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A Novel Multistep Mechanism for the Stereocontrolled Ring Opening of Hindered Sulfamidates: Mild, Green, and Efficient Reactivity with Alcohols

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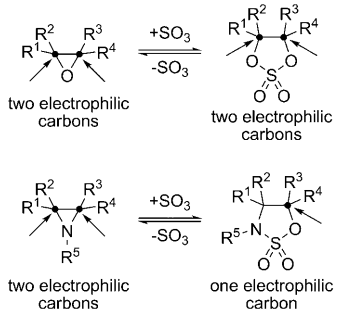
Abstract: Cyclic hindered sulfamidates exhibited an outstanding performance in their ring-opening reactions with alcohols and in the absence of any external activator. The mechanism of this unprecedented transformation was thoroughly studied both experimentally and theoretically. As a result, a nontrivial stepwise pathway involving solvent-induced conversion of the sulfamidates to activated aziridinium and then to oxazolinium cations, which are finally opened at their 5-position with inversion of configuration, is proposed. The presence of the SO_3 moiety in the sulfamidate was revealed as a "built-in activator". In fact, the spontaneous SO_3 cleavage takes place under the reaction conditions and avoids the subsequent step of hydrolysis after the ring opening of the sulfamidates. This is another important improvement of this methodology with respect to the standard basic conditions, allowing a greater compatibility with other functional groups. Furthermore, the carbamate group plays a key role in this mechanism. Briefly, a highly chemoselective and stereoespecific formal solvolysis of hindered sulfamidates with alcohols without further activation is described. This reaction takes place exclusively at the quaternary center with inversion of configuration, providing a new straightforward synthetic route to O-substituted α-methylisoserines.

Keywords: alcohols · neighboring-group effects · nucleophilic substitution · reaction mechanisms · sulfamidates

Introduction

Epoxides and aziridines are valuable intermediates in organic synthesis because they can undergo a great number of transformations.[1] Nucleophilic ring-opening reactions of these systems are especially important for the synthesis of many biologically interesting compounds,[1] such as amino acids, heterocycles, and alkaloids. As a result, several methods have been reported for the regioselective ring opening of epoxides and aziridines with various nucleophiles.[2] On the other hand, the importance of five-membered cyclic sulfates and sulfamidates in organic synthesis has profusely been described in the literature.[3] These systems compete with epoxides and aziridines in terms of reactivity and selectivity in ring-opening reactions with nucleophiles. Moreover, the chemical properties of these heterocycles are tightly connected since the epoxides/sulfates and aziridines/sulfamidates interconversions have previously been described[4] (Scheme 1).

Although the reactivity of epoxides, aziridines, sulfates, and sulfamidates towards sulfur, halogen, nitrogen, and carbon nucleophiles has been widely studied, procedures for



Scheme 1. Interconversions of epoxides–sulfates and aziridines–sulfamidates. The reactive positions of each substrate (apart from sulfur atom) are shown with arrows.

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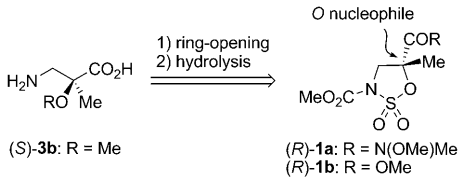
their opening with oxygenated nucleophiles (O nucleophiles) are scarce.[1g,2] This is mainly caused by the basic character of these reagents in their anionic form (alkoxides, phenoxides, carboxylates, etc.), which very often leads to competitive reactions (i.e., eliminations). In addition, O nucleophiles, such as alkoxides, are very hard and, as a consequence, incompatible with a broad range of functional groups (i.e., carbonyl compounds). As an alternative to the basic conditions, ring-opening reactions with O nucleophiles (i.e., alcohols or water) are frequently carried out in the presence of activating Lewis/Brønsted acids,[5] which in some cases interfere with other basic groups in the substrate. However, recently the ring opening of epoxides or aziridines under milder conditions (catalyst-free) with various nucleophiles has received particular attention.[6]

The reaction conditions (basic or acidic) play a key role in the regio- and stereochemical outcome of the ring-opening reaction, which allows for the direction of the nucleophilic attack to any of the different reactive positions of the heterocyclic substrates.[1g] As an example, and in connection with the results discussed later in this work, the nucleophilic ring opening of a 2-substituted aziridine-2-carboxylic acid derivatives has been carried out regioselectively at both the secondary and the quaternary carbon atoms depending on the incoming nucleophile and the reaction conditions.[7] However, the use of alcohols as O nucleophiles in a neutral medium (without acidic or basic additives) has not yet been explored in these reactions. To the best of our knowledge, only one example has been reported, which describes the regioselective ring opening in methanol of two aziridines activated by a strong electron-withdrawing group, such as the *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidoyl group.[8] However, no discussion on the regioselectivity and the stereochemical course of the reaction with these two substrates was done.

Given the importance of chiral compounds with quaternary carbon stereocenters[9] in the field of β-amino acids,[10] particularly of chiral α,α-disubstituted β-amino acids (namely $\beta^{2,2}$-amino acids[11]), we have focused our attention on the synthesis of isoserine derivatives[12] due to their implications as peptidomimetic units.[13] In this sense, and following our previously published protocol,[14] one attractive access to these $\beta^{2,2}$-amino acids with the isoserine skeleton involves the ring-opening reaction of hindered sulfamidates (*R*)-**1a**,**b** with O nucleophiles (Scheme 2).

