\text{M} + \text{H}]^+$, 100%) 378 ($[\text{M} + \text{Na}]^+$, 94%); HRMS (ESI^+); $\text{C}_{16}\text{H}_{18}\text{FNNaO}_5\text{S}$ $[\text{M} + \text{Na}]^+$; found 378.0797, requires 378.0782.

(±)-(2*S*,5*R*)-1-Aza-7-ethoxycarbonyl-2-(4-fluorophenyl)-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene (±)-9c

Yield (0.12 g, 53%); yellow solid; $R_{\text{f}} = 0.55$ (EtOAc : MeOH; 6 : 1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1224 (s, C–F), 1658 (s, C=O), 1709 (s, C=O); for (±)-9c purified by preparative TLC, δ_{H} (400 MHz, methanol- d_4): 1.28 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 2.95 (1H, dd, $J = 11.0$, 7.3 Hz, H_{4A}), 3.20 (1H, dd, $J = 11.0$, 7.6 Hz, H_{4B}), 4.14–4.24 (3H, m, OCH_2CH_3 , H5), 6.34 (1H, s, H2), 7.04 (2H, app t, $J = 8.8$ Hz, H3'), 7.47 (2H, dd, $J = 8.6$, 5.4 Hz, H2'); δ_{C} (125.8 MHz, methanol- d_4): 15.2 (OCH_2CH_3), 34.9 (C4), 59.7 (OCH_2CH_3), 64.6 (C2), 70.6 (C5), 91.9 (C7), 116.0 (d, $J = 21.9$ Hz, C3'), 129.6 (d, $J = 8.6$ Hz, C2'), 139.8 (C1'), 163.7 (d, $J = 244$ Hz, C4'), 167.3 (C9), 180.2 (C8), 195.1 (C6); m/z (ESI^-) 322

($[\text{M} - \text{H}]^-$, 100%); HRMS (ESI^-); $\text{C}_{15}\text{H}_{13}\text{FNO}_4\text{S}$ $[\text{M} - \text{H}]^-$; found 322.0569, requires 322.0555.

(±)-(2*RS*,5*R*)-2-(2-Chloro-4-fluorophenyl)-5-methoxycarbonyl-1,3-thiazolidine (±)-7e

Yield 51% (1.15 g); colourless oil; 0.9 : 1 *cis* and *trans* diastereomers; $R_{\text{f}} = 0.18$ (EtOAc : petrol; 1 : 5); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1227 (s, C–F), 1738 (s, C=O), 3324 (m, N–H); δ_{H} (400 MHz, CDCl_3) major isomer (*trans*): 2.66 (1H, br. s., NH), 3.06–3.14 (1H, m, H_{4A}), 3.33 (1H, dd, $J = 10.5$, 6.4 Hz, H_{4B}), 3.81 (3H, s, CO_2CH_3), 4.21 (1H, app t, $J = 6.6$ Hz, H5), 6.02 (1H, s, H2), 6.95 (2H, app td, $J = 8.3$, 2.7 Hz, H5'), 7.08–7.15 (2H, m, H3'), 7.57 (2H, dd, $J = 8.7$, 6.2 Hz, H6'); minor isomer (*cis*): 2.66 (1H, br. s., NH), 3.06–3.14 (1H, m, H_{4A}), 3.45 (1H, dd, $J = 10.3$, 6.9 Hz, H_{4B}), 3.80 (3H, s, CO_2CH_3), 3.96–4.04 (1H, m, H5), 5.88 (1H, s, H2), 7.03 (2H, app td, $J = 8.3$, 2.7 Hz, H5'), 7.08–7.15 (2H, m, H3'), 7.74 (2H, dd, $J = 8.7$, 6.0 Hz, H6'); δ_{C} (100.6 MHz, CDCl_3): major isomer (*trans*): 37.3 (C4), 52.6 (CO_2CH_3), 64.7 (C5), 66.5 (C2), 113.8 (d, $J = 21.5$ Hz, C5'), 117.0 (d, $J = 25.4$ Hz, C3'), 127.8 (d, $J = 8.7$ Hz, C6'), 133.5 (d, $J = 10.3$ Hz, C2'), 136.1 (d, $J = 4.0$ Hz, C1'), 161.6 (d, $J = 250$ Hz, C4'), 171.9 (CO_2CH_3); minor isomer (*cis*): 38.7 (C4), 52.6 (CO_2CH_3), 65.3 (C5), 67.6 (C2), 114.5 (d, $J = 20.7$ Hz, C5'), 117.1 (d, $J = 24.6$ Hz, C3'), 129.7 (d, $J = 8.7$ Hz, C6'), 131.9 (d, $J = 3.2$ Hz, C1'), 134.5 (d, $J = 10.3$ Hz, C2'), 162.1 (d, $J = 251$ Hz, C4'), 171.4 (CO_2CH_3); m/z (ESI^+) 276 ($[\text{M} + \text{H}]^+$, 100%); HRMS (ESI^+); $\text{C}_{11}\text{H}_{11}\text{ClFNNaO}_2\text{S}$ $[\text{M} + \text{Na}]^+$; found 298.0079, requires 298.0075.

