Generation of unnatural α,α-disubstituted amino acid derivatives from cyclic sulfamidates

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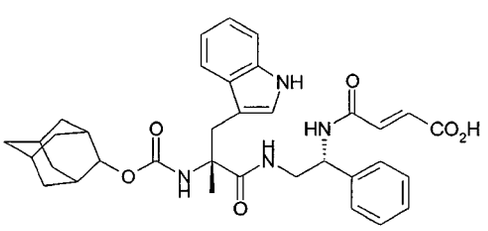
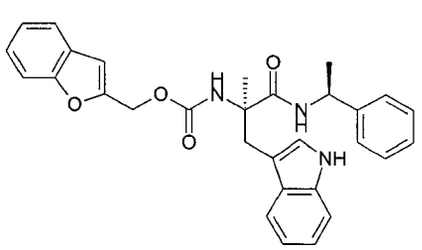
Cyclic sulfamidates function as excellent precursors to a variety of unnatural α,α-disubstituted amino acid derivatives by ring opening with a suitable nucleophile. Addition of various nucleophiles to a sulfamidate derived from 2-methylserine is described.

In connection with our interest in the preparation and application of α,α-disubstituted amino acid† derivatives for use as high affinity ligands for neuropeptide receptors such as cholecystokinin (CCK), tachykinin (NK) and bombesin (BB) receptors (Fig. 1), we report here the nucleophilic addition to cyclic sulfamidates derived from 2-methylserine.[1,2] We have shown that the incorporation of an α-methyl substituent into an α-amino acid has the potential to enhance *in vivo* stability, compared to the amino acid parent, and to stabilise preferred biologically active conformations due to restricted rotation.[3]

It has been known for some time that substituted aziridines can function as versatile intermediates for the synthesis of functionalised amino compounds by nucleophilic ring opening.[4] Previous work within our group has centred around the S_N2 ring opening reaction of 2-methylaziridine-2-carboxylic esters, of type **1**, in which a nucleophile attacks at C-β.[1] The presence of the 2-methyl substituent on the aziridine can promote undesired S_N1 ring opening resulting in attack at C-α due to the increased stability of the resultant tertiary carbocation. Conversely the presence of the 2-methyl substituent also helps to block C-α, favouring nucleophilic attack and hence ring opening at C-α. Selective formation of the desired C-β ring opened product was observed with amines and cuprates, however, competitive S_N1 ring opening and subsequent nucleophilic trapping at C-α was observed in several cases to yield a mixture of regioisomers **2** and **3** (Scheme 1).



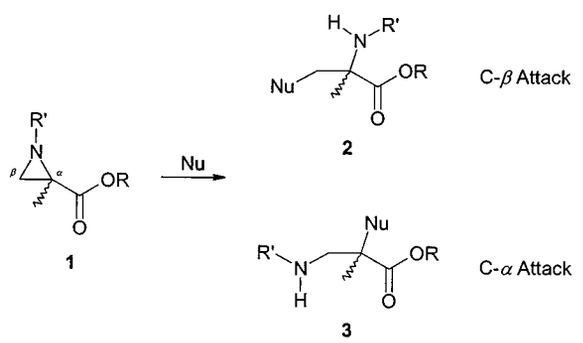
PD 136450
CCK-B Receptor antagonist.



PD 154075
NK_1 Receptor antagonist.

Fig. 1 Structures of high affinity CCK and NK receptor antagonists.

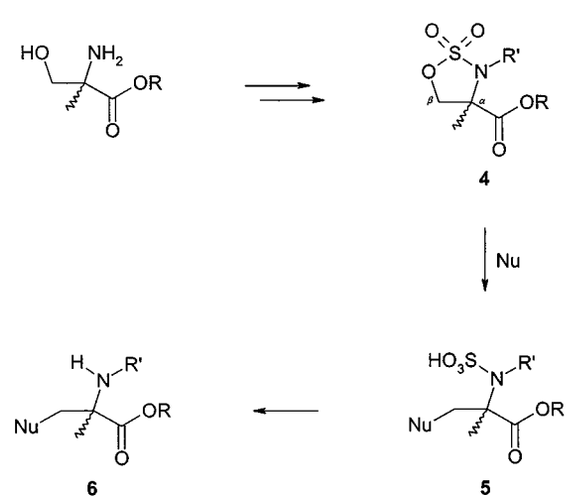
† In acyclic amino acids the α-carbon is the C-2 carbon.



Scheme 1

The competing S_N1 reaction could be suppressed to some extent by the use of a suitably large ester derivative; the *tert*-butyl ester was found to promote the C-β reaction in difficult cases. Our present work demonstrates that ring opening of cyclic sulfamidates, of type **4**, proceeds regioselectively by S_N2 reaction at C-β providing a synthetic methodology to unnatural α,α-disubstituted amino acid derivatives **6** (Scheme 2).

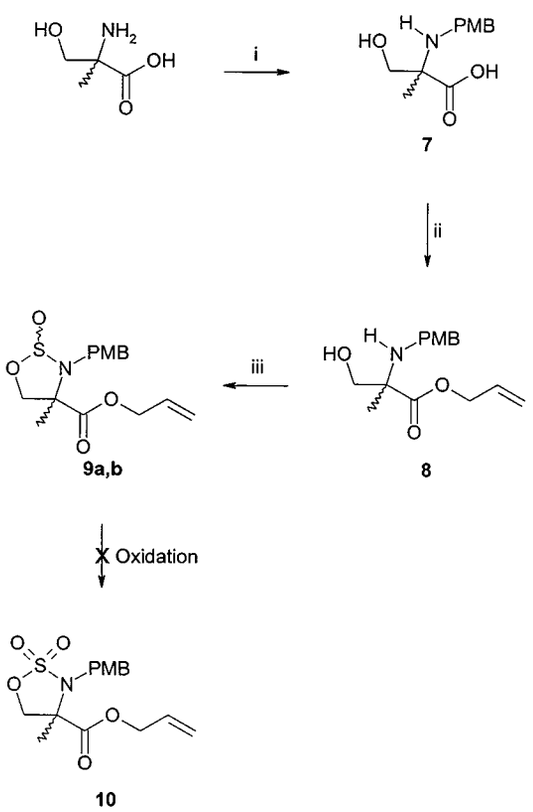
Previously, several examples of the use of cyclic sulfamidates,



Scheme 2

some derived from serine, as a 'β-alanyl cation' equivalent, have been described.[5–8] We reasoned that the combination of reduced ring strain, compared to the aziridine, and literature precedent for regioselective nucleophilic ring opening of cyclic sulfamidates could provide a potentially versatile entry into α,α-disubstituted amino acid derivatives. To the best of our knowledge, the nucleophilic ring opening of 2,2-disubstituted cyclic sulfamidates to generate amino acid derivatives **6** has not yet been considered (Scheme 2).