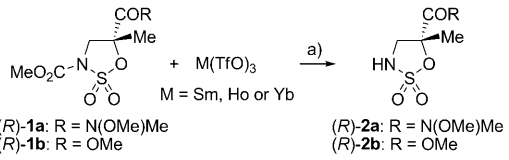


Scheme 2. Retrosynthesis of isoserine derived $\beta^{2,2}$-amino acids.

The quaternary carbon atom of these chiral building blocks (*R*)-**1a**,**b** is activated for nucleophilic displacement; therefore, the S_N2 reactivity with several nucleophiles in a basic medium was explored and further hydrolysis of ring-opening products allowed us to obtain interesting chiral compounds.[15] In this context, although chemoselectivity problems (elimination vs. substitution) with these substrates are well-known, we have recently published a highly chemoselective ring-opening reaction of sulfamidates (*R*)-**1a**,**b** with O nucleophiles in a basic medium.[16] Nevertheless, this method is limited to *O*-aryl or *O*-acyl-substituted α-methylisoserines (Scheme 2) and the use of alcohols as nucleophiles in acid or neutral media has not yet been explored in hindered sulfamidates. To the best of our knowledge, there is only one precedent in the literature dealing with the ring opening of a prolinol-derived sulfamidate with methanol as a solvent in the presence of one drop of trifluoroacetic acid.[17] Our previous results, together with the lack of antecedents on the ring opening of three- and five-membered cyclic systems with O nucleophiles in neutral media, encouraged us to undertake a study on the behavior of hindered sulfamidates (*R*)-**1a**,**b** towards alcohols.

Results and Discussion

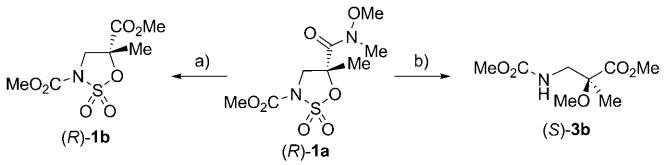
Reactivity of hindered sulfamidates: Firstly, and with the aim of fully inspecting the reactivity of these substrates, we started our study with the evaluation of alcohol-compatible Lewis acids. With this is mind, sulfamidates (*R*)-**1a**,**b**[14] were treated with stoichiometric amounts of several Lewis acids in methanol (Scheme 3). With $Sm(TfO)_3$, $Ho(TfO)_3$, or $Yb(TfO)_3$ only deprotection of the carbamate group was observed, giving compounds (*R*)-**2a**,**b**, whereas reaction with $Sc(TfO)_3$ and $In(TfO)_3$ did not progress and all of the starting material was recovered. These results are similar to those previously reported with MeONa as the nucleophile.[16] As will be discussed later on, the carbamate cleavage under these conditions has a decisive influence on the observed reactivity. Therefore, this strategy was abandoned because the desired ring-opening reaction was not observed at any extent.



Scheme 3. Reaction of sulfamidates (*R*)-**1a**,**b** with MeOH by using various Lewis acids. a) MeOH, 68 °C, 2 h (94–99 %).

In the next stage of our study, we tested the reaction of (*R*)-**1a** with methanol as a solvent in the presence of variable amounts of different Brønsted acids such as *p*-toluenesulfonic acid (*p*TsOH), Dowex 50W-X8, and triflic acid (TfOH). In all cases, the reactions quantitatively gave, as de-

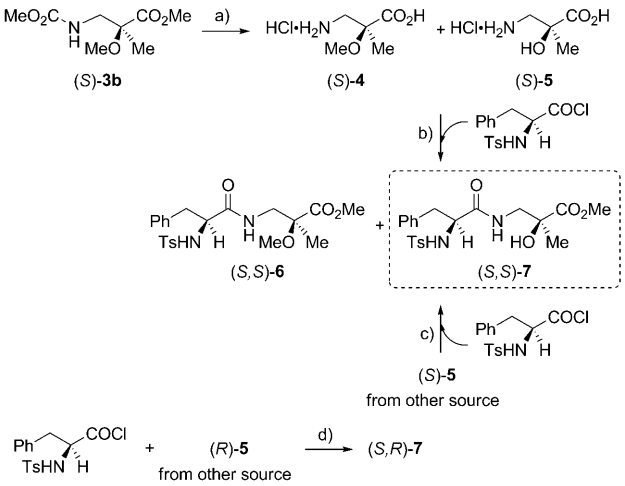
sired and in "one-pot", the product (*S*)-**3b**, arising from the amide–ester exchange, the subsequent ring opening with inversion of the configuration, and further sulfamic acid solvolysis reactions (Scheme 4). The amide–ester exchange to give (*R*)-**1b** occurs before the ring-opening reaction of this sulfamidate. This fact was demonstrated by carrying out the same reaction with (*R*)-**1a** at a lower temperature (40 °C), which only gave (*R*)-**1b** in good yield (Scheme 4).



Scheme 4. Sequential and one-pot ring-opening reactions of sulfamidate (*R*)-**1a** (optimized conditions). a) MeOH, TfOH (1.5 equiv), 40 °C, 24 h (98 %); b) MeOH, TfOH (1.5 equiv), 68 °C, 48 h (98 %).

