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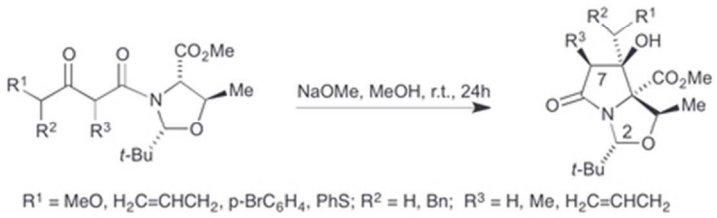

R^1 = MeO, $H_2C{=}CHCH_2$, p-BrC_6H_4, PhS; R^2 = H, Bn; R^3 = H, Me, $H_2C{=}CHCH_2$

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Diastereoselective Intramolecular Aldol Ring Closures of Threonine Derivatives Leading to Densely Functionalised Pyroglutamates Related to Oxazolomycin

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Abstract: Intramolecular aldol reactions on oxazolidine templates derived from threonine may be used to generate libraries of densely functionalised pyroglutamates with a high level of diastereoselectivity; the oxazolidine precursors themselves are suitable for further direct manipulation by side chain alkylation, permitting rapid access to cyclised products with several points of chemical diversity. Although these systems may be considered to be structural mimics of the functionalised pyroglutamate portion of oxazolomycin, little antibacterial activity against *S. aureus* and *E. coli* was found. These systems may additionally have application as three-dimensional fragments for drug discovery and development.

We have been interested in the development of methodology for rapid access to highly functionalised pyrrolidinones of particular relevance to the oxazolomycins (Figure 1)[1] and have established that Dieckmann[2] and aldol[3] ring closures may be used to access such systems. While a number of other groups have developed methodology to provide the relevant lactam-lactone spirocyclic and inthomycin subsets of the natural product,[4-11] we have established that some smaller structural mimics exhibit antibacterial activity[12-14] and therefore sought routes providing rapid access to other skeletal subsets of oxazolomycin which might similarly provide antibacterially active libraries. We recently reported that a biomimetic intramolecular aldol reaction using malonamide **2** (R^1 = H, R^2 = H, X = OMe) derived from oxazolidine template **1** may be used to generate densely functionalised pyroglutamates of type **3**, possessing two contiguous quaternary chiral centres.[15] Of interest to us was the possibility of extending this approach further, and we report here its application to threonine derivatives using systems of type **2** (R^1 = Me) giving a general approach which might be used to access diversely substituted systems, which have potential as three-dimensional scaffolds for fragment based drug discovery programmes, possessing well-defined structure, the capacity for synthetic manipulation and a natural product heritage.

Our first task was to establish a sequence which provided access to oxazolidines of type **2** (Scheme 1) with a diversity of substitution patterns, and which would ultimately translate into multiple ring substitution patterns on pyroglutamate **3**. Critical to the success of this strategy was

the simultaneous development of a direct method for the preparation of γ-substituted β-ketoesters by elaboration of Meldrum's acid,[16] substrates which are of particular interest due to their scope for further functionalisation; analogous ring openings on dioxinones have been recently reported.[17] Starting from substituted acetyl chlorides **4a-d**, conversion to the corresponding acylated Meldrum's acids **5a-d** proceeded in excellent yield (Scheme 2) using methodology which has recently been reported.[18] Further collapse of this system with *t*-butanol was very efficient, giving esters **6a-d**. In order to demonstrate that such intermediates could be used to perform the desired ring closing aldol reaction, one of them (**6a**) was hydrolysed to acid **7** and converted to malonamide **8** by DCC coupling with oxazolidine **1**. Furthermore, during the course of this work, we found that acyl Meldrum's acids **5b-d** could be opened directly with oxazolidine **1** (R=H),[15, 16, 19, 20] giving malonamides **9a-c** very efficiently; these sequences provided access to variously substituted analogues replacing the methoxy group at the chain terminus of **8**. We also expected that intermediates of type **6** would prove to be pivotal, since alkylation at either or both of the α- and γ-positions using standard conditions should be possible, providing access to diversely functionalised pyroglutamates after cyclisation. Thus, we found that successive treatment of **6a** with one equivalent of each of NaH and BuLi followed by benzyl bromide gave derivative **10**, which using the sequence outlined above, was readily converted to acid **11** and thence malonamide **12**, which was used without further purification. Furthermore, reaction of **6a-d** with *t*-BuOK followed by methyl iodide was found to give α-methyl adducts **13a-d** in very good yield (Scheme 2). Conversion to the acids **14a-d** and then to the epimeric malonamides **15a-d** and **15a□-d□** proved to be less efficient than some of the earlier examples, but gave sufficient material for further investigation; these compounds were obtained as an epimeric mixture at the side chain methyl group, whose ring stereochemistry could be assigned by nOe analysis, for which enhancements between *syn*-related groups on each side of the ring were easily detected (Figure 2). That this sequence could be used to access even more hindered systems was shown by converting α-methyl **13a** to α-methyl γ-benzyl adduct **16**, followed by further conversion as before to acid **17** and thence malonamide **18** as a mixture of diastereomers which were used without separation. We also found that ester **6d** could be similarly manipulated (Scheme 3), and base treatment followed by reaction with allyl bromide or benzyl bromide efficiently gave α-alkyl adducts **19a-b** in very good yield (Scheme 3), which could be converted as earlier to acids **20a-b** and malonamides **21a-b** as a diastereomeric mixture. These routes very efficiently provided the necessary malonamide substrates with a variety of substitution patterns, ready for investigation of the key aldol ring closure.

For the aldol cyclisation, we quickly found that treatment of **8** with NaOMe gave the desired product **22a** in 22% yield as a single diastereomer (Scheme 4), whose stereochemistry was assigned

by nOe analysis (Figure 3); however, this assignment proved to be more difficult than anticipated, and a detailed discussion of the approach is given below. Although the yield was not high, the outcome is remarkable since three contiguous chiral centres, one tertiary and two quaternary, were assembled in this single step. Malonamides **9a-c** behaved similarly, giving pyroglutamates **22b-d** in isolated yields of 30-46%, along with significant amounts of readily separated unreacted starting material. When this process was applied to the more elaborate malonamides **12, 15a** and **18**, which differ from **22a** by successive increases in substitution at the γ- and α- positions, pyroglutamates **22e, f** and **j** were readily obtained, again as single diastereomers at the bicyclic ring substituents (although **22j** was obtained as an epimeric mixture at the benzylic side chain position), albeit in yields of 6, 21 and 14%; these low yields are most likely to be due to the additional steric requirements of the ring closure along with the diastereomeric mixture of starting oxazolidine, but this outcome, giving up to 4 contiguous chiral centres under such mild conditions, is nonetheless remarkable. This approach could be similarly applied to **15b-d** and **21a,b**, all with more bulky groups at one or other of the γ- and α- positions, to afford products **22g-i** and **22k,l** in variable yield and as single stereoisomers, the stereochemistry of which was again established by nOe analysis (Figure 3); as before, this was not straightforward and a detailed discussion of the assignment is given below. The yield of products **22g-i** was particularly good, and this may be the result of a favourable Thorpe-Ingold effect which enhances the ring closure. Investigation of the ring closure conditions for **22b** indicated that a reaction temperature of 30^{o}C with a time of 24h gave best yields (46%), while higher or lower temperature or longer times only gave worse outcomes. Of interest is that the chemical shifts of C(2)H, C(4)H, C(4)Me in the ^{1}H NMR spectra of **22a-l** were remarkably consistent, with typical values of 5.03 ± 0.03, 4.77 ± 0.06, and 1.60 ± 0.07, suggesting a rigid structure with conservation of the indicated stereochemistry across the compound series. Moreover, C(7)H$_{endo}$ and C(7)H$_{exo}$ appeared at 3.0-3.3 and 2.4 respectively, consistent with the conserved C(7)Me$_{endo}$ stereochemistry for compounds **22g-22l**. This preference for the C(7)Me$_{endo}$ isomer presumably reflects the thermodynamic stability achieved by placing this methyl group opposite to the bulky C(6)alkyl substituent. This outcome suggests a preference for a transition state of type A rather than type B in the aldol ring closure (Figure 4), in which steric interactions involving the terminal functional group of the malonamide side chain are minimized, although it is not clear whether the final stereochemistry at C(7) arises during the ring closure, or from post-cyclisation equilibration. In terms of natural product synthesis, the formation of up to 4 contiguous chiral centres, two of which were tertiary and two quaternary, with excellent diastereocontrol, as well as the capacity to readily vary the substituent pattern, is noteworthy; the relative stereochemistry of these compounds is correct for 16-methyloxazolomycin.

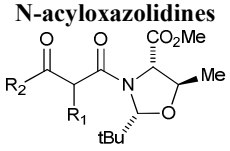
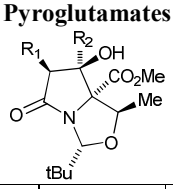
As noted above, the stereochemical assignment of these systems by nOe analysis proved not to be fully straightforward, despite the rigid bicyclic system which has normally been instrumental in providing the capacity to readily assign the product stereochemistry using this approach.[2] For example, for **22f**, the stereochemistry of the oxazolidine ring was readily confirmed by the presence of enhancements between C(2)*H* and C(4)*Me*, both known to be *syn*- related on the *N*-acyl-oxazolidine (Figure 3). The methyl ester was confirmed to be on the *exo* face through an enhancement to the C(2)*tBu*, and an enhancement between C(2)*H* and C(7)*Me* indicated that the C(7)*Me* group also occupied the *endo* face. The C(6)O*H* showed an enhancement to C(7)*Me*, indicating it had an *endo* position. However, the C(1□)H_2 unexpectedly showed enhancements to C(7)*Me*, C(7)*H* and C(4)*Me* (shown in red in Figure 3). A similar pattern was also observed in the pyroglutamate **22a** with enhancements between C(1□)H_2 and *endo*-C(7)*H*, *exo*-C(7)*H*, CO_2Me and C(4)*Me*. Since these signals did not appear to be consistent with either epimer, an examination of the energy minimised conformer of **22a** was undertaken that this suggested that the distance between C(4)Me and the closest C(1□)H could be as low as 3.25 Å. Similar unexpected enhancements for pyroglutamates **22b** and **22c** were also observed (Figure 3, indicated in red), suggesting functional group proximity in these sterically congested systems, leading to unexpected nOe effects.

Fortunately, compounds **22a**, **22c**, **22f**, **22h**, **22i**, **22j** and **22j**□ were crystalline, and single crystal X-ray analyses allowed unambiguous confirmation of their structure and stereochemistry (Figure 5).[21] Importantly, the stereochemistry of C(6) with OH in the *endo* position and the CH_2OMe in the *exo* position was observed in all cases. Additionally, the C(4)Me-C(1□)H_2 internuclear distances were between 2.35 and 2.75 Å, and the dihedral angles between C(6)CH_2 and C(7)H and C(7)Me for **22i**, for example, were 55° and 76° respectively, meaning that the C(6)R groups effectively bisect the C(7) substituents. All compounds showed the same short internuclear distance between the C(4)Me and the C(1□)H protons, and between all the C(7)H and C(6) substituents, explaining why the ring substituents are in sufficiently close proximity to produce nOe enhancements. This analysis also confirmed that the major and minor isomers **22j** and **22j**□ were epimeric at the C(1□) stereocentre, the major isomer having a 1□-*S* configuration, with the minor being 1□-*R* (Figure 5).

The *N*-acyloxazolidines and pyroglutamates synthesised were assayed against *S. aureus* D267 and *E. coli* X580 using the hole-plate method,[22] and the data is shown in Table 1. This phenotypic assay is not able to accurately measure MIC values for active compounds, but does allow a simple active/inactive result on antibacterial activity to be obtained quickly and easily. *N*-Acyloxazolidines **12** and **9b** were the only compounds displaying activity against Gram-positive *S. aureus*, with relative potencies of almost 10% relative to the cephalosporin C control. There were a

number of active hits against Gram-negative *E. coli*, including four *N*-acyloxazolidines (**15b**, **15b**□, **9b**, **9c**) and four pyroglutamates (**22b**, **22g**, **22c**, **22d**) which showed inhibition zones against *E. coli*, though for compounds **22b** and **22c** this activity was weak. The relative potencies here are much smaller (0.03-0.04%) due to the higher sensitivity of *E. coli* to the reference compound cephalosporin C. Broth bioassays also identified three compounds with activity against *H. influenza* Hi4, **12**, **22c**, and **22h** with MICs of 32, 64, and 16 μg/mL. We have recently demonstrated that the intrinsic antibacterial activity of simple pyroglutamates[23, 24] and tetramates is low,[25] but that homologation with longer chain side-units restores some activity.[12, 13, 26] Against this background, it is perhaps not surprising then that antibacterial biossay of a range of compounds prepared above did not show significant levels of activity, even though we have also shown that small changes such as the introduction of a methyl substituent improves bioactivity in simple tetramates.[27]

Table 1: Bioassay results for *N*-acyloxazolidines and pyroglutamates.

Compound number	R_1	R_2	*S. aureus* D267		*E. coli* X580	
			Zone size (mm)	Rel. potency (Ceph C, %)	Zone size (mm)	Rel. potency (Ceph C, %)
N-acyloxazolidines 						
8	H	CH_2OMe	0	-	0	-
9a	H	Butenyl	0	-	0	-
9b	H	$CH_2C_6H_4Br$	12.5	10.0%	12	0.04
9c	H	CH_2SPh	0	-	13	0.04
12	H	CH(Bn)OMe	13	9.7%	0	-
15a	Me	CH_2OMe	0	-	0	-
15b□	Me	Butenyl	0	-	12.5	0.03
15b	Me*	Butenyl	0	-	12	0.03
15c□	Me	$CH_2C_6H_4Br$	0	-	0	-
15c	Me*	$CH_2C_6H_4Br$	0	-	0	-
15d□	Me	CH_2SPh	0	-	0	-
15d	Me*	CH_2SPh	0	-	0	-
18	Me	CH(Bn)OMe	0	-	0	-
Compound number	**R_1**	**R_2**	***S. aureus* D267**		***E. coli* X580**	
			Zone size (mm)	**Rel. potency (Ceph C, %)**	**Zone size (mm)**	**Rel. potency (Ceph C, %)**
Pyroglutamates 						
22a	H	CH_2OMe	0	-	0	-
22b	H	Butenyl	0	-	12 (halo)	0.03
22c	H	$CH_2C_6H_4Br$	0	-	12 (halo)	0.04
22d	H	CH_2SPh	0	-	15	0.05
22e	H	CH(Bn)OMe	0	-	0	-
22f	Me	CH_2OMe	0	-	0	-

22g	Me	Butenyl	0	-	14	0.04
22h	Me	$CH_2C_6H_4Br$	0	-	0	-
22i	Me	CH_2SPh	0	-	0	-
22j	Me	CH(Bn)OMe	0	-	0	-
22j□	Me	CH(Bn*)OMe	0	-	0	-

In this work, we have shown that ring closing aldol reactions on a threonine-derived oxazolidine template, although not highly efficient in terms of chemical yield, nonetheless permits the rapid construction of diversely substituted diastereomerically pure pyroglutamates of relevance to the oxazolomycin series of natural products, although it does not appear that this subunit is of itself responsible for significant levels of antibacterial bioactivity. This work is a significant expansion of the approach reported earlier using the corresponding serine template **2** (R^1=H),[15] since additional and bulky side chain groups at R^2 and X of template **2** are tolerated, even in the presence of a methyl group at R^1. Such fragments are of interest for their relevance as novel three-dimensional fragments with potential application in drug discovery; by side chain manipulation, they may permit rapid "escape from flatland", which has been proposed to be beneficial for improved solubility and hydrophobicity and lower toxicity of drug discovery candidates.[28,29]

Experimental

For general experimental procedures, see our earlier report.[2] Acid chloride **4d** is commercially available.

General Procedure A: Acylation of Meldrum's acid

Pyridine (2.0 eq.) was added dropwise to a solution of Meldrum's acid (1.0 eq.) in DCM (10 mL/mmol of Meldrum's acid) at −10 °C and the resulting mixture was stirred for 20 min. A solution of the required acid chloride (1.0 eq.) in DCM (0.5 mL/mmol of acid chloride) was added dropwise and the resulting mixture was stirred for 1 h at −10 °C before being warmed to rt and stirred for a further 2 h. The mixture was quenched with 1M HCl (1 mL/mL DCM) and extracted with DCM (3×). The combined organic layers were washed with brine (50 mL), dried and concentrated *in vacuo* to give the crude product, which was used without further purification.

General Procedure B: Ring-opening/decarboxylation/esterification of Meldrum's acid derivatives

A solution of the Meldrum's acid derivative in 1:1 toluene:*t*BuOH (4 mL/mmol) was stirred at reflux for 2 h. The mixture was cooled to rt and concentrated *in vacuo* to give the crude product which was purified by column chromatography (petrol:EtOAc).

General Procedure C: Direct Meldrum opening with oxazolidine 1

The acylated Meldrum's acid (3.1 mmol) was dissolved in MeCN (15 mL) and oxazolidine **320/1** (2.8 mmol) in MeCN (8 mL) was added. The resulting mixture was stirred at 60 °C for 2 h and then concentrated *in vacuo*. Purification *via* column chromatography gave the product.

General Procedure D: Hydrolysis of β-keto-esters

A solution of the β-keto-ester in DCM (1 mL/mmol) was cooled to 0 °C and TFA (1 mL/mmol) was added dropwise. The solution was stirred for 3 h at rt before the solvent was removed *in vacuo* to give the β-keto-acid which was used without further purification.

General Procedure E: Synthesis of *N*-acyl-oxazolidines by amide coupling

A solution of oxazolidine **1** (1.0 eq.) in DCM (3 mL/mmol of **1**) was cooled to 0 °C before DCC (1.05 eq.) and DMAP (7 mol%) were added. A solution of the carboxylic acid (1.05 eq.) in DCM (1 mL/mmol of acid) was added and the mixture was stirred at 0 °C for 15 min and then at rt for 3-5 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give the crude product mixture.