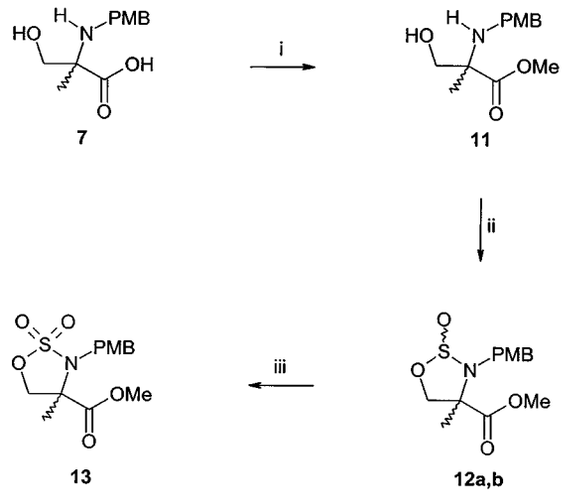
Our initial efforts were concentrated on the synthesis of 4-methoxybenzyl (PMB) protected sulfamidate **10** containing an allyl ester (Scheme 3). The allyl ester was chosen for its ease



Scheme 3 *Reagents and conditions*: i) 4-methoxybenzaldehyde, $NaCNBH_3$, THF, rt, 72 h, 86%; ii) K_2CO_3, allyl bromide, DMF, rt, 4.5 h, 79%; iii) $SOCl_2$, Et_3N, PhMe, 0 °C, 10 min, 96%.

of formation and deprotection under very mild conditions.[9] Starting from commercially available 2-methylserine, reductive amination with 4-methoxybenzaldehyde using sodium cyanoborohydride afforded amino acid **7** (86%).[10] Esterification was performed by slow addition of allyl bromide to a mixture of amino acid **7** and potassium carbonate in DMF to provide amino ester **8** (79%) which was then treated with thionyl chloride in the presence of triethylamine.[5] The resulting 3 : 2 mixture of diastereoisomers **9a** and **9b** (96%) were to be oxidised using the sodium periodate–ruthenium trichloride protocol which has been shown to give good yields for similar systems.[5,6] However, treatment of sulfamidites **9a** and **9b** under these conditions resulted in a complex mixture of products, presumably resulting from competing oxidation of the double bond of the allyl ester. Attempts to circumvent the unwanted side-reactions by use of alternative oxidants or by direct condensation of amino ester **8** with sulfuryl chloride all failed to yield the desired sulfamidate **10**.[6a–c,11]

With this knowledge, we turned our attentions to the synthesis of PMB-protected cyclic sulfamidate **13** containing a methyl ester (Scheme 4). Attempts to prepare amino ester **11** by treatment of amino acid **7** with methyl iodide in the presence of potassium carbonate resulted in the formation of a 1 : 2 mixture of *O*-methylated and *O*,*N*-dimethylated products in low yield



Scheme 4 *Reagents and conditions*: i) CH_2N_2, Et_2O, MeOH, 0 °C, 10 min, 71%; ii) $SOCl_2$, Et_3N, PhMe, 0 °C, 10 min, 93%; iii) $RuCl_3{\cdot}H_2O$, $NaIO_4$, MeCN, H_2O, 0 °C ⟶ rt, 30 min, 98%.

(50%) and so was not pursued. However, treatment of amino acid **7** with an ethereal solution of diazomethane did lead to a good yield of the desired amino ester **11** (71%).[12] Cyclisation of amino ester **11** with thionyl chloride in the presence of triethylamine furnished an excellent yield (93%) of sulfamidites **12a** and **12b** as a 5 : 2 mixture of diastereoisomers. Oxidation of sulfamidites **12a** and **12b** using sodium periodate and catalytic ruthenium trichloride afforded the desired cyclic sulfamidate **13** (98%, 62% from 2-methylserine) with no evidence of any competing side-reactions.

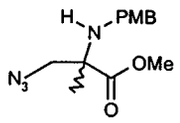
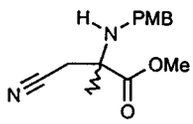
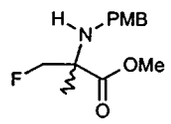
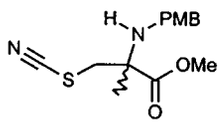
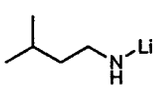
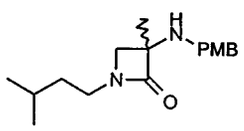
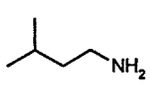
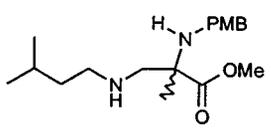
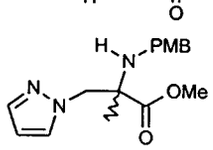
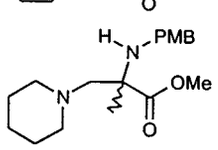
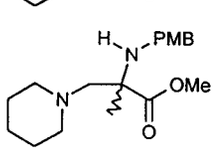
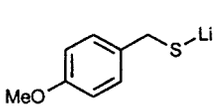
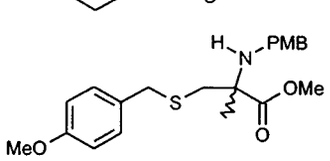
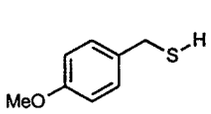
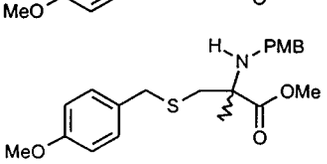
With quantities of cyclic sulfamidate **13** in hand we examined the nucleophilic ring opening and the subsequent hydrolysis of sulfamic acid **5**.[13] Initial investigations into the reaction conditions were carried out using sodium azide in DMF. We envisaged that isolation of the polar sulfamic acid intermediate **5** might prove difficult on a small scale and instead opted to hydrolyse this intermediate directly to the free base.[5,6] This was accomplished with a 20% (v/v) aqueous sulfuric acid solution; the more recent boron trifluoride–diethyl etherate protocol had not been disclosed at the time of this work.[14] Thus treatment of sulfamidate **13** with 1.2 equivalents of sodium azide in DMF solution at room temperature followed by hydrolysis using a biphasic sulfuric acid–dichloromethane mixture overnight and subsequent neutralisation and salt removal with solid sodium bicarbonate, furnished the desired azido derivative **14** in excellent yield (96%) and without the need for further purification. A summary of the various other nucleophilic species that were successfully added is presented below (Table 1).

As well as azide, both cyanide and fluoride were sufficiently nucleophilic at room temperature to provide good yields of derivatives **15** and **16** respectively (entries 1–3). Addition of ammonium or potassium thiocyanate however, required elevation of the reaction temperature to 60 °C for the preparation of thiocyanate derivative **17** (entry 4).

Initial attempts to get either amines or thiols to add by addition of the nucleophile to a solution of sulfamidate **13** did not result in ring opening. However, to our surprise, when the nucleophilic ring opening reaction was attempted with the preformed lithium salt of 3-methylbutylamine, β-lactam **18** was obtained (60%) instead of the anticipated amino derivative **19**.[15] β-Lactam **18** is presumably formed by initial attack of the amine at the ester functionality followed by intramolecular cyclisation of the resultant amide **25** (entry 5, Scheme 5).

