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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 554–561

Stereoselective synthesis of 4-substituted azetidine-2,3-diones by ring opening of 1,3-thiazolidine-derived spiro-β-lactams

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Received 13 December 2007; accepted 8 February 2008

Abstract—New 3-heterocycle substituted 1,3-thiazolidine-derived 4-spiro-β-lactams with a relative *trans*-configuration were stereoselectively synthesised by means of a *Staudinger* ketene–imine reaction between the ketene generated from the (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1** and imines **2b**–**e**. The 1,3-thiazolidine-derived 4-spiro-β-lactams were transformed into the corresponding enantiomerically pure 4-heterocycle substituted azetidine-2,3-diones by means of an oxidative cleavage of the 1,3-thiazolidine ring. The opening of the 1,3-thiazolidine ring was studied under different experimental conditions and a consistent mechanism is proposed.

1. Introduction

The stereoselective synthesis of β-lactams has received considerable attention over recent years because of their wide variety of biological activities,[1] in particular, asymmetric synthesis by means of a *Staudinger* ketene–imine reaction has been extensively studied.[2] Spiro-β-lactams are interesting compounds not only because of their antiviral[3a] and antibacterial activities,[3b] but also because they inhibit cholesterol absorption,[3c] indicating that they are potentially useful drugs. They can also act as β-turn mimetics,[4a] while the 4-spiro-β-lactams can be used as synthetic precursors for cyclic α,α-disubstituted β-amino acids and peptide derivatives.[4b]

Some β-lactams, such as the azetidine-2,3-diones or α-keto-β-lactams, are very interesting small heterocycles that could be useful intermediates because of the various possible transformations of the ketone and amide functional groups. The most significant of these transformations involves the synthesis of 3-hydroxy substituted β-lactams, which are important key fragments of many natural products.[5]

Continuing our studies of the synthesis[6] and reactivity[7] of hetero-spirocyclic β-lactams, we have recently synthesised new 1,3-thiazolidine-derived 4-spiro-β-lactams[8a,b] using a *Staudinger* ketene–imine reaction between imines and the non-symmetrical cyclic ketenes generated from *N*-acyl-1,3-thiazolidine-2-carboxylic acids by means of *Mukaiyama*'s reagent. Subsequently, we synthesised enantiomerically pure 1,3-thiazolidine-derived 4-spiro-β-lactams **3a** and **4a** starting from the optically active (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1** and benzyl-benzylidene-amine **2a** as indicated in Scheme 1.[8c]

Our studies led us to conclude that, when the imine-nitrogen atom is substituted with an electron-donor group (e.g., $PhCH_2$), the main diastereoisomer obtained has a relative *trans* configuration between the sulfur atom and the 3-C-phenyl group.[8b] Moreover, with the enantiomerically pure substrate **1**, the reactions afford only two diastereoisomers which have the same *trans* relative configuration but opposite configurations to the C-3 and the spiranic carbon atoms.

Our interest in compounds **3** and **4** was based on the presence of the spiro-fused 1,3-thiazolidine ring, whose selective opening made it possible to obtain α-keto-β-lactams and recover the chiral auxiliary. This transformation was accomplished in two steps: the spiro-β-lactams **3a** and **4a** were deprotected at the thiazolidine-*N*-atom under anhydrous conditions with gaseous HCl in AcOEt, and then heated in a $CHCl_3$/DMSO 90:10 solution for 6 h. These

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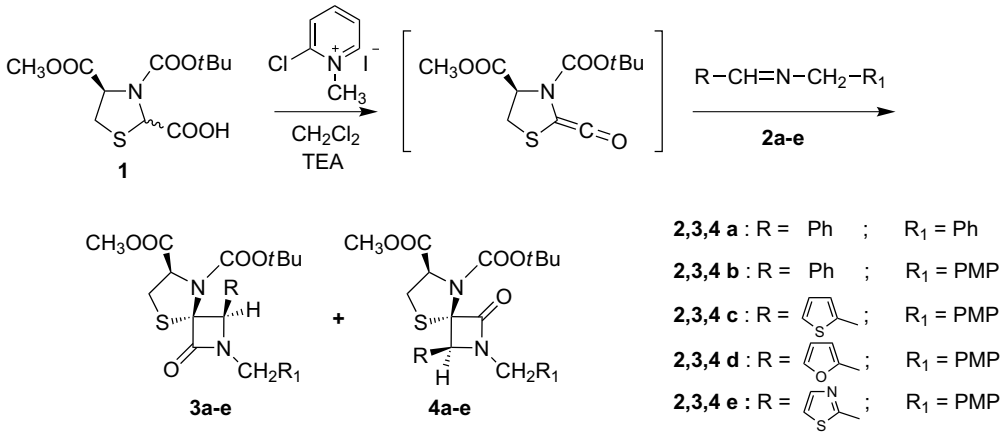
doi:10.1016/j.tetasy.2008.02.011



Scheme 1.

conditions allowed the corresponding α-keto-β-lactams to be obtained in good yields together with the dimethyl cystinate dihydrochloride.[8c] However, the mechanism of this reaction has not been completely clarified, and should be studied further.[8b]

In this context, and in view of the growing interest in the synthesis of enantiopure β-lactams, we herein report the asymmetric synthesis of new 1,3-thiazolidine-derived 4-spiro-β-lactams by means of a *Staudinger* ketene–imine reaction between the optically active (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1** and imines **2b–e**, which, respectively, derive from benzaldehyde, 2-thiophene-carbaldehyde, 2-furane-carbaldehyde, 2-thiazole-carbaldehyde and 4-methoxybenzylamine. The aim was to obtain 4-spiro-β-lactams that are substituted at the 3-position by a heterocycle and have a removable group, such as the *p*-methoxy-phenyl group, on the β-lactam-nitrogen, because the transformations of these compounds would allow new azetidine-2,3-diones to be obtained. At the same time, additional studies of 1,3-thiazolidine ring opening would enable us to propose a mechanism to explain the course of the reaction.