General Procedure F: Alkylation at the γ-position

A solution of β-keto-ester (1.0 eq.) in THF (2 mL/mmol) was added dropwise to a stirred suspension of NaH (1.0 eq.) in THF (10 mL/mmol). After stirring at 0 °C for 10 min, BuLi (1.6 M in hexanes, 1.05 eq.) was added dropwise. After a further 10 min at 0 °C, the stated alkylating agent (1.05 eq.) was added in one portion and the mixture allowed to warm to rt over 15 min. The mixture was quenched with 2M HCl (5 mL) and extracted with Et_2O (2×). The combined organic layers were washed with H_2O until the aqueous layer remained neutral, dried and concentrated *in vacuo* to give the crude product which was purified by column chromatography (petrol:EtOAc).

General Procedure G: Alkylation of the α-position giving 13a-d

A solution of β-keto-ester in THF (10 mL/mmol) was cooled to 0°C and *t*BuOK (1.05 eq.) was added. The mixture was then warmed to rt and stirred for 40 min before the addition of MeI (1.05 eq.). The mixture was stirred for a further 5 h at rt, after which time it was partitioned between Et_2O (1 mL/mL THF) and brine (1 mL/mL THF). The aqueous layer was extracted with Et_2O (2×) and the combined organic layers were dried and concentrated *in vacuo* to give the crude α-methyl-β-keto-ester which was purified by column chromatography (petrol:EtOAc).

General Procedure H: Aldol cyclisation of *N*-acyl-oxazolidines

NaOMe (1.1 eq.) was added portionwise to a stirred solution of *N*-acyl-oxazolidine (1.0 eq.) in MeOH (10 mL/mmol of oxazolidine) and the resulting mixture was stirred at rt for 24 h. The

mixture was partitioned between Et_2O (2 mL/mL MeOH) and sat. aq. NH_4Cl (2 mL/mL MeOH), and the aqueous layer was extracted with Et_2O (2×) before the combined organic layers were washed with brine (0.5 mL/mL Et_2O), dried and concentrated *in vacuo* to give the crude product mixture.

Methoxyacetyl chloride 4a[30]

Methoxyacetic acid (8.5 ml, 110 mmol) was added dropwise to a flask of stirring thionyl chloride (24.2 mL, 332 mmol) and stirred at rt for 15 min. The mixture was then heated to reflux at 110 °C for 2 h, allowed to cool and then purified by distillation at atmospheric pressure to give the product **4a** as a colourless oil (7.67 g, 64%); bp 98 ºC (lit.[28] bp 98 °C); δ_H (400 MHz, $CDCl_3$) 3.49 (3H, s, CH_3), 4.36 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 59.7 (*C*H_3), 77.5 (*C*H_2), 171.8 (*C*=O).

4-Pentenoyl chloride 4b[31]

A solution of 4-pentenoic acid (500 mg, 5 mmol) in DCM (3 mL) was stirred at rt, and oxalyl chloride (0.44 mL, 5.0 mmol) was added dropwise over 5 min. The resulting solution was heated to 40 °C for 2 h. The mixture was then concentrated *in vacuo* before a portion of DCM (2 mL) was added and the solution was reconcentrated to give **4b** as a pale pink oil (405 mg, 68%); δ_H (400 MHz, $CDCl_3$) 2.43-2.50 (2H, m, C(3)H_2), 3.00 (2H, t, *J* 7.2, C(2)H_2), 5.07-5.16 (2H, m, C(5)H_2), 5.74-5.86 (1H, m, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 28.9 (*C*(3)), 46.2 (*C*(2)), 116.9 (*C*(5)), 134.6 (*C*(6)), 173.2 (*C*(1)).

4-Bromophenylacetyl chloride 4c[32]

A solution of 4-bromophenylacetic acid (1.0 g, 4.65 mmol) in DCM (6 mL) was stirred at rt, and oxalyl chloride (0.6 mL, 6.9 mmol) was added dropwise over 5 min. The resulting solution was heated to 40 °C for 4 h. The mixture was then concentrated *in vacuo* before a portion of DCM (3 mL) was added and the solution reconcentrated to give **4c** as a colourless oil (1.13 g, quant); δ_H (400 MHz, $CDCl_3$) 4.11 (2H, s, CH_2), 7.16 (2H, d, *J* 8.2, C(2)*H*, C(6)*H*), 7.52 (2H, d, *J* 8.2, C(3)*H*, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 52.3 (*C*H_2), 122.4 (*C*(1)), 130.2 (*C*(4)), 131.2, 132.1 (*C*(2), *C*(3), *C*(5), *C*(6)), 171.5 (*C*=O); *m/z* (TOF FI^+) 233 (M^+, 100%).

5-(2□-Methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 5a[15]

Following General Procedure A, pyridine (3.46 mL, 43.0 mmol), Meldrum's acid (3.10 g, 21.5 mmol) and methoxyacetyl chloride **4a** (2.56 g, 23.7 mmol) were reacted to give **5a** as a dark brown oil (3.5 g, 75%) which was used without further purification; δ_H (400 MHz, $CDCl_3$) 1.75 (6H, s, C(C*H*$_3$)$_2$), 3.52 (3H, s, OC*H*$_3$), 4.86 (C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 26.9 (C(2)(*C*H$_3$)$_2$), 59.9 (O*C*H$_3$), 72.1 (*C*H$_2$), 90.1 (*C*(5)), 105.9 (*C*(2)), 162.9 (*C*=O), 194.1 (*C*OCH$_2$OMe); *m/z* (ESI$^+$) 215 ([M−H]$^-$, 40%).

5-(4□-Pentenoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 5b

Following General Procedure A, pyridine (0.49 mL, 6.13 mmol) was added to a solution of Meldrum's acid (447 mg, 3.1 mmol) in DCM (5 mL) at −10 °C and stirred for 20 min. A solution of acid chloride **4b** (405 mg, 3.41 mmol) in DCM (2 mL) was added dropwise and the resulting mixture was stirred for 1 h at −10 °C before being warmed to rt and stirred for a further 2 h. The mixture was quenched with 1M HCl (5 mL) and extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried and concentrated *in vacuo* to give **5b** as a yellow oil (644 mg, 84%) which was used without further purification; ν_{max} (film) 3080, 3002, 2922, 1739, 1667, 1574; δ_H (400 MHz, $CDCl_3$) 1.74 (3H, s, C*H*$_3$), 1.79 (3H, s, C*H*$_3$), 2.44-2.51 (2H, m, C(3□)*H*$_2$), 3.21 (2H, t, *J* 7.5, C(2□)*H*$_2$), 5.01-5.13 (2H, m, C(5□)*H*$_2$), 5.78-5.91 (1H, m, C(4□)*H*); δ_C (100 MHz, $CDCl_3$) 26.8, 27.6 (*C*H$_3$), 29.8 (*C*(3□)), 34.9 (*C*(2□)), 91.6 (*C*(5□)), 104.9 (C(2)), 116.2 (C(5□)), 136.0 (*C*(4□)), 170.5 (*C*(1), *C*(3)), 197.0 (*C*(1□)); *m/z* (ESI$^-$) 255 ([M−H]$^-$, 25%); HRMS (ESI$^+$) $C_{11}H_{14}NaO_5^+$ ([M+Na]$^+$) requires 249.0733, found 249.0739.

5-(4□-Bromophenylacetoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 5c

Following General Procedure A, pyridine (0.75 mL, 9.3 mmol) was added to a solution of Meldrum's acid (670 mg, 4.65 mmol) in DCM (20 mL) at −10 °C and stirred for 20 min. A solution of acid chloride **4c** (1.08 g, 4.65 mmol) in DCM (5 mL) was added dropwise and the resulting mixture was stirred for 1 h at −10 °C before being warmed to rt and stirred for a further 2 h. The mixture was quenched with 1M HCl (10 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried and concentrated *in vacuo* to give **5c** as a red solid (1.49 g, 93%); mp 112-115 ºC; ν_{max} (film) 3000, 1741, 1648; δ_H (400 MHz,

$CDCl_3$) 1.73 (6H, s, CH_3), 4.37 (2H, s, CH_2), 7.27 (2H, d, *J* 8.3, C(2□)*H*, C(6□)*H*), 7.46 (2H, d, *J* 8.3, C(3□)*H*, C(5□)*H*); δ_C (100 MHz, $CDCl_3$) 26.8 (*C*H_3), 40.2 (*C*H_2), 91.5 (*C*(5)), 105.1 (*C*(2)), 121.7 (*C*(4□)), 131.3 (*C*(2□), *C*(6□)), 131.8 (*C*(3□), *C*(5□)), 133.0 (*C*(1□)), 170.5 (*C*(4), *C*(6)), 193.8 (*C*=O); *m/z* (ESI^-) 388 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_{14}H_{13}BrO_5^+$ ($[M+Na]^+$) requires 362.9839, 364.9829, found 362.9826, 364.9807.

5-(1□-Hydroxy-2□-(phenylthio)ethylidene))-2,2-dimethyl-1,3-dioxane-4,6-dione 5d

Following General Procedure A, pyridine (0.86 mL, 10.7 mmol) and Meldrum's acid (771 mg, 5.35 mmol) in DCM (25 mL) were combined with a solution of acid chloride **4d** (1.00 g, 5.35 mmol) in DCM (5 mL) to give **5d** as an orange oil (1.62 g, quant); ν_{max} (film) 3000, 1737, 1666; δ_H (400 MHz, $CDCl_3$) 1.67 (6H, s, CH_3), 4.38 (2H, s, C(2□)H_2), 7.28-7.32 (3H, m, *Ph*), 7.47-7.51 (2H, m, *Ph*), 14.57 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 26.8 (*C*H_3), 36.4 (*C*(2□)), 91.1 (*C*(5)), 105.2 (*C*(2)), 127.0, 128.0, 132.1 (*o,m,p-Ph*), 133.5 (*i-Ph*), 170.4 (*C*(4), *C*(6)), 192.1 (*C*(1□)); *m/z* (ESI^-) 293 ($[M-H]^-$, 40%); HRMS (ESI^-) $C_{14}H_{13}O_5S^-$ ($[M-H]^-$) requires 293.0489, found 293.0489.

***t*-Butyl 4-methoxy-3-oxo-butanoate 6a**[15]

Following General Procedure B, a solution of **5a** (3.5 g, 16.2 mmol) in 1:1 toluene:^{t}BuOH (36 mL) was stirred at reflux for 2 h. The mixture was cooled to rt and concentrated *in vacuo* to give **6a** as a dark brown liquid (2.2 g, 73%); R_f 0.3 (eluent 9:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C(CH_3)$_3$), 3.41 (2H, s, C(2)H_2), 3.42 (3H, s, OCH_3), 4.08 (2H, s, C(4)H_2); δ_C (100 MHz, $CDCl_3$) 27.9 (C(*C*H_3)$_3$), 47.2 (*C*(2)), 59.3 (O*C*H_3), 77.3 (*C*(4)), 83.4 (*C*Me$_3$), 166.2 (*C*(1)), 202.0 (*C*(3)); *m/z* (ESI^+) 211 ($[M+Na]^+$, 50%), 399 ($[2M+Na]^+$, 75%).

***t*-Butyl 3-oxohept-6-enoate 6b**

Following General Procedure B, a solution of **5b** (312 mg, 1.4 mmol) in 1:1 toluene:*t*-BuOH (4 mL) was stirred at reflux for 2 h. The mixture was cooled to rt and concentrated *in vacuo* to give **6b** as a yellow liquid (290 g, quant.); R_f 0.55 (eluent 50:1 petrol:EtOAc); ν_{max} (film) 3080, 2981, 1734, 1643; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C(CH_3)$_3$), 2.32-2.39 (2H, m, C(5)H_2), 2.64 (2H, t, *J* 7.3, C(4)H_2), 3.36 (2H, s, C(2)*H*), 4.97-5.11 (2H, m, C(7)H_2), 5.75-5.89 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 27.4 (*C*(5)), 27.9 (C(*C*H_3)$_3$), 41.9 (*C*(4)), 50.7 (*C*(2)), 82.0 (*C*Me$_3$), 115.4 (*C*(7)),

136.7 (*C*(6)), 166.5 (*C*(1)), 202.3 (*C*(3)); *m/z* (ESI^+) 221 ($[M+Na]^+$, 75%), 419 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{18}NaO_3^+$ ($[M+Na]^+$) requires 221.1148, found 221.1144.

_t_-Butyl 4-(4□-bromophenyl)3-oxobutanoate 6c

Following General Procedure B, a solution of **5c** (750 mg, 2.19 mmol) in 1:1 toluene:*t*-BuOH (10 mL) was stirred at reflux for 2 h. The mixture was cooled to rt and concentrated *in vacuo* to give **6c** as a pale yellow oil (680 mg, quant); R_f 0.6 (eluent, 5:1 petrol:EtOAc) ν_{max} (film) 2979, 1731, 1648; δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C(CH_3)$_3$), 3.41 and 3.79 (2×2H, s, C(2)H_2, C(4)H_2), 7.10 (2H, d, *J* 7.3, C(2□)*H*, C(6□)*H*), 7.49 (2H, d, *J* 7.3, C(3□)*H*, C(5□)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (C(*C*H_3)$_3$), 49.1, 49.8 (*C*(2), *C*(4)), 82.3 (*C*Me$_3$), 121.4 (*C*(4□)), 131.3 (*C*(2□), *C*(6□)), 131.9 (*C*(3□), *C*(5□)), 132.3 (*C*(1□)), 166.2 (*C*(1)), 200.2 (*C*(3)); *m/z* (ESI^+) 335, 337 ($[M+Na]^+$, 95%); HRMS (ESI^+) $C_{14}H_{17}BrNaO_3^+$ ($[M+Na]^+$) requires 335.0253, 337.0233, found 335.0243, 337.0225.

_t_-Butyl (4-phenylthio)-3-oxo-butanoate 6d

Following General Procedure B, a solution of **5d** (714 mg, 2.42 mmol) in 1:1 toluene:*t*-BuOH (10 mL) was stirred at reflux for 2 h. The mixture was cooled to rt and concentrated *in vacuo* to give **6d** as a brown liquid (643 mg, quant); R_f 0.75 (eluent 5:1 40-60 petrol:EtOAc); ν_{max} (film) 3060, 2979, 1715, 1649; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C(CH_3)$_3$), 3.56 (2H, s, C(2)H_2), 3.82 (2H, s, C(4)H_2), 7.22-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (C(*C*H_3)$_3$), 43.9 (*C*(4)), 47.8 (*C*(2)), 82.3 (*C*Me$_3$), 127.1, 129.2, 129.7 (*o,m,p-Ph*), 134.3 (*i-Ph*), 166.2 (*C*(1)), 198.4 (*C*(3)); *m/z* (ESI^+) 289 ($[M+Na]^+$, 80%); HRMS (ESI^+) $C_{14}H_{18}NaO_3S^+$ ($[M+Na]^+$) requires 289.0867, found 289.0869.

4-Methoxy-3-oxobutanoic acid 7[15]

Following General Procedure D, a solution of **6a** (200 mg, 1.06 mmol) in DCM (1 mL) was cooled to 0 °C and TFA (1 mL) was added dropwise. The resulting solution was stirred for 24 h at rt before the solvent was removed *in vacuo* to give **7** as a yellow oil (140 mg, quant) in a 5:1 keto:enol ratio; δ_H (400 MHz, $CDCl_3$) keto-tautomer - 3.44 (3H, s, OCH_3), 3.57 (2H, s, C(2)H_2), 4.10 (2H, s, C(4)H_2), 9.73 (1H, br s, O*H*), enol-tautomer - 3.44 (3H, s, OCH_3), 4.02 (2H, s, C(4)H_2), 5.32 (1H, s, C(2)*H*), 9.73 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 45.1 (keto-*C*(2)) 59.2, 59.3 (2 × O*C*H_3), 71.1 (enol-*C*(4)), 77.2 (keto-*C*(4)), 87.8 (enol-*C*(2)), 171.9 (keto-*C*(1)), 201.8 (keto-*C*(8)).

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(4□-methoxy-3□-oxobutanoyl)-4-methoxycarbonyl-5-methyloxazolidine 8

Following General Procedure E, oxazolidine **1** (211 mg, 1.05 mmol) was reacted with DCC (227 mg, 1.01 mmol), DMAP (9 mg, 7 mol%) and the acid **7** (144 mg, 1.10 mmol). The crude mixture of **8** (350 mg) was used without purification; *m/z* (ESI^+) 338 ($[M+Na]^+$, 50%).

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(3□-oxohept-6□-enoyl)-4-methoxycarbonyl-5-methyloxazolidine 9a

Following General Procedure C, acylated Meldrum's acid **5b** (2.5 g, 11.0 mmol) was dissolved in MeCN (25 mL) and oxazolidine **1** (2.11 mg, 10.5 mmol) in MeCN (25 mL) was added. The resulting mixture was stirred at 60 °C for 2 h and then concentrated *in vacuo* and purified by column chromatography (SiO_2, eluent 20:2 to 5:1 petrol:EtOAc) to give **9a** as a yellow oil (1.86 g, 52%); R_f 0.2 (eluent 20:1 petrol:EtOAc); ν_{max} (film) 2958, 1753, 1667, 1632; δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.35 (3H, d, *J* 6.3, C(5)CH_3), 2.28-2.38 (2H, m, C(5□)H_2), 2.59-2.81 (2H, m, C(4□)H_2), 3.60 (2H, AB q, *J* 14.8, C(2□)H_2), 3.79 (3H, s, CO_2CH_3), 4.27 (1H, d, *J* 3.8, C(4)*H*), 4.72-4.79 (1H, m, C(5)*H*), 4.96-5.09 (2H, m, C(7□)H_2), 5.41 (1H, s, C(2)*H*), 5.74-5.86 (1H, m, C(6□)*H*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(5)*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 26.7 (*C*(5□)), 37.8 (*C*Me$_3$), 42.3 (*C*(4□)), 50.7 (*C*(2□)), 52.5 (CO_2CH_3), 65.3 (*C*(4)), 76.1 (*C*(5)), 96.1 (*C*(2)), 115.5 (*C*(7□)), 136.6 (*C*(6□)), 168.0 (*C*(1□)), 170.3 (*C*O_2Me), 203.8 (*C*(3□)); *m/z* (ESI^+) 326 ($[M+H]^+$, 55%), 348 ($[M+Na]^+$, 70%), 673 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 348.1777, found 348.1781.