The optical purity of *O*-methyl-α-methylisoserine derivative (*S*)-**3b** was determined by GC analysis (>93 % *ee*), a result that is equal to that measured for the starting material, sulfamidate (*R*)-**1a**, by the same methodology[14] (see the Supporting Information). To demonstrate that the nucleophilic attack of methanol proceeded with inversion of configuration at the quaternary sterogenic center of the sulfamidate, we carried out the hydrolysis of compound (*S*)-**3b** with an aqueous solution of 9 M HCl at reflux to give a mixture of compounds (*S*)-**4** and (*S*)-**5** (Scheme 5). Due to the impossibility of separating this mixture of $\beta^{2,2}$-amino acids, they were derivatized to the corresponding peptides (*S*,*S*)-**6** and (*S*,*S*)-**7** by reaction with (*S*)-*N*-(*p*-tosyl)phenylalaninyl chloride, with previous esterification. Once both compounds were separated by column chromatography, the spectroscopic data and optical activity of dipeptide (*S*,*S*)-**7** were compared to those measured for the diastereomers (*S*,*S*)-**7** and (*S*,*R*)-**7**, prepared separately from each enantiomer of α-methylisoserine (*S*)-**5** and (*R*)-**5**, which were synthesized by other published methodologies.[12c,14,16] This comparison allowed us to confirm the absolute configuration of (*S*)-**3b** (Scheme 5 and Supporting Information) and verify the high configurational stability of α-methylisoserine derivatives in strongly acidic aqueous media.

To expand the scope of these reactions, several alcohols were assayed, firstly under controlled-temperature conditions and then at higher temperatures. Therefore, a pool of the corresponding amide–ester exchange products (*R*)-**1c**–**k** were obtained in good yields (Table 1, entries conditions A). Both, the linear and branched primary alcohols gave good yields. In the case of a secondary alcohol, prolonged heating at 80 °C was necessary (Table 1, entry 17). The structure of (*R*)-**1c** was confirmed by X-ray analysis and the ORTEP structure is shown in Figure 1. To expand this methodology to other high boiling point alcohols, we optimized the amide–ester exchange reaction of (*R*)-**1a** by using toluene



Scheme 5. Determination of the absolute configuration of (*S*)-**3b**. a) HCl 9 M, reflux, 12 h (100 %); b) i) AcCl, MeOH, reflux, 10 h; ii) iPr$_2$EtN, CH_2Cl_2, 25 °C, 14 h; iii) column chromatography (61 % of (*S*,*S*)-**6**, 32 % of (*S*,*S*)-**7**); c) and d) the same conditions as b) (91 % of (*S*,*S*)-**7**, 87 % of (*S*,*R*)-**7**).

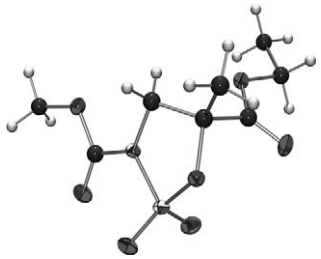
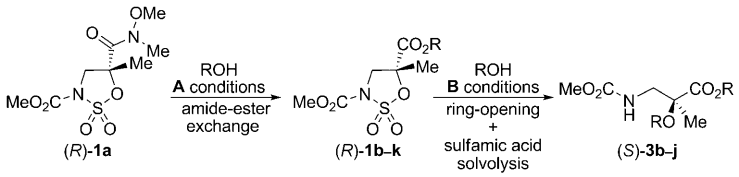


Figure 1. X-ray structure of sulfamidate (*R*)-**1c**.

as the solvent and only three equivalents of alcohol in the presence of more practical *p*TsOH. For example, a good yield of (*R*)-**1k** was obtained in the case of benzylic alcohol (Table 1, entry 19).

Once the ester sulfamidates (*R*)-**1b**–**k** were prepared, and to avoid possible transesterification products, we initially assayed the ring-opening reaction on these substrates with the same alcohol that was used to get the amide–ester exchange. Surprisingly, we found that this reaction could be accomplished simply by heating each substrate in the corresponding alcohol at 68–80 °C (the reaction progresses smoothly above 45 °C) in the absence of acid additives (conditions B in Table 1); this cleanly gave the corresponding ring-opening products (*S*)-**3b**–**j** with both linear and branched alcohols in excellent yields. It must be noted that even a secondary alcohol (isopropanol, Table 1, entry 18) reacted after prolonged heating at 80 °C (5 days) to give the corresponding ring-opening product in a good yield (65 %) and without secondary reactions. Moreover, this methodology also allowed us to carry out the reactions with alcohols sensitive to acid medium, such as the allylic alcohol (Table 1, entry 12). The enantiomeric purity values of these ring-opening prod-

Table 1. Reactions of (*R*)-**1a**,**b** and (*R*)-**1b**–**j** in acidic or neutral conditions.