2. Results and discussion

The starting material, (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1**, was prepared from (*R*)-cysteine methyl ester hydrochloride and glyoxylic acid followed by treatment with $(BOC)_2O$, as previously reported.[8c] Imines **2b**,[9] **2c**, **2d** and **2e** were prepared from the corresponding aldehydes and 4-methoxybenzylamine in dry CH_2Cl_2 over anhydrous Na_2SO_4 as a single (*E*) geometrical isomer, as determined by IR and ^1H NMR. Their stability under the experimental conditions of the *Staudinger* reaction (TEA in refluxing CH_2Cl_2 for 24 h) was also confirmed by means of suitable experiments insofar as the imines were stable under these conditions (as established by ^1H NMR analysis) but, when heated in refluxing CH_3OH in the presence of CH_3ONa, they equilibrated to afford a mixture of two tautomeric imines (Fig. 1).[10]

The reaction of amino acid **1**, imines **2b–e** and 2-chloro-1-methylpyridinium iodide (*Mukaiyama*'s reagent) in the presence of TEA in refluxing CH_2Cl_2 for 24 h gave the spiro-β-lactams as a mixture of two diastereoisomers, **3b–e** and **4b–e**, which were easily separated and purified by means of flash chromatography (Scheme 1).

The relative and absolute configurations of the new stereocentres of spiro-β-lactams **3b–e** and **4b–e** were assigned by comparing the NMR spectra of the products with those of the previously obtained compounds **3a** (whose structure was confirmed by means of X-ray analysis) and **4a**.[8c] The ^1H NMR spectra were complicated by the existence of rotamers arising from the presence of the *N*-Boc group, and hence were recorded at 80 °C in DMSO-d_6. In this way, it was possible to observe a complete correspondence between the multiplicities and chemical shifts of, for example, the H-7 proton (doublet, 4.30 δ in **3a**, doublet, 4.30–4.54 δ in **3b–e**; triplet, 4.75 δ in **4a**, triplet, 4.70–4.86 δ in **4b–e**), the $COOCH_3$ signal (3.65 δ in **3a**, 3.60–3.71 δ in **3b–e**; 3.39 δ in **4a**, 3.38–3.53 δ in **4b–e**), and the H-6 protons (3.31, 3.69 δ in **3a**, 3.27–3.38, 3.50–3.70 δ in **3b–e**;

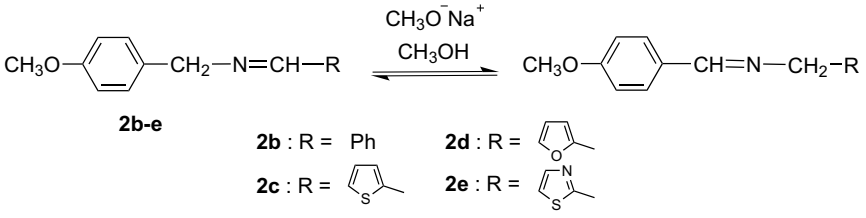


Figure 1.

Table 1.

	Total yield (%)	Ratio (%) (**3**):(**4**)
3–**4a**	63[8c]	64:36
3–**4b**	62	56:44
3–**4c**	77	36:64
3–**4d**	60	46:54
3–**4e**	72	69:31

3.25, 3.44 δ in **4a**, 3.20–3.25, 3.44–3.48 δ in **4b**–**e**). Table 1 shows the yields and the ratios of the new products **3b**–**e** and **4b**–**e** in comparison with **3a** and **4a**.

Also in this case, and with regard to the relative configuration of C-3 and C-4 carbon, the *Staudinger* reaction proceeded with total stereoselectivity, giving both spiro-β-lactams with a relative *trans* disposition. On the other hand, as shown in Table 1, the ratios between the adducts were generally lower than (and, in the case of the 2-thienyl and 2-furyl derivatives **3**/**4c**,**d** even opposite to) that observed for **3a**/**4a**. This result cannot be explained on the basis of the proposed mechanism of the ketene–imine reaction,[11,12] according to which the attack of nucleophilic imines such as (*E*)-**2b**–**e** occurs from the less hindered side of the ketene opposite to the *N*-Boc group (Fig. 2). The presence of a stereocentre in the 1,3-thiazolidine ring differentiates the two faces of the intermediate ketene, and so the β-lactams **3** deriving from the attack on the less hindered face should always be the more abundant adducts. Furthermore, the fact that the 2-thienyl and 2-furyl ring is smaller than the phenyl ring does not explain the reversed ratio because this does not happen in the case of the 2-thiazolyl ring.

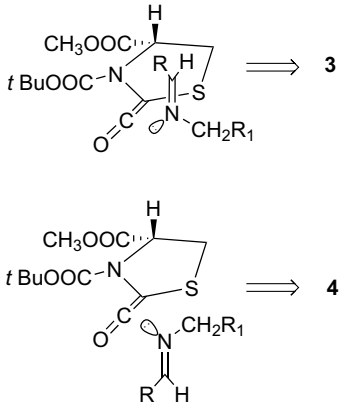


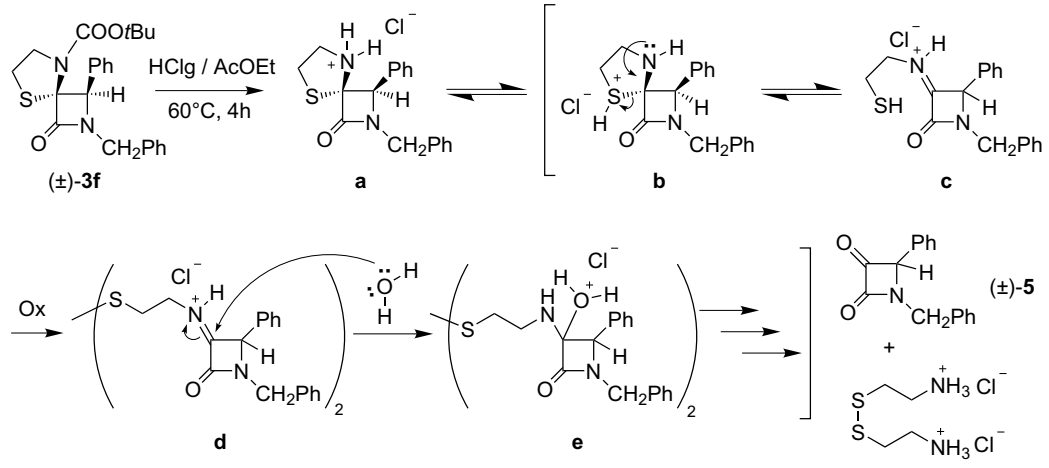
Figure 2.