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(3□-oxo-4□-(4□□-*p*-bromophenyl)butanoyl)-4-methoxycarbonyl-5-methyloxazolidine 9b

Following General Procedure C, acylated Meldrum's acid **5c** (700 mg, 2.05 mmol) was dissolved in MeCN (10 mL) and oxazolidine **1** (392 mg, 1.95 mmol) in MeCN (5 mL) was added. The resulting mixture was stirred at 60 °C for 2 h and then concentrated *in vacuo*. Purification *via* column chromatography (SiO_2, eluent 10:1 petrol:EtOAc) gave **9b** as a colourless oil (524 mg, 58%); R_f 0.45 (eluent 3:1 petrol:EtOAc); ν_{max} (film) 2957, 1747, 1685; δ_H (500 MHz, MeOD) 0.90 (9H, s, C(CH_3)$_3$), 1.32 (3H, d, *J* 6.0, C(5)CH_3), 3.77 (3H, s, CO_2CH_3), 3.87 (2H, AB q, *J* 16.4, C(4□)H_2), 4.31 (1H, d, *J* 3.4, C(4)*H*), 4.73-4.79 (1H, m, C(5)*H*), 5.36 (1H, s, C(2)*H*), 7.18 (2H, d, *J* 8.2, *o*-*Ph*), 7.50 (2H, d, *J* 8.2, *m*-*Ph*); δ_C (125 MHz, MeOD) 20.4 (C(5)*C*H$_3$), 26.4 (C(*C*H$_3$)$_3$), 38.8 (*C*Me$_3$), 53.3 (*C*(4□)), 66.5 (*C*(4)), 77.5 (*C*(5)), 97.2 (*C*(2)), 122.2 (*C*Br), 132.7, 132.9 (*o*,*m*-*Ph*), 134.5 (*i*-*Ph*), 171.0, 171.5 (CO_2CH_3, *C*(1□)), 203.4 (*C*(3□)); *m/z* (ESI^+) 462/464 ($[M+Na]^+$, 75%), 903 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}BrNNaO_6^+$ ($[M+Na]^+$) requires 462.0887, 464.0867, found 462.0869, 464.0850.

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(3□-oxo-4□-phenylthiobutanoyl)-4-methoxycarbonyl-5-methyloxazolidine 9c

Following General Procedure C, acylated Meldrum's acid **5d** (907 mg, 3.1 mmol) was dissolved in MeCN (15 mL) and oxazolidine **1** (563 mg, 2.8 mmol) in MeCN (8 mL) was added. The resulting mixture was stirred at 60 °C for 2 h and then concentrated *in vacuo*. Purification *via* column chromatography (SiO_2, eluent 20:1-5:1 petrol:EtOAc) gave **9c** as a yellow oil (558 mg, 45 %) as a mixture of keto and enol forms; R_f 0.37(eluent 5:1 pterol:EtOAc); ν_{max} (film) 2975, 2957, 1745, 1716, 1662; δ_H (400 MHz, MeOD) 0.87 (s, C(CH_3)$_3$), 1.21 (3H, d, *J* 6.3, C(5)CH_3), 3.77 (3H, s, CO_2CH_3), 3.93 (2H, AB q, *J* 15.4, C(4□)H_2), 4.16 (1H, d, *J* 3.8, C(4)*H*), 4.68-4.74 (1H, m, C(5)*H*), 5.33 (1H, s, C(2)*H*), 7.21-7.45 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.2 (C(5)*C*H$_3$), 25.3 (C(*C*H$_3$)$_3$), 37.8 (*C*Me$_3$), 43.1 (*C*(4□)) 52.3 (CO_2CH_3), 65.4 (*C*(4)), 76.3 (*C*(5)), 96.1 (*C*(2)), 126.9 (*p-Ph*), 129.2, 129.3 (*o*,*m-Ph*), 170.4, 170.5 (*C*O$_2$Me, C(1□)), 200.0 (*C*(3□)); *m/z* (ESI$^+$) 809 ([2M+Na]$^+$, 100%), 394 ([M+H]$^+$, 80%); HRMS (ESI$^+$) $C_{20}H_{28}NO_5S^+$ ([M+H]$^+$) requires 394.1680, found 394.1683.

***t*-Butyl 4-methoxy-5-phenyl-3-oxo-pentanoate 10**

Following General Procedure G, a stirred suspension of NaH (47 mg, 1.17 mmol) in THF (20 mL) was cooled to 0 °C and a solution of **6a** (200 mg, 1.06 mmol) in THF (2 mL) was added dropwise. Stirring was continued for 10 min at 0 °C before the dropwise addition of BuLi (0.7 mL, 1.6 M in hexanes, 1.12 mmol). After stirring for a further 10 min, BnBr (0.14 mL, 1.17 mmol) was added in one portion and the mixture was allowed to warm to rt over 15 min. The mixture was quenched with 2M HCl (7 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with H_2O until the aqueous layer remained neutral, dried and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent 10:1 40-60 petrol:EtOAc) gave **10** as a colourless oil (90 mg, 30%) as a 3:1 keto:enol mixture; R_f 0.5 (eluent 10:1 40-60 petrol:EtOAc); ν_{max} (film) 3064, 3030, 2980, 2829, 1717, 1650; δ_H (400 MHz, $CDCl_3$) keto: 1.47 (9H, s, C(CH_3)$_3$), 2.93 (1H, d, *J* 7.8, C(5)H_AH$_B$), 3.02 (1H, d, *J* 4.6, C(5)H$_A$$H_B$), 3.28 (1H, d, *J* 5.1, C(2)H_AH$_B$), 3.32 (3H, s, OCH_3), 3.46 (1H, d, *J* 15.9, C(2)H$_A$$H_B$), 3.92 (1H, dd, *J* 7.8, 4.6, C(4)*H*), 7.20-7.33 (5H, m, *Ph*), enol: 1.51 (9H, s, C(CH_3)$_3$), 2.90 (1H, d, *J* 7.8 C(5)H_AH$_B$), 3.06 (1H, d, *J* 4.3, C(5)H$_A$$H_B$), 3.32 (3H, s, OC$H_3$), 3.76 (1H, dd, *J* 8.6, 4.3, C(4)*H*), 5.11 (1H, s, C(2)*H*), 7.20-7.33 (5H, m, *Ph*); δ_C (100

MHz, $CDCl_3$) 28.0, 28.3 (C(CH_3)$_3$), 37.8 (*C*(5)), 46.7 (*C*(2) keto), 57.9, 58.7 (OCH_3), 81.8 (*C*Me$_3$), 87.6 (*C*(4) keto), 90.7 (*C*(2) enol), 126.7, 128.2, 128.4, 129.3, 129.4 (*o*,*m*,*p*-*Ph*), 136.8 (*i*-*Ph*), 166.4 (*C*(1)), 205.5 (*C*(3)); *m/z* (ESI$^+$) 301 ([M+Na]$^+$, 80%), 579 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{22}NaO_4^+$ ([M+Na]$^+$) requires 301.1410, found 301.1410.

4-Methoxy-3-oxo-5-phenylpentanoic acid 11

Following General Procedure D, a solution of **11** (90 mg, 0.32 mmol) in DCM (0.5 mL) was cooled to 0 °C and TFA (0.5 mL) was added dropwise. The resulting solution was stirred for 1.5 h at rt before the solvent was removed *in vacuo* to give **11** as an yellow oil (78 mg, quant); R_f 0.56 (eluent 3:1 40-60 petorl:EtOAc); ν_{max} (film) 2936, 1714, 1496, 1455; δ_H (400 MHz, $CDCl_3$) 2.91-2.91 (1H, m, C(5)H_AH_B), 3.03-3.09 (1H, m, C(5)H_AH_B), 3.35 (3H, s, OCH_3), 3.40 (1H, d, *J* 16.9, C(2)H_AH_B), 3.59 (1H, d, *J* 16.9, C(2)H_AH_B), 3.95 (1H, dd, *J* 7.3, 4.6, C(4)*H*), 7.16-7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 37.7 (*C*(5)), 44.5 (*C*(2)), 58.8 (OCH_3), 87.5 (*C*(4)), 126.9, 128.5, 129.4 (*o*,*m*,*p*-*Ph*), 136.3 (*i*-*Ph*), 171.5 (*C*(1)), 205.8 (*C*(3)); *m/z* (ESI$^+$) 245 ([M+Na]$^+$, 80%), 221 ([M−H]−, 100%); HRMS (ESI$^+$) $C_{12}H_{14}NaO_4^+$ ([M+H]$^+$) requires 245.0784, found 245.788.

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(4□-methoxy-5□-phenyl--3□-oxopentanoyl)-4-methoxycarbonyl-5-methyloxazolidine 12

Following General Procedure C for the synthesis of *N*-acyloxazolidines, oxazolidine **1** (67 mg, 0.33 mmol) was reacted with DCC (72 mg, 0.35 mmol), DMAP (3 mg, 7 mol%) and the acid **11** (78 mg, 0.35 mmol). The crude mixture of **12** (115 mg) was used without purification; ν_{max} (film) 3322, 2932, 2118, 1745, 1633; *m/z* (ESI$^+$) 428 ([M+Na]$^+$, 70%), 833 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{31}NNaO_6^+$ ([M+Na]$^+$) requires 428.2044, found 428.2041.

***t*-Butyl 4-methoxy-2-methyl-3-oxobutanoate 13a**[15]

Following General Procedure G, a solution of **6a** (2.0 g, 10.6 mmol) in THF (30 mL) was stirred at 0 °C and ^{t}BuOK (1.30 g, 11.7 mmol) was added. The mixture was then warmed to rt and stirred for 40 min before the addition of MeI (0.73 mL, 11.7 mmol). The mixture was left to stir for a further 5 h at rt. After this time the mixture was partitioned between Et_2O (30 mL) and brine (30 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic layers were dried and concentrated *in vacuo* to give **13a** as a yellow oil (1.60 g, 74%); R_f 0.4 (eluent 9:1 petrol:EtOAc);

δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 7.1, C(2)CH_3), 1.45 (9H, s, C(CH_3)$_3$), 3.41 (3H, s, OCH_3), 3.55 (1H, q, *J* 7.1, C(2)*H*), 4.07-4.15 (2H, m, C(4)H_2); δ_C (100 MHz, $CDCl_3$) 12.2 (C(2)*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 50.1 (*C*(2)), 59.2 (O*C*H$_3$), 76.8 (*C*(4)), 81.8 (*C*Me$_3$), 169.4 (*C*(1)), 204.5 (*C*(3)); *m/z* (ESI$^+$) 225 ([M+Na]$^+$, 80%), 427 ([2M+Na]$^+$, 100%).

_t_-Butyl 2-methyl-3-oxohept-6-enoate 13b[31]

Following General Procedure G, a solution of **6b** (277 mg, 1.4 mmol) in THF (7 mL) was stirred at 0 °C and *t*BuOK (180 mg, 1.46 mmol) was added. The mixture was then warmed to rt and stirred for 40 min before the addition of MeI (0.09 mL, 1.46 mmol). The mixture was left to stir for a further 5 h at rt. After this time the mixture was partitioned between Et_2O (15 mL) and brine (15 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic layers were dried and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent 100:1 to 50:1 petrol:EtOAc) gave **13b** as a yellow oil (128 mg, 43%); R_f 0.45 (eluent 50:1 petrol:EtOAc); ν_{max} (film) 2980, 1715, 1642; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 7.1, C(2)CH_3), 1.45 (9H, s, C(CH_3)$_3$), 2.30-2.37 (2H, m, C(5)H_2), 2.50-2.73 (2H, m, C(4)H_2), 3.42 (1H, q, *J* 7.1, C(2)*H*), 4.96-5.06 (2H, m, C(7)H_2), 5.74-5.85 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 12.6 (C(2)*C*H$_3$), 27.6 (*C*(5)), 27.9 (C(*C*H$_3$)$_3$), 40.4 (*C*(4)), 53.9 (*C*(2)), 81.7 (*C*Me$_3$), 115.3 (*C*(7)), 136.9 (*C*(6)), 169.7 (*C*(1)), 205.4 (*C*(3)); *m/z* (ESI$^+$) 235 ([M+Na]$^+$, 100%).

_t_-Butyl 4-(4□-bromophenyl)-2-methyl-3-oxobutanaoate 13c

Following General Procedure G, a solution of **6c** (638 mg, 2.19 mmol) in THF (15 mL) was stirred at 0 °C and *t*-BuOK (280 mg, 2.29 mmol) was added. The mixture was then warmed to rt and stirred for 40 min before the addition of MeI (0.14 mL, 2.29 mmol). The mixture was left to stir for a further 5 h at rt. After this time the mixture was partitioned between Et_2O (25 mL) and brine (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic layers were dried and concentrated *in vacuo* to give **13c** as a yellow oil (631 mg, 88%); R_f 0.75 (eluent 5:1 40-60 petrol:EtOAc); ν_{max} (film) 2983, 2937, 2360, 1745, 1715; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.1, C(2)CH_3), 1.46 (9H, s, C(CH_3)$_3$), 3.53 (1H, q, *J* 7.1, C(2)*H*), 3.76 (1H, d, *J* 16.4, C(4)H_AH_B), 3.84 (1H, d, *J* 16.4, C(4)H_AH_B), 7.08 (2H, d, *J* 8.5, C(2□)*H*, C(6□)*H*), 7.45 (2H, d, *J* 8.5, C(3□)*H*, C(5□)*H*); δ_C (100 MHz, $CDCl_3$) 12.7 (C(2)*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 47.7 (*C*(4)), 53.1 (*C*(2)), 82.1 (*C*Me$_3$), 121.2 (*C*(4□)), 131.1 (*C*(2□), *C*(6□)), 131.5 (*C*(3□), *C*(5□)), 132.6 (*C*(1□)), 169.4 (*C*(1)),

203.0 (*C*(3)); *m/z* (ESI$^+$) 349, 351 ([M+Na]$^+$, 80%), *m/z* (ESI$^+$) 675, 677, 679 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{19}BrO_3^+$ ([M+Na]$^+$) requires 349.0410, 351.0390, found 349.0396, 351.0378.

_t_-Butyl (4-phenylthio)-3-oxo-2-methylbutanoate 13d

Following General Procedure G, a solution of **6d** (717 mg, 2.56 mmol) in THF (20 mL) was stirred at 0 °C and *t*BuOK (328 mg, 2.68 mmol) was added. The mixture was then warmed to rt and stirred for 40 min before the addition of MeI (0.17 mL, 2.68 mmol). The mixture was left to stir for a further 5 h at rt. After this time the mixture was partitioned between Et_2O (20 mL) and brine (20 mL). The aqueous layer was extracted with Et_2O (2 × 10mL) and the combined organic layers were dried and concentrated *in vacuo* to give **13d** as a brown oil (620 mg, 86%); R_f 0.85 (eluent 5:1 petrol:EtOAc); ν_{max} (film) 3059, 1737, 1713; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.1, C(2)CH_3), 3.84 (1H, q, *J* 7.1, C(2)*H*), 3.81-3.92 (2H, m, C(4)H_2), 7.26-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.8 (C(2)*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 43.9 (*C*(4)), 50.9 (*C*(2)), 82.1 (*C*Me$_3$), 127.0 (*p-Ph*), 129.0, 129.1, 129.2, 129.7 (*o*,*m*,*p-Ph*), 134.6 (*i-Ph*), 169.2 (*C*(1)), 201.1 (*C*(3)); *m/z* (ESI$^+$) 303 ([M+Na]$^+$, 75%); HRMS (ESI$^+$) $C_{15}H_{20}NaO_3S^+$ ([M+Na]$^+$) requires 303.1025, found 303.1023.

4-Methoxy-2-methyl-3-oxobutanioic acid 14a[15]

Following General Procedure D, a solution of **13a** (282 mg, 1.39 mmol) in DCM (1.5 mL) was cooled to 0 °C and TFA (1.5 mL) was added dropwise. The resulting solution was stirred for 3 h at rt before the solvent was removed *in vacuo* to give **14a** as an orange oil (190 mg, 93%); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 7.3, C(2)CH_3), 3.44 (3H, s, OCH_3), 3.76 (1H, q, *J* 7.3, C(2)*H*), 4.13-4.17 (2H, m, C(4)H_2), 6.50 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 12.2 (C(2)*C*H$_3$), 48.5 (*C*(2)), 59.4 (O*C*H$_3$), 76.7 (*C*(4)), 175.2 (*C*(1)), 204.1 (*C*(3)).

2-Methyl-3-oxohept-6-enoic acid 14b

Following General Procedure D, a solution of **13b** (128 mg, 0.60 mmol) in DCM (0.7 mL) was cooled to 0 °C and TFA (0.7 mL) was added dropwise. The resulting solution was stirred for 1.5 h at rt before the solvent was removed *in vacuo* to give **14b** as a colourless oil (103 mg, quant); ν_{max} (film) 2984, 1712, 1642; δ_H (400 MHz, $CDCl_3$) 1.39 (3H×0.5, d, *J* 7.3, C(2)CH_3-keto), 1.42 (3H×0.5, s, C(2)CH_3-enol), 2.30-2.40 (2H, m, C(5)H_2), 2.50-2.81 (2H, m, C(4)H_2), 3.59 (1H×0.5, q, *J* 7.3, C(2)*H*-keto), 4.96-5.09 (2H, m, C(7)H_2), 5.74-5.87 (1H, m, C(6)H_2); δ_C (125 MHz, $CDCl_3$)

12.9 (C(2)*C*H$_3$-keto), 22.0 (C(2)*C*H$_3$-enol), 27.4, 27.8 (*C*(5)), 37.2, 41.1 (*C*(4)), 52.2 (*C*(2)), 115.2, 115.6 (*C*(7)), 136.5, 137.3 (*C*(6)), 178.9 (*C*(1)), 205.1 (*C*(3)); *m/z* (FI$^+$) 156 ([M]$^+$, 100%); HRMS (FI$^+$) $C_8H_{12}O_3^+$ ([M]$^+$) requires 156.0786, found 156.0784.

