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Highly chemoselective reactions on hindered sulfamidates with oxygenated nucleophiles

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Abstract—Although the chemoselectivity problems in substitution reactions, which arise from the use of oxygenated nucleophiles in a basic medium by generating anionic species are well-known, we report herein a highly chemoselective ring-opening reaction of hindered cyclic sulfamidates with O-nucleophiles. The reaction occurs with the inversion of configuration at the quaternary centre, allowing the stereoselective synthesis of an important class of $\beta^{2,2}$-amino acids, namely O-substituted α-methylisoserines.

1. Introduction

The important role that five-membered cyclic sulfamidates play in organic synthesis is due to the fact that most intermolecular ring-opening reactions of these systems with nucleophiles proceed by the S_N2 pathway.[1] Although the synthesis and reactivity of these type of sulfamidates have been described in detail,[2,3] little is known about hindered sulfamidates.[4] On this basis, and considering the importance of chiral compounds with quaternary carbon centres,[5] we have recently reported the behaviour of sulfamidates (*R*)-**1a**,**b** with several nucleophiles. Taking into account that within these chiral building blocks, the quaternary carbon centre is activated for nucleophilic displacement, the S_N2 reactivity with several nucleophiles (sulfur derivatives, azide, fluoride, benzoate, cyanide) in a basic medium was explored.[6] Further hydrolysis of the ring opened products allowed us to obtain interesting chiral α,α-disubstituted β-amino acids, namely $\beta^{2,2}$-amino acids[6,7] (Fig. 1).

Nevertheless, when basic nucleophiles were used, a competitive reaction pathway was observed which corresponded to the β-elimination process that allows the synthesis of α-unsaturated β-amino acid derivatives, which could also be obtained from these sulfamidates using a base in the absence of a nucleophile[6a] (Fig. 1).

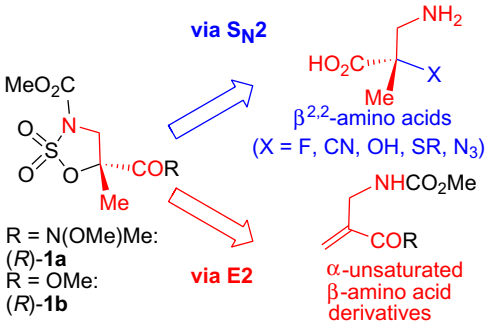

Figure 1. Reactions of chiral building blocks (*R*)-**1a**,**b**.

On the other hand, since Seebach and other authors discovered that β-peptides displayed interesting biological properties, the field of β-amino acids is a matter of continuous interest.[8]

Particularly attractive are the chiral $\beta^{2,2}$-amino acids,[9] since they bear a quaternary stereocentre at the α-position. In this context, the isoserine derivatives have received exceptional attention due to their implications as peptidomimetic units[10] and as important targets in the synthesis of β-lactams and of Taxol® analogues (taxoids).[11]

2. Results and discussion

Bearing these facts in mind, we focused our attention on O-substituted α-methylisoserine derivatives. Indeed, one

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of the best methods to obtain these compounds would involve the ring-opening reaction of the aforementioned hindered sulfamidates with oxygen nucleophiles (O-nucleophiles), although the problems arising from their use in a basic medium are well-known. It is important to notice that although we have reported the S_N2 reactivity of these hindered sulfamidates with several nucleophiles, only one example has been described with O-nucleophiles.[6a] As a result of this, we decided to undertake an in-depth study into the behaviour of five-membered cyclic sulfamidates (*R*)-**1a**,**b** with several O-nucleophiles under different basic conditions. (Table 1).

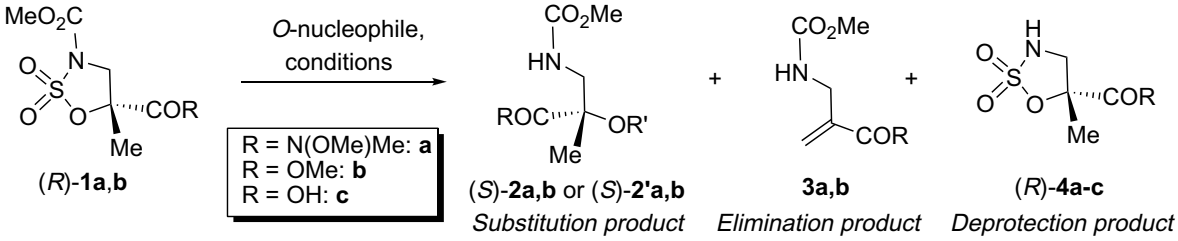
Taking into account the good results previously obtained with sulfamidate (*R*)-**1b** and cesium *p*-nitrobenzoate[6a] (Table 1, entry 2), we assayed the same reaction with sulfamidate (*R*)-**1a**. Now, the above-mentioned elimination was observed, giving a mixture of substitution and elimination products (*S*)-**2a** and **3a**, respectively (Table 1, entry 1). Other O-nucleophiles under similar conditions were tested, also giving a mixture of products in different proportions.