The mechanism of the 1,3-thiazolidine ring opening was thoroughly studied on the more easily available spiro-β-lactam **3f**[8b] (Scheme 2) starting from the following observations: (i) the reaction took place only on the spiro-β-lactam deprotected at the thiazolidine-*N*-atom and as an ammonium salt; and (ii) an oxidant was necessary to complete the reaction. Our first experiments verified that when DMSO was used as a co-solvent, it acted as an oxidant because Me_2S was identified as a reduction product by means of ^1H and ^{13}C NMR analysis, and the cystamine dihydrochloride was recovered as an oxidation product. Moreover, the reaction did not run if DMF was used as co-solvent instead of DMSO.

Further observations showed that the spiro-β-lactam has to be present as an ammonium salt and not as a free base, however the nature of its counter-ion does not influence the course of the reaction as turning the chloride counter-ion into the non-nucleophile perchlorate anion did not change the result of the reaction, thus proving that the counter-ion is not involved in the mechanism.

As thiols can be transformed into disulfides by means of various oxidising agents,[13] we also changed the nature of the oxidant from the nucleophile DMSO[14] to the non-nucleophile oxidant I_2,[15] but the reaction still took place. We attempted some other oxidants (PCC, $Ca(OCl)_2$[16]) and also atmospheric oxygen,[17] obtaining the α-keto-β-lactam **5**[8b] with variable experimental conditions and in variable yields (Table 2).

We finally verified the role of water, whose presence is fundamental and influences the reaction rate.[16a] We observed that, if water is added to the reaction mixture as wet alu-



Scheme 2.

Table 2.

Entry	Oxidant	Experimental conditions	Yield (%)
1	DMSO	$CHCl_3$, 45 °C, 6 h	72
2	I_2	CH_2Cl_2, 40 °C, 97 h	95
3	I_2	CH_2Cl_2, wet Al_2O_3, 40 °C, 7 h	80
4	PCC/Al_2O_3	CH_3COCH_3, 50 °C, 100 h	20
5	$Ca(OCl)_2$	CH_3COCH_3, wet Al_2O_3, 50 °C, 100 h	10
6	O_2	$CHCl_3$, 25 °C, 30 days	99

mina, the transformation with I_2 is complete in only 7 h instead of 97 h (Table 2, entries 2 and 3): these experimental conditions proved to be the best, also given the easy work-up. On the basis of all these considerations, we now propose the mechanism shown in Scheme 2.

We hypothesise initial prototropy of the ammonium ion between the nitrogen (structure **a**) and the sulfur atoms (structure **b**) of the thiazolidine ring.[18] This equilibrium allows the donation of the nitrogen electron pair and consequently the opening of the thiazolidine ring (structure **c**). At this point, the presence of an oxidant capable of oxidising the thiol group to the corresponding disulfide (structure **d**) avoids ring closure and shifts the equilibrium to the right. Finally, the nucleophilic addition of water (derived from atmospheric moisture or deliberately introduced) gives the corresponding hemiaminal (structure **e**) that evolves to the α-keto-β-lactam and cysteamine dimer.

We subsequently applied this 1,3-thiazolidine ring oxidative cleavage to the enantiopure spiro-β-lactams **4b–d** using I_2 as an oxidant in the presence of wet Al_2O_3, and obtained the corresponding new enantiopure α-keto-β-lactams **5b–d** (Scheme 3) in fair to good yields due to their instability. For this reason it was not possible to determine their ee by means of HPLC analysis, but they were measured by ^{1}H NMR spectroscopy, using (+)-Eu(hfc)$_3$ as a chiral shift reagent. In this way, the ee of compounds **5b–d** was calculated to be more than 98% (±2) by comparison with the ^{1}H NMR spectra of the racemic α-keto-β-lactams obtained from the equimolar mixtures of the diastereoisomeric spiro-β-lactams **3–4b–d**.

Additionally, the absence of racemisation[19a] through a keto–enol tautomerism, which could be observed in certain situations,[19b] was confirmed by means of ^{1}H NMR spectra of compound **5c** recorded at temperature ranging from $T = -10$ °C to room temperature in CCl_4 solution.

Surprisingly, in the case of the enantiopure **3e** our protocol failed since the *N*-Boc-deprotected spiro-β-lactam resulted stable to the next oxidation step and it was recovered unchanged as confirmed by means of its MS spectra (M^+−HCl: 404). We ascribed this result to the presence of the basic thiazole nitrogen which could be involved in an intramolecular hydrogen bond with a proton of the thiazolidine ammonium group affording compound **a′** (Fig. 3).

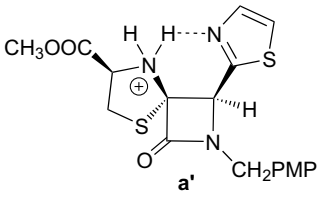


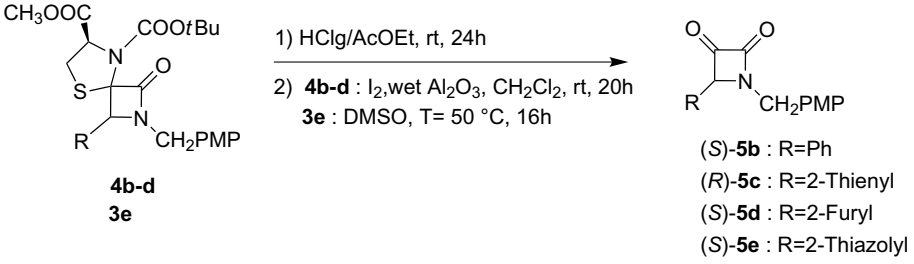
Figure 3.

