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Asymmetric synthesis of 1,3-thiazolidine-derived spiro-β-lactams via a Staudinger reaction between chiral ketenes and imines

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Abstract—Enantiomerically pure 1,3-thiazolidine-derived spiro-β-lactams were stereoselectively synthesised by means of a Staudinger ketene–imine reaction starting from optically active *N*-Boc-1,3-thiazolidine-2-carboxylic acid derivatives and imines. The reactions were stereoselective and afforded spiro-β-lactams with a relative *trans*-configuration. The absolute configuration of the new stereocentres was assigned on the basis of the well-accepted mechanism and confirmed by means of the X-ray crystal structure analysis. The spiro-β-lactams were transformed into enantiomerically pure chiral monocyclic β-lactams by opening the thiazolidine ring and recovering the chiral auxiliary.

1. Introduction

The stereoselective synthesis of β-lactams has received considerable attention over recent years and, in particular, asymmetric synthesis through a Staudinger reaction between a ketene and an imine has been extensively and successfully studied.[1] This is related to the renewed and growing interest in such heterocycles[2] because of their use in organic chemistry and recent discoveries of their biological activities as, for example, cholesterol absorption inhibitors,[3] thrombin inhibitors[4] and anti-hyperglycemic agents.[5]

More specifically, spiro-β-lactams are interesting because they can act as antiviral,[6] antibacterial agents[7] and also inhibit cholesterol absorption.[8] They are also β-turn mimetics,[9] with 4-spiro-β-lactams in particular being synthetic precursors of cyclic α,α-disubstituted β-amino acids and peptide derivatives.[10] The synthesis of 4-spiro-β-lactams has therefore received particular attention[11] because conformationally constrained amino acids and derived peptides may have valuable biological properties.

Continuing our studies of the synthesis[12] and reactivity[13] of spiro-β-lactams, we have recently reported the synthesis of new 1,3-thiazolidine-derived 4-spiro-β-lactams **3** and **4a–g** obtained by means of a Staudinger ketene–imine reaction between imines **2a–d** and the non-symmetrical cyclic ketenes α generated from *N*-acyl-1,3-thiazolidine-2-carboxylic acids **1a–c** by means of Mukaiyama's reagent (Scheme 1).[14]

Our interest in compounds **3** and **4** is based on the presence of the 2-spiro fused thiazolidine ring, which can be opened to obtain α-keto-β-lactams.[14b] The reactions afforded mixtures of diastereoisomeric 4-spiro-β-lactams **3** and **4** in a ratio depending on imine-nitrogen nucleophilicity and, therefore, the nature of the R_1 substituent. When the nitrogen atom was substituted with an electron-withdrawing group ($R_1 = PhSO_2$) the ratio was in favour of products **4** with a relative *cis*-configuration between the sulfur atom and *C*-phenyl group (**3**/**4** = 3/97). However when R_1 was an electron-donor group (e.g., $PhCH_2$), the principal products were compounds **3** with a relative *trans*-configuration (**3**/**4** = 68–93/32–7). This

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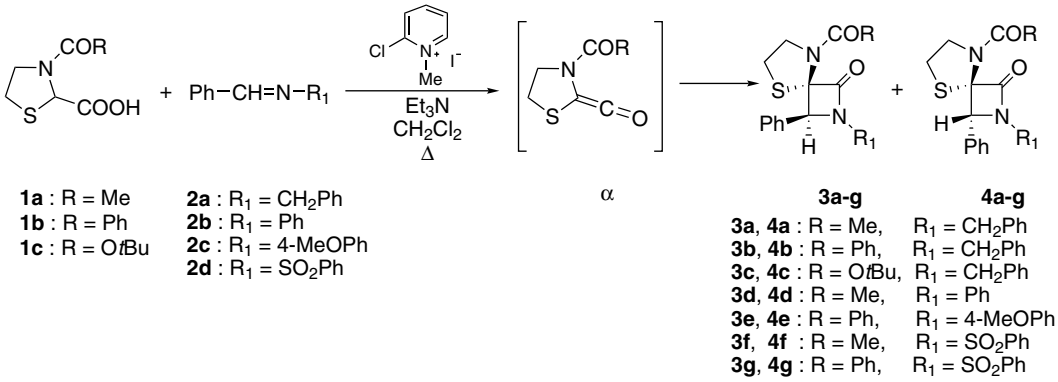


Scheme 1.

suggested that a different mechanism operates in the two cases.[14b]

In this context, and in view of the growing interest in the synthesis of enantiopure β-lactams, we planned the asymmetric synthesis of chiral, non-racemic 1,3-thiazolidine-derived spiro-β-lactams using the Staudinger reaction. Chiral ketenes or chiral imines are viable options for achieving asymmetric induction, although some catalytic approaches have recently been developed.[15]

We have previously reported a stereoselective synthesis of spiro-β-lactams obtained from *N*-(phenylmethylene)benzenesulfonammide **2d** and the ketene generated from (2*S*,4*R*)-4-acyloxy-*N*-acyl-L-prolines in the presence of acetic anhydride. In this case the stereocentre at the 4-position of the proline induced complete stereoselectivity for the new C-4 spiranic stereocentre, but not for the C-3 stereocentre: the imine attacks the ketene exclusively from the less hindered side of the proline ring, thus leading to a mixture of the *cis*- and *trans*-isomer with an (*S*)-absolute configuration at the C-4 spiranic carbon.[12a] We have also used chiral imines that bear a stereocentre in the α-position at the nitrogen atom, but the degree of diastereo- and enantioselectivity was low.[16]

Bearing in mind these previous results, we synthesised enantiomerically pure 1,3-thiazolidine-derived spiro-β-lactams by means of a Staudinger ketene–imine reaction using optically active *N*-Boc-1,3-thiazolidine-2-carboxylic acid derivatives **1d** and **1e** as the precursors of non-symmetrical chiral cyclic ketenes (Fig. 1).