It is important to note that the elimination products **3a** and **3b** can be exclusively obtained carrying out the reaction of sulfamidates (*R*)-**1a**,**b** with DBU at reflux in THF (Table 1, entries 3 and 4).[6a] In contrast, when KOH, LiOH, MeONa or BnONa were used in H_2O, MeOH/H_2O or THF none of the above reactions were observed and we only obtained deprotection products (*R*)-**4a**–**c** (Table 1, entries 6–8 and 11–13). Particularly interesting is the selectivity observed by using 1.1 or 10.0 equiv of LiOH in MeOH/H_2O (3:2), allowing the synthesis of sulfamidates (*R*)-**4a** or (*R*)-**4c**, respectively (Table 1, entries 7 and 8). Curiously, mixtures of elimination and deprotection products **3a**/(*R*)-**4a** were observed in the reaction of sulfamidate (*R*)-**1a** with bases such as NMe_4OH, ^{t}BuOK or MeONa, when DMF was used as a solvent (Table 1, entries 5, 9 and 10, respectively).

When we carried out the reaction of sulfamidate (*R*)-**1a** with PhONa, using DMF as a solvent, followed by acid hydrolysis, we obtained a mixture of the substitution product (*S*)-**2′a**, elimination product **3a** and carbamate group deprotection product (*R*)-**4a** (Table 1, entry 14). Fortunately, this problem was solved by changing the amide group to an ester group in the sulfamidate, therefore when using sulfamidate (*R*)-**1b** instead of (*R*)-**1a**, only the substitution product (*S*)-**2′b** was obtained (Table 1, entry 15). Therefore, the ester or amide substituent of the sulfamidate is responsible for the chemoselectivity observed; the ester group favours the substitution reaction pathway.

Taking into account the importance of these types of five-membered cyclic sulfamidates as chiral building blocks in the synthesis of interesting organic compounds that bear quaternary stereocentres,[6,7] this study allows easy access to differently protected and unprotected cyclic sulfamidate

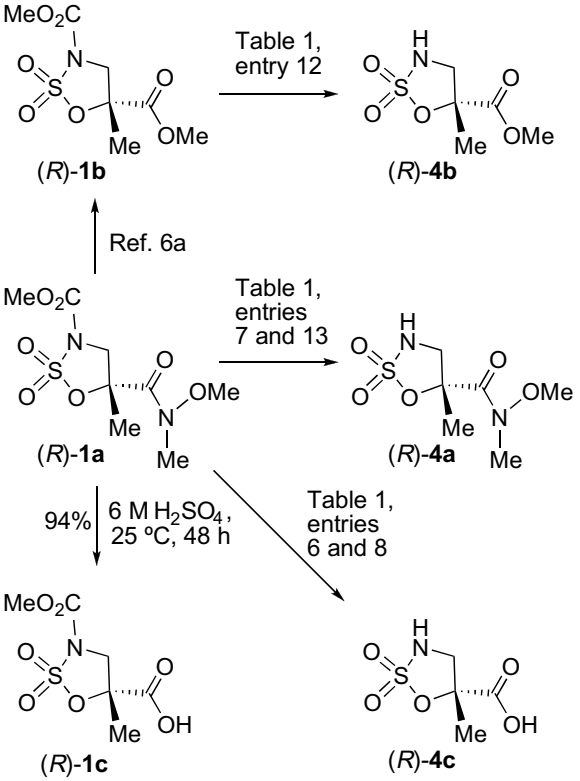
Table 1. Reactions of sulfamidates (*R*)-**1a**,**b** with several O-nucleophiles under basic conditions