4-(4□-Bromophenyl)-2-methyl-3-oxobutaoic acid 14c

Following General Procedure D, a solution of **13c** (631 mg, 1.92 mmol) in DCM (4 mL) was cooled to 0 °C and TFA (4 mL) was added dropwise. The resulting solution was stirred for 1.5 h at rt before the solvent was removed *in vacuo* to give **14c** as a yellow oil (499 mg, 95%) in a 3:1 mixture of keto and enol forms; ν_{max} (film) 2980, 1712; δ_H (400 MHz, $CDCl_3$) keto – 1.37 (3H, d, *J* 7.1, C(2)C*H*$_3$), 3.69 (1H, q, *J* 7.1, C(2)*H*), 3.84 (1H, d, *J* 16.0, C(4)*H*$_A$H$_B$), 3.90 (1H, d, *J* 16.0, C(4)H$_A$*H*$_B$), 7.06-7.12 (2H, m, *Ph*), 7.42-7.50 (2H, m, *Ph*), 12.40 (1H, br s, O*H*), enol – 1.47 (3H, s, C(2)C*H*$_3$), 3.66 (2H, s, C(4)*H*$_2$), 7.06-7.12 (2H, m, *Ph*), 7.42-7.50 (2H, m, *Ph*), 12.40 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 12.8 (C(2)CH3 keto), 22.0 (C(2)*C*H$_3$ enol), 48.0 (*C*(4) keto), 48.9 (*C*(4) enol), 51.5 (*C*(2) keto), 121.0, 121.4 (*C*(4□)), 131.1, 131.3, 131.6, 131.8, 131.9, 132.0, 133.3 (*Ph*, *C*(2) enol), 154.1, 154.2 (*C*(1□)), 175.4 (*C*(1)), 202.4 (*C*(3) keto), 202.4 (*C*(3) enol); *m/z* (ESI$^+$) 292, 294 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{11}BrNaO_3^+$ ([M+Na]$^+$) requires 292.9784, 294.9764, found 292.9780, 294.9763.

2-Methyl-3-oxo-4-(phenylthio)butanoic acid 14d

Following General Procedure D, a solution of **13d** (620 mg, 2.21 mmol) in DCM (4 mL) was cooled to 0 °C and TFA (4 mL) was added dropwise. The resulting solution was stirred for 2 h at rt before the solvent was removed *in vacuo* by co-evaporation with toluene to give **14d** as a brown oil (490 mg, quant) which was used without further purification; ν_{max} (film) 3059, 2985, 2940, 1707, 1583; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.1, C(2)C*H*$_3$), 3.86, 3.91 (2H, AB q, *J* 15.3, C(4)*H*$_2$), 4.03 (1H, q, *J* 7.1, C(2)*H*), 7.15-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (*C*H$_3$), 43.5 (*C*(4)), 49.1 (*C*(2)), 125.3, 127.3, 128.2, 129.2, 130.0 (*o*,*m*,*p*-*Ph*), 133.9 (*i*-*Ph*), 175.1 (*C*O$_2$H), 199.5 (*C*(3)); *m/z* (ESI$^+$) 223 ([M−H]$^-$, 40%).

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(4□-methoxy-2□-methyl-3□-oxobutanoyl)-4-methoxycarbonyl-5-methyloxazolidine 15a and 15a'

Following General Procedure E, oxazolidine **1** (248 mg, 1.23 mmol) was reacted with DCC (268 mg, 1.30 mmol), DMAP (10 mg, 7 mol%) and the acid **14a** (190 mg, 1.30 mmol). The crude

mixture of **15a** (340 mg) was used without purification; *m/z* (ESI^+) 352 ($[M+Na]^+$, 20%), 681 ($[2M+Na]^+$, 100%).

(2*R*,4*S*,5*R*,2□*R*)- and (2*R*,4*S*,5*R*,2□*S*)-2-*t*-Butyl-3-(3□-oxo-2□-methylhept-6□-enoyl)-4-methoxycarbonyl-5-methyloxazolidine 15b and 15b'

Following General Procedure E, oxazolidine **1** (522 mg, 2.6 mmol) was reacted with DCC (562 mg, 2.78 mmol), DMAP (23 mg, 7 mol%), and acid **14b** (434 mg, 2.78 mmol) in DCM (13 mL). Purification *via* column chromatography (SiO_2, eluent 10:1 petrol:EtOAc) gave **15b** as a colourless oil (130 mg, 14%); R_f 0.74 (eluent 3:1 petrol:EtOAc); $[\alpha]_D^{23}$ +2.42 (*c* 0.44 in $CHCl_3$); ν_{max} (film) 2977, 2958, 1747, 1729, 1664; δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(CH_3)$_3$), 1.32 (3H, d, *J* 6.1, C(5)CH_3), 1.50 (3H, d, *J* 6.8, C(2□)CH_3), 2.30 (2H, app. q, *J* 6.8, C(5□)H_2), 2.57-2.74 (2H, m, C(4□)H_2), 3.66 (1H, q, *J* 6.8, C(2□)*H*), 3.81 (3H, s, CO_2CH_3), 4.44 (1H, d, *J* 3.0, C(4)*H*), 4.73-4.82 (1H, m, C(5)*H*), 4.95-5.06 (2H, m, C(7□)H_2), 5.44 (1H, s, C(2)*H*), 5.72-5.84 (1H, m, C(6□)*H*); δ_C (125 MHz, $CDCl_3$) 15.0 (C(2□)*C*H$_3$), 20.2 (C(5)*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 27.2 (*C*(5□)), 37.8, 38.3 (*C*(4□), *C*Me$_3$), 52.8 (CO_2CH_3), 54.1 (*C*(2□)), 65.0 (*C*(4)), 76.0 (*C*(5)), 96.0 (*C*(2)), 115.3 (*C*(7□)), 136.7 (*C*(6□)), 170.2 (*C*O_2Me), 171.5 (*C*(1□)), 207.6 (*C*(3□)); *m/z* (ESI^+) 362 ($[M+Na]^+$, 40%), 701 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{29}NNaO_5^+$ ($[M+Na]^+$) requires 362.1938, found 362.1931; and **15b'** as a yellow oil (180 mg, 20%); R_f 0.1 (eluent 10:1 petrol:EtOAc); $[\alpha]_D^{23}$ −4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2977, 2958, 2936, 1747, 1728, 1663; δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C(CH_3)$_3$), 1.29 (3H, d, *J* 7.1, C(2□)CH_3), 1.35 (3H, d, *J* 6.3, C(5)CH_3), 2.29-2.38 (2H, m, C(5□)H_2), 2.58-2.77 (2H, m, C(4□)H_2), 3.49 (1H, q, *J* 7.1, C(2□)*H*), 3.81 (3H, s, CO_2CH_3), 4.11 (1H, d, *J* 4.3, C(4)*H*), 4.74-4.81 (1H, m, C(5)*H*), 4.93-5.05 (2H, m, C(7□)H_2), 5.42 (1H, s, C(2)*H*), 5.71-5.86 (1H, m, C(6□)*H*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(2□)*C*H$_3$), 20.3 (C(5)*C*H$_3$), 25.9 (C(*C*H$_3$)$_3$), 27.5 (*C*(5□)), 38.0 (*C*Me$_3$), 39.1 (*C*(4□)), 52.4, 52.9 (*C*(2□), CO_2CH_3), 65.8 (*C*(4)), 75.9 (*C*(5)), 96.2 (*C*(2)), 115.1 (*C*(7□)), 137.1 (*C*(6□)), 169.9 (*C*O_2Me), 172.4 (*C*(1□)), 204.2 (*C*(3□)); *m/z* (ESI^+) 362 ($[M+Na]^+$, 30%), 701, ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{29}NNaO_5^+$ ($[M+Na]^+$) requires 362.1938, found 362.1925.

(2*R*,4*S*,5*R*,2□*R*)- and (2*R*,4*S*,5*R*,2□*S*)-2-*t*-Butyl-3-(3□-oxo-4□-(4□□-bromophenyl)-2□-methylbutanoyl)-4-methoxycarbonyl-5-methyloxazolidine 15c and 15c'

Following General Procedure E, oxazolidine **1** (336 mg, 1.67 mmol) was reacted with DCC (344 mg, 1.67 mmol), DMAP (14 mg, 7 mol%), and acid **14c** (477 mg, 1.76 mmol). Purification *via* column chromatography (SiO_2, eluent 10:1 40-60 petrol:EtOAc) gave **15c** and **15c'** as a pale yellow oil (86 mg, 11%); R_f 0.4 (eluent 5:1 40-60 petrol:EtOAc); $[\alpha]_D^{23}$ +19.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film)

2957, 1748, 1713, 1662; δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(CH_3)$_3$), 1.19 (3H, d, *J* 6.1, C(5)CH_3), 1.53 (3H, d, *J* 6.9, C(2□)CH_3), 3.66 (1h, q, *J* 6.9, C(2□)*H*), 3.67 (3H, s, CO_2CH_3), 3.77-3.84 (2H, m, C(4□)H_2), 3.92 (1H, d, *J* 4.3, C(4)*H*), 4.65 (1H, qd, *J* 6.1, 4.3, C(5)*H*), 5.42 (1H, s, C(2)*H*), 7.05 (2H, d, *J* 8.3, C(2□□)*H*, C(6□□)*H*), 7.45 (2H, d, *J* 8.3, C(3□□)*H*, C(5□□)*H*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(2□)*C*H$_3$), 20.0 (C(5)*C*H$_3$), 25.9 (C(*C*H$_3$)$_3$), 38.0 (*C*Me$_3$), 45.7 (*C*(4□)), 52.8, 53.0 (CO_2CH_3, *C*(2□)), 65.0 (*C*(4)), 76.2 (*C*(5)), 96.1 (*C*(2)), 121.4 (*C*(4□□)), 131.3, 131.5, 131.7, 131.9 (*C*(2□□), *C*(6□□), *C*(3□□), *C*(5□□)), 132.3 (*C*(1□□), 170.0, 171.4 (*C*O_2Me, *C*(1□)), 205.0 (*C*(3□)); *m/z* (FI$^+$) 453 (M$^+$, 100%), 455 (M$^+$, 100%); HRMS (FI$^+$) $C_{21}H_{28}BrNO_5^+$ (M$^+$) requires 453.1151, 455.1133, found 453.1380, 455.1338; and **15c'** as a yellow solid (185 mg, 24%); R_f 0.2 (eluent 5:1 40-60 petrol:EtOAc); mp 148-150 ºC; $[\alpha]_D^{23}$ +1.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2958, 2359, 1747, 1733, 1662; δ_H (400 MHz, $CDCl_3$) 0.97 (9H, s, C(CH_3)$_3$), 1.32 (3H, d, *J* 6.9, C(2□)CH_3), 1.38 (3H, d, *J* 6.1, C(5)CH_3), 3.60 (1H, q, *J* 6.9, C(2□)*H*), 3.82 (3H, s, CO_2CH_3), 3.82-3.93 (2H, m, C(4□)H_2), 4.14 (1H, d, *J* 4.3, C(4)*H*), 4.75-4.83 (1H, m, C(5)*H*), 5.46 (1H, s, C(2)*H*), 7.10 (2H, d, *J* 8.3, C(2□□)*H*, C(6□□)*H*), 7.42 (2H, d, *J* 8.3, (C(3□□)*H*, C(5□□)*H*); δ_C (100 MHz, $CDCl_3$) 13.0 (C(2□)*C*H$_3$), 20.5 (C(5)*C*H$_3$), 26.0 (C(*C*H$_3$)$_3$), 38.2 (*C*Me$_3$), 45.9 (*C*(4□)), 52.6, 53.0 (CO_2CH_3, *C*(2□)), 65.8 (*C*(4)), 76.1 (*C*(5)), 96.4 (*C*(2)), 120.9 (*C*(4□□)), 131.2, 131.4, 131.5, 131.9 (*C*(2□□), *C*(6□□), *C*(3□□), *C*(5□□)), 132.9 (*C*(1□□)), 170.0, 172.1 (*C*O_2Me, *C*(1□□)), 201.7 (*C*(3□□)); *m/z* (FI$^+$) 453 (M$^+$, 100%), 455 (M$^+$, 100%); HRMS (FI$^+$) $C_{21}H_{28}BrNO_5^+$ (M$^+$) requires 453.1151, 455.1133, found 453.1393, 455.1442.

(2*R*,4*S*,5*R* ,2□*R*)- and (2*R*,4*S*,5*R* ,2□*S*)-2-*t*Butyl-3-(3□-oxo-2□-methyl-4□-phenylthiobutanoyl)4-methoxycarbonyl-5-methyloxazolidine 15d and 15d'

Following General Procedure E, oxazolidine **1** (422 mg, 2.1 mmol) was reacted with DCC (457 mg, 2.2 mmol), DMAP (18 mg, 7 mol%), and acid **14d** (495 mg, 2.2 mmol). Purification *via* column chromatography (SiO_2, eluent 10:1 petrol:EtOAc) gave **15d** as a yellow oil (117 mg, 14%); R_f 0.4 (eluent 20:1 petrol:EtOAc); $[\alpha]_D^{23}$ −12.2 (*c* 0.72 in $CHCl_3$); ν_{max} (film) 2975, 2957, 1746, 1717, 1661; δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(CH_3)$_3$), 1.27 (3H, d, *J* 6.3, C(5)CH_3), 1.48 (3H, d, *J* 7.1, C(2□)CH_3), 3.78 (3H, s, CO_2CH_3), 3.80-3.93 (3H, m, C(2□)*H*, C(4□)H_2), 4.27 (1H, d, *J* 4.3, C(4)*H*), 4.65-4.72 (1H, m, C(5)*H*), 5.47 (1H, s, C(2)*H*), 7.19-7.24 (1H, m, *Ph*), 7.27-7.30 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(2□)*C*H$_3$), 20.1 (C(5)*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 38.0 (*C*Me$_3$), 40.6 (*C*(4□)), 50.5 (*C*(2□)), 52.7 (CO_2CH_3), 65.3 (*C*(4)), 76.4 (*C*(5)), 96.1 (*C*(2)), 126.9 (*p-Ph*), 128.5, 129.3 (*o,m-Ph*), 134.0 (*i-Ph*), 170.1 (*C*O_2Me), 172.4 (*C*(1□)), 202.2 (*C*(3□)); *m/z* (ESI$^+$) 408 ([M+H]$^+$, 5%), 430 ([M+Na]$^+$, 45%), 837 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{29}NNaO_5S^+$ ([M+Na]$^+$) requires 430.1659, found 430.1647; and **15d'** as a yellow solid (140 mg, 16%); R_f 0.2

(eluent 20:1 petrol:EtOAc); mp 102-106 ºC; $[\alpha]_D^{23}$ −22.5 (*c* 0.39 in $CHCl_3$); ν_{max} (film) 2976, 2957, 1742, 1660; δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, C(CH_3)$_3$), 1.34 (3H, d, *J* 6.8, C(2□)CH_3), 1.37 (3H, d, *J* 6.1, C(5)CH_3), 3.81-3.88 (4H, m, CO_2CH_3, C(2□)*H*), 3.91, 3.98 (2H, AB q, *J* 15.8, C(4□)H_2), 4.14 (1H, d, *J* 4.0, C(4)*H*), 4.78-4.85 (1H, m, C(5)*H*), 5.43 (1H, s, C(2)*H*), 7.20 (1H, t, *J* 7.3, *p-Ph*), 7.28 (2H, app. t, *J* 7.6, *m-Ph*), 7.35 (2H, d, *J* 7.8, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 13.2 (C(2□)CH_3), 20.4 (C(5)CH_3), 26.0 (C(CH_3)$_3$), 38.1 (CMe_3), 42.0 (*C*(4□)), 50.8 (*C*(2□)), 53.1 (CO_2CH_3), 65.7 (*C*(4)), 76.0 (*C*(5)), 97.2 (*C*(2)), 126.7 (*p-Ph*), 129.0, 129.5 (*o*,*m-Ph*), 134.8 (*i-Ph*); *m/z* (ESI^+) 408 ($[M+H]^+$, 5%), 430 ($[M+Na]^+$, 55%), 837 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{29}NNaO_5S^+$ ($[M+Na]^+$) requires 430.1659, found 430.1646.

_t_-Butyl 4-methoxy-2-methyl-3-oxo-5-phenylpentanoate 16

A stirred suspension of NaH (43 mg, 1.00 mmol) in THF (20 mL) was cooled to 0 °C and a solution of **13b** (200 mg, 1.0 mmol) in THF (2 mL) was added dropwise. Stirring was continued for 10 min at 0 °C before the dropwise addition of BuLi (0.73 mL, 1.6 M in hexanes, 1.09 mmol). After stirring for a further 10 min, BnBr (0.13 mL, 1.09 mmol) was added in one portion and the mixture was allowed to warm to rt over 15 min. The mixture was quenched with 2M HCl (7 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with H_2O until the aqueous layer remained neutral, dried and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent 40:1 to 20:1 40-60 petrol:EtOAc) gave **16** as a colourless oil (117 mg, 40%) in a 47:43 dr; R_f 0.5 (eluent 50:1 40-60 petrol:EtOAc); ν_{max} (film) 3437, 3030, 2980, 2830, 1716, 1604; δ_H (100 MHz, $CDCl_3$) major diastereomer: 1.18 (3H, d, *J* 7.3, C(2)CH_3), 1.44 (9H, s, C(CH_3)$_3$), 2.88-2.93 (1H, m, C(5)H_AH_B), 3.11 (1H, dd, *J* 14.0, 4.2, C(5)H_AH_B), 3.32 (3H, s, OCH_3), 3.56-3.63 (1H, m, C(4)*H*), 7.19-7.33 (5H, m, *Ph*), minor diastereoisomer: 1.25 (3H, d, *J* 7.1, C(2)CH_3), 1.46 (9H, s, C(CH_3)$_3$), 2.88-2.93 (1H, m, C(5)H_AH_B), 3.04 (1H, dd, *J* 14.2, 4.0, C(5)H_AH_B), 3.27 (3H, s, OCH_3), 3.56-3.63 (1H, m, C(2)*H*), 2.97-4.03 (1H, m, C(4)*H*), 7.19-7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.5 (C(2)CH_3), 27.9 (C(CH_3)$_3$), 37.2 (*C*(5) major), 38.5 (*C*(5) minor), 49.4, 50.1 (*C*(2)), 58.6, 58.9 (OCH_3), 81.4, 81.8 (CMe_3), 86.9, 87.7 (*C*(4)), 126.6, 128.3, 128.4, 129.3, 129.6 (*o*,*m*,*p-Ph*), 137.2 (*i-Ph*), 169.3, 169.8 (*C*(1)), 207.2, 207.8 (*C*(3)); *m/z* (ESI^+) 315 ($[M+Na]^+$, 80%), 291 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_{17}H_{24}NaO_4^+$ ($[M+Na]^+$) requires 315.1567, found 315.1565.