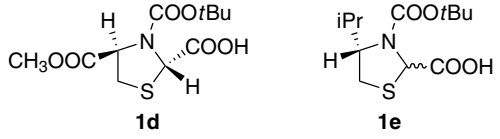


Figure 1.

2. Results and discussion

As amino acids **1a**–**c** have been synthesised by condensing the glyoxylic acid with cysteamine followed by N-acylation,[17] we decided to put a stereocentre at the 4-position of the thiazolidine ring. This meant using a 2-substituted-cysteamine (Fig. 2), the most widely available of which is the (*R*)-cysteine methyl ester.

The (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1d** was synthesised as described in Scheme 2.

(*R*)-Cysteine methyl ester hydrochloride and glyossilic acid were reacted in the presence of pyridine and, after 24 h at room temperature, afforded a mixture of the two amino acid diastereoisomers (2*S*,4*R*)-**1** and (2*R*,4*R*)-**1′** in a ratio of 58:42, as determined by ^{1}H NMR spectroscopy. Crystallisation of the mixture from water only allowed us to obtain the diastereoisomer *trans*-**1**. The relative (and subsequently absolute) configurations were assigned to compounds **1** and **1′** by comparing the proton chemical shifts with those reported for the corresponding 1,3-thiazolidine-2,4-dicarboxylic acids.[18] This assignment was confirmed by means of NOE experiments using a mixture of the two diastereoisomers insofar as it was not possible to isolate the more soluble diastereoisomer **1′** because the two compounds are in equilibrium.[18] The NOE experiments revealed a relationship between H-2 and H-4 in the less abundant diastereoisomer **1′** thus confirming a relative *cis*-configuration. Subsequently, compound **1** was treated with $(BOC)_2O$ to afford **1d**. The *N*-Boc protecting group was introduced on the thiazolidine-2-carboxylic acid in

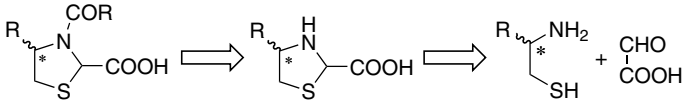
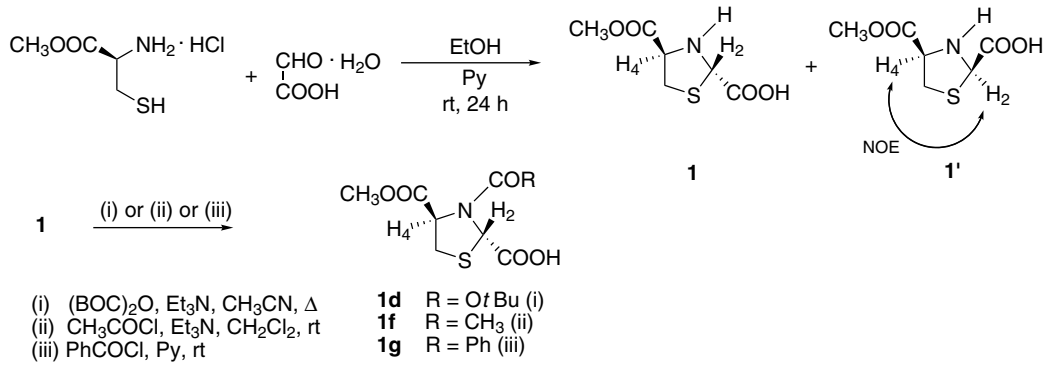


Figure 2.



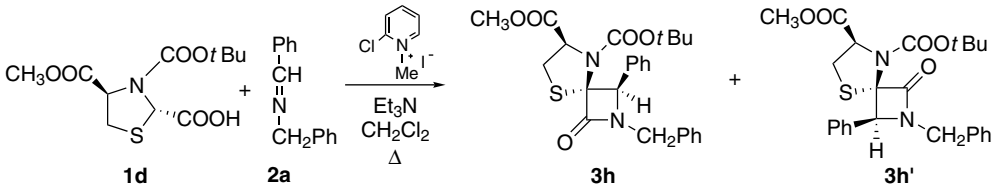
Scheme 2.

order to remove it and facilitate the opening of the ring.[14b]

The reaction of an equimolar quantity of amino acid **1d**, imine **2a** and 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) in the presence of triethylamine in refluxing CH_2Cl_2 for 8 h gave the spiro-β-lactams as a 1.8:1 mixture of diastereoisomers **3h** and **3h′**, which were separated by means of column chromatography (Scheme 3).

The relative configuration of C-3 and C-4 of the azetidinone ring was established by comparing the ^1H NMR spectra with those of the previously obtained compounds.[14] The ^1H NMR spectra were complicated by the existence of rotamers (64:36 ratio) arising from the *N*-Boc group, and so were recorded at 80 °C in DMSO-d_6. The Staudinger reaction proceeded with total stereoselectivity, giving both the β-lactams with a relative *cis*-disposition of *N*-Boc and the phenyl group (*trans* according to the CIP rules).

The absolute configuration of the stereocentres of spiro-β-lactams was assigned on the basis of the generally accepted mechanism of the Staudinger ketene–imine reaction. According to experimental and theoretical studies,[11,19] with a nucleophilic imine such as (*E*)-**2a**, this [2+2] ketene–imine cycloaddition is a two-step reaction leading to the formation of a zwitterionic intermediate. The mechanism involves the attack of the imine lone pair from the less hindered side of the ketene opposite the *N*-acyl group. The presence of a stereocentre in the ketene differentiates the two faces of the thiazolidine ring and, depending on which face is attacked, allows



Scheme 3.