Entry	Sulfamidate	O-Nucleophile	Conditions	R′O–	Products	Yield[a] (%)
1	(*R*)-**1a**	*p*NO_2–BzOH/CsF	(i) *p*NO_2–BzOH/CsF (1.1 equiv), DMF, 50 °C, (ii) 20% H_2SO_4/CH_2Cl_2 (1:1), 25 °C	*p*NO_2–BzO–	(*S*)-**2a**/**3a**	71/27
2	(*R*)-**1b**	*p*NO_2–BzOH/CsF	(i) *p*NO_2–BzOH/CsF (1.1 equiv), DMF, 50 °C, (ii) 20% H_2SO_4/CH_2Cl_2 (1:1), 25 °C	*p*NO_2–BzO–	(*S*)-**2b**	99[b]
3[b]	(*R*)-**1a**	—	DBU, THF, reflux	—	**3a**	88[b]
4	(*R*)-**1b**	—	DBU, THF, reflux	—	**3b**	80[b]
5	(*R*)-**1a**	NMe_4OH	NMe_4OH (1.1 equiv), DMF, 25 °C	—	**3a**/(*R*)-**4a**	38/31
6	(*R*)-**1a**	KOH	KOH (20 equiv), H_2O, 50 °C	—	(*R*)-**4c**	83
7	(*R*)-**1a**	LiOH	LiOH·H_2O (1.1 equiv), MeOH/H_2O (3:2), 25 °C	—	(*R*)-**4a**	98
8	(*R*)-**1a**	LiOH	LiOH·H_2O (10.0 equiv), MeOH/H_2O (3:2), 25 °C	—	(*R*)-**4c**	89[c]
9	(*R*)-**1a**	^{t}BuOK	^{t}BuOK (1.1 equiv), DMF, 50 °C	—	**3a**/(*R*)-**4a**	31/63
10	(*R*)-**1a**	MeONa	MeONa (1.1 equiv), DMF, 25 °C	—	**3a**/(*R*)-**4a**	38/31
11	(*R*)-**1a**	MeONa	MeONa (1.1 equiv), MeOH, 25 °C	—	(*R*)-**4a**/(*R*)-**4b**	62/38
12	(*R*)-**1b**	MeONa	MeONa (1.1 equiv), MeOH, 25 °C	—	(*R*)-**4b**	93
13	(*R*)-**1a**	BnONa	BnONa (1.1 equiv), THF, 25 °C	—	(*R*)-**4a**	96
14	(*R*)-**1a**	PhONa	(i) PhONa (1.1 equiv), DMF, 50 °C, (ii) 20% H_2SO_4/CH_2Cl_2 (1:1), 25 °C	PhO–	(*S*)-**2′a**/**3a**/(*R*)-**4a**	47/25/28
15	(*R*)-**1b**	PhONa	(i) PhONa (1.1 equiv), DMF, 50 °C, (ii) 20% H_2SO_4/CH_2Cl_2 (1:1), 25 °C	PhO–	(*S*)-**2′b**	94

[a] Yield determined after column chromatography.
[b] Yield of product obtained in Ref. 6a.
[c] Yield of product obtained in Ref. 6c.

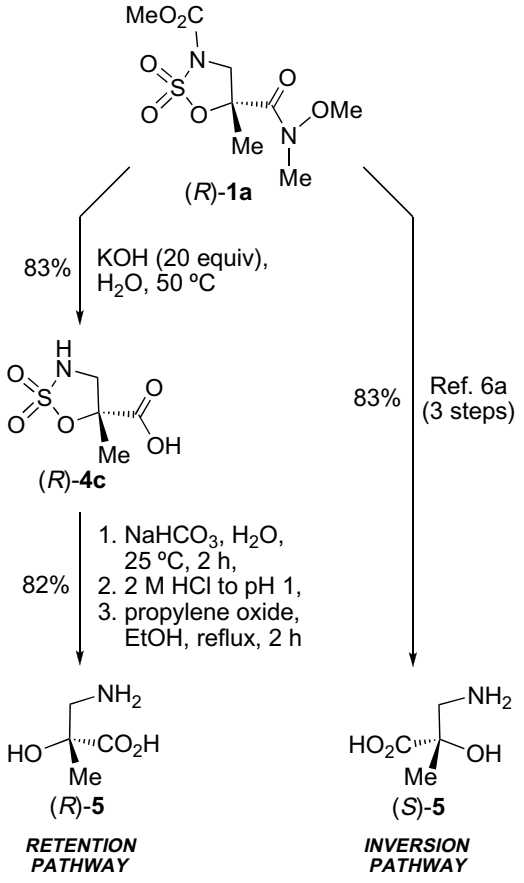
derivatives to design a future regioselective synthesis. To this end, the carbamate group of sulfamidates (*R*)-**1a**,**b** could be deprotected with the NH function to give compounds (*R*)-**4a**,**b**, respectively (Table 1, entries 7, 13 and 12). Moreover, the carbamate and amide groups of sulfamidate (*R*)-**1a** could be deprotected to give the unprotected cyclic sulfamidate (*R*)-**4c** in a different way to that previously reported[6c] (Table 1, entries 6 and 8). To complete the list of sulfamidate derivatives, we have converted the amide group of (*R*)-**1a** into the carboxylic acid function, without altering the carbamate group, using acid hydrolysis with aqueous H_2SO_4, to afford sulfamidate (*R*)-**1c** (Scheme 1).