We were able to obtain amino derivative **19** by changing the reaction conditions. When the nucleophilic ring opening reaction was performed with amine in the presence of caesium carbonate the desired amino derivative **19** was obtained in excellent yield (96%, entry 6). Addition of caesium carbonate

Table 1 Addition of various nucleophiles to sulfamidate **13**

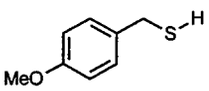
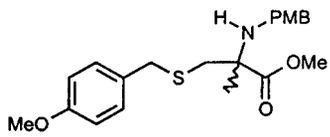
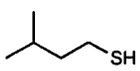
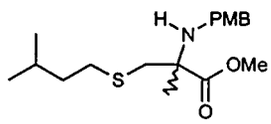
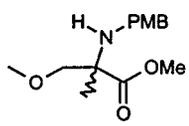
Entry	Nucleophilic source	Conditions	Product		Yield (%)
1	NaN_3	DMF, rt, 4 h		**14**	96
2	NaCN	DMF, rt, 90 min		**15**	100
3	TBAF	DMF, rt, 4 h		**16**	70
4	NH_4SCN	DMF, 60 °C, 6 h		**17**	68
5		THF, −78 °C, 16 h		**18**	60
6		Cs_2CO_3, DMF, rt, 36 h		**19**	96
7		Cs_2CO_3, DMF, rt, 18 h		**20**	74
8		Cs_2CO_3, DMF, rt, 24 h		**21**	25
9		Cs_2CO_3, MeCN, rt, 96 h		**21**	96
10		THF, −78 °C, 16 h		**22**	100
11		Cs_2CO_3, DMF, rt, 2 h		**22**	94

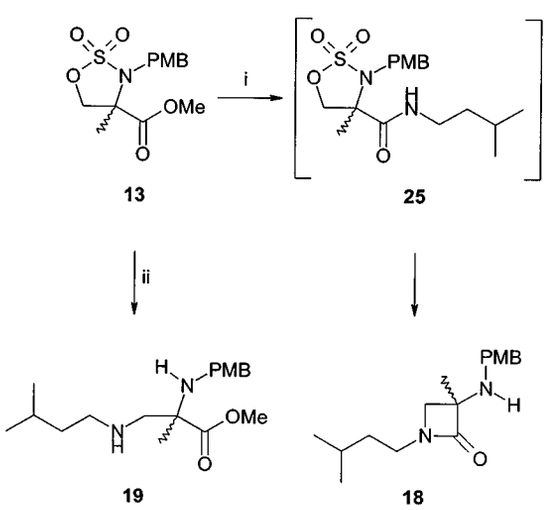
also enabled pyrazole to be used as a nucleophile (74%, entry 7). Reactions 6 and 7 were also attempted in the presence of potassium carbonate, triethylamine, 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,1,3,3-tetramethylguanidine (TMG), but none of these reagents resulted in isolation of significant amounts of the desired products. When sulfamidate **13** was treated with piperidine, the starting material was seen to be consumed in a few hours but only a low yield (25%) of the desired piperidyl derivative **21** was isolated from the complex reaction mixture. However, when the reaction solvent was changed from DMF to acetonitrile, consumption of sulfamidate **13** took considerably longer (96 h) but an increased yield (96%) of amino derivative **21** was obtained (entries 8 and 9).

Addition of the preformed lithium salt of 4-methoxytoluene-α-thiol provided a quantitative yield of the desired thio derivative **22** after hydrolysis (entry 10).[15] This reaction could also be mediated by the presence of caesium carbonate or TMG in good yields (94% and 98% respectively, entries 11 and 12). Addition of an aliphatic thiol also proceeded well using caesium carbonate in DMF to provide thio derivative **23** (95%, entry 13).

Addition of oxygen nucleophiles proved to be more

Table 1 (*Contd.*)

Entry	Nucleophilic source	Conditions	Product		Yield (%)
12		TMG, DMF, rt, 2 h		**22**	98
13		Cs_2CO_3, DMF, rt, 45 min		**23**	95
14	MeONa	THF, 0 °C, 16 h		**24**	27



Scheme 5 *Reagents and conditions*: i) lithium 3-methylbutylamide, THF, −78 °C ⟶ rt, 16 h, 60%; ii) 3-methylbutylamine, Cs_2CO_3, DMF, rt, 36 h, 96%.

problematic. The reaction of an alcohol or carboxylic acid under basic conditions, with either caesium carbonate or potassium *tert*-butoxide as base, gave no ring opened products. Use of sodium methoxide did however result in isolation of a small amount (27%) of the desired methoxy derivative **24** from a rather complex reaction mixture. Amino ester **11** (38%) was also isolated from the reaction, presumably formed by direct attack at sulfur and subsequent hydrolysis (entry 14). Formation of amino ester **11** cannot be explained by hydrolysis of unreacted sulfamidate **13** since this was shown to be stable to the acidic hydrolysis conditions.

Numerous attempts were made to add carbon nucleophiles other than cyanide to sulfamidate **13**. Not too surprisingly, alkyllithiums, and Grignard reagents resulted in complex reaction mixtures due to competing processes such as attack at the ester carbonyl. Addition of copper catalysed Grignard reagents, higher-order cuprates, zincates, deprotonated malonates and silyl enol ethers resulted only in recovery of starting sulfamidate **13**. These findings are consistent with the fact that very few literature examples of carbon addition to sulfamidate systems have been described. In each of the successful examples in which carbon addition could be accomplished either no other electrophilic sites were present in the molecule or the product underwent further intramolecular reaction.[5,11]

In conclusion we have demonstrated the utility of cyclic sulfamidates for the synthesis of unnatural α,α-disubstituted amino acid derivatives. We have applied this chemistry to commercially available racemic 2-methylserine, but it is equally applicable to enantiomerically pure 2-methylserine and hence the synthesis of single enantiomer α,α-disubstituted amino acid derivatives. The nucleophilic substitution takes place at a *neopentyl* centre in good to excellent yields and with complete regioselectivity. Further investigation of carbon and oxygen based nucleophiles as well as the synthesis of potential drug candidates using this methodology is currently in progress.

Experimental

General procedures

All reactions requiring anhydrous conditions were conducted using oven-dried apparatus under an atmosphere of nitrogen at room temperature, unless otherwise stated. Syringes and needles used for the transfer of reagents were dried in a similar fashion and allowed to cool in a dessicator. Anhydrous solvents were purchased in septum-capped bottles (puriss) from Fluka Chemicals Ltd., Glossop, U.K., all other reagents were used as received. Reactions were monitored by TLC using commercially available (Merck) glass backed plates containing a fluorescent indicator. Visualisation of the reaction components was carried out using 254 nm light and potassium permanganate, cerium sulfate, phosphomolybdic acid or bromocresol green stains. Chromatographic purification of compounds was carried out on normal phase Merck no. 9385 (230–400 mesh) silica gel.

Melting points were determined on a Reichart Thermovar hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer System 2000 FT spectrometer by placing the compound neat on a sodium chloride disk. Peak intensities have been specified as strong (s), medium (m), weak (w) or broad (br). All ^1H and ^{13}C-NMR spectra were obtained using $CDCl_3$ solutions with TMS as the internal standard, unless otherwise specified, on a Varian Unity *plus* 400 spectrometer with coupling constants (*J*) being given in Hz. Mass spectra were carried out on a Micromass platform and high resolution spectra were performed at the National Service Centre, University College Swansea on a Thermoquest Finnigan MAT900XT spectrometer.

(±)-3-Hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid 7

4-Methoxybenzaldehyde (5.04 cm^3, 41.40 mmol) was added dropwise to a stirred solution of 2-methylserine (Sigma, 4.481 g, 37.60 mmol) and sodium cyanoborohydride (1 mol dm^{-3} in THF, 37.6 cm^3, 37.60 mmol) in methanol (56 cm^3) at room temperature. After 72 h the resulting precipitate was removed by filtration and washed with cold ether (3 × 10 cm^3) affording, after drying under vacuum, an analytically pure white solid, the

title compound **7** (5.125 g, 57%). The resultant organic solutions were combined and concentrated by evaporation. Purification of the crude residue by column chromatography with 40% ethyl acetate–40% dichloromethane–20% methanol as the eluant afforded further white solid, the *title compound* **7** (3.488 g, 39%); R_f 0.25 (20% methanol–dichloromethane); mp 130–135 °C; ν_{max}(neat)/cm^{-1} 3358br, 2963m, 2839m, 1614s, 1517s, and 1254m; Found: (M+H)$^+$, 240.1239. $C_{12}H_{18}NO_4$ requires 240.12364; δ_H(400 MHz, DMSO) 7.38 (2H, d, *J* 9, Ar), 6.94 (2H, d, *J* 9, Ar), 3.92 (1H, d, *J* 13, NCH_aH$_b$), 3.86 (1H, d, *J* 13, NCH$_a$$H_b$), 3.75 (3H, s, OMe), 3.64 (1H, d, *J* 11, OCH_aH$_b$), 3.56 (1H, d, *J* 11, OCH$_a$$H_b$), 3.32 (1H, br s, NH) and 1.28 (3H, s, Me); δ_C(101 MHz, DMSO) 172.4 (CO_2H), 160.2 (qAr), 132.0 (Ar), 127.8 (qAr), 114.7 (Ar), 66.7 (HOCH_2), 65.1 (*C*Me), 56.1 (OMe), 47.0 (NCH_2) and 19.2 (Me); *m*/*z*(EI+) 240[(M + H)$^+$, 100%].