4-Methoxy-2-methyl-3-oxo-5-phenylpentanoic acid 17

Following General Procedure D, a solution of **16** (357 mg, 1.22 mmol) in DCM (1.7 mL) was cooled to 0 °C and TFA (1.7 mL) was added dropwise. The resulting solution was stirred for 1.5 h at rt before the solvent was removed *in vacuo* to give **17** in a 53:47 dr as an orange oil (283 mg, 98%); ν_{max} (film) 2939, 1713, 1496, 1455; δ_H (400 MHz, $CDCl_3$) 1.24 (3H × 0.53, d, *J* 7.3, C(2)CH_3 major), 1.28 (3H × 0.47, d, *J* 7.1, C(2)CH_3 minor), 2.89-3.00 (1H, m, C(5)H_AH_B), 3.06-3.15 (1H, m, C(5)H_AH_B), 3.28 (3H × 0.47, s, OCH_3 min), 3.30 (3H × 0.53, s, OCH_3 maj), 3.60-3.72 (1H, m, C(2)*H*), 3.99-4.05 (1H, m, C(4)*H*), 7.18-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.4 (C(2)*C*H_3), 37.4, 38.2 (C(5)), 48.2, 48.9 (*C*(2)), 58.6, 58.9 (O*C*H_3), 87.0, 87.7 (*C*(4)), 126.6, 126.7, 128.4, 128.5, 129.3, 129.4, 129.6 (*o,m,p-Ph*), 136.8, 137.1 (*i-Ph*), 175.5, 176.2 (*C*(1)), 206.8, 207.1 (*C*(3)); *m/z* (ESI^+) 259 ($[M+Na]^+$, 80%), 235 ($[M-H]^-$, 80%); HRMS (ESI^+) $C_{13}H_{16}NaO_4^+$ ($[M+Na]^+$) requires 259.0941, found 259.0947.

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(4□-methoxy-5□-phenyl-2□-methyl-3□-oxopentanoyl)-4-methoxycarbonyl-5-methyloxazolidine 18

Following General Procedure E, oxazolidine **1** (229 mg, 1.14 mmol) was reacted with DCC (247 mg, 1.20 mmol), DMAP (10 mg, 7 mol%) and the acid **17** (236 mg, 1.20 mmol). The crude mixture of **18** (438 mg) was used without purification; R_f 0.25 (eluent 8:1 40-60 petrol:EtOAc); ν_{max} (film) 3339, 3030, 2934, 2118, 1822, 1741, 1651; *m/z* (ESI^+) 442 ($[M+Na]^+$, 60%), 861 ($[2M+Na]^+$, 90%), 418 ($[M-H]^-$, 30%); δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(CH_3)$_3$), 1.19 (3H, d, *J* 6.8, C(2□)CH_3), 1.50 (3H, d, *J* 6.1, C(5)CH_3), 2.63 (1H, q, *J* 6.8, C(2□)*H*), 2.88 (1H, dd, *J* 14.0, 5.2, C(5□)H_AH_B), 3.12 (1H, dd, *J* 14.0, 5.2, C(5□)H_AH_B), 3.30 (3H, s, OCH_3), 3.72 (3H, s, CO_2CH_3), 3.93 (1H, dd, *J* 5.2, 4.4, C(4□)*H*), 4.27 (1H, d, *J* 7.1, C(4)*H*), 4.51-4.58 (1H, m, C(5)*H*), 5.50 (1H, s, C(2)*H*), 7.12-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.2 (C(2□)*C*H_3), 21.0 (*C*(5)CH_3), 25.8/26.0 (C(*C*H_3)$_3$), 37.2/38.6 (*C*Me_3), 37.9 (*C*(5□)), 50.1 (*C*(2□)), 58.0/58.2 (O*C*H_3), 66.2 (*C*(4)), 77.6 (*C*(5)), 86.3 (*C*(4□)), 96.6 (*C*(2)), 126.3, 126.6, 128.3, 128.6, 129.1, 129.3, 129.4, 129.8 (*o,m,p-Ph*), 136.5 (*i-Ph*), 170.4 (*C*O_2Me), 172.8 (*C*(1□)), 206.8 (*C*(3□)); HRMS (ESI^+) $C_{23}H_{33}NNaO_6^+$ ($[M+Na]^+$) requires 422.2200, found 422.2198.

***t*-Butyl 3-oxo-2-allyl-4-(phenylthio)-butanoate 19a**

A stirred suspension of NaH (33 mg, 0.83 mmol) in THF (6 mL) was cooled to 0 °C and a solution of **6d** (200 mg, 0.75 mmol) in THF (2 mL) was added dropwise. Stirring was continued for 10 min

at 0 °C before the dropwise addition of BuLi (0.53 mL, 1.48 M in hexanes, 0.79 mmol). After stirring for a further 10 min, allyl bromide (0.07 mL, 0.83 mmol) was added in one portion and the mixture was allowed to warm to rt over 15 min. The mixture was quenched with 2 M HCl (7 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with H_2O until the aqueous layer remained neutral, dried and concentrated *in vacuo* to give *t*-butyl 3-oxo-2-allyl-4-(phenylthio)-butanoate **19a** as a yellow oil (232 mg, quant.): R_f 0.2 (eluent 50:1 petrol:EtOAc); ν_{max} (film) 2978, 2927, 1738, 1710; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, $C(CH_3)_3$), 2.37-2.47 (1H, m, C(1□)H_AH_B), 2.51-2.62 (1H, m, C(1□)H_AH_B), 3.55 (1H, d, *J* 15.4, C(4)H_AH_B), 3.69 (1H, d, *J* 15.4, C(4)H_AH_B), 3.79 (1H, app. t, *J* 7.5, C(2)*H*), 5.07-5.17 (2H, m, C(3□)H_2), 5.76-5.89 (1H, m, C(2□)*H*), 7.26-7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.0 ($C(CH_3)_3$), 33.8 (*C*(1□)), 47.6 (*C*(4)), 56.0 (*C*(2)), 82.0 (CMe_3), 118.0 (*C*(3□)), 128.7, 128.9, 129.1 (*o*,*m*,*p*-*Ph*), 133.9 (*C*(2□)), 134.6 (*i*-*Ph*), 166.3 (*C*(1)), 198.2 (*C*(3)); *m/z* (ESI^+) 329 ($[M+Na]^+$, 15%), 635 ($[2M+Na]^+$, 20%); HRMS (ESI^+) $C_{17}H_{22}NaO_3S^+$ ($[M+Na]^+$) requires 329.1182, found 329.1182.

_t_-Butyl 3-oxo-2-benzyl-4-(phenylthio)-butanoate 19b

A stirred suspension of NaH (17 mg, 0.41 mmol) in THF (4 mL) was cooled to 0 °C and a solution of **6d** (100 mg, 0.38 mmol) in THF (1 mL) was added dropwise. Stirring was continued for 10 min at 0 °C before the dropwise addition of BuLi (0.27 mL, 1.48 M in hexanes, 0.39 mmol). After stirring for a further 10 min, BnBr (0.05 mL, 0.41 mmol) was added in one portion and the mixture was allowed to warm to rt over 15 min. The mixture was quenched with 2 M HCl (7 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with H_2O until the aqueous layer remained neutral, dried and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent 50:1 40-60 petrol:EtOAc) gave *t*-butyl 3-oxo-2-benzyl-4-(phenylthio)-butanoate **19b** as a yellow oil (91 mg, 54%) in a 4:1 mixture with unreacted starting material; R_f 0.2 (eluent 50:1 petrol:EtOAc); ν_{max} (film) 2978, 2931, 1737, 1709; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, $C(CH_3)_3$), 2.96 (1H, dd, *J* 14.4, 7.2, C(1□)H_AH_B), 3.22 (1H, dd, *J* 14.4, 7.6, C(1□)H_AH_B), 3.52 (1H, d, *J* 15.3, C(4)H_AH_B), 3.63 (1H, d, *J* 15.3, C(4)H_AH_B), 4.04 (1H, app. t, *J* 7.4, C(2)*H*), 7.14-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 ($C(CH_3)_3$), 35.9 (*C*(5)), 48.2 (*C*(2)), 57.9 (*C*(4)), 82.0 (CMe_3), 126.7-129.6 (*o*,*m*,*p*-*Ph*, -S*Ph*), 133.8 (*i*-S*Ph*), 138.0 (*i*-*Ph*), 166.1 (*C*(1)),

198.1 (*C*(3)); *m/z* (ESI$^-$) 355 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{21}H_{24}NaO_3S^+$ ([M+Na]$^+$) requires 379.1228, found 379.1338.

2-Allyl-3-oxo-4-(phenylthio)-butanoic acid 20a

Following Procedure D, a solution of **19a** (232 mg, 0.75 mmol) in DCM (1.0 mL) was cooled to 0 °C and TFA (1.0 mL) was added dropwise. The resulting solution was stirred for 1.5 h at rt before the solvent was removed *in vacuo* to give **21a** as a pale yellow oil (190 mg, quant.); ν_{max} (film) 3077, 2923, 1704; δ_H (400 MHz, $CDCl_3$) 2.43-2.64 (2H, m, C(1□)H_2), 3.75-3.79 (3H, m, C(4)H_2, C(2)*H*), 5.09-5.20 (2H, m, C(3□)H_2), 5.76-5.89 (1H, m, C(2□)*H*), 7.28-7.42 (5H, m, *Ph*), 8.57 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 33.7 (*C*(1□)), 45.0 (*C*(4)), 56.5 (*C*(2)), 118.5 (*C*(3□)), 129.0, 129.2, 129.3, 130.0, 130.7 (*o,m,p-Ph*), 133.3, 134.0 (*C*(2□), *i-Ph*), 198.8 (*C*(3)); *m/z* (ESI$^+$) 273 ([M+Na]$^+$, 100%), (ESI$^-$) 249 ([M−H]$^-$, 60%); HRMS (ESI$^+$) $C_{13}H_{24}NaO_3S^+$ ([M+Na]$^+$) requires 273.0556, found 273.0561.

2-Benzyl-3-oxo-4-(phenylthio)-butanoic acid 20b

According to Procedure D, a solution of **19b** (90 mg, 0.26 mmol) in DCM (0.5 mL) was cooled to 0 °C and TFA (0.5 mL) was added dropwise. The resulting solution was stirred for 1.5 h at rt before the solvent was removed *in vacuo* to give **20b** as a yellow oil (71 mg, 92%) in a 3:1 mixture of keto:enol tautomers; ν_{max} (film) 3061, 3028, 2928, 1705; δ_H (400 MHz, $CDCl_3$) keto form - 2.89-3.28 (2H, m, CH_2Ph), 3.66-3.72 (2H, m, C(4)H_2), 4.03 (1H, app. t, *J* 7.6, C(2)*H*), 7.15-7.45 (10H, m, *Ph*, S*Ph*); enol form - 2.89-3.28 (2H, m, CH_2Ph), 4.30 (1H, app. t, *J* 7.5, C(2)*H*), 4.83 (1H, s, C(4)*H*), 7.15-7.45 (10H, m, *Ph*, S*Ph*); δ_C (100 MHz, $CDCl_3$) 34.0, 35.9 (*C*H_2Ph), 45.9 (*C*(4) keto), 57.1 (*C*(2) enol), 58.3 (*C*(2) keto), 90.1 (*C*(4) enol), 126.8, 126.9, 127.2, 127.5, 128.3, 128.4, 128.5, 128.6, 129.0, 129.1, 129.7, 130.0 (*o,m,p-Ph*, -S*Ph*), 133.4, 134.0 (*i-Ph*), 137.7, 140.0 (*i*-S*Ph*), 171.8, 173.8 (*C*(1)), 198. 3, 198.8 (*C*(3)); *m/z* (ESI$^+$) 323 ([M+Na]$^+$, 100%), (ESI$^-$) 299 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{17}H_{16}NaO_3S^+$ ([M+Na]$^+$) requires 323.0712, found 323.0716.

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(2□-allyl-3□-oxo-4□-phenylthio-butanoyl)-4-methoxycarbonyl-5-methyloxazolidine 21a

Following General Procedure E, oxazolidine **1** (169 mg, 0.84 mmol) was reacted with DCC (183 mg, 0.88 mmol), DMAP (7 mg, 7 mol%) and acid **20a** (211 mg, 0.84 mmol). Purification *via* column chromatography gave **21a** as a mixture of indeterminate dr as a pale yellow oil (100 mg, 27%); R_f 0.2 (eluent 20:1 petrol:EtOAc); ν_{max} (film) 2956, 2926, 2871, 2855, 1746, 1714, 1667, 1625; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, C(CH_3)$_3$), 1.32-1.40 (3H, m, C(5)CH_3) 2.41-2.73 (2H, m, C(1□□)H_2), 3.72-3.82 (4H, m, CO_2CH_3), C(4□)H_AH_B), 3.90-3.95 (1H, m, C(2□)*H*), 4.00 (1H, d, *J* 15.2, C(4□)H$_A$$H_B$), 3.81 and 4.26 (1H, d, *J* 2.8 and 3.5, C(4)*H*), 4.66-4.72 and 4.73-4.79 (1H, m, C(5)*H*), 5.07-5.20 (2H, m, C(3□□)H_2), 5.38-5.43 (1H, m, C(2)*H*), 5.75-5.91 (1H, m, C(2□□)*H*), 7.25-7.34 (3H, m, *o*,*p*-*Ph*), 7.34-7.46 (2H, m, *m*-*Ph*); δ_C (100 MHz, $CDCl_3$) 19.9, 20.0 (C(5)*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 33.9 (*C*(1□□)), 37.7 (*C*Me$_3$), 46.9, 48.4 (*C*(4□)), 52.6, 52.7 (CO_2CH_3), 55.9, 46.0 (*C*(2□)), 65.1 (*C*(4)), 75.9 (*C*(5)), 95.9 (*C*(2)), 117.9, 118.0 (*C*(3□□)), 127.8, 127.9 (*p*-*Ph*), 128.7, 128.9, 129.0, 129.2 (*o*,*m*-*Ph*), 132.4, 133.7 (*i*-*Ph*), 134.0, 134.2 (*C*(2□□)), 167.9 (*C*(1□)), 170.1 (CO_2Me), 185.8 (*C*(3□)); *m/z* (ESI$^+$) 456([M+Na]$^+$, 100%), (ESI$^-$) 432 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{23}H_{31}NNaO_5S^+$ ([M+Na]$^+$) requires 456.1815, found 456.1809.

(2*R*,4*S*,5*R*)-2-*t*-Butyl-3-(2□-benzyl-3□-oxo-4□-phenylthio-butanoyl)-4-methoxycarbonyl-5-methyloxazolidine 21b

Following General Procedure E, oxazolidine **1** (47 mg, 0.24 mmol) was reacted with DCC (51 mg, 0.25 mmol), DMAP (2 mg, 7 mol%) and acid **20b** (71 mg, 0.24 mmol). Purification *via* flash column chromatography (SiO_2, eluent 20:1 petrol:EtOAc) gave **21b** in a 1:1 dr as a colourless oil (20 mg, 17%); R_f 0.2 (eluent 20:1 petrol:EtOAc); ν_{max} (film) 3029, 2975, 2956, 2933, 2873, 1745, 1715, 1667, 1625; δ_H (500 MHz, $CDCl_3$) 0.87 (9H, s, C(CH_3)$_3$), 1.16 and 1.22 (3H, d, *J* 6.3, C(5)CH_3), 2.98-3.11 (1H, m, C$H_A$$H_B$Ph), 3.16-3.30 (1H, m, CH$_A$$H_B$Ph), 3.61-3.82 (5H, m, CO_2CH_3, C(4□)H_2-epimer A, C(4□)H_AH_B-epimer B, C(4)*H*-A), 3.95 (0.5 × 1H, d, *J* 15.1, C(4□)H$_A$$H_B$-B), 4.07-4.12 (0.5 × 2H, m, C(4)*H*-B, C(2□)*H*-A), 4.17 (0.5 × 1H, app. t, *J* 7.6, C(2□)*H*-B), 4.63-4.68 and 4.69-4.73 (1H, m, C(5)*H*), 5.20 and 5.39 (1H, s, C(2)*H*), 7.14-7.32 (10H, m, *Ph*, S*Ph*); δ_C (125 MHz, $CDCl_3$) 19.8, 19.9 (C(5)*C*H$_3$), 25.7, 25.7 (C(*C*H$_3$)$_3$), 36.0, 36.3, 37.6, 37.7 (*C*H$_2$Ph, *C*Me$_3$), 48.2, 48.6 (*C*(4□)), 52.5, 52.7 (CO_2CH_3), 57.5, 57.8 (*C*(2□)), 64.9, 64.9 (*C*(4)), 75.7, 75.8 (*C*(5)), 95.8, 95.9 (*C*(2)), 126.8-129.2 (*o*,*m*,*p*-*Ph*, -S*Ph*), 133.0, 133.5 (*i*-S*Ph*), 137.5, 137.6 (*i*-*Ph*), 167.5, 168.1 (*C*(1□)), 170.0, 170.1 (CO_2Me), 199.6, 200.1 (*C*(3□)); *m/z* (ESI$^-$) 482 ([M−H]$^-$, 100%), (ESI$^+$) 506 ([M+Na]$^+$, 60%); HRMS (ESI$^+$) $C_{27}H_{33}NNaO_5S^+$ ([M+Na]$^+$) requires 506.1972, found 506.1980.