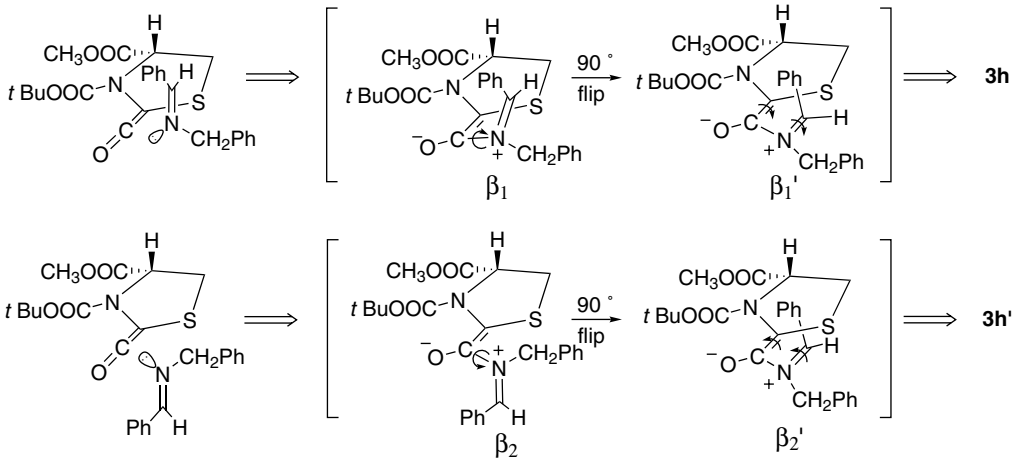


Figure 3.

the zwitterionic intermediates β_1 or β_2 to be obtained. After a 90° flip to the corresponding β_1' and β_2', the conrotatory ring-closure of these zwitterionic intermediates leads to β-lactams **3h** and **3h′**, which, respectively, have the absolute (3*R*,4*R*,7*R*)- and (3*S*,4*S*,7*R*)-configurations (Fig. 3).

There was therefore also an asymmetric induction because the diastereoisomer **3h** derives from the attack of the imine on the face of the ketene opposite the 4-methoxycarbonyl group. These assignments were confirmed by means of the X-ray structure determination of the more abundant diastereoisomer **3h** (Fig. 4).

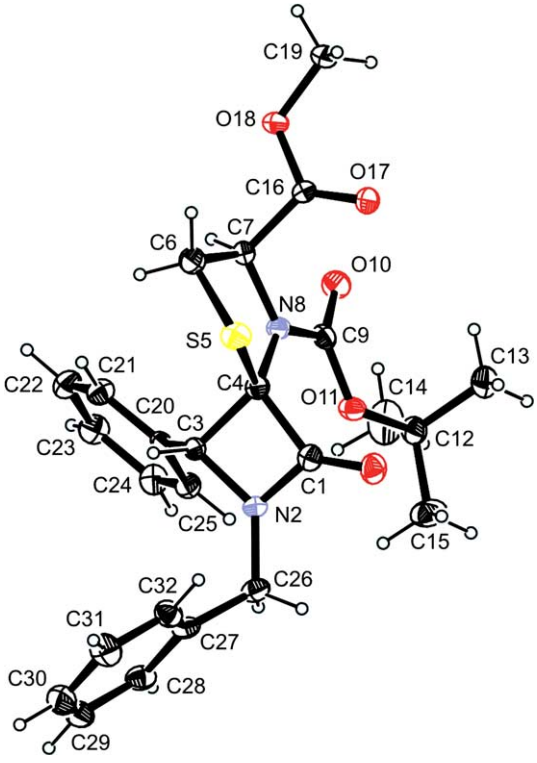
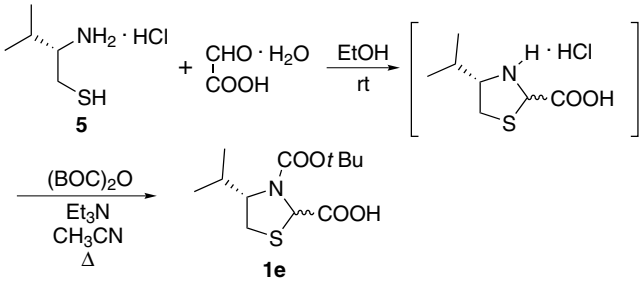


Figure 4. ORTEP plot of **3h** with atom numbering scheme. Displacement ellipsoids at 20% probability level.

A similar result was obtained using the (4*S*)-4-(1-methylethyl)-1,3-thiazolidine-2,3-dicarboxylic acid 3-(1,1-dimethylethyl) ester **1e**, which has a substituent with different electronic and steric properties. Product **1e** was prepared by condensing (2*S*)-2-(1-methylethyl)-cysteamine hydrochloride[20] **5** and glyoxylic acid, followed by treatment with $(BOC)_2O$ (Scheme 4).

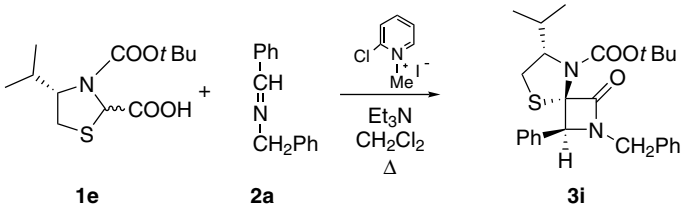


Scheme 4.

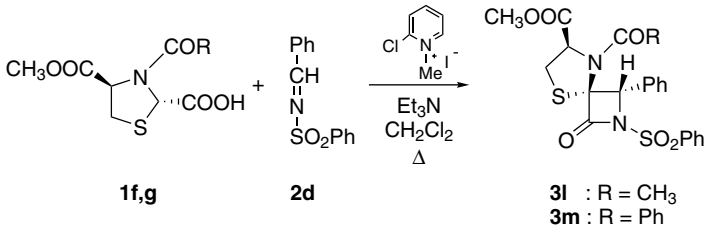
^{1}H NMR analysis showed that a single diastereoisomer was obtained, but its relative configuration was not determined because the stereochemistry at C-2 of the thiazolidine ring is lost during the cycloaddition. The reaction of **1e** and imine **2a** under the usual experimental conditions affords a single diastereoisomer **3i**, to which the absolute (3*S*,4*S*,7*S*)-configuration was assigned on the basis of the ^{1}H NMR spectra and the above mechanistic considerations (Scheme 5).