This possibility was confirmed by an examination of the corresponding **a′** Dreiding Molecular Model, which pointed out the proximity of these two atoms and the possible formation of a stable six-membered ring. Under our usual experimental conditions the deprotection of thiazolidine-*N*-atom is carried out with an excess of gaseous HCl in ethyl acetate. During this first step the thiazole nitrogen atom is protonated but when, at the end of the reaction, the solvent is evaporated off, this weakly basic nitrogen[20] could lose HCl. The concomitant formation of the intramolecular hydrogen bond could prevent the *N–S* prototropy and the consequent oxidative cleavage (second step). To verify our hypothesis, we carried out the reaction on **3e** without the elimination of the excess of gaseous HCl and with the addition of DMSO as oxidant (see Section 4). Indeed, under these conditions, the corresponding α-keto-β-lactam **5e** was obtained (Scheme 3).

Finally we tried to deprotect the β-lactam-*N*-atom directly during the oxidative cleavage of the spiro-β-lactams with the aim of obtaining *N*-unsubstituted azetidin-2,3-diones, a class of compounds rarely present in the literature.[21,22] Unfortunately, starting from compounds **3b–c** and using CAN[23] or $Na_2S_2O_8$[24] as oxidant, we were unable to obtain the desired product because in all cases we observed the complete degradation of the spiro-β-lactam.

3. Conclusions

We have stereoselectively synthesised new enantiomerically pure 1,3-thiazolidine-derived 4-spiro-β-lactams substituted



Scheme 3.

with a heterocycle at the 3-position by reacting a non-symmetrical, optically active cyclic ketene with C-heterocyclic substituted imines. The reaction was stereoselective as only *trans*-diastereoisomers were obtained. The pairs of adducts were separated and transformed into the corresponding 4-heterocycle substituted azetidine-2,3-diones by means of a new oxidative cleavage of the 1,3-thiazolidine ring. The mechanism of this transformation was studied and completely clarified. In this way, by starting from the diastereoisomeric spiro-β-lactam **3** and/or **4**, it is possible to obtain both of the enantiomers of the corresponding α-keto-β-lactam **5**.

4. Experimental

4.1. General

Melting points were measured using a *Büchi* apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise specified) on a *Bruker AMX 300* spectrometer; chemical shifts (δ) are given in ppm relative to TMS and all of the coupling constants are in Hertz. Optical rotations were measured at 25 °C on a *Jasco P-1030* polarimeter. The MS spectra were determined using a *VG Analytical 7070 EQ* mass spectrometer with an attached *VG analytical 11/250* data system. The IR spectra were determined using a *Jasco FT-IR-4100* spectrometer, in cm^{-1}.

Compound (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1**[8c] was prepared according to the reported method.

4.2. General procedure for the synthesis of imines 2b–e

A mixture of carboxaldehyde (10 mmol), 4-methoxybenzylamine (10 mmol), dry dichloromethane (20 mL) and anhydrous sodium sulfate was stirred for 24 h at room temperature. The mixture was filtered and the filtrate evaporated to give the crude imines **2b–e**, which were judged >95% pure by ^{1}H NMR.

4.3. Benzylidene-(4-methoxybenzyl)-amine 2b[9]

Oil (95%); bp 150 °C/0.1 mmHg. ^{1}H NMR: δ 3.79 (3H, s, OCH_3); 4.77 (2H, s, CH_2); 6.89 (2H, d, $J = 8.6$, H_o-Bz); 7.26 (2H, d, $J = 8.6$, H_m-Bz); 7.41 (3H, m, Ph); 7.78 (2H, m, Ph); 8.37 (1H, s, CH). ^{13}C NMR: δ 55.11 (OCH_3); 64.31 (CH_2); 113.83, 128.13, 128.30, 128.89, 130.54, 131.31, 136.15, 158.61, 161.39. MS-EI (*m*/*z*): 225 (M^+), 139. IR (Nujol): 1643 ($\nu_{C=N}$).

4.4. (4-Methoxybenzyl)-thiophen-2-ylmethyleneamine 2c

Colourless solid (84%); mp 58–60 °C (*n*-hexane). ^{1}H NMR: δ 3.84 (3H, s, OCH_3); 4.78 (2H, s, CH_2); 6.93 (2H, d, $J = 8.6$, H_o-Bz); 7.11 (1H, dd, $J = 4.9$, 3.6, H_4-Thio); 7.28 (2H, d, $J = 8.6$, H_m-Bz); 7.36 (1H, d, $J = 3.6$, H_3-Thio); 7.44 (1H, d, $J = 4.9$, H_5-Thio); 8.46 (1H, s, CH). ^{13}C NMR: δ 55.19 (OCH_3); 63.75 (CH_2); 113.86; 127.25, 128.85, 129.19, 130.43, 131.03, 142.48, 154.68, 158.65. MS-EI (*m*/*z*): 231 (M^+), 121. IR (Nujol): 1626 ($\nu_{C=N}$).

4.5. Furan-2-ylmethylene-(4-methoxybenzyl)-amine 2d

Oil (70%); bp 175 °C/0.6 mmHg. ^{1}H NMR: δ 3.79 (3H, s, OCH_3); 4.72 (2H, s, CH_2); 6.46 (1H, dd, $J = 3.4$, 1.6, H_4-Fur); 6.76 (1H, d, $J = 3.4$, H_3-Fur); 6.88 (2H, d, $J = 8.6$, H_o-Bz); 7.24 (2H, d, $J = 8.6$, H_m-Bz); 7.5 (1H, d, $J = 1.6$, H_5-Fur); 8.13 (1H, s, CH). ^{13}C NMR: δ 54.94 (OCH_3); 64.18 (CH_2); 111.32, 113.66, 129.15, 130.62, 144.38, 149.72, 151.4, 158.49. MS-EI (*m*/*z*): 215 (M^+), 121. IR (Nujol): 1646 ($\nu_{C=N}$).