Entry	Substrate	Alcohol	R	Conditions[a]	Products	Yield [%][b]
1	(*R*)-**1a**	methanol	Me	A	(*R*)-**1b**	98
2	(*R*)-**1b**	methanol	Me	B	(*S*)-**3b**	93
3	(*R*)-**1a**	ethanol	Et	A	(*R*)-**1c**	94
4	(*R*)-**1c**	ethanol	Et	B	(*S*)-**3c**	94
5	(*R*)-**1a**	propanol	Pr	A	(*R*)-**1d**	93
6	(*R*)-**1d**	propanol	Pr	B	(*S*)-**3d**	91
7	(*R*)-**1a**	butanol	Bu	A	(*R*)-**1e**	89
8	(*R*)-**1e**	butanol	Bu	B	(*S*)-**3e**	93
9	(*R*)-**1a**	pentanol	Bu(CH_2)-	A	(*R*)-**1f**	90
10	(*R*)-**1f**	pentanol	Bu(CH_2)-	B	(*S*)-**3f**	88
11	(*R*)-**1a**	allylic alcohol	allyl	A	(*R*)-**1g**	86
12	(*R*)-**1g**	allylic alcohol	allyl	B	(*S*)-**3g**	84
13	(*R*)-**1a**	isobutanol	*i*Bu	A	(*R*)-**1h**	91
14	(*R*)-**1h**	isobutanol	*i*Bu	B	(*S*)-**3h**	90
15	(*R*)-**1a**	isopentanol	*i*Bu(CH_2)-	A	(*R*)-**1i**	93
16	(*R*)-**1i**	isopentanol	*i*Bu(CH_2)-	B	(*S*)-**3i**	92
17	(*R*)-**1a**	isopropanol	*i*Pr	A	(*R*)-**1j**	79[c]
18	(*R*)-**1j**	isopropanol	*i*Pr	B	(*S*)-**3j**	65[d]
19	(*R*)-**1a**	benzylic alcohol	Bn	A*	(*R*)-**1k**	89

[a] Conditions: A) alcohol, TfOH (1.5 equiv), 40 °C, 24 h; B) alcohol, 68–80 °C, 48 h; A*) alcohol (3.0 equiv), *p*TsOH·H_2O (1.5 equiv), toluene, reflux, 24 h. [b] Yield determined after column chromatography. [c] To carry out the amide–ester exchange it was necessary to heat at 80 °C for 48 h. [d] To carry out the ring-opening reaction it was necessary to heat at 80 °C for 120 h.

ucts were the same as those obtained for (*S*)-**3b** ($ee > 93\,\%$) even in the most problematic cases with less nucleophilic, bulkier, or more branched alcohols (see the Supporting Information for a thorough study on enantioselectivity).

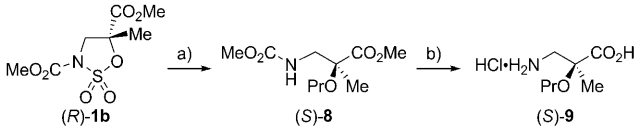
The possibility of acid traces present in the alcohols as the true activators was discarded by carrying out the reaction with HPLC-grade MeOH distilled over CaH_2. Under these conditions, the same results in terms of yield and enantioselectivity were obtained.

Moreover, and according to our previous results,[14] we confirmed that the presence of an ester group is required to accomplish the ring opening of sulfamidate, since the reaction of (*R*)-**1a** at reflux in methanol for 48 h did not progress at all. On the other hand, we carried out the reaction in different solvents, obtaining good results only with neat alcohols.[18]

As an important synthetic advantage, the absence of acidic promotors allowed us the chemoselective synthesis of O-substituted α-methylisoserine derivatives bearing different groups in ester or ether substituents (i.e., avoiding transesterification). Indeed, the treatment of sulfamidate (*R*)-**1b** with propanol as the solvent at 55 °C gave a good yield of compound (*S*)-**8**, which could be easily converted into the corresponding $\beta^{2,2}$-amino acid (*S*)-**9** (Scheme 6). Thus, depending on the reaction conditions (presence or absence of acidic activators), the reactivity of these hindered sulfamidates with alcohols can be completely directed towards transesterification, ring opening, both processes simultaneously, or carbamate deprotection.

It is important to note that, to the best of our knowledge, this is the first time that a ring-opening reaction of sulfamidates has been reported with alcohols as nucleophiles in neutral and mild conditions. Therefore, this methodology is synthetically useful and highly environmentally friendly, given that a full atom economy is achieved and no extra disposals apart from the alcoholic solvent are generated in the reaction.

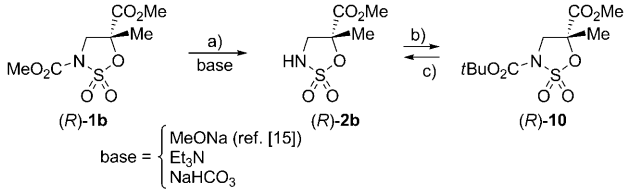
Once the synthetic scope of the ring-opening reaction was explored, we were intrigued by the high enantioselectivity achieved in the process, which was confirmed to take place with inversion of the configuration of the quaternary carbon atom. Alcohols have been traditionally considered as poor nucleophiles, especially when reacting towards sterically hindered electrophiles like quaternary carbon atoms. Therefore, and although the ring opening of sulfamidates (*R*)-**1a**,**b** has been demonstrated, by both experimental and theoretical studies, to take place by means of a S_N2 process with strong nucleophiles (RS^-, N_3^-, CN^-, F^-),[14,15a] such a mechanism is, a priori, highly unfeasible with alcohols. In turn, terms like "solvolysis" easily come to mind when looking at the aforementioned reaction conditions. But, how does this solvolysis really take place? Is the commonly referred formation of ion pairs after heterolytic cleavage enough to explain the observed enantioselectivity and the inversion of configuration? To shed some light on these questions, we performed a thorough study combining experimental studies and theoretical calculations, which allowed us to confidently propose a mechanism to explain the enantioselective ring-opening reaction of hindered sulfamidates with alcohols.



Scheme 6. Chemoselective ring-opening reaction of sulfamidate (*R*)-**1b**. a) *n*PrOH, 55 °C, 4 d (82 %); b) HCl 6 M, 90 °C, 48 h (95 %).