As previously reported,[11b,c] the Staudinger ketene–imine reaction depends on the steric hindrance of the ketene intermediate. In our cycloadditions, we also noted a decrease in the total yield going from the 4-unsubstituted 1,3-thiazolidine-2-carboxylic acid (91%)[14b] to the more encumbered 4-substituted 1,3-thiazolidine-2-carboxylic acid (63% for **1d** and 42% for **1e**). On the other hand, the presence of this substituent makes the reactions more diastereoselective because a 100:0 = *trans*:*cis* ratio was obtained. Furthermore, the formation of only one spiro-β-lactam in the reaction of **1e** shows that the isopropyl group generates a greater steric hindrance than the methoxycarbonyl group on the thiazolidine ring.

Amino acids **1d** and **1e** were also reacted with *N*-(phenylmethylene)benzenesulfonamide **2d**, but no spiro-β-lactams were detected in the reaction mixtures. With this electron-poor imine, a concerted [2+2] cycloaddition rather than a two-step mechanism mainly affording the *cis*-isomer was proposed to explain the opposite diastereoselectivity with substrates **1a** and **b**.[14b] The complete lack of reactivity may be due to the fact that a concerted mechanism prevents an approach between the imine and the more crowded ketenes derived from **1d** and **1e** (with both the *N*-Boc and 4-methoxycarbonyl or 4-*iso*-propyl groups present). To confirm this hypothesis, amino acid **1** was transformed into the 3-acetyl **1f** and 3-benzoyl **1g** derivatives using conventional methods (Scheme 2), and reacted with imine **2d**. The reactions afforded spiro-β-



Scheme 5.



Scheme 6.

lactams **3l** and **3m** in only 8% and 5% yield, respectively, thus showing a close relationship with the steric hindrance of the N-substituent (Scheme 6).

The relative *cis*-configuration was assigned to compounds **3l** and **3m** on the basis of the ^{1}H NMR spectra. It was not possible to determine the absolute configuration but the (3*S*,4*R*,7*R*) configuration was proposed on the basis of an attack of the imine on the face of the ketene opposite the 4-metoxycarbonyl group,[14b] as already verified in our previous research.[12c]

Finally, our protocol for opening the thiazolidine ring[14b] was applied to spiro-β-lactams **3h** and **3h′**, which were, respectively, transformed into the corresponding (4*R*)-4-phenyl-1-(phenylmethyl)azetidine-2,3-dione **7** and (4*S*)-4-phenyl-1-(phenylmethyl)azetidine-2,3-dione **7′**. In this transformation, we observed a steric influence of the methoxycarbonyl group on the reaction times: compound **3h** was deprotected at the thiazolidine-*N*-atom under anhydrous conditions with gaseous HCl in AcOEt to 60 °C for 24 h, thus affording the corresponding spiro-β-lactam hydrochloride **6** (Scheme 7).

After heating **6** to 60 °C in a $CHCl_3$/DMSO solution for 60 h, the (4*R*)-4-phenyl-1-(phenylmethyl) azetidine-2,3-dione **7** was obtained in 58% total yield from **3h**; similarly, the spiro-β-lactam **3h′** afforded **7′** in a 54% total yield. The enantiomeric excess of β-lactams **7** and **7′** (and therefore the absence of epimerisation during the transformation or a keto-enol tautomerism) were determined by means of ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as a chiral shift reagent.

In this way, both of the enantiomers of this useful β-lactam[21] were synthesised for the first time. Furthermore, the (*R*)-cystine dimethyl ester dihydrochloride could be recycled as a chiral auxiliary after its reduction to (*R*)-cysteine methyl ester hydrochloride.[22] This method is a mild and general procedure for the preparation of monocyclic azetidine-2,3-diones, which are useful intermediates in organic synthesis.

3. Conclusions

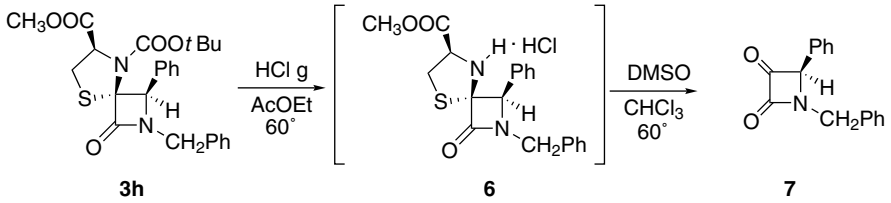
We stereoselectively synthesised enantiomerically pure 1,3-thiazolidine-derived spiro-β-lactams by means of the [2+2] cycloaddition reaction of non-symmetrical, optically active cyclic ketenes with an imine, thus confirming the generality of the reported 1,3-thiazolidine-derived spiro-β-lactam synthesis. The presence of the stereocentre afforded complete diastereoselectivity (only *trans* diastereoisomers) and enantioselectivity (with substrate **1e**). When two stereoisomers were obtained (substrate **1d**), they were separated and transformed into the enantiomer pair of 4-phenyl-1-(phenylmethyl)azetidine-2,3-dione. In this way, the Staudinger ketene–imine cycloaddition, followed by thiazolidine ring cleavage, proved to be a general method for obtaining these heterocycles.

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 AC 300 spectrometer; chemical shifts (δ) are given in parts per million relative to TMS and all of the coupling constants are in Hertz. Optical rotation values were measured at 25 °C on a Perkin–Elmer 241 spectropolarimeter. 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 Perkin–Elmer 1725X FT-IR spectrometer in reciprocal centimetres.

Compound (2*S*)-2-(1-methylethyl)-cysteamine hydrochloride **5**[20] was prepared according to the reported method. Imines **2a** and **d**, 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) and the shift reagent (+)-Eu(hfc)$_3$ were obtained from commercial sources.