4.6. (4-Methoxybenzyl)-thiazol-2-ylmethyleneamine 2e

Oil (98%). ^{1}H NMR: δ 3.81 (3H, s, OCH_3); 4.82 (2H, s, CH_2); 6.7 (2H, d, $J = 8.7$, H_o-Bz); 7.23 (2H, d, $J = 8.7$, H_m-Bz); 7.41 (1H, dd, $J = 3.2$, 1.0, H_4-Thiaz); 7.92 (1H, d, $J = 3.2$, H_5-Thiaz); 8.49 (1H, d, $J = 1.0$, CH). ^{13}C NMR: δ 55.06 (OCH_3); 63.57 (CH_2); 113.59, 121.43, 129.3, 129.82, 143.76, 155.27, 158.74, 166.98. MS-EI (*m*/*z*): 232 (M^+), 121. IR (Nujol): 1640 ($\nu_{C=N}$).

4.7. General procedure for the reactions of 1 with 2b–e and Mukaiyama's reagent

A mixture of **1** (1.1 mmol), imine **2b–e** (1.0 mmol), 2-chloro-*N*-methylpyridium iodide (1.2 mmol) and Et_3N (3.0 mmol) in dry CH_2Cl_2 (15 mL) was heated at reflux temperature for 12–20 h under a nitrogen atmosphere. After cooling, the solution was washed with 5% aq HCl, 5% aq $NaHCO_3$ and then with H_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude products were purified by flash chromatography (SiO_2, *n*-hexane/AcOEt = 50:50).

4.8. (3*R*,4*R*,7*R*)-2-(4-Methoxybenzyl)-1-oxo-3-phenyl-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 3b

(Yield: 35%). Amorphous solid. $[\alpha]_D^{20} = -154.8$ (*c* 0.64, $CHCl_3$). ^{1}H NMR (DMSO-d_6, $T = 80$ °C): δ 1.19 (s, 9H, $(CH_3)_3C$), 3.30 (dd, 1H, H-6, $J_{gem} = 12.6$, $J_{vic} = 1.2$); 3.67 (s, 3H, $COOCH_3$); 3.69 (dd, 1H, H-6, $J_{gem} = 12.6$, $J_{vic} = 7.8$); 3.78 (s, 3H, OCH_3); 4.24 (d, 1H, CH_2Ph, $J = 15.0$); 4.32 (d, 1H, H-7, $J = 6.8$); 4.74 (s, 1H, H-3); 4.83 (d, 1H, CH_2Ph, $J = 15.0$); 6.91 (d, 2H, CH_2*Ph*, $J = 8.6$); 7.17 (d, 2H, CH_2*Ph*, $J = 8.6$); 7.28–7.34 (m, 5H, Ph). ^{13}C NMR show the presence of rotamers about the carbamate bond: δ 27.7 (q, $(CH_3)_3C$); 31.8, 32.7 (t, C-6); 44.6, 44.9 (t, CH_2Ph); 52.5 (q, $COOCH_3$); 55.1 (q, OCH_3); 63.1, 64.0 (d, C-7); 75.0 (d, C-3); 81.3 (s, $(CH_3)_3C$); 83.2, 83.8 (s, C-4); 113.0–151.0 (Ph); 159.2, 164.0, 170.3 (s, CO). IR (Nujol): 1711 (ν_{CO}, NCO*t*Bu, N–CO), 1774 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.51; H 5.95; N, 5.55. MS-FAB$^+$ (*m*/*z*): 498 (M^+), 443, 335, 277, 235.

4.9. (3*S*,4*S*,7*R*)-2-(4-Methoxybenzyl)-1-oxo-3-phenyl-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 4b

(Yield: 27%) Amorphous solid. $[\alpha]_D^{20} = +46.9$ (*c* 0.71, $CHCl_3$). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.31 (s, 9H, $(CH_3)_3C$), 3.26 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 7.1$); 3.41 (s, 3H, $COOCH_3$); 3.45 (dd, 1H, H-6, $J_{gem} = 11.7$, $J_{vic} = 6.6$); 3.78 (s, 3H, OCH_3); 4.13 (d, 1H, CH_2Ph, $J = 15.0$); 4.67 (s, 1H, H-3); 4.7 (t, 1H, H-7, $J = 6.9$); 4.79 (d, 1H, CH_2Ph, $J = 15.0$); 6.89 (d, 2H, CH_2Ph, $J = 8.6$); 7.12 (d, 2H, CH_2Ph, $J = 8.6$); 7.31–7.41 (m, 5H, Ph). ^{13}C NMR show the presence of rotamers about the carbamate bond: δ 27.7 (q, (CH_3)$_3$C); 31.5, 32.3 (t, C-6); 44.2 (t, CH_2Ph); 52.1 (q, $COOCH_3$); 55.1 (q, OCH_3); 65.1, 65.6 (d, C-7); 73.6, 74.2 (d, C-3); 82.0 (s, $(CH_3)_3C$); 83.7 (s, C-4); 112.4–151.2 (Ph); 159.2, 164.9, 170.0 (s, CO). IR (Nujol): 1712 (ν_{CO}, NCOO*t*Bu, N–CO), 1770 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.55; H 5.93; N, 5.60. MS-FAB$^+$ (*m*/*z*): 498 (M^+), 443, 399, 335, 277, 235.