(±)-(2*RS*,5*R*)-2-(2-Chloro-4-fluorophenyl)-(3-ethoxy-3-oxopropanoyl)-5-methoxycarbonyl-1,3-thiazolidine (±)-8e

Yield (0.73 g, 94%); 0.7 : 1 separable *cis* and *trans* diastereomers; major isomer (*trans*, a mixture of conformers): white solid, mp 82–84 °C; $R_{\text{f}} = 0.16$ (EtOAc : petrol; 1 : 3); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1225 (s, C–F), 1668 (s, C=O), 1743 (s, C=O); δ_{H} (400 MHz, CDCl_3): 1.23 (3H, t, $J = 7.1$ Hz, OCH_2CH_3 major conformer), 1.31 (3H, t, $J = 7.2$ Hz, OCH_2CH_3 minor conformer), 3.06–3.48 (4H, m, H_{4A}, H_{4B}, H_{2''A}, H_{2''B}), 3.81 (3H, s, CO_2CH_3 major conformer), 3.87 (3H, s, CO_2CH_3 minor conformer), 4.10 (2H, q, $J = 7.1$ Hz, OCH_2CH_3 major conformer), 4.18–4.27 (2H, m, OCH_2CH_3 minor conformer), 5.20–5.23 (1H, m, H5 minor conformer), 5.30–5.34 (1H, m, H5 major conformer), 6.44 (1H, s, H2 major conformer), 6.47 (1H, s, H2 minor conformer), 6.94 (1H, app td, $J = 8.4$, 2.6 Hz, H5' minor conformer), 7.03 (1H, $J = 8.3$, 2.6 Hz, H5' major conformer), 7.12–7.18 (2H, m, H3' minor conformer, H6' major conformer), 7.21 (1H, dd, $J = 8.2$, 2.6 Hz, H3' major conformer), 7.33 (1H, dd, $J = 8.6$, 5.9 Hz, H6' minor conformer); δ_{C} (100.6 MHz, CDCl_3): 13.9 and 14.0 (OCH_2CH_3), 30.6 and 32.5 (C4), 42.1 and 43.1 (C2''), 52.9 and 53.5 (CO_2CH_3), 61.6 and 61.9 (OCH_2CH_3), 62.0 and 62.9 (C2), 64.3 and 64.6 (C5), 113.8 (d, $J = 20.7$ Hz, C5') and 114.5 (d, $J = 21.5$ Hz, C5'), 117.5 (d, $J = 24.6$ Hz, C3') and 118.0 (d, $J = 24.6$ Hz, C3'), 125.7 (d, $J = 8.7$ Hz, C6') and 126.4 (d, $J = 8.7$ Hz, C6'), 132.6 (d, $J = 10.3$ Hz, C2'), 134.6 (d, $J = 3.2$ Hz, C1') and 134.7 (d, $J = 3.2$ Hz, C1'), 161.6 (d, $J = 250$ Hz, C4') and 162.1 (d, $J = 252$ Hz, C4'), 164.5 and 165.1 (C1''), 166.0 and 167.5 (C3''), 169.2 and 170.1 (CO_2CH_3); m/z (ESI^+) 390 ($[\text{M} + \text{H}]^+$, 100%),