Scheme 7.

4.2. (2*S*,4*R*)-1,3-Thiazolidine-2,4-dicarboxylic acid 4-methyl ester, 1

To a stirred solution of (*R*)-cysteine methyl ester hydrochloride (4 g, 23.3 mmol) and glyoxylic acid monohydrate (2.15 g, 23.3 mmol) in ethyl alcohol (50 mL), pyridine (3.76 mL, 46.6 mmol) was added. After being stirred for 24 h at room temperature, the solvent was evaporated off and the residue treated with water: the crystalline mass was filtered and dried. Product **1** was obtained as a colourless solid (2.85 g, 64%). Mp 133–134 °C. ^{1}H NMR: δ 3.07 (dd, 1H, H-5, $J_{gem} = 10.5$, $J_{vic} = 5.3$); 3.18 (dd, 1H, H-5, $J_{gem} = 10.5$, $J_{vic} = 6.7$); 3.72 (s, 3H, OCH_3); 4.41 (t, 1H, H-4, $J = 6.0$); 5.04 (s, 1H, H-2). ^{13}C NMR: δ 36.7 (t, C-5); 52.0 (q, OCH_3); 65.3 (d, C-4); 65.8 (d, C-2); 171.1, 171.9 (s, CO). $[\alpha]_D^{20} = -216.8$ (*c* 1.03, CH_3OH). IR (Nujol): 1703 (ν_{CO}, COOH), 1742 (ν_{CO}, $COOCH_3$), 3220 (ν_{OH}). Anal. Calcd for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33. Found: C, 37.67; H, 4.76; N, 7.40. MS-EI (*m*/*z*): 191 (M^+), 160, 146, 132, 59, 45.

4.3. (2*S*,4*R*)-1,3-Thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester, 1d

A mixture of **1** (1.2 g, 6.28 mmol), $(BOC)_2O$ (2.74 g, 12.56 mmol) and Et_3N (1.74 mL, 12.56 mmol) in 40 mL of acetonitrile was refluxed for 7 h. After evaporation of the solvent, the residue was treated with 30 mL of a cold 5% aq HCl solution and extracted with toluene. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Compound **1d** was obtained as an amorphous solid (1.68 g, 92%). ^{1}H and ^{13}C NMR show the presence of rotamers about the carbamate bond in a 79:21 ratio. ^{1}H NMR: δ 1.38 (s, 9H, $(CH_3)_3C$); 3.15 (d, 1H, H-5, $J_{gem} = 12.5$); 3.39 (dd, 1H, H-5, $J_{gem} = 12.5$, $J_{vic} = 7.2$); 3.73, 3.85 (s, 3H, OCH_3); 4.95, 5.03 (m, 1H, H-4); 5.25, 5.30 (s, 1H, H-2). ^{13}C NMR: δ 28.0, 28.3 (q, $(CH_3)_3C$); 32.5, 33.8 (t, C-5); 52.7 (q, OCH_3); 59.7, 60.4 (d, C-4); 62.4, 62.7 (d, C-2); 82.3 ($(CH_3)_3C$); 170.4, 173.7, 174.3 (s, CO). $[\alpha]_D^{20} = -72.7$ (*c* 0.22, CH_3OH). IR (Nujol): 1660 (ν_{CO}, N–CO); 1708 (ν_{CO}, COOH), 1741 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{11}H_{17}NO_6S$: C, 45.36; H, 5.84; N, 4.81. Found: C, 45.31; H, 5.63; N, 4.70. MS-FAB$^+$ (*m*/*z*): 291 (M^+), 247, 192.

4.4. (4*S*)-4-(1-Methylethyl)-1,3-thiazolidine-2,3-dicarboxylic acid 3-(1,1-dimethylethyl) ester, 1e

To a stirred solution of (2*S*)-2-(1-methylethyl)-cysteamine hydrochloride **5** (1.0 g, 6.42 mmol) in ethyl alcohol (25 mL), glyoxylic acid monohydrate (0.59 g, 6.42 mmol) was added under a nitrogen atmosphere. After 24 h at room temperature, the solvent was evaporated off and the residue treated with water and dichloromethane. The aqueous phase was separated and evaporated affording (4*S*)-4-(1-methylethyl)-1,3-thiazolidine-2-carboxylic acid hydrochloride as a yellow oil, which was used without further purification (1.23 g, 90%). A mixture of this compound (1.23 g, 5.8 mmol), $(BOC)_2O$ (2.54 g, 11.6 mmol) and Et_3N (1.78 mL, 12.76 mmol) in 70 mL of acetonitrile was refluxed for 7 h. After evaporation of the solvent, the residue was treated with 30 mL of a cold 10% aq HCl solution and extracted with toluene. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue yellow oil was treated with dichloromethane and a 5% aq $NaHCO_3$ solution. The aqueous phase was separated, acidified with acetic acid and extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Compound **1e** was obtained as a pale yellow oil (0.72 g, 45%). ^{1}H NMR: δ 0.87 (d, 3H, $(CH_3)_2C$, $J = 6.7$); 0.97 (d, 3H, $(CH_3)_2C$, $J = 6.7$); 1.39 (s, 9H, $(CH_3)_3C$); 2.05 (m, 1H, $CH(CH_3)_2$); 2.91 (dd, 1H, H-5, $J_{gem} = 11.3$, $J_{vic} = 6.6$); 2.99 (dd, 1H, H-5, $J_{gem} = 11.3$, $J_{vic} = 6.2$); 4.06 (m, 1H, H-4); 5.39 (s, 1H, H-2). $[\alpha]_D^{20} = 56.4$ (*c* 0.15, CH_3OH). IR (Nujol): 1650 (ν_{CO}, N–CO); 1710 (ν_{CO}, COOH). Anal. Calcd for $C_{12}H_{21}NO_4S$: C, 52.36; H, 7.64; N, 5.09. Found: C, 52.31; H, 7.44; N, 4.95.