4.10. (3*S*,4*R*,7*R*)-2-(4-Methoxybenzyl)-1-oxo-3-thiophen-2-yl-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 3c

(Yield: 28%). Amorphous solid. $[\alpha]_D^{20} = -176.6$ (*c* 0.56, $CHCl_3$). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.27 (s, 9H, $(CH_3)_3C$), 3.32 (d, 1H, H-6, $J_{gem} = 12.6$); 3.60 (dd, 1H, H-6, $J_{gem} = 12.6$, $J_{vic} = 7.7$); 3.69 (s, 3H, $COOCH_3$); 3.78 (s, 3H, OCH_3); 4.22 (d, 1H, CH_2Ph, $J = 15.1$); 4.45 (d, 1H, H-7, $J = 7.7$); 4.81 (d, 1H, CH_2Ph, $J = 15.1$); 4.88 (s, 1H, H-3); 6.92 (d, 2H, CH_2Ph, $J = 8.6$); 7.0–7.04 (m, 2H, H-3, H-4 Thioph); 7.18 (d, 2H, CH_2Ph, $J = 8.6$); 7.5 (dd, 1H, H-5 Thioph, $J = 4.3$, 2.0). ^{13}C NMR show the presence of rotamers about the carbamate bond: δ 27.8 (q, (CH_3)$_3$C); 31.8, 32.6 (t, C-6); 44.3 (t, CH_2Ph); 52.5 (q, $COOCH_3$); 55.1 (q, OCH_3); 63.1, 63.9 (d, C-7); 70.6 (d, C-3); 81.3 (s, $(CH_3)_3C$); 81.5, 83.1 (s, C-4); 113.0–151.3 (Ph + Thioph); 159.1, 163.3, 170.3 (s, CO). IR (Nujol): 1713 (ν_{CO}, NCOO*t*Bu, N–CO), 1775 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{24}H_{28}N_2O_6S_2$: C, 57.14; H, 5.55; N, 5.55. Found: C, 57.06; H 5.37; N, 5.45. MS-FAB$^+$ (*m*/*z*): 504 (M^+), 449, 405, 283, 242.

4.11. (3*R*,4*S*,7*R*)-2-(4-Methoxybenzyl)-1-oxo-3-thiophen-2-yl-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 4c

(Yield: 49%) Amorphous solid. $[\alpha]_D^{20} = +50.5$ (*c* 0.92, $CHCl_3$). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.39 (s, 9H, $(CH_3)_3C$), 3.22 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 7.3$); 3.42 (s, 3H, $COOCH_3$); 3.44 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 6.6$); 3.78 (s, 3H, OCH_3); 4.09 (d, 1H, CH_2Ph, $J = 15.1$); 4.71 (d, 1H, CH_2Ph, $J = 15.1$); 4.8 (t, 1H, H-7, $J = 6.9$); 4.88 (s, 1H, H-3); 6.91 (d, 2H, CH_2Ph, $J = 8.6$); 7.04 (dd, 1H, H-4 Thioph, $J = 5.0$, 3.8); 7.12 (d, 2H, CH_2Ph, $J = 8.6$); 7.2 (d, 1H, H-3 Thioph, $J = 3.8$); 7.53 (d, 1H, H-5 Thioph, $J = 5.0$). ^{13}C NMR show the presence of rotamers about the carbamate bond: δ 27.6, 27.9 (q, (CH_3)$_3$C); 32.3, 33.0 (t, C-6); 43.9 (t, CH_2Ph); 52.3 (q, $COOCH_3$); 55.1 (q, OCH_3); 64.9 (d, C-7); 69.1, 69.6 (d, C-3); 82.2 (s, $(CH_3)_3C$); 83.7 (s, C-4); 113.0–151.1 (Ph + Thioph); 159.2, 164.1, 170.0 (s, CO). IR (Nujol): 1712 (ν_{CO}, NCOO*t*Bu, N–CO), 1769 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{24}H_{28}N_2O_6S_2$: C, 57.14; H, 5.55; N, 5.55. Found: C, 57.08; H 5.47; N, 5.52. MS-FAB$^+$ (*m*/*z*): 504 (M^+), 449, 405, 283, 242.

4.12. (1*R*,4*R*,7*R*)-1-Furan-2-yl-2-(4-methoxybenzyl)-3-oxo-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 3d

(Yield: 28%). Oil. $[\alpha]_D^{20} = -80.1$ (*c* 0.14, $CHCl_3$). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.27 (s, 9H, $(CH_3)_3C$), 3.28 (d, 1H, H-6, $J_{gem} = 12.5$); 3.50 (dd, 1H, H-6, $J_{gem} = 12.5$, $J_{vic} = 7.5$); 3.66 (s, 3H, $COOCH_3$); 3.75 (s, 3H, OCH_3); 4.19 (d, 1H, CH_2Ph, $J = 15.1$); 4.41 (d, 1H, H-7, $J = 7.5$); 4.64 (s, 1H, H-3); 4.71 (d, 1H, CH_2Ph, $J = 15.1$); 6.29 (d, 1H, H-3 Fur, $J = 3.3$); 6.39 (dd, 1H, H-4 Fur, $J = 3.3$, 1.9); 6.88 (d, 2H, CH_2Ph, $J = 8.6$); 7.14 (d, 2H, CH_2Ph, $J = 8.6$); 7.54 (d, 1H, H-5 Fur, $J = 1.9$). ^{13}C NMR show the presence of rotamers about the carbamate bond: δ 28.1 (q, (CH_3)$_3$C); 32.1, 32.9 (t, C-6); 44.6, 44.8 (t, CH_2Ph); 52.9 (q, $COOCH_3$); 55.6 (q, OCH_3); 63.6, 64.3 (d, C-7); 68.9, 69.1 (d, C-3); 81.3 (s, $(CH_3)_3C$); 83.1 (s, C-4); 110.1–145.0 (Ph + Fur); 159.8, 163.2, 170.8 (s, CO). IR (Nujol): 1711 (ν_{CO}, NCOO*t*Bu, N–CO), 1772 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{24}H_{28}N_2O_7S$: C, 59.02; H, 5.74; N, 5.74. Found: C, 58.89; H 5.65; N, 5.70. MS-FAB$^+$ (*m*/*z*): 488 (M^+), 410, 387, 354, 325, 267.