Scheme 1. Chiral building blocks with cyclic sulfamidate skeleton.

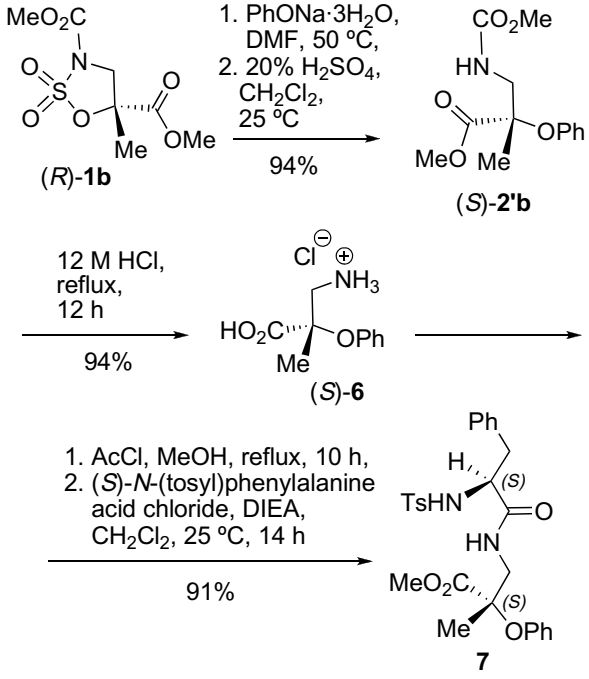
To show the synthetic application of the reactions of these sulfamidates in basic medium and since α-methylisoserine is an important β[2,2]-amino acid,[12] whose (*S*)-isomer, namely (*S*)-**5**, was previously obtained from sulfamidate (*R*)-**1a** in three steps[6a] with an overall yield of 83%, we carried out the hydrolysis of (*R*)-**4c** to give the α-methylisoserine (*R*)-**5** with an excellent yield. Therefore, and taking into account that (*R*)-**4c** comes from sulfamidate (*R*)-**1a** (Table 1, entries 6 and 8), we have developed an interesting stereodivergent synthesis of enantiomerically pure (*S*)- and (*R*)-α-methylisoserine starting from sulfamidate (*R*)-**1a** with a methodology that involves the inversion or retention of configuration at the quaternary stereocentres (Scheme 2).

Moreover, in spite of the inconveniences of the basic medium, the use of some O-nucleophiles was appropriate to obtain O-substituted α-methylisoserine derivatives. For



Scheme 2. Stereodivergent synthesis of (*S*)- and (*R*)-α-methylisoserine.

example, the required amino acid *O*-phenyl-α-methylisoserine (*S*)-**6** was easily obtained as a hydrochloride salt



Scheme 3. Synthesis of (*S*)-*O*-phenyl-α-methylisoserine.

by acid hydrolysis of (*S*)-**2′b** (Scheme 3). The absolute configuration of this new $\beta^{2,2}$-amino acid was unambiguously determined by their transformation into dipeptide **7**, after previous esterification with acetyl chloride in methanol (Scheme 3). This chiral derivative **7** has two stereogenic centres, whose absolute configurations were found to be (*S*,*S*) by X-ray analysis[13] of the corresponding monocrystals (Fig. 2). Additionally, the ^{1}H NMR study of **7** (focused on the methyl group of the tosyl substituent) allowed us to determine the high enantiomeric purity (ee > 93%) of $\beta^{2,2}$-amino acid (*S*)-**6**.

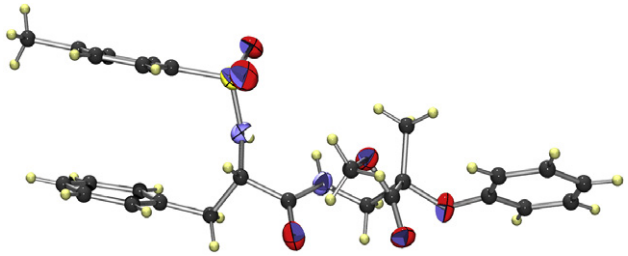


Figure 2. ORTEP3 representation of compound **7**.