412.0 ($[M + Na]^+$ 65%); HRMS (ESI^+); $C_{16}H_{17}ClFNNaO_5S$ $[M + Na]^+$; found 412.0398, requires 412.0392. Minor isomer (*cis*, a mixture of conformers): colourless oil; $R_f = 0.24$ (EtOAc : petrol; 1 : 3); ν_{max}/cm^{-1} (neat) 1224 (s, C–F), 1664 (s, C=O), 1740 (s, C=O); δ_H (400 MHz, $CDCl_3$): 1.21–1.30 (3H, m, OCH_2CH_3), 3.07–3.54 (4H, m, H_{4A} , H_{4B} , $H_{2''A}$, $H_{2''B}$), 3.85 (3H, s, CO_2CH_3 major conformer), 3.89 (3H, s, CO_2CH_3 minor conformer), 4.09–4.22 (2H, m, OCH_2CH_3), 4.91 (1H, dd, $J = 9.2$, 6.5 Hz, H5 major conformer), 5.06 (1H, app t, $J = 5.0$ Hz, H5 minor conformer), 6.38 (1H, s, H2 major conformer), 6.52 (1H, s, H2 minor conformer), 6.95 (1H, app t, $J = 8.3$ Hz, H5' minor conformer), 7.08 (1H, app td, $J = 8.3$, 2.3 Hz, H5' major conformer), 7.17 (1H, dd, $J = 8.1$, 2.4 Hz, H3'), 7.84 (1H, dd, $J = 8.7$, 6.0 Hz, H6' minor conformer), 8.28 (1H, dd, $J = 8.7$, 6.0 Hz, H6' major conformer); δ_C (100.6 MHz, $CDCl_3$): 14.0 (OCH_2CH_3), 31.2 and 33.8 (C4), 41.8 and 42.8 (C2''), 52.8 and 53.3 (CO_2CH_3), 61.7 (OCH_2CH_3), 62.9 and 64.5 (C2), 64.2 and 65.2 (C5), 114.3 (d, $J = 20.7$ Hz, C5') and 114.7 (d, $J = 20.7$ Hz, C5'), 116.7 (d, $J = 25.4$ Hz, C3') and 117.4 (d, $J = 25.4$ Hz, C3'), 128.3 (d, $J = 8.0$ Hz, C6') and 128.9 (d, $J = 8.7$ Hz, C6'), 132.7 (d, $J = 10.3$ Hz, C2'), 133.7 (d, $J = 4.0$ Hz, C1'), 162.2 (d, $J = 252$ Hz, C4'), 165.1 and 165.3 (C1''), 166.2 and 166.8 (C3''), 170.3 and 170.4 (CO_2CH_3); m/z (ESI^+) 390 ($[M + H]^+$ 100%), 412.0 ($[M + Na]^+$ 71%); HRMS (ESI^+); $C_{16}H_{17}ClFNNaO_5S$ $[M + Na]^+$; found 412.0393, requires 412.0392.