4.13. (1*S*,4*S*,7*R*)-1-Furan-2-yl-2-(4-methoxybenzyl)-3-oxo-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 4d

(Yield: 32%). Oil. $[\alpha]_D^{20} = +15.0$ (*c* 1.02, $CHCl_3$). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.40 (s, 9H, $(CH_3)_3C$), 3.22 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 6.6$); 3.45 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 6.4$); 3.53 (s, 3H, $COOCH_3$); 3.79 (s, 3H, OCH_3); 4.11 (d, 1H, CH_2Ph, $J = 15.2$); 4.66 (s, 1H, H-3); 4.68 (d, 1H, CH_2Ph, $J = 15.2$); 4.86 (t, 1H, H-7, $J = 6.6$); 6.44 (dd, 1H, H-4 Fur, $J = 3.3$, 1.7); 6.50 (d, 1H, H-3 Fur, $J = 3.3$); 6.90 (d, 2H, CH_2Ph, $J = 8.6$); 7.14 (d, 2H, CH_2Ph, $J = 8.6$); 7.56 (d, 1H, H-5 Fur, $J = 1.7$). ^{13}C NMR show the presence of rotamers about the carbamate bond: δ 27.8, 28.1 (q, (CH_3)$_3$C); 32.1, 32.7 (t, C-6); 44.1, 44.4 (t, CH_2Ph); 52.9 (q, $COOCH_3$); 55.5 (q, OCH_3); 65.1, 65.5 (d, C-7); 66.3, 67.8 (d, C-3); 82.6 (s, $(CH_3)_3C$); 83.5 (s, C-4); 109.3–149.1 (Ph + Fur); 160.2, 163.1, 171.0 (s, CO). IR (Nujol): 1709 (ν_{CO}, NCOO*t*Bu, N–CO), 1772 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{24}H_{28}N_2O_7S$: C, 59.02; H, 5.74; N, 5.74. Found: C, 58.95; H 5.68; N, 5.71. MS-FAB$^+$ (*m*/*z*): 488 (M^+), 387, 325, 267.

4.14. (3*S*,4*R*,7*R*)-2-(4-Methoxy-benzyl)-1-oxo-3-thiazol-2-yl-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 3e

(Yield: 50%). Amorphous solid. $[\alpha]_D^{20} = -149.1$ (*c* 0.83, $CHCl_3$). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.21 (s, 9H, $(CH_3)_3C$), 3.38 (dd, 1H, H-6, $J_{gem} = 12.4$, $J_{vic} = 1.0$); 3.66 (dd, 1H, H-6, $J_{gem} = 12.4$, $J_{vic} = 7.6$); 3.70 (s, 3H, $COOCH_3$); 3.79 (s, 3H, OCH_3); 4.45 (d, 1H, CH_2Ph,

$J = 15.0$); 4.54 (d, 1H, H-7, $J = 7.6$); 4.88 (d, 1H, CH_2Ph, $J = 15.0$); 4.93 (s, 1H, H-3); 6.93 (d, 2H, CH_2Ph, $J = 8.6$); 7.24 (d, 2H, CH_2Ph, $J = 8.6$); 7.69 (d, 1H, H-4 Thiaz, $J = 3.2$); 7.83 (d, 1H, H-5 Thiaz, $J = 3.2$). ^{13}C NMR shows the presence of rotamers about the carbamate bond: δ 27.1, 27.5 (q, (CH_3)$_3$C); 31.8, 32.5 (t, C-6); 44.7 (t, CH_2Ph); 52.3 (q, $COOCH_3$); 54.9 (q, OCH_3); 62.9, 63.6 (d, C-7); 70.5, 71.0 (d, C-3); 81.3 (s, (CH_3)$_3C$); 82.6 (s, C-4); 112.3–150.9 (Ph + Thiaz); 159.0, 163.6, 169.6 (s, CO). IR (Nujol): 1708 (ν_{CO}, NCOO*t*Bu, N–CO), 1775 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{23}H_{27}N_3O_6S_2$: C, 54.65; H, 5.35; N, 8.32. Found: C, 54.44; H 5.27; N, 8.15. MS-FAB$^+$ (*m*/*z*): 505 (M^+), 450, 406, 284, 242.

4.15. (3*R*,4*S*,7*R*)-2-(4-Methoxy-benzyl)-1-oxo-3-thiazol-2-yl-5-thia-2,8-diazaspiro[3.4]octane-7,8-dicarboxylic acid 8-*tert*-butyl ester 7-methyl ester 4e

(Yield: 22%). Amorphous solid. $[\alpha]_D^{20} = +35.1$ (*c* 0.79, $CHCl_3$). ^{1}H NMR (DMSO-d_6, $T = 80$ °C): δ 1.38 (s, 9H, (CH_3)$_3$C), 3.25 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 6.9$); 3.49 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 6.6$); 3.50 (s, 3H, $COOCH_3$); 3.78 (s, 3H, OCH_3); 4.27 (d, 1H, CH_2Ph, $J = 15.0$); 4.75 (d, 1H, CH_2Ph, $J = 15.0$); 4.85 (t, 1H, H-7, $J = 6.7$); 4.99 (s, 1H, H-3); 6.90 (d, 2H, CH_2Ph, $J = 8.7$); 7.14 (d, 2H, CH_2Ph, $J = 8.7$); 7.72 (d, 1H, H-4 Thiaz, $J = 3.2$); 7.82 (d, 1H, H-5 Thiaz, $J = 3.2$). ^{13}C NMR shows the presence of rotamers about the carbamate bond: δ 27.4, 27.8 (q, (CH_3)$_3$C); 31.9, 32.4 (t, C-6); 44.6 (t, CH_2Ph); 52.4 (q, $COOCH_3$); 55.1 (q, OCH_3); 64.7, 65.1 (d, C-7); 69.8, 71.4 (d, C-3); 82.4 (s, (CH_3)$_3C$); 83.67(s, C-4); 113.6–151.9 (Ph + Thiaz); 159.2, 164.1, 169.6 (s, CO). IR (Nujol): 1708 (ν_{CO}, NCOO*t*Bu, N–CO), 1775 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{23}H_{27}N_3O_6S_2$: C, 54.65; H, 5.35; N, 8.32. Found: C, 54.52; H 5.19; N, 8.23. MS-FAB$^+$ (*m*/*z*): 505 (M^+), 450, 406, 284, 242.

4.16. General procedure for the oxidative thiazolidine ring opening of spiro-β-lactams 4b–d

A solution of spiro-β-lactams **4b–d** (1 mmol) in 10 mL of 1 M HCl_g in AcOEt was stirred at room temperature for 24 h under a nitrogen atmosphere. After the evaporation of the solvent, the residue was treated with 10 mL of CH_2Cl_2, I_2 (2 mmol) and wet Al_2O_3 (1.0 g) at room temperature for 20 h. The alumina was filtered off and the organic solvent was washed with 10% aq $Na_2S_2O_3$ and then with H_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Monobactams **5b–d** were purified as indicated below.