(±)-3-Hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid allyl ester 8

Potassium carbonate (0.892 g, 6.46 mmol) was added to a stirred suspension of (±)-3-hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid **7** (1.030 g, 4.30 mmol) in DMF (86 cm^3) at room temperature. After 1 h a solution of allyl bromide (0.41 cm^3, 4.73 mmol) in DMF (9 cm^3) was added by syringe pump over 3 h. On completion of the addition and a further 90 min, the bulk of the DMF was removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using 75% ethyl acetate–heptane as the eluant afforded a colourless oil, the *title compound* **8** (0.948 g, 79%); R_f 0.15 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3331br, 2938m, 1732s, 1613m, 1514s, 1456m, 1249s and 1123m; Found: (M + H)$^+$, 280.1536. $C_{15}H_{22}NO_4$ requires 280.15496; δ_H(400 MHz) 7.25 (2H, d, *J* 9, Ar), 6.86 (2H, d, *J* 9, Ar), 6.00–5.90 (1H, m, C*H*CH$_2$), 5.36 (1H, ddt, *J* 17, 2 and 2, CHCH_aH$_b$), 5.28 (1H, ddd, *J* 10, 1 and 1, CHCH$_a$$H_b$), 4.67 (2H, ddd, *J* 6, 2 and 2, OCH_2CH), 3.80 (3H, s, OMe), 3.73 (1H, d, *J* 11, NCH_aH$_b$), 3.62–3.60 [3H, m, NCH$_a$$H_b$, including at 3.62 (2H, s, HOCH_2)], 2.60 (1H, br s, NH) and 1.39 (3H, s, CMe); δ_C(101 MHz) 175.0 (CO_2CH_2), 158.9 (qAr), 132.0 (*C*HCH$_2$), 131.9 (qAr), 129.6 (Ar), 118.8 (CH*C*H$_2$), 114.0 (Ar), 66.1 (HOCH_2), 65.7 (CO_2CH$_2$), 63.2 (*C*Me), 55.4 (ArO*Me*), 47.4 (NCH_2) and 20.2 (Me); *m*/*z* (EI+) 581 [(2M + Na)$^+$, 30%], 302 [(M+Na)$^+$, 100] and 280 [(M + H)$^+$, 40%].

(±)-3-(4-Methoxybenzyl)-4-methyl-2λ^4-1,2,3-oxathiazolidine-4-carboxylic acid allyl ester 9a and 9b

Thionyl chloride (2.04 cm^3, 28.02 mmol) was added dropwise to a stirred solution of (±)-3-hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid allyl ester **8** (7.116 g, 25.47 mmol) and triethylamine (7.81 cm^3, 56.04 mmol) in toluene (320 cm^3) at 0 °C. After 5 min at 0 °C the reaction was allowed to warm to room temperature and water was added. The bulk of the solvents were removed by evaporation under reduced pressure before the resulting concentrate was extracted with ethyl acetate (3 × 150 cm^3). The combined organic extracts were then washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using firstly 25% ethyl acetate–heptane and then 35% ethyl acetate–heptane as the eluant afforded a colourless oil, the *title compound* **9** (7.957 g, 96%), as a 3:2 mixture of diastereoisomers; R_f 0.51 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 2954m, 1737s, 1613m, 1514s, 1250s, 1163s, 963m and 830m; Found: (M + H)$^+$, 326.1047. $C_{15}H_{20}NO_5S$ requires 326.10630; *m*/*z* (EI+) 673 [(2M + Na)$^+$, 80%], 348 [(M+Na)$^+$, 100] and 326 [(M + H)$^+$, 15]; Major diastereoisomer δ_H(400 MHz) 7.37 (2H, d, *J* 9, Ar), 6.87 (2H, d, *J* 9, Ar), 5.99–5.86 (1H, m, C*H*CH$_2$), 5.52–5.27 (2H, m, CHCH_2), 4.88 (1H, d, *J* 9, NCH_aH$_b$), 4.72 (1H, d, *J* 9, NCH$_a$$H_b$), 4.68–4.63 (2H, m, OC$H_2$CH), 4.44 (1H, d, *J* 14, OCH_aH$_b$C), 4.22 (1H, d, *J* 14, OCH$_a$$H_b$C), 3.81 (3H, s, OMe) and 1.63 (3H, s, CMe); δ_C(101 MHz) 171.7 (CO_2Me), 159.5 (qAr), 131.3 (*C*HCH$_2$), 130.3 (Ar), 128.5 (qAr), 119.4 (CH*C*H$_2$), 114.0 (Ar), 78.4 (O*C*H$_2$CMe), 67.7 (*C*Me), 66.6 (O*C*H$_2$CH), 55.3 (ArO*Me*), 45.8 (N*C*H$_2$Ar) and 20.5 (Me); Discernible data for minor diastereoisomer δ_H(400 MHz) 7.30 (2H, d, *J* 9, Ar), 6.88 (2H, d, *J* 9, Ar), 5.34 (1H, d, *J* 8, NCH_aH$_b$), 4.45 (1H, d, *J* 14, OCH_aH$_b$), 4.33 (1H, d, *J* 14, OCH$_a$$H_b$), 4.15 (1H, d, *J* 8, NCH$_a$$H_b$) and 1.52 (3H, s, CMe); δ_C(101 MHz) 171.2 (*C*O$_2$Me), 131.4 (*C*HCH$_2$), 130.2 (Ar), 128.7 (qAr), 119.2 (CH*C*H$_2$), 114.1 (Ar), 79.4 (O*C*H$_2$-CMe), 66.6 (O*C*H$_2$CH), 65.8 (*C*Me), 45.7 (N*C*H$_2$Ar) and 21.0 (Me).

(±)-3-Hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid methyl ester 11

Diazomethane (solution in ether[12]) was added portionwise to a stirred solution (±)-3-hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid **7** (1.000 g, 4.18 mmol) in methanol (60 cm^3) at 0 °C. When sufficient diazomethane solution had been added to give a pale yellow reaction mixture, acetic acid was added to quench the excess reagent. After a further 10 minutes the (now colourless) solution was concentrated by evaporation. Purification of the crude residue by column chromatography with 80% ethyl acetate–heptane as the eluant afforded a white solid, the *title compound* **11** (0.752 g, 71%); R_f 0.36 (ethyl acetate); mp 42–44 °C; ν_{max}(neat)/cm^{-1} 3333br, 2924m, 2852m, 1721s, 1612m, 1514s, 1248s and 1035m; Found: (M + H)$^+$, 254.1389. $C_{13}H_{20}NO_4$ requires 254.13930; δ_H(400 MHz) 7.25 (2H, d, *J* 8, Ar), 6.87 (2H, d, *J* 8, Ar), 3.80 (3H, s, ArO*Me*), 3.77 (3H, s, CO_2Me), 3.71 (1H, d, *J* 11, NCH_aH$_b$), 3.60 (2H, s, HOCH_2), 3.59 (1H, d, *J* 11, NCH$_a$$H_b$), 2.27 (1H, br s, NH), 1.37 (3H, s, Me) and 1.25 (1H, br s, OH); δ_C(101 MHz) 175.5 (*C*O$_2$Me), 159.1 (qAr), 131.4 (qAr), 129.6 (Ar), 114.1 (Ar), 66.0 (HOCH_2), 63.3 (*C*Me), 55.4 (ArO*Me*), 52.4 (OMe), 47.4 (NCH_2) and 19.9 (Me); *m*/*z* (EI+) 276 [(M+Na)$^+$, 70%] and 254 [(M + H)$^+$, 100)].