(±)-(2*S*,5*R*)-1-Aza-2-(2-Chloro-4-fluorophenyl)-7-ethoxycarbonyl-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene (±)9e

Yield (74 mg, 45%); yellow solid, mp 96–98 °C; $R_f = 0.57$ (EtOAc : MeOH; 6 : 1); ν_{max}/cm^{-1} (neat) 1230 (s, C–F), 1658 (s, C=O), 1707 (s, C=O); δ_H (500 MHz, CD_2Cl_2): 1.37 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.01 (1H, dd, $J = 11.0$, 8.8 Hz, H_{4A}), 3.30 (1H, dd, $J = 11.0$, 6.9 Hz, H_{4B}), 4.39 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 4.91–4.95 (1H, m, H5), 6.41 (1H, s, H2), 7.03 (1H, app td, $J = 8.4$, 2.6 Hz, H5'), 7.17 (1H, dd, $J = 8.4$, 2.6 Hz, H3'), 7.42 (1H, dd, $J = 8.6$, 6.0 Hz, H6'); δ_C (125 MHz, CD_2Cl_2): 14.5 (OCH_2CH_3), 33.0 (C4), 59.9 (OCH_2CH_3), 62.4 (C2), 66.6 (C5), 99.5 (C7), 114.9 (d, $J = 21.9$ Hz, C5'), 117.8 (d, $J = 25.8$ Hz, C3'), 128.0 (d, $J = 8.6$ Hz, C6'), 133.6 (d, $J = 10.5$ Hz, C2'), 135.4 (d, $J = 3.8$ Hz, C1'), 162.6 (d, $J = 250$ Hz, C4'), 167.5 (C9), 168.3 (C8), 186.5 (C6); m/z (ESI^-) 356 ($[M - H]^-$, 100%); HRMS (ESI^-); $C_{15}H_{14}O_4NClFS$ $[M - H]^-$; found 358.03120, requires 358.03106.

(±)-(2*S*,5*R*)-1-Aza-2-bromophenyl-7-ethoxycarbonyl-6-hydroxy-8-oxo-3-thiabicyclo[3.3.0]oct-6-ene (±)9b

Yield (47 mg, 39%); yellow solid, mp 148 °C; $R_f = 0.26$ (EtOAc : MeOH; 9 : 1); ν_{max}/cm^{-1} (neat) 1618 (C=C), 1657 (s, C=O), 1712 (s, C=O); δ_H (500 MHz, CD_2Cl_2): 1.37 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.02 (1H, dd, $J = 11.2$, 8.2 Hz, H_{4A}), 3.29 (1H, dd, $J = 11.2$, 7.1 Hz, H_{4B}), 4.38 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 4.76 (1H, app t, $J = 7.6$ Hz, H5), 6.22 (1H, s, H2), 7.35 (2H, d, $J = 8.3$ Hz, H2'), 7.49 (2H, d, $J = 8.5$ Hz, H3'); δ_C (125 MHz, CD_2Cl_2): 14.5 (OCH_2CH_3), 33.4 (C4), 62.3 (OCH_2CH_3), 62.4 (C2), 65.8 (C5), 99.7 (C7), 122.4 (C1'), 128.8 (C2'), 132.2 (C3'), 140.3 (C4'), 167.5 (C9), 169.1 (C8), 186.6 (C6); m/z (ESI^-) 382.0 and 384.0

($[M - H]^-$, 100%); HRMS (ESI^-); $C_{15}H_{13}O_4NBrS$ $[M - H]^-$; found 381.97573 and 383.97348, requires 381.97541, 383.97337.

Acknowledgements

We are particularly grateful for access to chiral chromatography made available by Professors Martin Smith and Mike Willis (University of Oxford). We also wish to acknowledge financial support from the FfWG and from an MRC Confidence in Concept award. SI thanks HEC Pakistan for a scholarship.