4.5. (2*S*,4*R*)-3-Acetyl-1,3-thiazolidine-2,4-dicarboxylic acid 4-methyl ester, 1f

To a stirred suspension of acid **1** (1.5 g, 7.85 mmol) in dichloromethane (8 mL), Et_3N (2.4 mL, 17.3 mmol) was added, after which acetyl chloride (0.62 mL, 8.65 mmol) in dichloromethane (4 mL) was added dropwise. The obtained solution was stirred for 24 h. After evaporation of the solvent, the residue was treated with 15 mL of 10% aq HCl. The precipitate was filtered and recrystallised from *i*-PrOH–*i*-Pr_2O to afford a colourless solid (1.05 g, 56%). Mp 186–188 °C. ^{1}H and ^{13}C NMR show the presence of rotamers about the amide bond in a 72:28 ratio. ^{1}H NMR: δ 2.14, 2.16 (s, 3H, $COCH_3$); 3.21, 3.42 (d, 1H, H-5, $J = 12.3$, 11.9); 3.60, 3.70 (dd, 1H, H-5, $J_{gem} = 12.3$, 11.9, $J_{vic} = 6.3$, 7.2); 3.78, 3.85 (s, 3H, OCH_3); 4.93, 5.17 (d, 1H, H-4, $J = 7.2$, 6.3); 5.33, 5.39 (s, 1H, H-2). ^{13}C NMR: (DMSO-d_6) δ 22.3, 23.0 (q, $COCH_3$); 32.3, 34.3 (t, C-5); 52.6, 53.3 (q, OCH_3); 60.8 (d, C-4); 62.5, 63.3 (d, C-2); 168.7, 169.6, 170.2, 170.7, 171.2, 171.9 (s, CO). $[\alpha]_D^{20} = -133.0$ (*c* 0.79, CH_3OH). IR (Nujol): 1610 (ν_{CO}, N–CO); 1725 (ν_{CO}, COOH), 1738 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_8H_{11}NO_5S$: C, 41.20; H, 4.75; N, 6.01. Found: C, 41.15; H, 4.53; N, 5.92. MS-EI (*m*/*z*): 188 (M^+−COOH), 174, 146.

4.6. (2*S*,4*R*)-3-Benzoyl-1,3-thiazolidine-2,4-dicarboxylic acid 4-methyl ester, 1g

To a stirred solution of acid **1** (1.0 g, 5.2 mmol) in pyridine (4 mL), benzoyl chloride (0.6 mL, 5.2 mmol) was added dropwise. The obtained solution was stirred at room temperature for 18 h. After evaporation of the solvent, the residue was treated with 10% aq HCl and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CH_2Cl_2/CH_3OH = 98/2$–$50/50$). Product **1g** was obtained as a colourless solid after recrystallisation from trichloroethylene (1.07 g, 70%). Mp 143–145 °C. ^{1}H NMR: δ 3.30 (d, 1H, H-5, $J = 11.9$); 3.64 (dd, 1H, H-5, $J_{gem} = 11.9$, $J_{vic} = 6.4$);

3.71 (s, 3H, OCH_3); 4.84 (d, 1H, H-4, $J = 6.4$); 5.58 (s, 1H, H-2); 7.42 (s, 5H, Ph). ^{13}C NMR show the presence of rotamers about the amide bond: (DMSO-d_6) δ 31.7, 33.8 (t, C-5); 51.8, 52.6 (q, OCH_3); 60.2, 61.1 (d, C-4); 62.3, 64.0 (d, C-2); 126.3–132.8 (Ph); 166.5, 168.6, 170.5 (s, CO). $[\alpha]_D^{20} = 191.9$ (c 1.03, CH_3OH). IR (Nujol): 1644 (ν_{CO}, N–CO); 1697 (ν_{CO}, COOH), 1742 (ν_{CO}, $COOCH_3$). Anal. Calcd for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74. Found: C, 52.58; H, 4.24; N, 4.73. MS-EI (m/z): 295 (M^+), 264, 250, 236, 190.

4.7. General procedure for the reactions of 1d–g with 2a and 2d and Mukaiyama's reagent

A mixture of **1d**–**g** (1.0 mmol), imine **2a** and **2d** (1.0 mmol), 2-chloro-*N*-methylpyridium iodide (1.16 mmol) and Et_3N (3.0 mmol) in dry CH_2Cl_2 (15 mL) was heated at reflux temperature for 8–12 h under a nitrogen atmosphere. After cooling, the solution was washed with H_2O, 5% aq HCl, and then with H_2O. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by column chromatography (SiO_2, toluene/AcOEt = 95:5) and recrystallised as indicated.

4.8. (3*R*,4*R*,7*R*)-8-(*tert*-Butoxycarbonyl)-7-methoxycarbonyl-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3,4]octan-1-one, 3h

(Yield: 40.5%). Mp 108–109 °C (*i*-Pr_2O). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.17 (s, 9H, $(CH_3)_3C$), 3.31 (dd, 1H, H-6, $J_{gem} = 12.6$, $J_{vic} = 1.1$); 3.65 (s, 3H, OCH_3); 3.69 (dd, 1H, H-6, $J_{gem} = 12.6$, $J_{vic} = 7.8$); 4.30 (d, 1H, CH_2Ph, $J = 15.2$); 4.30 (d, 1H, H-7, $J = 7.1$); 4.75 (s, 1H, H-3); 4.92 (d, 1H, CH_2Ph, $J = 15.2$); 7.24–7.38 (m, 10H, Ph). ^{13}C NMR show the presence of rotamers about the carbamate bond in a 64:36 ratio: δ 27.7 (q, $(CH_3)_3C$); 31.8, 32.7 (t, C-6); 45.2, 45.6 (t, CH_2Ph); 52.5 (q, OCH_3); 63.3, 64.1 (d, C-7); 75.3 (d, C-3); 81.4 (s, $(CH_3)_3C$); 83.2 (s, C-4); 125.9–134.9 (Ph); 151.1, 164.1, 170.4 (s, CO). $[\alpha]_D^{20} = -180.2$ (c 0.95, $CHCl_3$). IR (Nujol): 1690 (ν_{CO}, NCO*t*-Bu), 1766 (ν_{CO}, $COOCH_3$, N–CO). Anal. Calcd for $C_{25}H_{28}N_2O_5S$: C, 64.08; H, 6.02; N, 5.98. Found: C, 63.81; H, 5.89; N, 5.85. MS-FAB$^+$ (m/z): 469 (M^+), 413, 367, 335, 309, 277. Single crystals suitable for X-ray structure determination were obtained by precipitation from *i*-Pr_2O.