The ring-opening mechanism: Despite of their small size, a big number of reaction channels starting from sulfamidates (*R*)-**1a**,**b** can be expected because of their high functionalization. Indeed, methods to carry out many of these reactions selectively (nucleophilic substitution, elimination, deprotection, and functional-group interconversions) have been previously described.[14–16] Moreover, a great dependence on apparently expectant neighboring groups, such as the ester or amide substituents, on some reactions (i.e., S_N2 vs. E2 with basic nucleophiles) has been observed and studied.[14] Regarding the ring-opening reaction of substrates (*R*)-**1a**,**b** with alcohols described in this work, the presence of both an ester group and a carbamate group has been observed to be mandatory for the reaction to take place. Leaving aside the activating effect of the ester groups towards nucleophilic substitution at the quaternary position with respect to amides, which has been extensively studied for both cyclic sulfates and sulfamidates in our previous works,[3h,14] the unexpected key role of the carbamate in the ring-opening reaction of (*R*)-**1b**–**k** with alcohols is challenging and points to a nontrivial mechanism. With this in mind, some experimental findings must be taken into account:

1) The methyl carbamate group is required to achieve the ring-opening reaction (i.e., sulfamidate (*R*)-**2b** does not react at all) and it remains unaltered irrespective of the alcohol used as the nucleophile.
2) When the ring-opening reaction was assayed on the *tert*-butyloxycarbonyl (Boc)-derived sulfamidate (*R*)-**10**, (Scheme 7 and Figure 2), only a small amount of the ring-opening product (~20%, not isolated) could be detected by ^{1}H NMR spectroscopy at short reaction times (12 h), with the deprotection product (*R*)-**2b** the major product when the reaction was completed. Bearing in mind the high lability of the Boc group in acidic media, this result points to the generation of "acid" to some extent at the early stages of the reaction. Indeed, a variation in the pH of the reaction mixture was observed qualitatively by using an indicator paper from neutral to slightly acid upon the completion of the reaction. This acidification could be the result of the reaction of SO_3 (released in some way along the reaction pathway) with methanol to produce methoxysulfonic acid and/or dimethyl sulfate. Unfortunately, any attempt to inhibit the ring-opening reaction of sulfamidate (*R*)-**1b** in the presence of variable amounts of base (triethylamine or sodium bicarbonate) resulted in rapid transformation to (*R*)-**2b** (Scheme 7).
3) After carrying out the ring-opening reaction of sulfamidate (*R*)-**1b** in [D_4]MeOH, residual signals in the ^{13}C spectra (Figure 3b) were tentatively assigned to traces of [D_6]dimethyl sulfate or [D_6]dimethylether (multiplet at $\delta = 60$ ppm)[19] and the [D_3]methoxysulfonate anion (multiplet at $\delta = 55$ ppm), which would be in agreement with the aforementioned generation of acidic species from SO_3 and [D_4]MeOH.
4) Sulfamidate (*R*)-**1b** is stable when heated in neat non-nucleophilic solvents (i.e., toluene, chloroform, and acetonitrile) both in neutral and acidic (stoichiometric *p*TsOH) conditions. Therefore, the role of the generated acid mentioned above is not clear at this point. Conversely, the presence of a protic solvent like methanol, and not an initial activation with an "exogen acid" seems to be required for the reaction to take place.
5) Markedly, the sulfamic acid ($-NSO_3^-H^+$) generated after the ring opening of sulfamidates, which must be cleaved before isolating the final products (commonly by acid hydrolysis or treatment with $BF_3{\cdot}Et_2O$/thiol), appears to be spontaneously lost without observing any intermediate along the whole reaction pathway. This is an unprecedented finding which, apart from being useful synthetically, points to a somewhat different mechanism in which the SO_3 moiety is removed very quickly after (or maybe at the same time) the ring-opening reaction occurs.



Scheme 7. Deprotection/protection of hindered sulfamidates under basic conditions. a) MeOH, 68 °C, 48 h (81–93% conv.); b) Boc_2O, Et_3N, CH_2Cl_2, 25 °C, 32 h (76%); c) MeOH, 68 °C, 48 h (72% conv.).

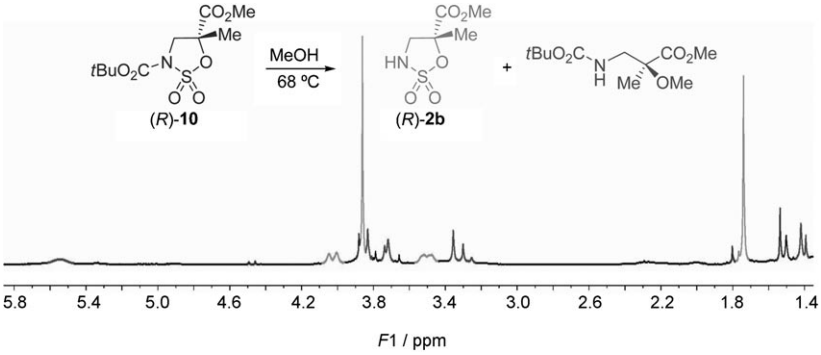


Figure 2. Reaction of sulfamidate (*R*)-**10** with methanol after 48 h at reflux. The ^{1}H NMR spectrum of the crude mixture shows the clean cleavage of the carbamate group in the sulfamidate together with a small amount of the N-protected ring-opening product (the conformational isomerism of the Boc group is revealed in some duplicated signals).