3. Conclusions

An in-depth study on the reactions of ester or amide-derived sulfamidates with O-nucleophiles in basic medium has helped enhance the understanding of the reactivity of these systems, with it now being possible to direct the chemoselectivity of the reactions. The most important conclusion is related to the development of a practical method for the ring-opening reaction of hindered sulfamidates using O-nucleophiles, which occurs with the inversion of configuration at the quaternary stereocentre, allowing the synthesis of interesting $\beta^{2,2}$-amino acid derivatives with isoserine skeleton.

4. Experimental

4.1. General procedures

Melting points are uncorrected. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. The chemical reagents were purchased from Aldrich Chemical Co. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Kieselgel 60 (230–400 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, concentrated under reduced pressure using a rotary evaporator. NMR spectra were recorded at 300 or 400 MHz (^{1}H) and at 75 or 100 MHz (^{13}C) and signals are reported in ppm downfield from TMS. The value of coupling constants (*J*) is reported in Hertz. Mass spectra were obtained by electrospray ionization (ESI). Optical rotations were measured on a polarimeter in an 1 dm cell of 1 mL capacity. Microanalyses were in good agreement with the calculated values.

4.2. Methyl (*R*)-5-hydroxycarbonyl-5-methyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-3-carboxylate (*R*)-1c

Sulfamidate (*R*)-**1a** (103 mg, 0.36 mmol) was suspended in a 6 M aqueous H_2SO_4 solution (5 mL) and the mixture was stirred at room temperature for 48 h. Then, H_2O (5 mL) and AcOEt (15 mL) were added and the phases were separated. The corresponding aqueous phase was extracted with AcOEt (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, and evaporated to give compound (*R*)-**1c** (81 mg, 94%), as a colourless oil. Anal. Calcd for $C_6H_9NO_7S$: C, 30.13; H, 3.79; N, 5.86; S, 13.40. Found: C, 30.24; H, 3.81; N, 5.88; S, 13.37. $[\alpha]_D^{25} = -4.3$ (*c* 1.30, MeOH). ESI+ (*m*/*z*): 240.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.79 (s, 3H, CH_3), 3.70–4.05 (m, 4H, $CH_2N + CO_2CH_3$), 4.51 (d, 1H, $J = 10.5$ Hz, CH_2N), 8.01 (br s, 1H, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.7 (CH_3), 53.0 (CH_2N), 55.0 (CO_2CH_3), 83.5 (CCH_3), 150.2 (NCO), 170.9 (CO_2).

4.3. (*S*)-2-Methoxycarbonylaminomethyl-2-(*p*-nitrobenzoyloxy)-*N*-methoxy-*N*-methylpropanamide (*S*)-2a

Sulfamidate (*R*)-**1a** (226 mg, 0.80 mmol), CsF (134 mg, 0.88 mmol), and *p*-nitrobenzoic acid (147 mg, 0.88 mmol) were dissolved in DMF (5 mL) and the mixture was heated at 50 °C for approx. 1 h, when the total disappearance of starting material was observed by TLC or GC–MS. After evaporating the solvent, the residue was dissolved in a mixture of aqueous 20% H_2SO_4/CH_2Cl_2 (1:1, 10 mL) and it was stirred at room temperature for 10 h. Once the phases were separated, the aqueous phase was extracted with AcOEt (3 × 15 mL), the combined organic phases were dried (Na_2SO_4), and evaporated to give a residue which was purified by silica gel column chromatography (hexane/AcOEt, 4:6). In this way, compounds (*S*)-**2a** (213 mg, 71%) and **3a** (44 mg, 27%) were obtained as colourless oils. Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38. Found: C, 48.85; H, 5.01; N, 11.29. $[\alpha]_D^{25} = -11.8$ (*c* 0.94, MeOH). ESI+ (*m*/*z*): 370.3 + K. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.78 (s, 3 H, CH_3), 3.18 (s, 3H, NCH_3), 3.62 (s, 6H, $NOCH_3 + CO_2CH_3$), 3.72–3.92 (m, 2H, CH_2N), 5.38 (br s, 1H, NH), 8.10–8.37 (m, 4H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.2 (CH_3), 34.0 (NCH_3), 47.1 (CH_2N), 52.6 (CO_2CH_3), 61.2 ($NOCH_3$), 83.4 (CCH_3), 123.9, 131.2, 135.6, 150.9 (Ph), 157.7 (NCO), 164.0 ($PhCO_2$), 171.5 (CON).