(2*R*,4*R*,5*R*,6*R*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-methoxymethyl-8-oxo-3-oxabicylco[3.3.0]octane 22a

Following General Procedure H, **8** (440 mg, 1.40 mmol) and NaOMe (83 mg, 1.53 mmol) were reacted to give the crude reaction mixture. Purification *via* column chromatography (SiO_2, eluent 3:1 40-60 petrol:EtOAc) gave **22a** as a white solid (99 mg, 22%); R_f 0.1 (eluent 3:1 40-60 petrol:EtOAc); mp 144-147 ºC; $[\alpha]_D^{23}$ +26.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3404 (br), 2956, 1704; δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(C*H*$_3$)$_3$), 1.63 (3H, d, *J* 6.6, C(4)C*H*$_3$), 2.34 (1H, d, *J* 16.2, C(7)*H*$_A$H$_B$), 3.06 (1H, d, *J* 16.2, C(7)H$_A$*H*$_B$), 3.09 (1H, s, O*H*), 3.35 (1H, d, *J* 9.7, C*H*$_A$H$_B$OMe), 3.36 (3H, s, OCH$_3$), 3.50 (1H, d, *J* 9.7, CH$_A$*H*$_B$OMe), 3.77 (3H, s, CO$_2$C*H*$_3$), 4.76 (1H, q, *J* 6.6, C(4)*H*), 5.04 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 15.5 (C(4)*C*H$_3$), 25.6 (C(*C*H$_3$)$_3$), 37.0 (*C*Me$_3$), 45.8 (*C*(7)), 52.6 (CO$_2$*C*H$_3$), 59.3 (O*C*H$_3$), 74.3 (*C*H$_2$OMe), 78.6 (*C*(4)), 79.0, 82.2 (*C*(5), *C*(6)), 171.5 (*C*O$_2$Me), 178.2 (*C*(8)); *m/z* (ESI$^-$) 314 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{15}H_{26}NO_6^+$ ([M+H]$^+$) requires 316.1755, found 316.1754.

(2*R*,5*R*,4*R*,6*R*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(but-3□-enyl)-8-oxo-oxabicyclo[3.3.0]octane 22b

Following General Procedure H, *N*-acyloxazolidine **15b** (143 mg, 0.44 mmol) and NaOMe (26 mg, 0.48 mmol) were reacted to give a crude mixture which was purified *via* column chromatography (SiO_2, eluent 20:1-6:1) to give unreacted **9a** (74 mg, 51%) and **22b** as a colourless oil (67 g, 46%); R_f 0.6 (eluent 2:1 petrol:EtOAc); $[\alpha]_D^{23}$ +18.0 (*c* 0.95 in $CHCl_3$); ν_{max} (film) 3418 (OH), 3078, 2955, 1702 (ester C=O), 1642 (amide C=O); δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(C*H*$_3$)$_3$), 1.33-1.43 (1H, m, C(1□)*H*$_A$H$_B$), 1.70 (3H, d, *J* 6.6, C(4)C*H*$_3$), 1.90-1.98 (1H, m, C(1□)H$_A$*H*$_B$), 1.99-2.10 (1H, m, C(2□)*H*$_A$H$_B$), 2.30-2.37 (1H, m, C(2□)H$_A$*H*$_B$), 2.37 (1H, d, *J* 15.8, C(7)*H*$_A$H$_B$), 3.04 (1H, d, *J* 15.8, C(7)H$_A$*H*$_B$), 3.14 (1H, br s, O*H*), 3.80 (3H, s, CO$_2$C*H*$_3$), 4.79 (1H, q, *J* 6.6, C(4)*H*), 4.98-5.10 (2H, m, C(4□)*H*$_2$), 5.06 (1H, s, C(2)*H*), 5.76-5.87 (1H, m, C(3□)*H*); δ_C (100 MHz, $CDCl_3$) 15.3 (C(4)*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 28.6 (*C*(2□)), 35.0 (*C*(1□)), 37.4 (*C*Me$_3$), 47.4 (*C*(7)), 52.7 (CO$_2$*C*H$_3$), 78.5 (*C*(4)), 80.9, 84.8 (*C*(6), *C*(5)), 96.2 (*C*(2)), 115.5 (*C*(4□)), 137.8 (*C*(3□)), 172.0, 178.5 (*C*O$_2$Me, *C*(8)); *m/z* (ESI$^+$) 348 ([M+Na]$^+$, 90%), 673 ([2M+Na]$^+$, 100%), 324 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{17}H_{27}NNaO_5^+$ ([M+H]$^+$) requires 348.1781, found 348.1771.

(2*R*,4*R*,5*R*,6*R*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(*p*-bromophenyl)-8-oxo-3-oxabicyclo[3.3.0]octane 22c

Following General Procedure H, *N*-acyl-oxazolidine **9b** (460 mg, 1.05 mmol) and NaOMe (62 mg, 1.15 mmol) were reacted to give a product which was purified *via* column chromatography (SiO_2,

eluent DCM) to give unreacted **9b** (115 mg) and **22c** as a yellow solid (198 mg, 42%); R_f 0.1 (eluent DCM); mp 122-125 ºC; $[\alpha]_D^{23}$ −4.6 (*c* 0.63 in $CHCl_3$); ν_{max} (film) 3414, 2956, 2874, 1703, 1488; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, C(C*H*$_3$)$_3$), 1.76 (3H, d, *J* 6.6, C(4)C*H*$_3$), 1.85 (1H, d, *J* 15.9, C(1□)*H*$_A$H$_B$), 2.45 (1H, d, *J* 13.4, C(7)*H*$_A$H$_B$), 3.04-3.09 (2H, m, C(1□)H$_A$*H*$_B$, C(7)H$_A$*H*$_B$), 3.19 (1H, br s, O*H*), 3.83 (3H, s, CO_2CH_3), 4.79 (1H, q, *J* 6.6, C(4)*H*), 4.99 (1H, s, C(2)*H*), 7.04 (2H, d, *J* 8.3, *o-Ph*), 7.39 (2H, d, *J* 8.3, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 15.3 (C(4)*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 37.4 (*C*Me$_3$), 41.3 (*C*(7)), 47.2 (*C*(1□)), 52.9 (CO_2CH_3), 78.6 (*C*(4)), 80.6 (*C*(5)), 83.9 (*C*(6)), 96.2 (*C*(2)), 121.2 (*i-Ph*), 131.7, 131.9 (*o*,*m-Ph*), 143.4 (*C*Br), 172.0 (CO_2Me), 178.0 (*C*(8)); *m/z* (ESI$^-$) 438/440 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NNaO_5^+$ ([M+Na]$^+$) requires 462.0887, 464.0867, found 462.0879, 464.0855.

(2*R*,4*R*,5*R*,6*R*)-1-Aza-2-*t*-butyl-4methyl-5-methoxycarbonyl-6-hydroxy-6-(phenylthio-methyl)-8-oxo-3-oxabicyclo[3.3.0]octane 22d

Following General Procedure H, *N*-acyl-oxazolidine **9c** (550 mg, 1.39 mmol) and NaOMe (84 mg, 1.55 mmol) were reacted to give a crude mixture which was purified *via* column chromatography (SiO_2, eluent 5:1 petrol:EtOAc) to give **22d** as a pale yellow oil (167 mg, 30%); R_f 0.25 (eluent 5:1 petrol:EtOAc); $[\alpha]_D^{23}$ +8.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3400, 2956, 2874, 1743, 1703, 1584, 1481; δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(C*H*$_3$)$_3$), 1.69 (3H, d, *J* 6.6, C(4)C*H*$_3$), 2.33 (1H, d, *J* 15.8, C(7)*H*$_A$H$_B$), 2.89 (1H, d, *J* 15.8, C(7)H$_A$*H*$_B$), 3.03 (1H, d, *J* 13.9, C(1□)*H*$_A$H$_B$), 3.34 (1H, s, O*H*), 3.37 (1H, d, *J* 13.9, C(1□)H$_A$*H*$_B$), 3.82 (3H, s, CO_2CH_3), 4.75 (1H, q, *J* 6.6, C(4)*H*), 5.05 (1H, s, C(2)*H*), 7.22-7.33 (3H, m, *Ph*), 7.38-7.41 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4 (C(4)*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 37.4 (*C*Me$_3$), 41.8 (*C*(1□)), 47.8 (*C*(7)), 53.0 (CO_2CH_3), 78.5 (*C*(4)), 80.1 (*C*(5)), 83.6 (*C*(6)), 96.6 (*C*(2)), 127.4 (*p-Ph*), 129.4, 130.5 (*o*,*m-Ph*), 135.0 (*i-Ph*), 171.6 (CO_2Me), 177.7 (*C*(8)); *m/z* (ESI$^+$) 392 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NO_5S^+$ ([M−H]$^-$) requires 392.01537, found 392.1533.

(2*R*,4*R*,5*R*,6*R*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(1□-methoxy-2□-phenylethyl)-8-oxo-3-oxabicyclo[3.3.0]octane 22e

Following General Procedure H, *N*-acyl-oxazolidine **12** (107 mg, 0.26 mmol) and NaOMe (16 mg, 0.29 mmol) were reacted to give the crude reaction mixture. Purification *via* column chromatography (SiO_2, eluent 20:1 40-60 petrol:EtOAc) gave **22e** as a colourless oil (6.5 mg, 6 %); R_f 0.05 (eluent 8:1 40-60 petrol:EtOAc); $[\alpha]_D^{23}$ +11.6 (*c* 0.32 in $CHCl_3$); ν_{max} (film) 2956, 1698; δ_H (500 MHz, $CDCl_3$) 0.92 (9H, s, C(C*H*$_3$)$_3$), 1.68 (3H, d, *J* 6.6, C(4)C*H*$_3$), 1.78 (1H, d, *J* 16.1, C(7)*H*$_A$H$_B$), 2.77 (1H, dd, *J* 14.7, 6.0, C(2□)*H*$_A$H$_B$), 3.13 (3H, s, OC*H*$_3$), 3.15 (1H, dd, *J* 14.7, 4.1,

C(2□)H_AH_B), 3.27-3.32 (1H, m, C(7)H_AH_B), 3.71 (1H, dd, *J* 6.0, 4.1, C(1□)*H*), 3.76 (3H, s, CO_2CH_3), 4.75 (1H, q, *J* 6.6, C(4)*H*), 5.00 (1H, s, C(2)*H*), 7.22-7.31 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.4 (C(4)CH_3), 25.8 (C(CH_3)$_3$), 35.5 (*C*(2□)), 37.2 (*C*Me$_3$), 44.1 (*C*(7)), 52.4 (CO_2CH_3), 57.8 (OCH_3), 78.1 (*C*(5)), 78.9 (*C*(4)), 81.9 (*C*(1□)), 87.4 (*C*(6)), 96.4 (*C*(2)), 126.6 (*p-Ph*), 128.2, 128.6, 129.3, 129.6 (*o*,*m-Ph*), 138.3 (*i-Ph*), 171.5 (CO_2Me), 178.5 (*C*(8)); *m/z* (ESI$^+$) 406 ([M+H]$^+$, 30%), 428 ([M+Na]$^+$, 80%), 404 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{22}H_{31}NNaO_6^+$ ([M+H]$^+$) requires 428.2044, found 428.2026.

(2*R*,4*R*,5*R*,6*R*,7*S*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-methoxymethyl-7-methyl-8-oxo-3-oxabicyclo[3.3.0]octane 22f

Following General Procedure H, **15a** (280 mg, 0.85 mmol) and NaOMe (50 mg, 0.94 mmol) were reacted to give the crude reaction mixture. Purification *via* column chromatography (SiO_2, eluent 3:1 40-60 petrol:EtOAc) gave **22f** as a colourless solid (30 mg, 21%); R_f 0.1 (eluent 3:1 40-60 petrol:EtOAc); mp 120-130 ºC; $[\alpha]_D^{23}$ −31.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3457 (br), 2956, 1725; δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, C(CH_3)$_3$), 1.05 (3H, d, *J* 7.1, C(7)CH_3), 1.68 (3H, d, *J* 6.6, C(4)CH_3), 2.53 (1H, s, O*H*), 3.19 (1H, q, *J* 7.1, C(7)*H*), 3.33 (3H, s, OCH_3), 3.40 (1H, d, *J* 9.9, CH_AH_BOMe), 3.47 (1H, d, *J* 9.9, CH_AH_BOMe), 3.76 (3H, s, CO_2CH_3), 4.72 (1H, q, *J* 6.6, C(4)*H*), 5.03 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 6.6 (C(7)CH_3), 15.5 (C(4)CH_3), 25.7 (C(CH_3)$_3$), 37.3 (*C*Me$_3$), 45.4 (*C*(7)), 52.6 (CO_2CH_3), 59.2 (OCH_3), 72.4 (CH_2OMe), 77.2 (*C*(5)), 78.9 (*C*(4)), 85.2 (*C*(6)), 96.6 (*C*(2)), 171.5 (CO_2Me), 180.5 (*C*(8)); *m/z* (ESI$^+$) 352 ([M+Na]$^+$, 90%), (ESI$^-$) 328 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{16}H_{27}NNaO_6^+$ ([M+Na]$^+$) requires 352.1731, found 352.1725.

(2*R*,5*R*,4*R*,6*R*,7*S*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(but-3□-enyl)-7-methyl-8-oxo-oxabicyclo[3.3.0]octane 22g

Following General Procedure H, *N*-acyl-oxazolidine **15b** (258 mg, 0.76 mmol) and NaOMe (45 mg, 0.84 mmol) were reacted to give a crude mixture which was purified *via* column chromatography (SiO_2, eluent 10:1 petrol:EtOAc) to give **22g** as a colourless oil (132 mg, 51%); R_f 0.56 (eluent 3:1 40-60 petrol:EtOAc); $[\alpha]_D^{23}$ +1.88 (*c* 0.65 in $CHCl_3$); ν_{max} (film) 3454 (OH), 3071, 2957, 2251, 1725; δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.11 (3H, d, *J* 7.2, C(7)CH_3), 1.68 (3H, d, *J* 6.6, C(4)CH_3), 1.70-1.80 (2H, m, C(1□)H_2), 2.08-2.20 (1H, m, C(2□)H_AH_B), 2.21-2.31 (1H, m, C(2□)H_AH_B), 3.11 (1H, q, *J* 7.2, C(7)*H*), 3.79 (3H, s, CO_2CH_3), 4.81 (1H, q, *J* 6.6, C(4)*H*), 4.94-5.07 (2H, m, C(4□)H_2), 5.01 (1H, s, C(2)*H*), 5.73-5.85 (1H, m, C(3□)*H*); δ_C (125 MHz, $CDCl_3$) 7.4 (C(7)CH_3), 15.9 (C(4)CH_3), 28.3 (*C*(2□)), 35.0 (*C*(1□)), 37.3 (*C*(CH_3)$_3$), 48.3 (*C*(7)), 52.7 (CO_2CH_3), 78.8 (*C*(4)), 79.1 (*C*(5)), 86.3 (*C*(6)), 96.1, (*C*(2)), 115.3 (*C*(4□)), 137.8 (*C*(3□)), 172.0

(CO_2Me), 180.0 (C(8)); *m/z* (ESI$^+$) 362 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{29}NNaO_5^+$ ([M+Na]$^+$) requires 362.1938, found 362.1923; and unreacted **15b** (50 mg, 38%).

(2*R*,4*R*,5*R*,6*R*,7*S*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(*p*-bromophenyl)-7-methyl-8-oxo-3-oxabicyclo[3.3.0]octane 22h

Following General Procedure H, *N*-acyl-oxazolidine **15c** (242 mg, 0.53 mmol) and NaOMe (32 mg, 0.58 mmol) were reacted the crude material, which was purified by column chromatography (SiO_2, eluent 5:1 petrol:EtOAc) to give **22h** as a colourless solid (124 mg, 72%); R_f 0.35 (eluent 5:1 petrol:EtOAc); mp 150-153 ºC; $[\alpha]_D^{23}$ +1.82 (*c* 0.37 in $CHCl_3$); ν_{max} (film) 3458, 2955, 2873, 1708, 1659; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 7.1, C(7)CH_3), 0.92 (9H, s, C(CH_3)$_3$), 1.66 (3H, d, *J* 6.6, C(4)CH_3), 2.09 (1H, br s, OH), 2.63 (1H, d, *J* 14.2, C(1□)H_AH$_B$), 3.17 (1H, d, *J* 14.2, C(1□)H$_A$$H_B$), 3.21 (1H, q, *J* 7.1, C(7)*H*), 3.85 (3H, s, CO_2CH_3), 4.83 (1H, q, *J* 6.6, C(4)*H*), 5.00 (1H, s, C(2)*H*), 7.14 (2H, d, *J* 8.3, *o-Ph*), 7.43 (2H, d, *J* 8.3, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 7.5 (C(7)CH_3), 15.5 (C(4)CH_3), 25.8 (C(CH_3)$_3$), 37.4 (CMe_3), 41.1 (C(1□)), 48.2 (C(7)), 52.9 (CO_2CH_3), 78.8 (C(4)), 79.1 (C(5)), 85.4 (C(6)), 96.6 (C(2)), 121.4 (*i-Ph*), 131.5 (*o-Ph*), 132.5 (*m-Ph*), 134.0 (CBr), 172.1 (CO_2Me), 180.3 (C(8)); *m/z* (ESI$^+$) 476/478 ([M+Na]$^+$, 35%), 929, 931, 933 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{28}BrNNaO_5^+$ ([M+Na]$^+$) requires 476.1043, 478.1024, found 476.1047, 478.1032.