(±)-3-(4-Methoxybenzyl)-4-methyl-2λ^4-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester 12a and 12b

Thionyl chloride (0.63 cm^3, 8.57 mmol) was added dropwise to a stirred solution of (±)-3-hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid methyl ester **11** (2.177 g, 7.79 mmol) and triethylamine (2.39 cm^3, 17.15 mmol) in toluene (160 cm^3) at 0 °C. After 5 min at 0 °C the reaction was allowed to warm to room temperature and water was added. The bulk of the solvents were removed by evaporation under reduced pressure before the resulting concentrate was extracted with ethyl acetate (3 × 50 cm^3). The combined organic extracts were then washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using 75% ethyl acetate–heptane as the eluant afforded a colourless oil, the title compound **12** (2.177 g, 93%), as a 5:2 mixture of diastereoisomers; R_f 0.40 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 2990m, 2955m, 1739s, 1613s, 1514s, 1463m, 1250s and 1163s; Found: M$^+$, 299.0825. $C_{13}H_{17}NO_5S$ requires 299.08281; *m*/*z* (EI+) 621 [(2M + Na)$^+$, 100%], 322 [(M+Na)$^+$, 70], 317 [(M+NH$_4$)$^+$, 20] and 300 [(M + H)$^+$, 15]; Major diastereoisomer δ_H(400 MHz) 7.36 (2H, d, *J* 9, Ar), 6.87 (2H, d, *J* 9, Ar), 4.85 (1H, d, *J* 9, NCH_aH$_b$), 4.70 (1H, d, *J* 9, NCH$_a$$H_b$), 4.43 (1H, d, *J* 14, OCH_aH$_b$), 4.22 (1H, d, *J* 14, OCH$_a$$H_b$), 3.80 (3H, s, ArO*Me*), 3.75 (3H, s, CO_2Me) and 1.61 (3H, s, Me); δ_C(101 MHz) 172.5 (CO_2Me), 159.5 (qAr), 130.3 (Ar), 128.6 (qAr), 114.0 (Ar), 78.4 (OCH_2), 67.6 (*C*Me), 55.3 (ArO*Me*), 53.0 (OMe), 45.8 (NCH_2) and 20.6 (Me); Discernible data for minor diastereoisomer δ_H(400 MHz) 7.30 (2H, d, *J* 9, Ar), 6.88 (2H, d, *J* 9, Ar), 5.33 (1H, d, *J* 9, NCH_aH$_b$), 4.43 (1H, d, *J* 14, OCH_aH$_b$), 4.33 (1H, d, *J* 14, OCH$_a$$H_b$), 4.14 (1H, d, *J* 9,

NCH_aH_b), 3.80 (3H, s, ArO*Me*), 3.77 (3H, s, CO_2Me) and 1.51 (3H, s, Me); δ_C(101 MHz) 172.0 (*C*O_2Me), 130.2 (Ar), 128.6 (qAr), 114.1 (Ar), 79.4 (OCH_2), 65.6 (*C*Me), 52.9 (CO_2*Me*), 45.7 (NCH_2) and 20.9 (Me).

(±)-3-(4-Methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester 13

Water (42 cm^3) was added dropwise to a stirred suspension of (±)-2-hydroxy-3-(4-methoxybenzyl)-4-methyl-2λ^4-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **12** (3.002 g, 10.03 mmol), sodium periodate (2.359 g, 11.03 mmol) and ruthenium trichloride hydrate (0.021 g, 0.10 mmol) in acetonitrile (67 cm^3) at 0 °C. After 5 min the cold bath was removed and the reaction was allowed to warm slowly. After a further 15 min saturated aqueous sodium hydrogen carbonate solution was added and the reaction mixture was extracted with ethyl acetate (3 × 100 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using 50% ethyl acetate–heptane as the eluant afforded a white solid, the *title compound* **13** (3.098 g, 98%); R_f 0.35 (50% ethyl acetate–heptane); mp 102–105 °C; ν_{max}(neat)/cm^{-1} 2956m, 1746s, 1611m, 1514s, 1455m, 1339s, 1187s and 974m; Found: C, 49.71; H, 5.40; N, 4.55; S, 10.17; $C_{13}H_{17}NO_6S$ requires C, 49.51; H, 5.40; N, 4.44; S, 10.17%; Found: M$^+$, 315.0781. $C_{13}H_{17}NO_6S$ requires 315.07771; δ_H(400 MHz) 7.34 (2H, d, *J* 8, Ar), 6.88 (2H, d, *J* 8, Ar), 4.82 (1H, d, *J* 9, NCH_aH_b), 4.49 (1H, d, *J* 15, OCH_aH_b), 4.38 (1H, d, *J* 15, OCH_aH_b), 4.27 (1H, d, *J* 9, NCH_aH_b), 3.80 (3H, s, ArO*Me* or OMe), 3.75 (3H, s, OMe or ArO*Me*) and 1.50 (3H, s, CMe); δ_C(101 MHz) 170.5 (*C*O_2Me), 159.6 (qAr), 130.1 (Ar), 127.1 (qAr), 114.0 (Ar), 73.9 (OCH_2), 65.9 (*C*Me), 55.3 (ArO*Me*), 53.3 (OMe), 46.7 (NCH_2) and 20.3 (Me); *m*/*z* (EI+) 653 [(2M + Na)$^+$, 90%], 648 [(2M + NH_4)$^+$, 15], 338 [(M+NH_4)$^+$, 100] and 333 [(M+NH_4)$^+$, 15].

(±)-3-Azido-2-(4-methoxybenzylamino)-2-methylpropionic acid methyl ester 14

Sodium azide (10.2 mg, 0.16 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (41.3 mg, 0.13 mmol) in DMF (0.8 cm^3) at room temperature. After 4 h the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure affording a colourless oil, the *title compound* **14** (34.8 mg, 96%); R_f 0.41 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 2953m, 2837m, 2104s, 1732s, 1613m, 1513s, 1248s and 1035m; Found: (M + H)$^+$, 279.1460. $C_{13}H_{19}N_4O_3$ requires 279.14587; δ_H(400 MHz) 7.26 (2H, d, *J* 9, Ar), 6.86 (2H, d, *J* 9, Ar), 3.80 (3H, s, ArO*Me* or CO_2Me), 3.78 (3H, s, CO_2Me or ArO*Me*), 3.64 (1H, d, *J* 12, NCH_aH_bC), 3.60 (1H, d, *J* 12, NCH_aH_bC), 3.57 (1H, d, *J* 12, NCH_aH_bAr), 3.43 (1H, d, *J* 12, NCH_aH_bAr), 1.88 (1H, br s, NH) and 1.40 (3H, s, Me); δ_C(101 MHz) 174.8 (*C*O_2Me), 158.9 (qAr), 131.8 (qAr), 129.6 (Ar), 114.0 (Ar), 62.7 (*C*Me), 57.5 (NCH_2C), 55.4 (ArO*Me*), 52.4 (OMe), 47.8 (NCH_2Ar) and 20.9 (Me); *m*/*z* (EI+) 579 [(2M + Na)$^+$, 40%], 301 [(M+Na)$^+$, 90] and 279 [(M + H)$^+$, 100].