4.4. (*R*)-5-Methyl-5-(*N*-methoxy-*N*-methylcarbamoyl)-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine (*R*)-4a

Method 1 (Table 1, entry 7): Sulfamidate (*R*)-**1a** (125 mg, 0.44 mmol) and $LiOH{\cdot}H_2O$ (19 mg, 0.44 mmol) were dissolved in a mixture of $MeOH/H_2O$ (3:1, 10 mL). The resulting solution was stirred at room temperature for 4 h. After evaporating the solvent, the residue was dissolved in CH_2Cl_2 (15 mL), the base was neutralized with an aqueous 2 M HCl solution (10 mL) and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were dried over Na_2SO_4, and evaporated to give compound

(*R*)-**4a** (99 mg, 98%), as a colourless oil. *Method 2 (Table 1, entry 13)*: To a solution of sulfamidate (*R*)-**1a** (92 mg, 0.33 mmol) in THF (3 mL), a filtered solution of BnONa in THF (0.40 M, 2.5 mL, 1.00 mmol) was added [this last reagent was in situ prepared by reacting BnOH (204 μL, 1.98 mmol) with Na (57 mg, 2.48 mmol) in THF (5 mL) under an inert atmosphere]. The resulting mixture was stirred at room temperature for 24 h. Then, Et_2O (15 mL) was added and the solution was neutralized with an aqueous 2 M HCl solution (10 mL). Once the organic phase was separated, the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, concentrated, and the residue was purified by a silica gel column chromatography (hexane/AcOEt, 7:3), to give compound (*R*)-**4a** (70 mg, 96%), as a colourless oil. Anal. Calcd for $C_6H_{12}N_2O_5S$: C, 32.14; H, 5.39; N, 12.49; S, 14.30. Found: C, 32.26; H, 5.41; N, 12.52; S, 14.27. $[\alpha]_D^{25} = -46.3$ (*c* 1.04, $CHCl_3$). ESI+ (*m*/*z*): 225.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.77 (s, 3H, CH_3), 3.12–3.42 (m, 4H, $CH_2N + NCH_3$), 3.80 (s, 3H, $NOCH_3$), 4.35–4.51 (m, 1H, CH_2N), 5.01 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.8 (CH_3), 33.7 (NCH_3), 52.5 (CH_2N), 61.7 ($NOCH_3$), 90.7 (*C*CH_3), 167.8 (CON).

4.5. Methyl (*R*)-5-methyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-5-carboxylate (*R*)-4b

To a solution of sulfamidate (*R*)-**1a** (87 mg, 0.31 mmol) in MeOH (10 mL), MeONa (33 mg, 0.62 mmol) was added and the mixture was stirred at room temperature for 24 h. After evaporating the solvent, the residue was dissolved in CH_2Cl_2 (15 mL) and neutralized with an aqueous 2 M HCl solution (10 mL). Once the organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, concentrated, and the residue was purified by a silica gel column chromatography (hexane/AcOEt, 7:3), to give compound (*R*)-**4b** (60 mg, 93%), as a colourless oil. Anal. Calcd for $C_5H_9NO_5S$: C, 30.77; H, 4.65; N, 7.18; S, 16.43. Found: C, 30.89; H, 4.63; N, 7.16; S, 16.45. $[\alpha]_D^{25} = -24.4$ (*c* 1.30, $CHCl_3$). ESI+ (*m*/*z*): 196.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.75 (s, 3H, CH_3), 3.44–3.58 (m, 1H, CH_2N), 3.87 (s, 3H, CO_2CH_3), 3.94–4.09 (m, 1H, CH_2N), 4.91 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.5 (CH_3), 52.1 (CH_2N), 53.7 (CO_2CH_3), 88.0 (*C*CH_3), 169.8 (CO_2).

4.6. (*R*)-5-Methyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-5-carboxylic acid (*R*)-4c

To a suspension of sulfamidate (*R*)-**1a** (87 mg, 0.31 mmol) in H_2O (10 mL), KOH (347 mg, 6.20 mmol) was added and the mixture was stirred at 50 °C for 2 h. After evaporating the solvent, the residue was dissolved in CH_2Cl_2 (15 mL) and neutralized with an aqueous 2 M HCl solution (10 mL). Once the organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, and concentrated to give compound (*R*)-**4c** (47 mg, 83%), as a white solid. Anal. Calcd for $C_4H_7NO_5S$: C, 26.52; H, 3.89; N, 7.73; S, 17.70. Found: C, 26.69; H, 3.93; N, 7.79; S, 17.75. $[\alpha]_D^{25} = -8.0$ (*c* 0.99, MeOH). Analytical data are according to those described in the literature.[6c]

4.7. (*S*)-2-Methoxycarbonylaminomethyl-2-phenyloxy-*N*-methoxy-*N*-methylpropanamide (*S*)-2′a