(2*R*,4*R*,5*R*,6*R*,7*S*)-1-Aza-2-*t*-butyl-4methyl-5-methoxycarbonyl-6-hydroxy-6-(phenylthio-methyl)-7-methyl-8-oxo-3-oxabicyclo[3.3.0]octane 22i

Following General Procedure H, *N*-acyl-oxazolidine **15d** (122 mg, 0.3 mmol) and NaOMe (18 mg, 0.33 mmol) were reacted to give **22i** as a yellow solid (92 mg, 75%); R_f 0.25 (eluent 5:1 petrol:EtOAc); mp 150-152 ºC; $[\alpha]_D^{23}$ +6.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3367 (br), 2956, 2938, 2873, 1722, 1695; δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C(CH_3)$_3$), 1.02 (3H, d, *J* 7.1, C(7)CH_3), 1.68 (3H, d, *J* 6.6, C(4)CH_3), 2.82 (1H, br s, O*H*), 3.17 (1H, q, *J* 7.1, C(7)*H*), 3.31 (2H, s, CH_2SPh), 3.83 (3H, s, CO_2CH_3), 4.77 (1H, q, *J* 6.6, C(4)*H*), 5.02 (1H, s, C(2)*H*), 7.25-7.34 (3H, m, *m,p-Ph*), 7.41 (2H, d, *J* 8.3, *o-Ph*); δ_C (125 MHz, $CDCl_3$) 7.2 (C(7)CH_3), 15.7 (C(4)CH_3), 25.7 (C(CH_3)$_3$), 37.3 (CMe_3), 41.4 (CH_2Ph), 47.9 (C(7)), 52.9 (CO_2CH_3), 78.3 (C(4)), 78.8 (C(5)), 85.1 (C(6)), 96.4 (C(2)), 127.4, 129.3 (*m,p-Ph*), 130.6 (*o-Ph*), 135.6 (*i-Ph*), 171.6 (CO_2Me), 179.6 (C(8)); *m/z* (ESI$^-$) 406 ([M−H]$^-$, 40%); HRMS (ESI$^-$) $C_{21}H_{28}NO_5S^-$ ([M−H]$^-$) requires 406.1694, found 406.1707.

(2*R*,4*R*,5*R*,6*R*,7*R*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(1□-methoxy-2□-phenylethyl)-7-methyl-8-oxo-3-oxabicyclo[3.3.0]octane 22j

Following General Procedure H, *N*-acyl-oxazolidine **18** (400 mg, 0.95 mmol) and NaOMe (57 mg, 1.05 mmol) were reacted to give the crude reaction mixture. Purification *via* column chromatography (SiO_2, eluent 20:1 40-60 petrol:EtOAc) gave **22j** as a white solid (54 mg, 14%); R_f 0.1 (eluent 8:1, 40-60 petrol:EtOAc); mp 198-201 ºC; $[\alpha]_D^{23}$ +4.9 (*c* 0.63 in $CHCl_3$); ν_{max} (film) 3315, 2937, 1736, 1682; δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s, C(C*H*$_3$)$_3$), 1.15 (3H, d, *J* 7.0, C(7)C*H*$_3$), 1.72 (3H, d, *J* 6.6, C(4)C*H*$_3$), 2.63-2.77 (2H, m, C(2□)*H*$_2$), 2.96 (3H, s, OC*H*$_3$), 3.20 (1H, q, *J* 7.0, C(7)*H*), 3.23 (1H, s, O*H*), 3.66 (1H, dd, *J* 10.0, 2.4, C(1□)*H*), 3.83 (3H, s, CO_2CH_3), 4.80 (1H, q, *J* 6.6, C(4)*H*), 5.06 (1H, s, C(2)*H*), 7.21-7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.6 (C(7)*C*H$_3$), 16.2 (C(4)*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 37.3 (*C*Me$_3$), 38.4 (*C*(2□)), 45.2 (*C*(7)), 52.8 (CO_2CH_3), 61.7 (OCH$_3$), 76.7 (*C*(5)), 79.3 (*C*(4)), 83.3 (*C*(1□)), 87.3 (*C*(6)), 96.1 (*C*(2)), 126.7 (*p-Ph*), 128.6, 129.3 (*o*,*m-Ph*), 138.4 (*i-Ph*), 172.4 (*C*O$_2$Me), 179.6 (*C*(8)); *m/z* (ESI$^+$) 418 ([M−H]$^-$, 95%); HRMS (ESI$^+$) $C_{23}H_{34}NO_6^+$ ([M+H]$^+$) requires 420.2381, found 420.2375; and a 58:42 mixture of the starting material **18** and **22j'** as a colourless gum; R_f 0.25 (eluent 8:1 40-60 petrol:EtOAc); ν_{max} (film) 3447, 2936, 1728; δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, C(CH$_3$)$_3$), 1.21 (3H, d, *J* 7.3, C(7)C*H*$_3$), 1.58 (3H, d, *J* 6.8, C(4)C*H*$_3$), 2.75 (1H, dd, *J* 14.4, 6.6, C(2□)*H*$_A$H$_B$), 3.06 (3H, s, OC*H*$_3$), 3.24 (1H, dd, *J* 14.4, 4.6, C(2□)H$_A$*H*$_B$), 3.57 (1H, q, *J* 7.1, C(7)*H*), 3.76 (3H, s, CO_2CH_3), 3.77-3.81 (1H, m, C(1□)*H*), 4.73 (1H, q, *J* 6.8 C(4)*H*), 4.99 (1H, s, C(2)*H*), 7.12-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(7)*C*H$_3$), 15.4 (C(4)*C*H$_3$), 25.8/26.0 (C(*C*H$_3$)$_3$), 36.9 (*C*(2□)), 38.6 (*C*Me$_3$), 44.9 (*C*(7)), 52.4 (CO_2CH_3), 58.0 (OCH$_3$), 76.54 (*C*(5)), 79.0 (*C*(4)), 82.7 (*C*(1□)), 88.7 (*C*(6)), 96.4 (*C*(2)), 140.1 (*i-Ph*), 171.6 (*C*O$_2$Me), 180.7 (*C*(8)); *m/z* (ESI$^+$) 420 ([M+H]$^+$, 60%), 442 ([M+Na]$^+$, 90%), 418 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{23}H_{34}NO_6^+$ ([M+H]$^+$) requires 420.2381, found 420.2374.

(2*R*,4*R*,5*R*,6*R*,7*S*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(phenylthio-methyl)-7-allyl-8-oxo-3-oxabicyclo[3.3.0]octane 22k

Following General Procedure H, *N*-acyloxazolidine **21a** (100 mg, 0.23 mmol) and NaOMe (14 mg, 0.25 mmol) were reacted to give a crude mixture which was purified *via* column chromatography (SiO_2, eluent 10:1 petrol:EtOAc) to give **22k** as an off-white solid (8 mg, 8%); R_f 0.1 (eluent 10:1 petrol:EtOAc); mp 95-97 ºC; $[\alpha]_D^{23}$ −5.92 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3430, 2955, 2923, 2854, 1725; δ_H (500 MHz, $CDCl_3$) 0.93 (9H, s, C(C*H*$_3$)$_3$), 1.65 (3H, d, *J* 6.6, C(4)C*H*$_3$), 2.29-2.38 (1H, m, C(1□□)*H*$_A$H$_B$), 2.46-2.57 (1H, m, C(1□□)H$_A$*H*$_B$), 2.89 (1H, s, O*H*), 3.18 (1H, app. t, *J* 6.2, C(7)*H*), 3.30 (1H, d, *J* 14.2, C(1□)*H*$_A$H$_B$), 3.40 (1H, d, *J* 14.2, C(1□)H$_A$*H*$_B$), 3.83 (3H, s, CO_2CH_3), 4.81 (1H, q, *J* 6.6, C(4)*H*), 5.00-5.13 (2H, m, C(3□□)*H*$_2$), 5.05 (1H, s, C(2)*H*), 5.93-6.03 (1H, m,

C(2□□)*H*), 7.24-7.41 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.1 (C(4)*C*H_3), 25.6 (C(*C*H_3)$_3$), 28.1 (*C*(1□□)), 37.1 (*C*Me$_3$), 41.3 (*C*(1□)), 52.3 (*C*(7)), 53.0 (CO_2CH_3), 78.6, 78.7 (*C*(4), *C*(5)), 85.7 (*C*(6)), 96.0 (*C*(2)), 117.1 (*C*(3□□)), 127.3, 129.3, 130.3 (*o*,*m*,*p*-*Ph*), 135.6, 136.5 (*i*-*Ph*, *C*(2□□)), 171.7 (CO_2Me), 178.1 (*C*(8)); *m/z* (ESI$^+$) 456 ([M+Na]$^+$, 75%), (ESI$^-$) 432 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{23}H_{31}NNaO_5S^+$ ([M+Na]$^+$) requires 456.1815, found 456.1811.

(2*R*,4*R*,5*R*,6*R*,7*S*)-1-Aza-2-*t*-butyl-4-methyl-5-methoxycarbonyl-6-hydroxy-6-(phenylthio-methyl)-7-benzyl-8-oxo-3-oxabicyclo[3.3.0]octane 22l

Following General Procedure H, *N*-acyloxazolidine **21b** (20 mg, 4.0 μmol) and NaOMe (3 mg, 5.0 μmol) were reacted to give a crude mixture which was purified *via* column chromatography (SiO_2, eluent 10:1 petrol:EtOAc) to give **22l** as a colourless oil (3 mg, 15%); R_f 0.3 (eluent 6:1 petrol:EtOAc); $[\alpha]_D^{23}$ +7.56 (*c* 0.15 in $CHCl_3$); ν_{max} (film) 3437, 2956, 2924, 2854, 1722; δ_H (500 MHz, $CDCl_3$) 0.94 (9H, s, C(C*H*$_3$)$_3$), 1.65 (3H, d, *J* 6.6, C(4)C*H*$_3$), 2.89 (1H, dd, *J* 14.8, 7.4, C*H*$_A$H$_B$Ph), 2.98 (1H, d, *J* 14.3, C(1□)*H*$_A$H$_B$), 3.08 (1H, d, *J* 14.3, C(1□)H$_A$*H*$_B$), 3.16 (1H, dd, *J* 14.8, 6.0, CH$_A$*H*$_B$Ph), 3.42 (1H, app. t, *J* 6.6, C(7)*H*), 3.79 (3H, s, CO_2CH_3), 4.91 (1H, q, *J* 6.6, C(4)*H*), 5.05 (1H, s, C(2)*H*), 7.16-7.30 (10H, m, *Ph*, S*Ph*); δ_C (125 MHz, $CDCl_3$) 16.9 (C(4)*C*H$_3$), 25.6 (C(*C*H$_3$)$_3$), 29.6 (*C*H$_2$Ph), 37.1 (*C*Me$_3$), 41.6 (*C*(1□)), 52.9 (CO_2CH_3), 54.8 (*C*(7)), 78.4, 79.2 (*C*(4), *C*(5)), 85.0 (*C*(6)), 95.1 (*C*(2)), 126.3, 127.2, 128.5, 129.2, 129.3, 130.0 (*o*,*m*,*p*-*Ph*, -S*Ph*), 135.4 (*i*-S*Ph*), 139.7 (*i*-*Ph*), 171.9 (CO_2Me), 177.2 (*C*(8)); *m/z* (ESI$^+$) 506 ([M+Na]$^+$, 95%), (ESI$^-$) 506 ([M−Na]$^-$, 100%); HRMS (ESI$^+$) $C_{27}H_{33}NNaO_5S^+$ ([M+Na]$^+$) requires 506.1972, found 506.1976.

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21. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 952079-95083 and 980818-980819) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
22. Bioassay of products:[33-35] Microbiological assays were performed by the hole- plate method with the test organism *Staphylococcus aureus* N.C.T.C. 6571 or *E. coli* X580. Solutions (100 µl) of the compounds to be tested (4mg/ml) were loaded into wells in bioassay plates, and incubated overnight at 37°C. The diameters of the resultant inhibition zones were measured (±1mm), and relative potency estimated by reference to standards prepared with Cephalosporin C; this is expressed as zone diameter per M, of the analyte relative to cephalosporin C standard.
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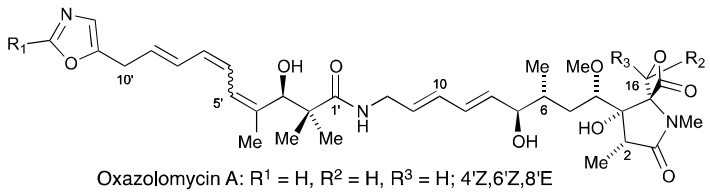
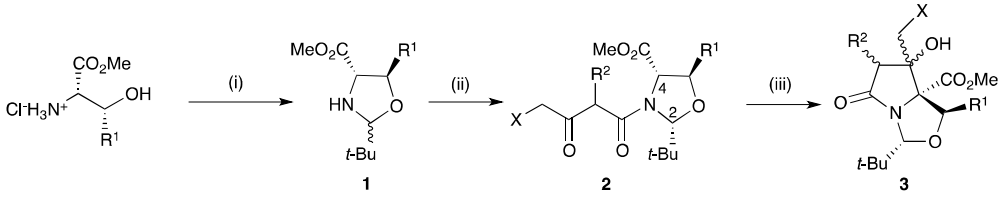


Oxazolomycin A: R^1 = H, R^2 = H, R^3 = H; 4'Z,6'Z,8'E
Oxazolomycin B: R^1 = H, R^2 = H, R^3 = H; 4'E,6'E,8'E
Oxazolomycin C: R^1 = H, R^2 = H, R^3 = H; 4'Z,6'E,8'E
16-Methyloxazolomycin: R^1 = H, R^2 = H, R^3 = Me; 4'Z,6'Z,8'E
Curromycin A: R^1 = Me , R^2 = H, R^3 = CH_3OCH_2; 4'Z,6'Z,8'E
Curromycin B: R^1 = Me, R^2 = H, R^3 = Me; 4'Z,6'Z,8'E
KSM-2690 B: R^1 = H, R^2 = H, R^3 = Me; 4'Z,6'Z,8'E
KSM-2690 C: R^1 = H, R^2 = H, R^3 = Me; 4'Z,6'E,8'E

FIgure 1



(i) Me_3CCHO, petrol (40/60), reflux, 16-20h; (ii) $XCH_2C(O)CH(R^2)CO_2H$, DCCI, DMAP; (iii) KO*t*-Bu, *t*-BuOH

Scheme 1

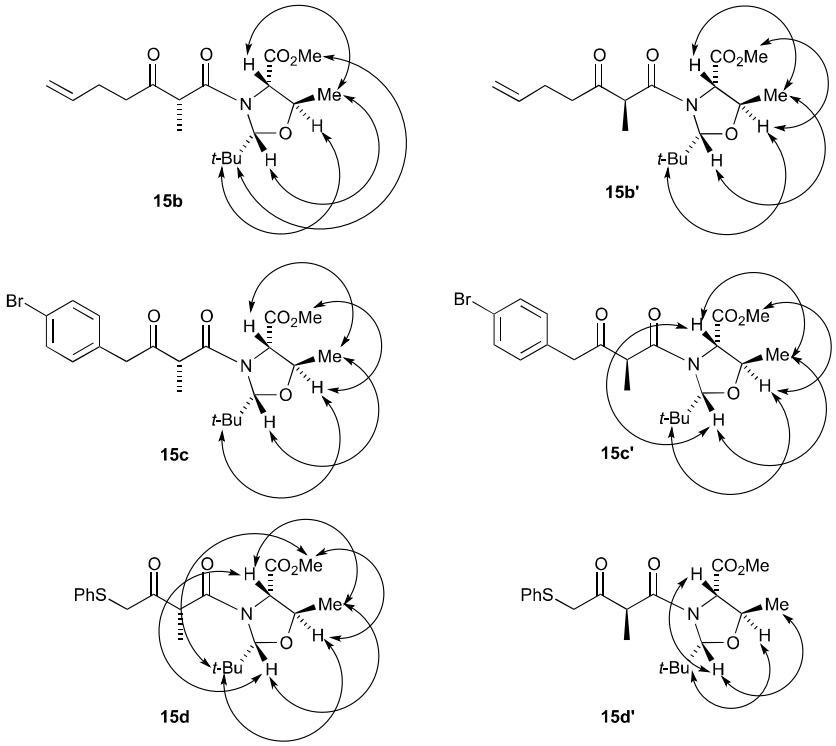
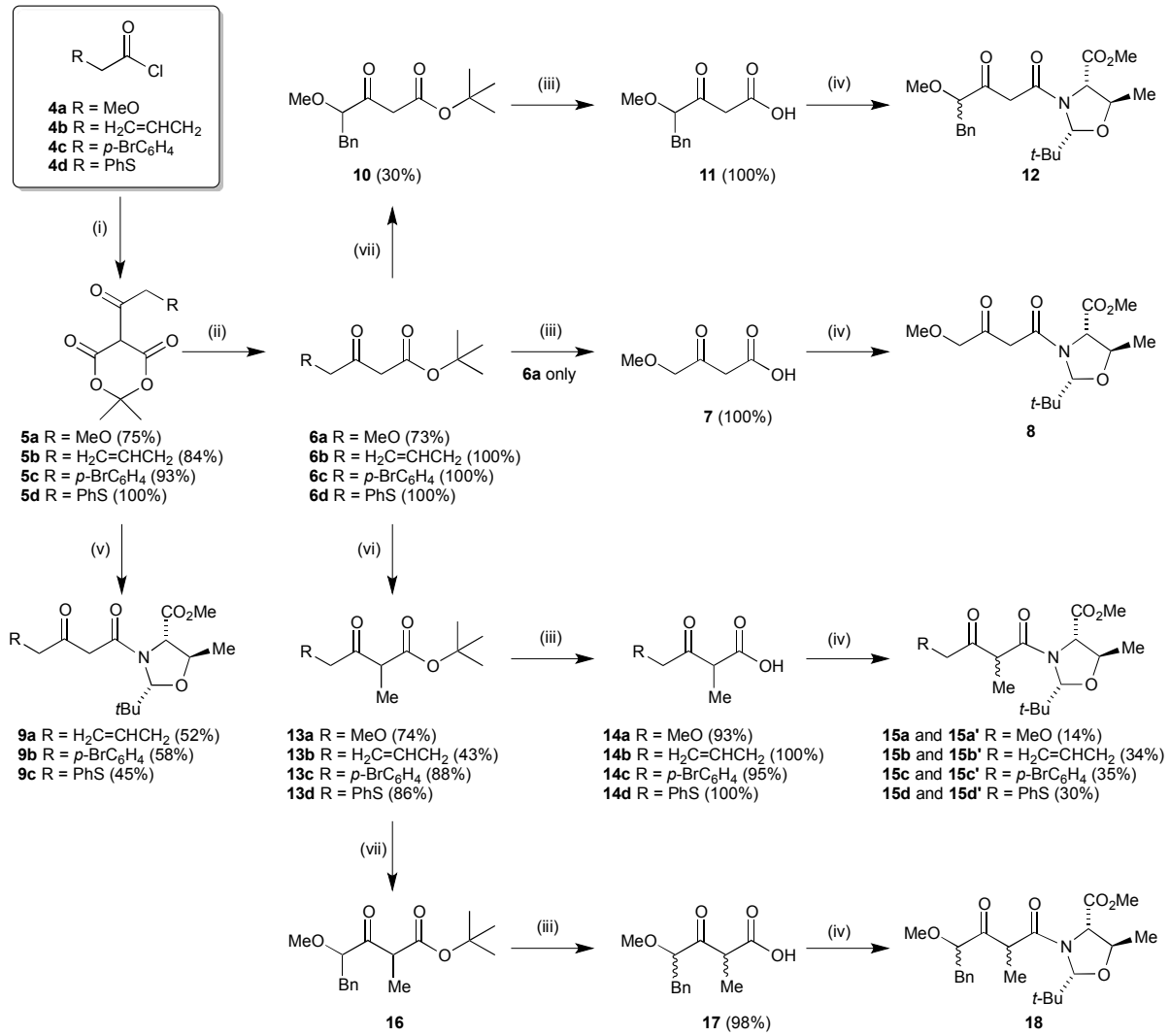
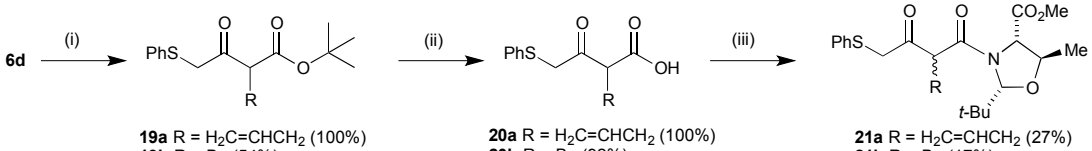