(±)-3-Cyano-2-(4-methoxybenzylamino)-2-methylpropionic acid methyl ester 15

Sodium cyanide (14.5 mg, 0.30 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (46.7 mg, 0.15 mmol) in DMF (0.8 cm^3) at room temperature. After 90 min the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure affording a colourless oil, the *title compound* **15** (40.0 mg, 100%); R_f 0.33 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3335m, 2955m, 2248m, 1732s, 1613m, 1514s, 1248s and 1115s; Found: (M + H)$^+$, 263.1408. $C_{14}H_{19}N_2O_3$ requires 263.13967; δ_H(400 MHz) 7.26 (2H, d, *J* 8, Ar), 6.86 (2H, d, *J* 8, Ar), 3.78 (6H, s, ArO*Me* and OMe), 3.62 (1H, d, *J* 12, NCH_aH_b), 3.55 (1H, d, *J* 12, NCH_aH_b), 2.83 (1H, d, *J* 17, $NCCH_aH_b$), 2.77 (1H, d, *J* 17, $NCCH_aH_b$) and 1.53 (3H, s, CMe); δ_C(101 MHz) 174.1 (*C*O_2Me), 159.1 (qAr), 131.3 (qAr), 129.6 (Ar), 116.9 (NC), 114.0 (Ar), 60.4 (*C*Me), 55.4 (ArO*Me*), 52.7 (OMe), 48.0 (NCH_2), 26.6 ($NCCH_2$) and 24.1 (Me); *m*/*z* (EI+) 285 [(M+Na)$^+$, 100%].

(±)-3-Fluoro-2-(4-methoxybenzylamino)-2-methylpropionic acid methyl ester 16

Tetrabutylammonium fluoride (1 mol dm^{-3} in THF, 0.160 cm^3, 0.16 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (41.2 mg, 0.13 mmol) in DMF (0.8 cm^3) at room temperature. After 4 h the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by passage through a short pad of silica gel using ethyl acetate as the eluant afforded a colourless oil, the *title compound* **16** (23.4 mg, 70%); R_f 0.36 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3341w, 2954m, 1737s, 1613m, 1514s, 1463m, 1248s and 1034m; Found: (M + H)$^+$, 256.1357. $C_{13}H_{19}NO_3F$ requires 256.13497; δ_H(400 MHz) 7.27 (2H, d, *J* 8, Ar), 6.86 (2H, d, *J* 8, Ar), 4.53 (1H, dd, J_{HF} 47 and *J* 9, FCH_aH_b), 4.45 (1H, dd, J_{HF} 47 and *J* 9, FCH_aH_b), 3.80 (3H, s, ArO*Me* or OMe), 3.78 (3H, s, OMe or ArO*Me*), 3.66 (2H, s, NCH_2), 1.95 (1H, br s, NH) and 1.38 (3H, s, CMe); δ_C(101 MHz) 174.5 (*C*O_2Me), 158.9 (qAr), 132.2 (qAr), 129.6 (Ar), 114.0 (Ar), 87.2 (D, J_{CF} 176, FCH_2), 62.5 (d, J_{CF} 18, *C*Me), 55.4 (ArO*Me*), 52.4 (OMe), 47.8 (NCH_2) and 19.1 (d, J_{CF} 6, Me); *m*/*z* (EI+) 278 [(M+Na)$^+$, 100%] and 256 [(M + H)$^+$, 10].

(±)-2-(4-Methoxybenzylamino)-2-methyl-3-thiocyanatopropionic acid methyl ester 17

Ammonium thiocyanate (35.0 mg, 0.46 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (48.8 mg, 0.15 mmol) in DMF (1.0 cm^3) at room temperature. The reaction was heated to 60 °C and after 6 h the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The com-

bined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using 5% methanol–ethyl acetate as the eluant afforded a colourless oil, the *title compound* **17** (29.9 mg, 68%); R_f 0.18 (5% methanol–ethyl acetate); ν_{max}(neat)/cm^{-1} 3323w, 2952m, 2058w, 1737s, 1609s, 1513s, 1246s and 1172s; Found: (M + H)$^+$, 295.1108. $C_{14}H_{19}N_2O_3S$ requires 295.11177; δ_H(400 MHz) 7.24 (2H, d, *J* 9, Ar), 6.84 (2H, d, *J* 9, Ar), 4.99 (1H, d, *J* 16, SCH_aH$_b$), 4.19 (1H, d, *J* 16, SCH$_a$$H_b$), 3.78 (3H, s, ArO*Me* or OMe), 3.73 (3H, s, OMe or ArO*Me*), 3.50 (1H, d, *J* 11, NCH_aH$_b$Ar), 3.17 (1H, d, *J* 11, NCH$_a$$H_b$Ar), 1.53 (3H, s, CMe) and 1.23 (1H, br s, NH); δ_C(101 MHz) 173.5 (*C*O$_2$Me), 164.2 (NCS), 158.6 (qAr), 130.9 (qAr), 128.3 (Ar), 113.9 (Ar), 70.7 (*C*Me), 55.3 (ArO*Me*), 52.9 (OMe), 47.0 (N*C*H$_2$Ar), 38.1 (SCH$_2$) and 23.2 (Me); *m*/*z* (EI+) 611 [(2M + Na)$^+$, 5%], 589 [(2M+H)$^+$, 10], 317 [(M+Na)$^+$, 5] and 295 [(M + H)$^+$, 100].

(±)-3-(4-Methoxybenzylamino)-3-methyl-1-(3-methylbutyl)-azetidin-2-one 18

Lithium 3-methylbutylamide (0.5 mol dm^{-3} in THF,[15] 0.388 cm^3, 0.19 mmol) was added to a solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (51.0 mg, 0.16 mmol) in THF (0.75 cm^3) at −78 °C. After the addition was complete the cold bath was removed and the reaction was allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride solution (2 drops) was added to the reaction before the solvents were removed by evaporation under reduced pressure. The resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure affording a colourless oil, the *title compound* **18** (27.8 mg, 60%); R_f 0.10 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3310br, 2957m, 1740s, 1612w, 1513m, 1465w, 1247m and 1035w; Found: (M + H)$^+$, 291.2065. $C_{17}H_{27}N_2O_2$ requires 291.20741; δ_H(400 MHz) 7.27 (2H, d, *J* 9, Ar), 6.85 (2H, d, *J* 9, Ar), 3.79 (3H, s, OMe), 3.78 (1H, d, *J* 12, NCH_aH$_b$Ar), 3.71 (1H, d, *J* 12, NCH$_a$$H_b$Ar), 3.35 (1H, d, *J* 6, NCH_aH$_b$C), 3.31–3.18 (2H, m, CH$_2$CH_2N), 3.10 (1H, d, *J* 6, NCH$_a$$H_b$C), 1.64–1.54 (1H, m, Me$_2$C*H*), 1.48 (3H, s, CMe), 1.42 (2H, dt, *J* 7 and 7, CHCH_2N), 0.94 (3H, s, *Me*CH) and 0.92 (3H, s, *Me*CH); δ_C(101 MHz) 172.2 (NCO), 158.9 (qAr), 132.0 (qAr), 129.5 (Ar), 113.9 (Ar), 70.5 (*C*Me), 55.3 (ArO*Me*), 52.2 (*C*H$_2$CMe), 48.0 (N*C*H$_2$Ar), 39.6 (CH$_2$*C*H$_2$N), 36.4 (Me$_2$CH*C*H$_2$), 26.0 (Me$_2$*C*H), 22.4 (*Me*CH), 22.4 (*Me*CH) and 21.2 (C*Me*); *m*/*z* (CI+) 291 [(M + H)$^+$, 100%].