4.9. (3*S*,4*S*,7*R*)-8-(*tert*-Butoxycarbonyl)-7-methoxycarbonyl-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3,4]octan-1-one, 3h′

(Yield: 22.5%). Mp 102–103 °C (*i*-Pr_2O/hexane). ^1H NMR (DMSO-d_6, $T = 80$ °C): δ 1.31 (s, 9H, $(CH_3)_3C$), 3.25 (dd, 1H, H-6, $J_{gem} = 11.7$, $J_{vic} = 7.1$); 3.39 (s, 3H, OCH_3); 3.44 (dd, 1H, H-6, $J_{gem} = 11.7$, $J_{vic} = 6.7$); 4.19 (d, 1H, CH_2Ph, $J = 15.2$); 4.70 (s, 1H, H-3); 4.75 (t, 1H, H-7, $J = 6.9$); 4.80 (d, 1H, CH_2Ph, $J = 15.2$); 7.20–7.40 (m, 10H, Ph). ^{13}C NMR show the presence of rotamers about the carbamate bond in a 66:34 ratio: δ 28.3 (q, $(CH_3)_3C$); 32.0, 32.9 (t, C-6); 45.3 (t, CH_2Ph); 52.5 (q, OCH_3); 65.0, 65.6 (d, C-7); 74.3, 74.9 (d, C-3); 82.6 (s, $(CH_3)_3C$); 83.9 (s, C-4); 127.1–135.2 (Ph); 151.8, 165.9, 170.5 (s, CO). $[\alpha]_D^{20} = +59.6$ (c 0.98, $CHCl_3$). IR (Nujol): 1690 (ν_{CO}, NCO*t*-Bu), 1747 (ν_{CO}, $COOCH_3$), 1766 (ν_{CO}, N–CO). Anal. Calcd for $C_{25}H_{28}N_2O_5S$: C, 64.08; H, 6.02; N, 5.98. Found: C, 64.95; H, 5.92; N, 5.95. MS-FAB$^+$ (m/z): 469 (M^+), 413, 367, 335, 309, 277.

4.10. (3*S*,4*S*,7*S*)-8-(*tert*-Butoxycarbonyl)-7-(1-methylethyl)-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3,4]octan-1-one, 3i

(Yield: 42%). Mp 120–121 °C (*i*-Pr_2O/hexane). ^1H NMR: δ 0.83 (d, 3H, $(CH_3)_2CH$, $J = 7.0$); 0.93 (d, 3H, $(CH_3)_2CH$, $J = 7.0$); 1.22 (s, 9H, $(CH_3)_3C$); 2.49 (m, 1H, $(CH_3)_2CH$); 2.96 (d, 1H, H-6, $J = 12.0$); 3.23 (dd, 1H, H-6, $J_{gem} = 12.0$, $J_{vic} = 7.1$); 3.87 (dd, 1H, H-7, $J = 7.1$, 4.4); 4.23 (d, 1H, CH_2Ph, $J = 15.0$); 4.75 (s, 1H, H-3); 5.21 (d, 1H, CH_2Ph, $J = 15.0$); 7.23–7.56 (m, 10H, Ph). ^{13}C NMR: δ 17.7 (q, $(CH_3)_2CH$); 20.1 (q, $(CH_3)_2CH$); 27.8 (q, $(CH_3)_3C$); 30.2 (t, C-6); 30.5 (d, $(CH_3)_2CH$); 45.7 (t, CH_2Ph); 66.7 (d, C-7); 75.0 (d, C-3); 81.1 (s, $(CH_3)_3C$); 84.0 (s, C-4); 126.1–135.0 (Ph); 151.8, 166.4 (s, CO). $[\alpha]_D^{20} = +159.2$ (c 1.03, $CHCl_3$). IR (Nujol): 1694 (ν_{CO}, NCO*t*-Bu), 1772 (ν_{CO}, N–CO). Anal. Calcd for $C_{26}H_{32}N_2O_3S$: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.92; H, 7.05; N, 6.15. MS-ESI (m/z): 475 (M^++Na), 397, 375.

4.11. (3*S*,4*R*,7*R*)-8-Acetyl-7-methoxycarbonyl-3-phenyl-2-(phenylsulfonyl)-5-thia-2,8-diazaspiro[3,4]octan-1-one, 3l

Oil. (Yield: 8%). ^1H NMR: δ 2.07 (s, 3H, $COCH_3$); 2.77 (dd, 1H, H-6, $J_{gem} = 11.8$, $J_{vic} = 6.0$); 3.05 (d, 1H, H-6, $J = 11.8$); 3.81 (s, 3H, OCH_3); 4.67 (d, 1H, H-7, $J = 6.0$); 5.51 (s, 1H, H-3); 7.23–7.39 (m, 5H, Ph); 7.56 (t, 2H, H_mPhSO_2); 7.69 (t, 1H, H_pPhSO_2); 8.00 (d, 2H, H_oPhSO_2). Anal. Calcd for $C_{21}H_{20}N_2O_6S_2$: C, 54.77; H, 4.38; N, 6.08. Found: C, 54.65; H, 4.30; N, 5.92.