4.17. Procedure for the oxidative thiazolidine ring opening of spiro-β-lactam 3e

A solution of spiro-β-lactams **3e** (0.15 mmol) in 5 ml of 1 M HCl_g in AcOEt was stirred at room temperature for 24 h under a nitrogen atmosphere. DMSO (0.2 mL) was added and the mixture was heated at $T = 50$ °C for 16 h. After the evaporation of the solvent, the residue was treated with CH_2Cl_2 and washed with a saturated aqueous NaCl solution. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Monobactam **5e** was purified as indicated below.

4.18. (*S*)-1-(4-Methoxybenzyl)-4-phenyl-azetidine-2,3-dione 5b

Colourless solid (75%); mp 58–60 °C (CCl_4/(*iso*Pr)$_2$O). $[\alpha]_D^{20} = +17.5$ (*c* 0.64, CH_2Cl_2). ^{1}H NMR: δ 3.79 (s, 3H, OCH_3); 4.11 (d, 1H, CH_2Ph, $J = 14.6$); 4.87 (s, 1H, H-4); 5.14 (d, 1H, CH_2Ph, $J = 14.6$); 6.85 (d, 2H, CH_2Ph, $J = 8.7$); 7.09 (d, 2H, CH_2Ph, $J = 8.7$); 7.3–7.5 (m, 5H, Ph). ^{13}C NMR: δ 45.1 (t, CH_2Ph); 55.5 (q, OCH_3); 73.8 (d, C-4); 113.8–131.6 (Ph); 160.2, 193.8 (s, CO). IR (Nujol): 1745, 1822 (ν_{CO}). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.60; H, 5.34; N, 4.98. Found: C, 72.55; H 5.23; N, 4.88. MS-FAB$^+$ (*m*/*z*): 281 (M^+), 221.

4.19. (*R*)-1-(4-Methoxybenzyl)-4-thiophen-2-yl-azetidine-2,3-dione 5c

Purified by means of column chromatography (SiO_2, hexane/AcOEt = 7:3). Colourless solid (55%); mp 128–130 °C (CCl_4). $[\alpha]_D^{20} = +84.9$ (*c* 0.17, $CHCl_3$). ^{1}H NMR: δ 3.82 (s, 3H, OCH_3); 4.19 (d, 1H, CH_2Ph, $J = 14.3$); 5.16 (s, 1H, H-4); 5.25 (d, 1H, CH_2Ph, $J = 14.3$); 6.99 (d, 2H, CH_2Ph, $J = 8.5$); 7.16 (d, 1H, H-3 Thioph, $J = 3.4$); 7.22 (t, 1H, H-4 Thioph, $J = 4.8$); 7.31 (d, 2H, CH_2Ph, $J = 8.5$); 7.52 (d, 1H, H-5 Thioph, $J = 5.0$). ^{13}C NMR: δ 45.2 (t, CH_2Ph); 55.7 (q, OCH_3); 69.2 (d, C-4); 114.6–130.6 (Ph + Thioph); 162.5, 189.8 (s, CO). IR (Nujol): 1756, 1820 (ν_{CO}). Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.72; H, 4.53; N, 4.88. Found: C, 62.58; H 4.44; N, 4.76. MS-FAB$^+$ (*m*/*z*): 287 (M^+), 230, 219.

4.20. (*S*)-4-Furan-2-yl-1-(4-methoxybenzyl)-azetidine-2,3-dione 5d

Purified by means of column chromatography (SiO_2, hexane/AcOEt = 1:1). (Yield: 34%). Amorphous solid. $[\alpha]_D^{20} = +38.4$ (*c* 0.42, CH_2Cl_2). ^{1}H NMR: δ 3.85 (s, 3H, OCH_3); 4.24 (d, 1H, CH_2Ph, $J = 14.7$); 5.0 (s, 1H, H-4); 5.1 (d, 1H, CH_2Ph, $J = 14.7$); 6.39 (d, 1H, H-3 Fur, $J = 3.3$); 6.43 (t, 1H, H-4 Fur, $J = 3.2$); 6.91 (d, 2H, CH_2Ph, $J = 8.6$); 7.18 (d, 2H, CH_2Ph, $J = 8.6$); 7.46 (br s, 1H, H-5 Fur). ^{13}C NMR: δ 46.3 (t, CH_2Ph); 55.3 (q, OCH_3); 67.3 (d, C-4); 109.8–131.1 (Ph + Fur); 159.5, 195.5 (s, CO). IR (Nujol): 1749, 1821 (ν_{CO}). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.80; N, 5.17. Found: C, 66.28; H 4.64; N, 4.97. MS-FAB$^+$ (*m*/*z*): 271 (M^+), 213.

4.21. (*S*)-1-(4-Methoxybenzyl)-4-thiazol-2-yl-azetidine-2,3-dione 5e

Purified by means of column chromatography (SiO_2, toluene/AcOEt = 75:25). (Yield: 30%). Amorphous solid. $[\alpha]_D^{20} = -20.7$ (*c* 0.52, CH_2Cl_2). ^{1}H NMR: δ 3.80 (s, 3H, OCH_3); 4.39 (d, 1H, CH_2Ph, $J = 15.0$); 4.77 (s, 1H, H-4); 4.93 (d, 1H, CH_2Ph, $J = 15.0$); 6.80 (d, 2H, CH_2Ph, $J = 8.6$); 7.21 (d, 2H, CH_2Ph, $J = 8.6$); 7.46 (d, 1H, H-4 Thiaz, $J = 3.2$); 7.83 (d, 1H, H-5 Thiaz, $J = 3.2$). IR (Nujol): 1741, 1820 (ν_{CO}). Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C,

58.33; H, 4.17; N, 9.72. Found: C, 58.24; H 4.04; N, 9.56. MS-FAB$^+$ (m/z): 288 (M^+), 230.

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