Sulfamidate (*R*)-**1a** (162 mg, 0.57 mmol) and $PhONa{\cdot}3H_2O$ (107 mg, 0.63 mg) were dissolved in DMF (5 mL) and the mixture was heated at 50 °C for approx. 1 h, when the total disappearance of starting material was observed by TLC or GC–MS. After evaporating the solvent, the residue was dissolved in a mixture of aqueous 20% H_2SO_4/CH_2Cl_2 (1:1, 10 mL) and it was stirred at room temperature for 10 h. Once the phases were separated, the aqueous phase was extracted with AcOEt (3 × 15 mL), the combined organic phases were dried over Na_2SO_4, and evaporated to give a residue which was purified by silica gel column chromatography (hexane/AcOEt, 6:4). In this way, compounds (*S*)-**2′a** (80 mg, 47%), **3a** (29 mg, 25%) and (*R*)-**4a** (36 mg, 28%) were obtained as colourless oils. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.92; H, 6.82; N, 9.42. $[\alpha]_D^{25} = -42.8$ (*c* 1.03, $CHCl_3$). ESI+ (*m*/*z*): 297.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.58 (s, 3H, CH_3), 3.26–3.32 (m, 3H, NCH_3), 3.51–3.89 (m, 8H, $CH_2N + NOCH_3 + CO_2CH_3$), 5.17–5.30 (m, 1H, NH), 6.80–7.06 (m, 3H, Ph), 7.19–7.32 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.4, 20.5 (CH_3), 38.3 (NCH_3), 46.5 (CH_2N), 52.2, 52.3 (CO_2CH_3), 60.4, 60.8 ($NOCH_3$), 82.0, 82.2 (*C*CH_3), 118.9, 122.5, 129.5, 154.8 (Ph), 157.3 (NCO), 173.7 (CON).

4.8. Methyl (*S*)-2-methoxycarbonylaminomethyl-2-phenyloxypropanoate (*S*)-2′b

Following the same protocol described for compound (*S*)-**2′a** and starting from sulfamidate (*R*)-**1b** (114 mg, 0.45 mmol), compound (*S*)-**2′b** (113 mg, 94%) was obtained, after purification by a silica gel column chromatography (hexane/AcOEt, 7:3). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.60; H, 6.39; N, 5.26. $[\alpha]_D^{25} = -6.9$ (*c* 1.88, $CHCl_3$). ESI+ (*m*/*z*): 268.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.49 (s, 3H, CH_3), 3.53–3.88 (m, 8H, $CH_2N + CO_2CH_3 + CO_2CH_3$), 5.30 (br s, 1H, NH), 6.77–6.92 (m, 2H, Ph), 6.93–7.07 (m, 1H, Ph), 7.19–7.33 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.4 (CH_3), 48.4 (CH_2N), 52.2 (CO_2CH_3), 52.6 (CO_2CH_3), 81.0 (*C*CH_3), 119.4, 122.7, 129.2, 154.5 (Ph), 157.2 (NCO), 172.6 (CO_2).

4.9. (*R*)-2-Aminomethyl-2-hydroxypropanoic acid (*R*)-5

To a suspension of sulfamidate (*R*)-**4c** (106 mg, 0.58 mmol) in H_2O (3 mL), $NaHCO_3$ (122 mg, 1.45 mmol) was added and the mixture was stirred at room temperature for 2 h. Then, an aqueous 2 M HCl solution was added until pH 1 and the resulting mixture was evaporated to obtain the corresponding 2-methylisoserine amino acid as a hydrochloride salt. This salt was dissolved in ethanol/propylene oxide (3:1, 2 mL) and the solution was refluxed for 2 h. After that, 2-methylisoserine (*R*)-**5** partially precipitated as a white solid (22 mg), which was filtered and the filtrate was evaporated, dissolved in H_2O (2 mL), and eluted

through a reverse-phase Sep-pak C_{18} cartridge to obtain, after evaporating the H_2O, the corresponding amino acid (*R*)-**5** (35 mg) as a white solid (total amount: 57 mg, 82%). Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.26; H, 7.63; N, 11.72. $[\alpha]_D^{25} = -2.6$ (*c* 1.01, H_2O). Analytical data are in good agreement with those described in the literature.[6a]