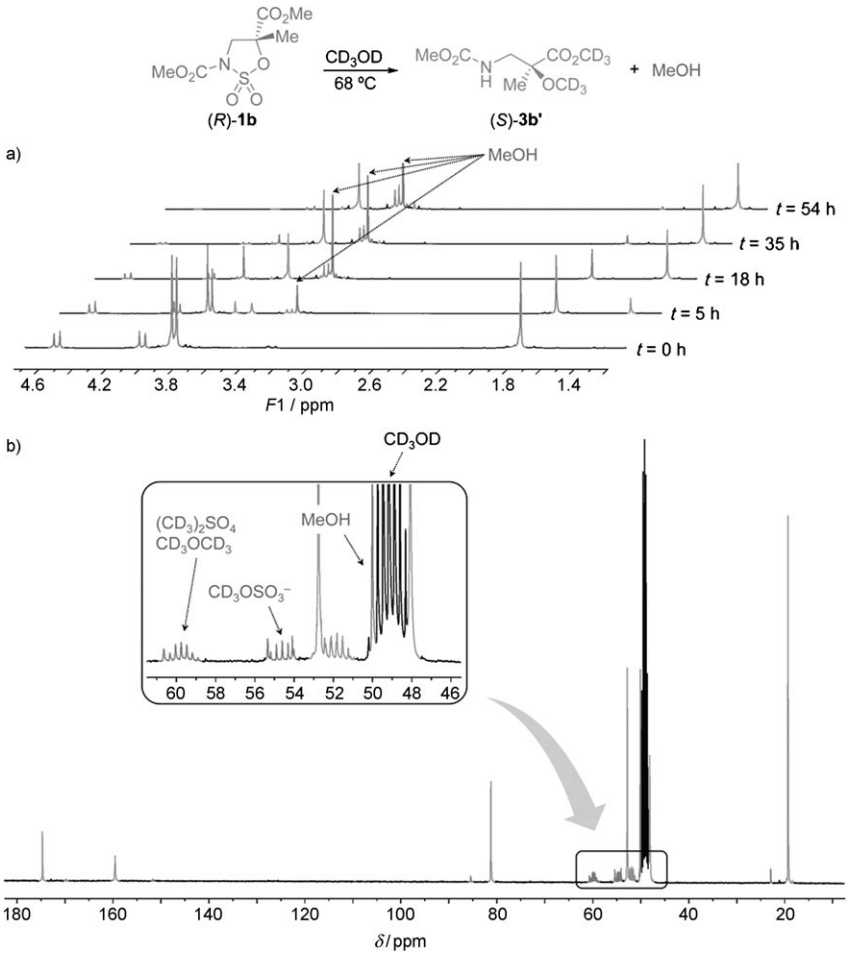


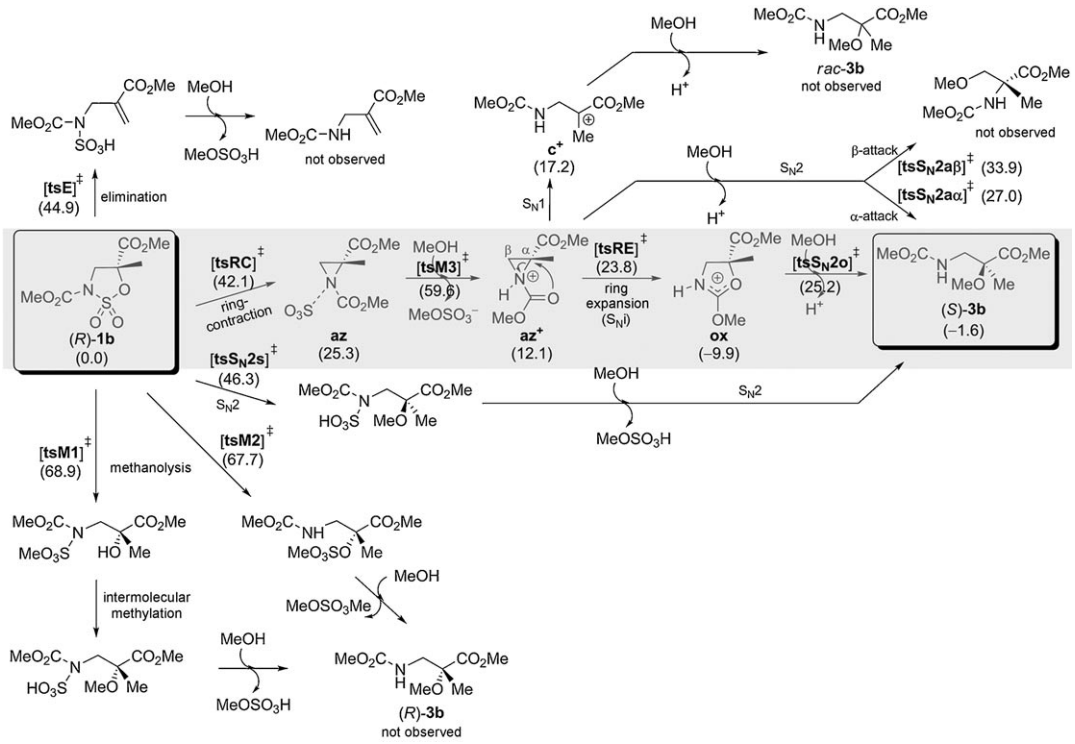
Figure 3. Reaction of sulfamidate (*R*)-**1b** with CD_3OD monitored by NMR spectroscopy. a) The stacked ^1H NMR spectra show the clean and direct conversion of (*R*)-**1b** into (*S*)-**3b′** and the simultaneous (but faster) disappearance of the ester signals in both the reactant and the product (CO_2Me, $\delta = 3.89$ and 3.75 ppm, respectively) due to transesterification with CD_3OD (with the subsequent evolution of MeOH). As a consequence, a slight growing of the ether signal (OCH_3, $\delta = 3.31$ ppm) arising from the competitive ring opening with the generated MeOH is also appreciated. b) The ^{13}C NMR spectrum shows the presence of small amounts of deuterated dimethyl ether and sulfonic derivatives at the end of the reaction.