(±)-2-(4-Methoxybenzylamino)-2-methyl-3-(3-methylbutylamino)propionic acid methyl ester 19

Caesium carbonate (89 mg, 0.27 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (43.2 mg, 0.14 mmol) and 3-methylbutylamine (0.032 cm^3, 0.27 mmol) in DMF (1.0 cm^3) at room temperature. After 36 h the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using ethyl acetate as the eluant afforded a colourless oil, the *title compound* **19** (34.8 mg, 96%); R_f 0.17 (ethyl acetate); ν_{max}(neat)/cm^{-1} 3330w, 2953s, 2836m, 1732s, 1613m, 1513s, 1465m and 1248s; Found: (M + H)$^+$, 323.2329. $C_{18}H_{31}N_2O_3$ requires 323.23363; δ_H(400 MHz) 7.26 (2H, d, *J* 9, Ar), 6.85 (2H, d, *J* 9, Ar), 3.79 (3H, s, ArO*Me* or OMe), 3.74 (3H, s, OMe or ArO*Me*), 3.61 (1H, d, *J* 12, NCH_aH$_b$Ar), 3.56 (1H, d, *J* 12, NCH$_a$$H_b$Ar), 2.81 (1H, d, *J* 12, NCH_aH$_b$C), 2.74 (1H, d, *J* 12, NCH$_a$$H_b$C), 2.56–2.54 (2H, m, CH$_2CH_2$N), 1.63–1.55 (3H, m, Me$_2$C*H* and 2 × NH), 1.38 (3H, s, CMe), 1.35–1.25 (2H, m, CH_2CH$_2$N), 0.87 (3H, s, *Me*CH) and 0.86 (3H, s, *Me*CH); δ_C(101 MHz) 176.7 (*C*O$_2$Me), 158.7 (qAr), 132.8 (qAr), 129.5 (Ar), 113.9 (Ar), 62.8 (*C*Me), 56.7 (N*C*H$_2$C), 55.3 (ArO*Me*), 51.9 (OMe), 48.6 (CH$_2$*C*H$_2$N), 47.7 (N*C*H$_2$Ar), 39.2 (CH*C*H$_2$), 26.1 (Me$_2$*C*H), 22.8 (*Me*CH), 22.7 (*Me*CH) and 21.3 (Me); *m*/*z* (EI+) 667 [(2M + Na)$^+$, 35%], 345 [(M+Na)$^+$, 40] and 323 [(M + H)$^+$, 100].

(±)-2-(4-Methoxybenzylamino)-2-methyl-3-pyrazol-1-ylpropionic acid methyl ester 20

Caesium carbonate (112.0 mg, 0.34 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (54.0 mg, 0.17 mmol) and pyrazole (23.3 mg, 0.34 mmol) in DMF (1.0 cm^3) at room temperature. After 18 h the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using 60% ethyl acetate–heptane as the eluant afforded a colourless oil, the *title compound* **20** (38.0 mg, 74%); R_f 0.15 (40% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3331w, 2951w, 2837w, 1731s, 1612m, 1513s, 1458m and 1248s; Found: (M + H)$^+$, 304.1652. $C_{16}H_{22}N_3O_3$ requires 304.16626; δ_H(400 MHz) 7.49 (1H, d, *J* 2, C*H*NCH$_2$), 7.40 (1H, d, *J* 2, CHNN), 7.26 (2H, d, *J* 9, Ar), 6.86 (2H, d, *J* 9, Ar), 6.23 (1H, dd, *J* 2 and 2, C*H*CHN), 4.38 (2H, s, NCH$_2$C), 3.80 (3H, s, ArO*Me* or OMe), 3.73 (3H, s, OMe or ArO*Me*), 3.66 (2H, s, NCH_2Ar), 1.96 (1H, br s, NH) and 1.35 (3H, s, CMe); δ_C(101 MHz) 175.0 (*C*O$_2$Me), 158.8 (qAr), 139.6 (*C*HNCH$_2$), 132.2 (qAr), 130.5 (Ar), 129.5 (CHNN), 113.9 (Ar), 105.6 (*C*HCHN), 63.3 (*C*Me), 58.5 (N*C*H$_2$C), 55.3 (ArO*Me*), 52.4 (OMe), 47.7 (N*C*H$_2$Ar), and 20.5 (Me); *m*/*z* (EI+) 326 [(M+Na)$^+$, 15%] and 304 [(M + H)$^+$, 100].

(±)-2-(4-Methoxybenzylamino)-2-methyl-3-piperidin-1-ylpropionic acid methyl ester 21

Caesium carbonate (74.0 mg, 0.23 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (47.7 mg, 0.15 mmol) and piperidine (0.150 cm^3, 1.51 mmol) in acetonitrile (1.0 cm^3) at room temperature. After 96 h the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using 45% ethyl acetate–heptane as the eluant afforded a colourless oil, the *title compound* **21** (46.3 mg, 96%); R_f 0.19 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3320w, 2934s, 2851m, 1732s, 1612m, 1513s, 1248s and 1099s;

Found: $(M + H)^+$, 321.2172. $C_{18}H_{29}N_2O_3$ requires 321.21797; δ_H(400 MHz) 7.28 (2H, d, *J* 9, Ar), 6.86 (2H, d, *J* 9, Ar), 3.80 (3H, s, ArO*Me* or OMe), 3.71 (3H, s, OMe or ArO*Me*), 3.62 (2H, s, NCH_2Ar), 2.58 (1H, d, *J* 14, NC$H_a$$H_b$C), 2.50 (1H, d, *J* 14, NCH$_a$$H_b$C), 2.42–2.40 (4H, m, $CH_2CH_2NCH_2CH_2$), 1.50–1.45 (4H, m, $CH_2CH_2NCH_2CH_2$) and 1.27–1.32 [5H, m, $CH_2CH_2CH_2N$, including at 1.32 (3H, s, CMe)]; δ_C(101 MHz) 176.8 (CO_2Me), 158.6 (qAr), 133.2 (qAr), 129.3 (Ar), 113.8 (Ar), 67.7 (NCH_2C), 63.1 (*C*Me), 56.5 ($CH_2CH_2NCH_2CH_2$), 55.3 (ArO*Me*), 51.7 (OMe), 47.7 (NCH_2Ar), 26.4 (CH_2CH_2-NCH_2CH_2), 24.1 ($CH_2CH_2CH_2N$), 20.4 (Me); *m*/*z* (EI+) 663 [$(2M + Na)^+$, 50%], 343 [$(M+Na)^+$, 30] and 321 [$(M + H)^+$, 100].

(±)-2-(4-Methoxybenzylamino)-3-(4-methoxybenzylsulfanyl)-2-methylpropionic acid methyl ester 22

Method A. Lithium 4-methoxytoluene-α-thiolate (0.5 mol dm^{-3} in THF,[15] 0.315 cm^3, 0.16 mmol) was added to a solution of (±)-*N*-(4-methoxybenzyl)-4-methyl-2,2-dioxo-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (45.1 mg, 0.14 mmol) in THF (0.75 cm^3) at −78 °C. After the addition was complete the cold bath was removed and the reaction was allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride solution (2 drops) was added to the reaction before the solvents were removed by evaporation under reduced pressure. The resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure affording a colourless oil, the *title compound* **22** (58.2 mg, 100%).