4.12. (3*S*,4*R*,7*R*)-8-Benzoyl-7-methoxycarbonyl-3-phenyl-2-(phenylsulfonyl)-5-thia-2,8-diazaspiro[3,4]octan-1-one, 3m

(Yield: 5%). Mp 221–223 °C (Toluene). ^1H NMR: δ 2.91 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 5.8$); 3.11 (dd, 1H, H-6, $J_{gem} = 11.6$, $J_{vic} = 2.5$); 3.63 (s, 3H, OCH_3); 4.85 (dd, 1H, H-7, $J_{gem} = 5.8$, $J_{vic} = 2.5$); 5.66 (s, 1H, H-3); 7.28–7.47 (m, 10H, Ph); 7.57 (t, 2H, H_mPhSO_2); 7.69 (t, 1H, H_pPhSO_2); 8.06 (d, 2H, H_oPhSO_2). ^{13}C NMR: δ 32.7 (t, C-6); 53.1 (q, OCH_3); 66.0 (d, C-7); 67.9 (d, C-3); 86.6 (s, C-4); 127.5–137.4 (Ph); 163.2, 168.8, 170.3 (s, CO). $[\alpha]_D^{20} = -85.3$ (c 0.30, $CHCl_3$). IR (Nujol): 1663 (ν_{CO}, N–COPh); 1747 (ν_{CO}, $COOCH_3$), 1806 (ν_{CO}, N–CO). Anal. Calcd for $C_{26}H_{22}N_2O_6S_2$: C, 59.76; H, 4.24; N, 5.36. Found: C, 59.69; H, 4.10; N, 5.13. MS-EI (m/z): 522 (M^+), 491, 463, 417, 381.

4.13. (4*R*)-4-Phenyl-1-(phenylmethyl) azetidine-2,3-dione, 7

A solution of **3h** (200 mg, 0.43 mmol) in 8 mL of 2 M HCl in AcOEt, was heated at 60 °C for 24 h under

a nitrogen atmosphere. After evaporation of the solvent, the residue was treated with 10 mL of $CHCl_3$ and 0.1 mL of DMSO and heated at 60 °C for 60 h. After evaporation of the solvent, the residue was treated with a mixture of methyl alcohol/diethyl ether and (*R*)-cystine dimethyl ester dihydrochloride was collected by filtration (81 mg, 55%). The solution was evaporated to dryness and compound **7** purified by flash chromatography (SiO_2, hexane/AcOEt = 3/1). Product **7** was obtained as an oil (63 mg, 58%). ^1H NMR: δ 4.1 (d, 1H, CH_2, $J = 14.5$); 4.85 (s, 1H, H-4); 5.13 (d, 1H, CH_2, $J = 14.5$); 7.11–7.32 (m, 10H, Ph). ^{13}C NMR: δ 45.7 (t, CH_2); 73.8 (d, C-4); 126.4–133.7 (Ph); 164.0, 202.0 (CO). $[\alpha]_D^{20} = -21.9$ (*c* 0.59, $CHCl_3$), Ee >99% [^1H NMR with (+)-Eu(hfc)$_3$]. IR (Nujol): 1743 (ν_{CO}, CO-3); 1825 (ν_{CO}, CO-2). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.31; H, 5.01; N, 5.42. MS-FAB$^+$ (*m*/*z*): 252 (M^+), 194.

4.14. (4*S*)-4-Phenyl-1-(phenylmethyl) azetidine-2,3-dione, 7′

(Yield 54%). ^1H NMR: δ 4.12 (d, 1H, CH_2, $J = 14.4$); 4.85 (s, 1H, H-4); 5.12 (d, 1H, CH_2, $J = 14.4$); 7.10–7.32 (m, 10H, Ph). ^{13}C NMR: δ 45.8 (t, CH_2); 73.7 (d, C-4); 126.4–133.7 (Ph); 164.0, 202.0 (CO). $[\alpha]_D^{20} = +20.35$ (*c* 0.50, $CHCl_3$), Ee >99% [^1H NMR with (+)-Eu(hfc)$_3$]. IR (Nujol): 1740 (ν_{CO}, CO-3); 1822 (ν_{CO}, CO-2). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.28; H, 5.00; N, 5.33. MS-FAB$^+$ (*m*/*z*): 252 (M^+), 194.

4.15. Single crystal X-ray structural determination of 3h

The intensity data for **3h** were collected on a Bruker Smart Apex CCD area detector using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data reduction was made using SAINT programs; absorption corrections based on multiscan were obtained by SADABS.[23] The structures were solved by SIR-92[24] and refined on F^2 by full-matrix least-squares using SHELXL-97.[25] All the non-hydrogen atoms were refined anisotropically, hydrogen atoms were included as 'riding' and not refined. The ORTEP-III program was used for molecular diagrams.[26]

Crystal data and results of the refinement: colourless plate $0.35 \times 0.32 \times 0.05$ mm, $M_r = 468.55$, orthorhombic, space group $P2_12_12_1$, $a = 10.722(2)$ Å, $b = 14.398(3)$ Å, $c = 15.979(3)$ Å, $V = 2466.9(9)$ Å^3, $Z = 4$, $T = 293(2)$ K, $\mu = 0.168$ mm^{-1}. 30,123 measured reflections, 4859 independent reflections, 4084 reflections with $I > 2\sigma(I)$, $3.80° < 2\theta < 52.00°$, $R_{int} = 0.0777$. Refinement on 4859 reflections, 298 parameters. Flack parameter[27] for determination of the absolute configuration = 0.09(11). Final $R = 0.0578$, $wR = 0.1272$ for data with $F^2 > 2\sigma(F^2)$, $S = 1.099$, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.18$, $\Delta\rho_{min} = -0.20$ e Å^{-3}. The puckering analysis[28] of the five-membered ring gives the parameters $Q = 0.478(3)$ Å, $\varphi = 322.3(4)°$, corresponding to a nearly envelope conformation.

Crystallographic data (excluding structure factors) for **3h** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 279055. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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