6) The pseudo-first-order kinetics of the ring-opening reaction of (*R*)-**1b** with methanol (measured by GC analysis) and [D_4]MeOH (measured by ^1H NMR spectroscopy, Figure 3a) were studied at different initial concentrations of substrate and effective (also called "apparent") kinetic constants were obtained (see the Supporting Information).[20,21]

In view of all these experimental results, and despite the nondetection of any intermediates along the reaction pathway, the possibility of a stepwise mechanism was considered. The spontaneous conversion of sulfamidates into aziridines with release of SO_3 in neutral media has been previously reported,[4g,h] being also a common secondary reaction in the preparation of sulfamidates.[4i,j] In addition, the thermal, nucleophilic, or acid-catalyzed ring expansion of *N*-acylaziridines into oxazolines to obtain protected 1,2-aminoalcohols is a common strategy in organic synthesis,[22] which has been studied both experimentally and theoretically.[23] Finally, there are many examples in the literature describing the regioselective ring opening of oxazolines with nucleophiles at the 5-position in acidic media (in competition with the usual reactivity at the 2-position).[24]

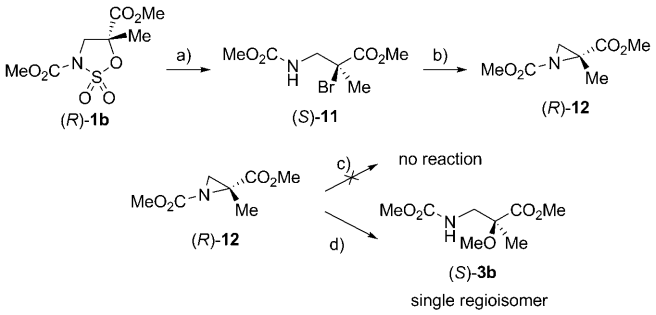
Therefore, a stepwise mechanism involving the ring contraction of sulfamidate (*R*)-**1b** into the corresponding aziridine derivative and its subsequent regioselective ring expansion to an oxazolinium, followed by the regioselective nucleophilic attack at the 5-position with inversion of the quaternary carbon atom (Scheme 8), is a reasonable pathway to be considered together with the direct S_N2 ring opening of the sulfamidate. This novel mechanism could explain the key role of the neighboring carbamate group in the stereoselective ring-opening reaction of hindered sulfamidates with alcohols (i.e., by forming an oxazolinic intermediate).

The regioselective nucleophilic ring opening of the sulfamidate-derived aziridine is another possibility that must be taken into account. With this in mind, 2-methylaziridine (*R*)-**12**,[25] which was prepared by intramolecular ring closure of bromide (*S*)-**11** in the presence of *t*BuOK as a base, was treated with methanol at reflux under different conditions. Noticeably, and according to previous results reported for analogue 2-aziridinecarboxylic acids,[5i] this substrate remained unaltered under neutral conditions, but when an equimolecular amount of *p*TsOH was added a full conversion into (*S*)-**3b**, as a single regioisomer with a high enantiomeric purity, was observed (Scheme 9). It must be noted that, as mentioned in the Introduction, 2-methylaziridine-2-carboxilic acid derivatives have been opened regioselectively at both the secondary (mainly with hard nucleophiles and/or in basic conditions[7a–c]) and the quaternary (mostly with soft nucleophiles and/or with acid activation[7c–f]) positions. Therefore, these results are in good agreement with those previously reported for similar substrates and reinforce the possibility of acid-activated aziridine (*R*)-**12** (i.e., its related aziridinium cation) as an inter-



Scheme 8. Possible reaction channels calculated from sulfamidate (*R*)-**1b**. The minimum-energy pathway is depicted in red and relative energies (ΔG, in parentheses) are given in kcal mol^{-1}.

mediate involved in the ring-opening reaction of sulfamidate (*R*)-**1b**.



Scheme 9. Synthesis and ring-opening reaction of sulfamidate-derived aziridine (*R*)-**12**. a) i) Bu_4NBr, CH_3CN, 25 °C, 20 h; ii) 20 % H_2SO_4/CH_2Cl_2 1:1, 25 °C, 8 h (76 %); b) *t*BuOK, THF, 0 °C, 12 h (43 %, unoptimized conditions); c) MeOH, 68 °C, 48 h; d) MeOH, *p*TsOH·H_2O (1.0 equiv), 68 °C, 48 h (86 % conv., *ee* > 93 % determined by GC analysis, see the Supporting Information).