Method B. Caesium carbonate (93.0 mg, 0.28 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (44.9 mg, 0.14 mmol) and 4-methoxytoluene-α-thiol (0.040 cm^3, 0.28 mmol) in DMF (0.75 cm^3) at room temperature. After 2 h the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using firstly 25% ethyl acetate–heptane and then 50% ethyl acetate–heptane as the eluant afforded a colourless oil, the *title compound* **22** (51.1 mg, 94%).

Method C. 1,1,3,3-Tetramethylguanidine (0.024 cm^3, 0.19 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (40.4 mg, 0.13 mmol) and 4-methoxytoluene-α-thiol (0.027 cm^3, 0.19 mmol) in DMF (0.8 cm^3) at room temperature. After 2 h the solvent was removed by evaporation under reduced pressure and the resulting residue was hydrolysed and purified according to *Method B* to afford a colourless oil, the *title compound* **22** (48.9 mg, 98%); R_f 0.30 (40% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3321w, 2951w, 1730m, 1611m, 1512s, 1464m, 1248s and 1174m; Found: $(M + H)^+$, 390.1750. $C_{21}H_{28}NO_4S$ requires 390.17404; δ_H(400 MHz) 7.26–7.20 (4H, m, Ar), 6.86–6.81 (4H, m, Ar), 3.79 (6H, s, 2 × ArO*Me*), 3.73 (3H, s, OMe), 3.67 (2H, s, NCH_2Ar), 3.55 (2H, s, ArCH_2S), 2.87 (1H, d, *J* 13, SC$H_a$$H_b$C), 2.72 (1H, d, *J* 13, SCH$_a$$H_b$C), 1.96 (1H, br s, NH) and 1.40 (3H, s, CMe); δ_C(101 MHz) 175.8 (CO_2Me), 158.8 (qAr), 158.7 (qAr), 132.3 (qAr), 130.3 (qAr), 130.1 (Ar), 129.6 (Ar), 114.0 (Ar), 113.9 (Ar), 62.7 (*C*Me), 55.3 (ArO*Me*), 55.3 (ArO*Me*), 52.2 (O*Me*), 47.8 (NCH_2), 40.4 (CCH_2S), 37.0 (SCH_2CMe) and 22.5 (Me); *m*/*z* (CI+) 390 [$(M + H)^+$, 100%].

(±)-2-(4-Methoxybenzylamino)-2-methyl-3-(3-methylbutylsulfanyl)propionic acid methyl ester 23

Caesium carbonate (107.0 mg, 0.33 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (51.6 mg, 0.16 mmol) and 3-methylbutanethiol (0.041 cm^3, 0.33 mmol) in DMF (0.75 cm^3) at room temperature. After 45 min the solvent was removed by evaporation under reduced pressure and the resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the crude residue by column chromatography using 25% ethyl acetate–heptane as the eluant afforded a colourless oil, the *title compound* **23** (51.5 mg, 95%); R_f 0.50 (50% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3330w, 2954m, 1732s, 1613m, 1513s, 1466m, 1248s and 1172m; Found: $(M + H)^+$, 340.1957. $C_{18}H_{30}NO_3S$ requires 340.19480; δ_H(400 MHz) 7.28–7.26 (2H, m, Ar), 6.85 (2H, d, *J* 9, Ar), 3.79 (3H, s, ArO*Me* or OMe), 3.75 (3H, s, OMe or ArO*Me*), 3.60 (2H, s, NCH_2Ar), 2.97 (1H, d, *J* 13, SCH_a-H_bC), 2.80 (1H, d, *J* 13, SCH$_a$$H_b$C), 2.52 (2H, td, *J* 8 and 2, CH_2CH_2S), 2.01 (1H, s, NH), 1.69–1.58 (1H, m, Me_2CH), 1.47–1.42 [5H, m, CH_2CH_2S, including at 1.45 (3H, s, CMe)], 1.45 (3H, s, CMe), 0.89 (3H, s, *Me*CH) and 0.87 (3H, s, *Me*CH); δ_C(101 MHz) 175.8 (CO_2Me), 158.8 (qAr), 132.4 (qAr), 129.6 (Ar), 113.9 (Ar), 62.8 (*C*Me), 55.3 (ArO*Me*), 52.1 (O*Me*), 47.9 (NCH_2Ar), 41.8 (SCH_2C), 39.9 (CH_2CH_2S), 31.8 ($CHCH_2$), 27.4 (Me_2CH), 22.4 (Me), 22.3 (Me) and 22.3 (Me); *m*/*z* (EI+) 701 [$(2M + Na)^+$, 95%], 362 [$(M+Na)^+$, 100] and 340 [$(M + H)^+$, 90].

(±)-3-Methoxy-2-(4-methoxybenzylamino)-2-methylpropionic acid methyl ester 24

Sodium methoxide (0.5 mol dm^{-3} in methanol, 0.322 cm^3, 0.16 mmol) was added to a stirred solution of (±)-3-(4-methoxybenzyl)-4-methyl-2,2-dioxo-2λ^6-1,2,3-oxathiazolidine-4-carboxylic acid methyl ester **13** (42.3 mg, 0.13 mmol) in THF at 0 °C. The reaction was allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride solution (2 drops) was added to the reaction before the solvents were removed by evaporation under reduced pressure. The resulting residue was stirred vigorously overnight between dichloromethane (1 cm^3) and 20% (v/v) sulfuric acid solution (1 cm^3). Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased), the reaction mixture was then extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were washed (brine), dried (magnesium sulfate), filtered and then the solvents were removed by evaporation under reduced pressure. Purification of the residue by column chromatography using firstly 70% ethyl acetate–heptane and then ethyl acetate as the eluant afforded two compounds; first elution, the *title compound* **24** (9.5 mg, 27%); R_f 0.10 (40% ethyl acetate–heptane); ν_{max}(neat)/cm^{-1} 3345w, 2950m, 1737s, 1612m, 1513s, 1456m, 1248s and 1109m; Found: $(M + H)^+$, 268.1536. $C_{14}H_{22}NO_4$ requires 268.15496; δ_H(400 MHz) 7.28 (2H, d, *J* 9, Ar), 6.85 (2H, d, *J* 9, Ar), 3.79 (3H, s, ArOMe or OMe), 3.75 (3H, s, OMe or ArOMe), 3.64 (2H, s, NCH_2Ar), 3.53 (1H, d, *J* 9, OC$H_a$$H_b$C), 3.42 (1H, d, *J* 9,

OCH_aH_bC), 3.32 (3H, s, $MeOCH_2$), 2.10 (1H, br s, NH) and 1.37 (3H, s, CMe); δ_C(101 MHz) 175.6 (CO_2Me), 158.7 (qAr), 132.5 (qAr), 129.6 (Ar), 113.8 (Ar), 78.6 (OCH_2C), 62.8 (CMe), 59.4 ($MeOCH_2$), 55.3 (ArOMe), 52.1 (OMe), 47.7 (NCH_2Ar) and 19.5 (CMe); *m*/*z* (EI+) 557 [$(2M + Na)^+$, 40%], 290 [$(M+Na)^+$, 100] and 268 [$(M + H)^+$, 25]; second elution, (±)-3-hydroxy-2-(4-methoxybenzylamino)-2-methylpropionic acid methyl ester **11** (12.4 mg, 38%).

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