References

- R. Schobert and A. Schlenk, *Bioorg. Med. Chem.*, 2008, **16**, 4203–4221.
- B. J. L. Royles, *Chem. Rev.*, 1995, **95**, 1981–2001.
- M. D. Andrews, A. G. Brewster, K. M. Crapnell, A. J. Ibbett, T. Jones, M. G. Moloney, K. Prout and D. Watkin, *J. Chem. Soc., Perkin Trans. 1*, 1998, 223–235.
- M. Anwar, A. R. Cowley and M. G. Moloney, *Tetrahedron: Asymmetry*, 2010, **21**, 1758–1770.
- L. Josa-Culleré, M. G. Moloney and A. L. Thompson, *Synlett*, 2016, DOI: 10.1055/s-0035-1561942.
- Y.-C. Jeong, M. Anwar, T. M. Nguyen, B. S. W. Tan, C. L. L. Chai and M. G. Moloney, *Org. Biomol. Chem.*, 2011, **9**, 6663–6669.
- D. Seebach, A. R. Sting and M. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2708–2748.
- L. Lazar and F. Fulop, *Eur. J. Org. Chem.*, 2003, 3025–3042.
- J. H. Bailey, D. Cherry, J. Dyer, M. G. Moloney, M. J. Bamford, S. Keeling and R. B. Lamont, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2783–2792.
- S. A. Hermitage and M. G. Moloney, *Tetrahedron: Asymmetry*, 1994, 1463–1464.
- W. Flitsch, *Chem. Ber.*, 1970, **103**, 3205–3213.
- M. Anwar and M. G. Moloney, *Chem. Biol. Drug Des.*, 2013, **81**, 645–649.
- F. Fulop, J. Mattinen and K. Pihlaja, *Tetrahedron*, 1990, **46**, 6545–6552.
- M. D. Andrews, A. Brewster and M. G. Moloney, *Tetrahedron: Asymmetry*, 1994, **5**, 1477–1478.
- Single crystal X-ray diffraction data were collected at 150 K with an Oxford Diffraction (Rigaku) SuperNova diffractometer (using $\lambda = 1.54180$ Å) and processed with CrysAlisPro as per the ESI (CIF).† The structure was solved with SIR92²⁵ and refined with CRYSTALS.^{26,27} Full crystallographic data (in CIF format) is available as ESI† and has been deposited with the Cambridge Crystallographic Data Centre (reference code CCDC 1452987).
- F. Fulop and K. Pihlaja, *Tetrahedron*, 1993, **49**, 6701–6706.
- F. Fulop, K. Pihlaja, J. Mattinen and G. Bernath, *J. Org. Chem.*, 1987, **52**, 3821–3825.

- 18 F. Fulop, K. Pihlaja, K. Neuvonen, G. Bernath, G. Argay and A. Kalman, *J. Org. Chem.*, 1993, **58**, 1967–1969.
- 19 M. Zaghouani and B. Nay, *Nat. Prod. Rep.*, 2016, **33**, 540–548.
- 20 Y.-C. Jeong and M. G. Moloney, *J. Org. Chem.*, 2011, **76**, 1342–1354.
- 21 B. Barnickel, F. Bayliffe, R. Diestel, K. Kempf, S. Laschat, S. Pachali, F. Sasse, A. Schlenk and R. Schobert, *Chem. Biodiversity*, 2010, **7**, 2830–2845.
- 22 M. Sodeoka, R. Sampe, S. Kojima, Y. Baba, N. Morisaki and Y. Hashimoto, *Chem. Pharm. Bull.*, 2001, **49**, 206–212.
- 23 B. Biersack, R. Diestel, C. Jagusch, F. Sasse and R. Schobert, *J. Inorg. Biochem.*, 2009, **103**, 72–76.
- 24 M.-H. Lebrun, P. Duvert, F. Gaudemer, A. Gaudemer, C. Deballon and P. Boucly, *J. Inorg. Biochem.*, 1985, **24**, 167–181.
- 25 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.
- 26 R. I. Cooper, A. L. Thompson and D. J. Watkin, *J. Appl. Crystallogr.*, 2010, **43**, 1100–1107.
- 27 P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Crystallogr.*, 2003, **36**, 1487–1487.