Figure 2



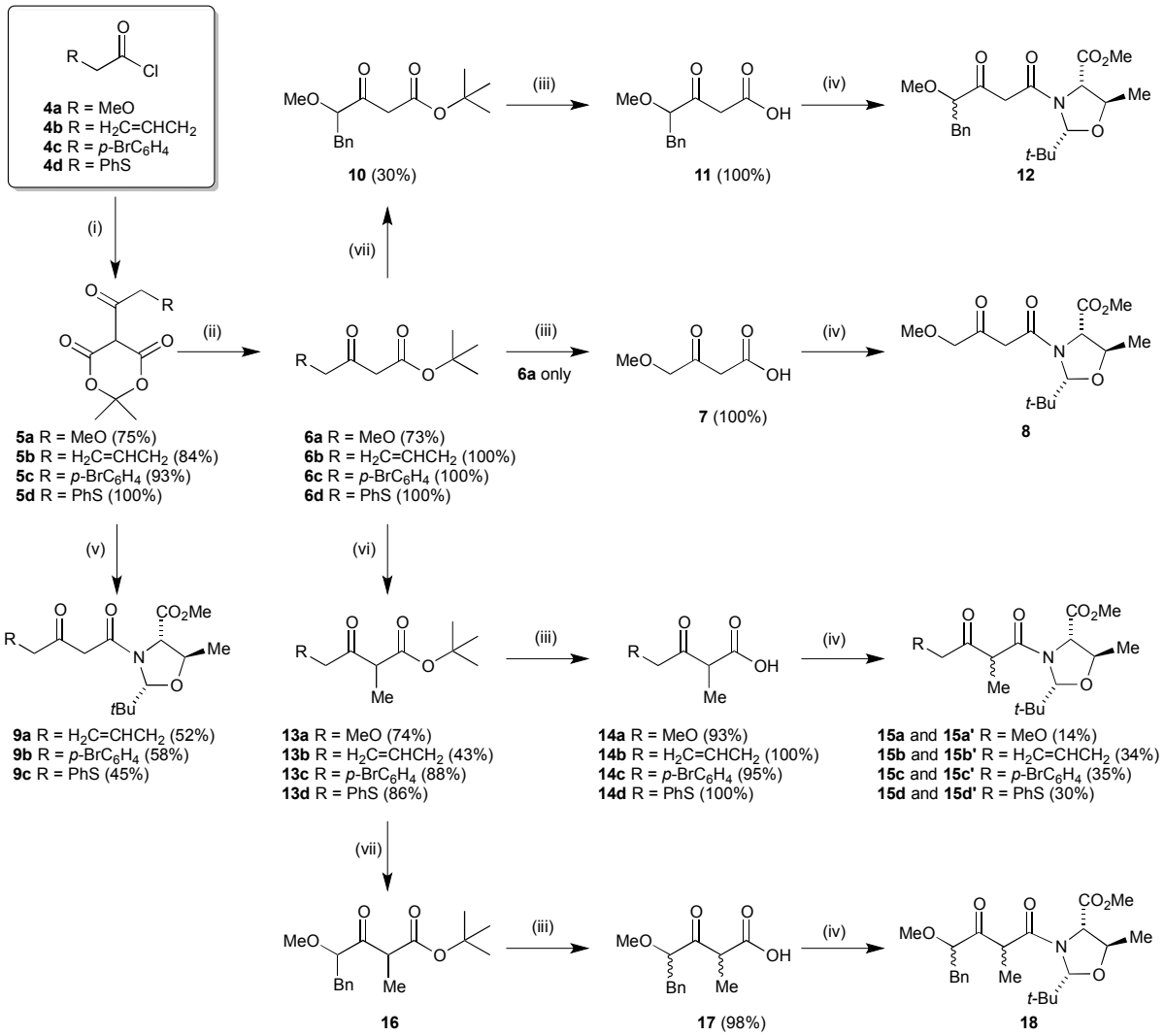
Reagents: (i) Meldrum's acid, py, DCM, -10°C to r.t.; (ii) *t*-BuOH, reflux, 24h; (iii) CF_3CO_2H, DCM, 0°C ; (iv) **1**, DCC, DMAP, DCM ; (v) **1**, MeCN, 60 °C, 2h; (vi) *t*-BuOK, THF then MeI, THF; (vii) NaH, THF then BuLi then BnBr, THF

Scheme 2



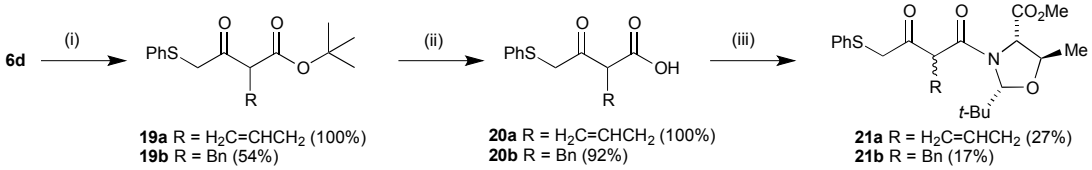
Reagents: (i) *t*-BuOK, THF then RX, THF; (ii) CF_3CO_2H, DCM, 0°C ; (iii) **1**, DCC, DMAP, DCM

Scheme 3



Reagents: (i) Meldrum's acid, py, DCM, -10°C to r.t.; (ii) *t*-BuOH, reflux, 24h; (iii) CF_3CO_2H, DCM, 0°C ; (iv) **1**, DCC, DMAP, DCM ; (v) **1**, MeCN, 60 °C, 2h; (vi) *t*-BuOK, THF then MeI, THF; (vii) NaH, THF then BuLi then BnBr, THF

Scheme 2



Reagents: (i) *t*-BuOK, THF then RX, THF; (ii) CF_3CO_2H, DCM, 0°C ; (iii) **1**, DCC, DMAP, DCM

Scheme 3

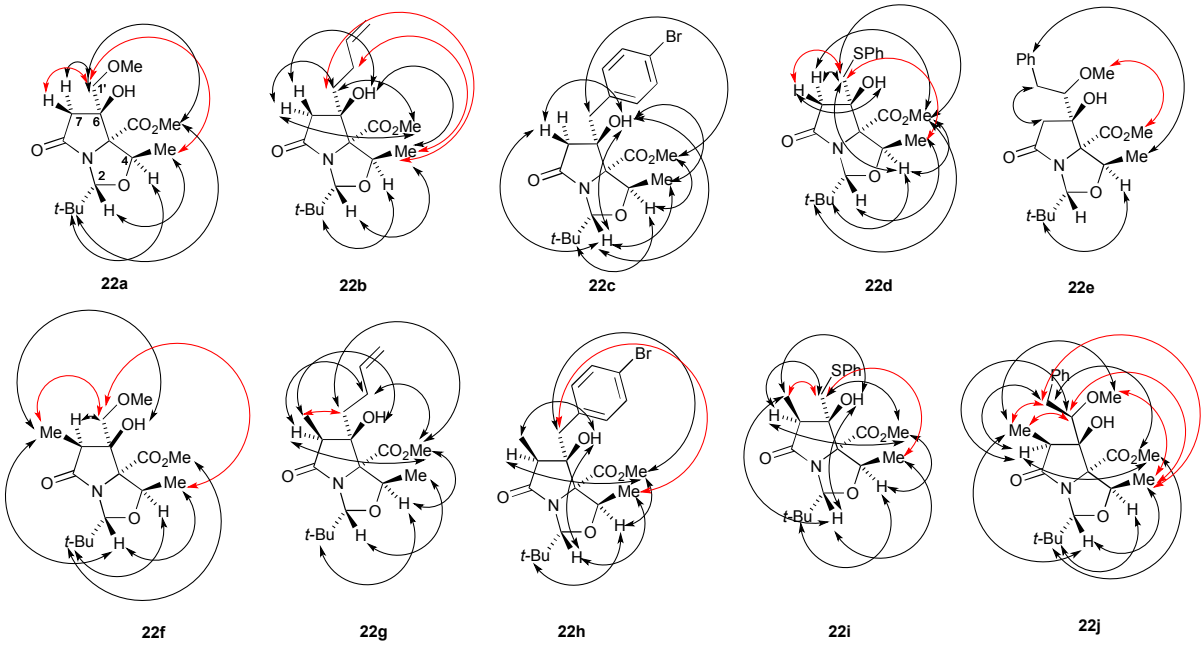
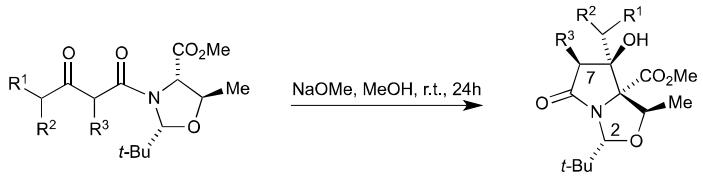


Figure 3



8 R_1 = MeO, R_2 = H, R_3 = H
9a R_1 = H_2C=$CHCH_2$, R_2 = H, R_3 = H
9b R_1 = *p*-BrC_6H_4, R_2 = H, R_3 = H
9c R_1 = PhS, R_2 = H, R_3 = H
12 R_1 = MeO, R_2 = Bn, R_3 = H
15a R_1 = MeO, R_2 = H, R_3 = Me
15b R_1 = H_2C=$CHCH_2$, R_2 = H, R_3 = Me
15c R_1 = *p*-BrC_6H_4, R_2 = H, R_3 = Me
15d R_1 = PhS, R_2 = H, R_3 = Me
18 R_1 = MeO, R_2 = Bn, R_3 = Me
21a R_1 = PhS, R_2 = H, R_3 = H_2C=$CHCH_2$
21b R_1 = PhS, R_2 = H, R_3 = Bn

22a R_1 = MeO, R_2 = H, R_3 = H (22%)
22b R_1 = H_2C=$CHCH_2$, R_2 = H, R_3 = H (46%)
22c R_1 = *p*-BrC_6H_4, R_2 = H, R_3 = H (42%)
22d R_1 = PhS, R_2 = H, R_3 = H (30%)
22e R_1 = MeO, R_2 = Bn, R_3 = H (6%)
22f R_1 = MeO, R_2 = H, R_3 = Me (11%)
22g R_1 = H_2C=$CHCH_2$, R_2 = H, R_3 = Me (51%)
22h R_1 = *p*-BrC_6H_4, R_2 = H, R_3 = Me (72%)
22i R_1 = PhS, R_2 = H, R_3 = Me (75%)
22j and **22j'** R_1 = MeO, R_2 = Bn, R_3 = Me (14%)
22k R_1 = PhS, R_2 = H, R_3 = H_2C=$CHCH_2$ (8%)
22l R_1 = PhS, R_2 = H, R_3 = Bn (15%)

Scheme 4

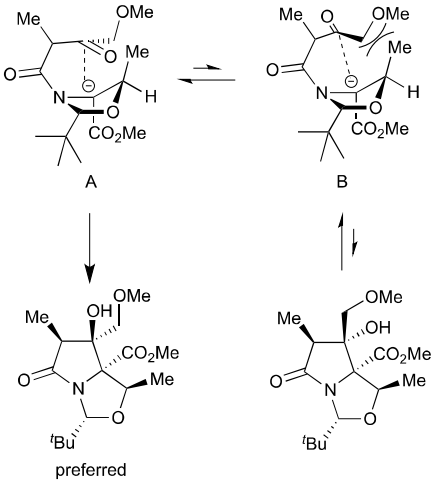
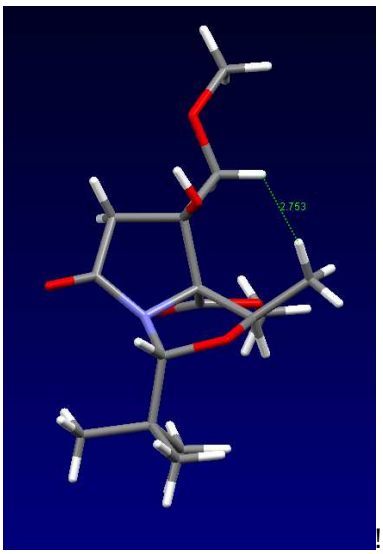
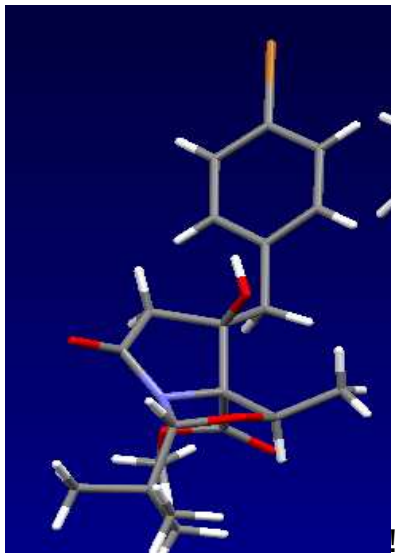


Figure 4



22a



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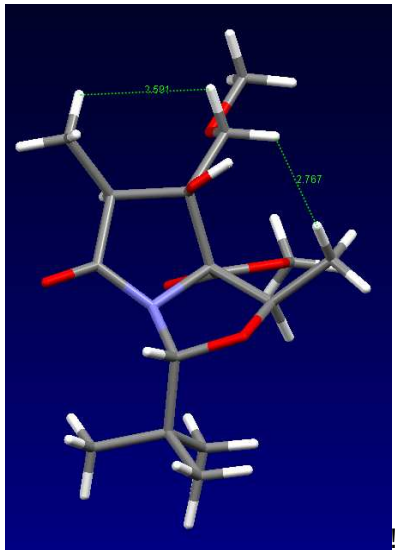
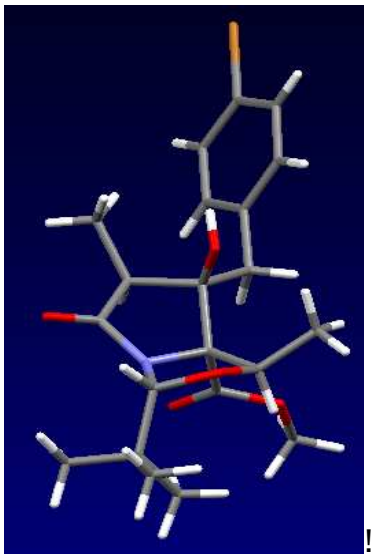
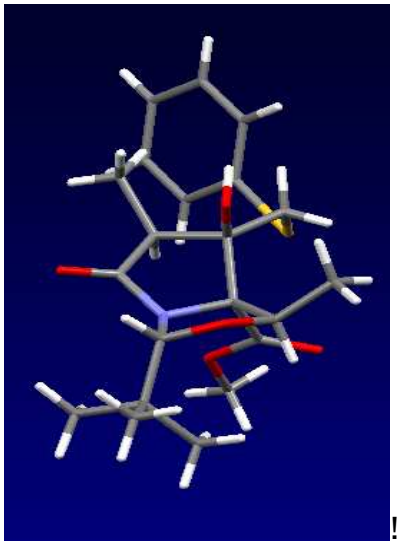


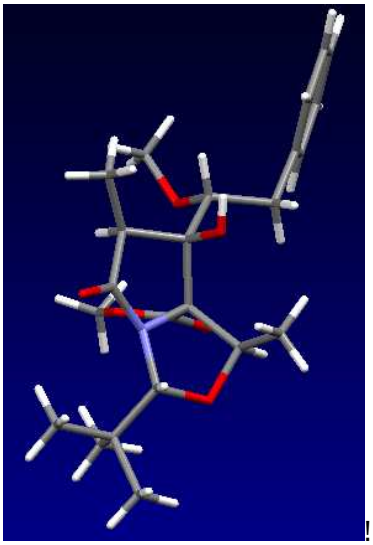
22f



22h



22i



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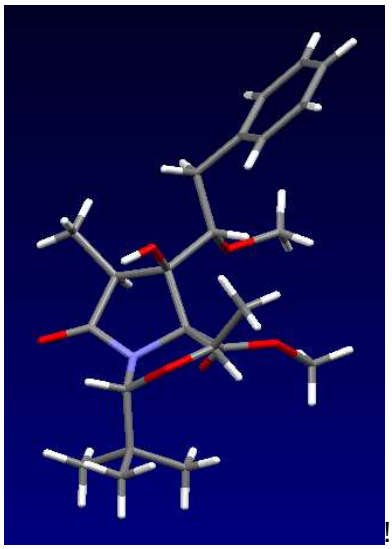

22j'

Figure 5