4.10. (*S*)-2-Aminomethyl-2-phenyloxypropanoic acid hydrochloride (*S*)-6

Compound (*S*)-**2′b** (109 mg, 0.41 mmol) was suspended in aqueous 12 M HCl (5 mL) and the mixture was refluxed for 12 h. After that, the solvent was evaporated, and the residue was dissolved in H_2O (2 mL), and eluted through a reverse-phase Sep-pak C_{18} cartridge to obtain, after evaporating the H_2O, the corresponding compound (*S*)-**6** (89 mg, 94%) as a white solid. Anal. Calcd for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.09; N, 6.05. Found: C, 52.01; H, 6.12; N, 6.03. $[\alpha]_D^{25} = -16.8$ (*c* 1.38, H_2O). ESI+ (*m*/*z*): 196.2. ^{1}H NMR (300 MHz, D_2O) δ (ppm): 1.50 (s, 3H, CH_3), 3.42–3.50 (m, 2H, CH_2N), 6.91–7.04 (m, 2 H, Ph), 7.06–7.20 (m, 1H, Ph), 7.25–7.40 (m, 2H, Ph). ^{13}C NMR (75 MHz, D_2O) δ (ppm): 21.6 (CH_3), 48.2 (CH_2N), 81.1 (CCH_3), 122.6, 126.5, 132.2, 155.9 (Ph), 176.6 (CO_2).

4.11. (*S*)-*N*-(Tosyl)phenylalaninyl-(*S*)-*O*-phenyl-α-methylisoserine methyl ester 7

4.11.1. Synthesis of compound 7. Compound (*S*)-**6** (78 mg, 0.34 mmol) was dissolved in a mixture of MeOH/HCl, previously prepared by the addition of AcCl (4 mL) over MeOH (16 mL) at 0 °C. After refluxing for 10 h, the solvent was evaporated, the residue was suspended in CH_2Cl_2 (10 mL) under an inert atmosphere, and *N*-(tosyl)phenylalanine acid chloride (150 mg, 0.44 mmol) and DIEA (176 μL, 1.00 mmol) were added. The resulting solution was stirred at room temperature for 14 h. The reaction was quenched by the addition of aqueous 0.5 M HCl (4 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, concentrated, and the crude reaction was purified by a silica gel column chromatography (hexane/AcOEt, 7:3), to give dipeptide **7** (156 mg, 91%) as a white solid. Anal. Calcd for $C_{27}H_{30}N_2O_6S$: C, 63.51; H, 5.92; N, 5.49; S, 6.28. Found: C, 63.69; H, 5.94; N, 5.51; S, 6.26. Mp: 141–143 °C. $[\alpha]_D^{25} = -35.8$ (*c* 1.38, $CHCl_3$). ESI+ (*m*/*z*): 511.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.42 (s, 3H, CCH_3), 2.38 (s, 3H, PhCH_3), 2.74–2.89 (m, 1H, CH_2Ph), 3.03 (dd, 1H, $J = 14.0$ Hz, $J = 5.5$ Hz, CH_2Ph), 3.71 (d, 2H, $J = 6.1$ Hz, CH_2N), 3.75 (s, 3H, CO_2CH_3), 3.90 (td, 1H, $J = 8.2$ Hz, $J = 5.9$ Hz, CHCON), 5.21 (d, 1H, $J = 6.4$ Hz, $NHSO_2$), 6.81–7.32 (m, 13H, NHCO + *Ph*CH_3 + Ph + Ph), 7.41–7.51 (m, 2H, *Ph*CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.2 (CCH_3), 21.4 (PhCH_3), 38.2 (CH_2Ph), 46.4 (CH_2N), 52.7 (CO_2CH_3), 58.1 (CH), 81.0 (CCH_3), 120.0, 123.0, 127.0, 128.8, 129.0, 129.3, 129.7, 135.2, 135.4, 143.6, 154.5 (Ph), 170.7 (CON), 172.5 (CO_2).

4.11.2. Crystal data for compound 7. Molecular formula: $C_{27}H_{30}N_2O_6S$, $M_w = 510.61$, colourless prism of 0.55 × 0.20 × 0.05 mm, $T = 298$ K, monoclinic, space group $P2_1$, $Z = 2$, $a = 9.7005(6)$ Å, $b = 10.4209(7)$ Å, $c = 13.3439(9)$ Å, $V = 1291.76(15)$ Å^3, $d_{calcd} = 1.313$ g cm^{-3}, $F(000) = 528$, $\lambda = 0.71073$ Å (Mo Kα), $\mu = 0.316$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.44–28.03°, 6240 collected reflections, 2993 unique, full-matrix least-squares (SHELXL97), $R_1 = 0.0636$, $wR_2 = 0.1861$, ($R_1 = 0.0952$, $wR_2 = 0.2470$ all data), goodness of fit = 1.229, residual electron density between 0.753 and −0.912 e Å^{-3}. Absolute structure parameter (Flack) 0.2(2). Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number CCDC 667615.

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