Theoretical calculations: To evaluate the experimentally based mechanistic hypothesis mentioned above, several reaction pathways starting from sulfamidate (*R*)-**1b** were calculated by using DFT methods (see the Supporting Information). Solvent effects were envisaged to have a decisive influence on the relative stability of the calculated species, particularly of those charged; hence, bulky solvent effects were considered for all the structures through the polarizable continuum model by using methanol parameters. In addition, and given that the methoxide anion failed experimentally to achieve the ring opening of sulfamidate (*R*)-**1b**, all nucleophilic displacements were calculated by using methanol as the nucleophile. Apart from the ring-opening reaction mechanism (S_N2 and stepwise pathways), other possible reactions (although not observed experimentally) were theoretically explored (Scheme 8 and Supporting Information). Figure 4 shows the most remarkable geometrical features of selected minimum-energy transition states (TSs) and intermediates, with a detailed description of all the calculated structures available in the Supporting Information.

In view of the experimental results, the rate-determining step of the global reaction should be the first one starting from sulfamidate (*R*)-**1b**. This point was confirmed theoretically by inspecting all the reaction barriers involved in the whole process. Thus, the activation energy calculated for the ring contraction of sulfamidate into aziridine (**tsRC**, $\Delta G^{\neq} = 42.1$ kcal mol^{-1}) was lower than those associated with the S_N2 reaction (**tsS$_N$2s**, $\Delta G^{\neq} = 46.3$ kcal mol^{-1}), elimination (**tsE**, $\Delta G^{\neq} = 44.9$ kcal mol^{-1}), and much lower than the methanolysis of the S–O (**tsM1**) and S–N (**tsM2**) bonds ($\Delta G^{\neq} = 68.9$ and 67.7 kcal mol^{-1}, respectively). This first step of the mechanism could provide a useful explanation to sulfamidate/aziridine ring contraction, a reaction observed for a long time, the mechanism of which had not been described previously.[4g,h]

To test the influence of the carbamate group on the activation energy of both the ring contraction and S_N2 process-

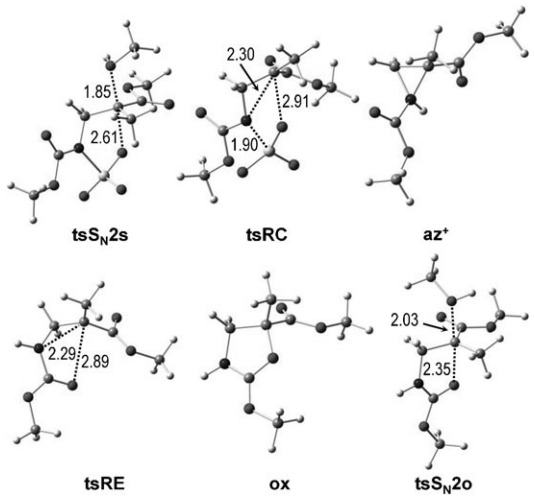


Figure 4. Most relevant minimum-energy structures and TSs at the B3LYP/6-31+G(d,p) level calculated for all the proposed pathways starting from sulfamidate (*R*)-**1b**. Distances are given in Å.

es, the energy barriers of these pathways were calculated from sulfamidate (*R*)-**2b** (**tsRC′** and **tsS$_N$2s′**, $\Delta G^{\neq}=41.2$ and 47.6 kcal mol^{-1}, respectively), and were very similar to those calculated from (*R*)-**1b**. Therefore, the carbamate group does not confer an extra inductive activation to the sulfamidate moiety, although the ring-opening reaction does not take place experimentally in the absence of the former. This result indicates that a direct S_N2 is not the most feasible ring-opening mechanism of sulfamidate (*R*)-**1b**, and encouraged us to further explore its energy surface to gain insights into the whole mechanism.

Markedly, the heterolytic cleavage of the C–O bond in the ring-contraction process did not result in any stable "naked" carbocationic structure, or in any ionic pair between the quaternary carbon atom and the NSO_3^- moieties. In contrast, as demonstrated by IRC calculations, the N atom attacks at the quaternary position at the same time that the C–O bond is breaking to form the corresponding aziridine (**az**) in a concerted way.

It is important to note that, after formation of the aziridine–SO_3 complex, the SO_3 moiety lies greatly separated from the molecule ($d_{N-S}=2.23$ Å), which is in agreement with the experimental spontaneous cleavage of the sulfamic acid. Therefore, the next calculated step was the conversion of the aziridine–SO_3 complex (**az**) into the corresponding aziridinium cation **az$^+$** (13.1 kcal mol^{-1} lower in energy) after protonation with the sulfonic acid generated in the reaction of methanol with SO_3 (**tsM3**). The activation energy of this process calculated from the aziridine–SO_3 complex was $\Delta G^{\neq}=34.3$ kcal mol^{-1}.

This activated aziridinium cation[26] could undergo a regioselective ring-expansion reaction into the corresponding oxazolinium cation (**tsRE**, $\Delta G^{\neq}=11.7$ kcal mol^{-1}) together with the ring-opening reaction with methanol at both the secondary (**tsS$_N$2aβ**, β-attack, $\Delta G^{\neq}=21.8$ kcal mol^{-1}, disfavored) and quaternary (**tsS$_N$2aα**, α-attack, $\Delta G^{\neq}=14.9$ kcal mol^{-1}, favored) positions by means of a S_N2 mechanism. Theoretical calculations on regioselective ring-opening reactions of aziridinium systems have been extensively studied.[27] Thus, and according to previous theoretical studies,[24] the formation of the oxazolinium derivative (**ox**) by means of a S_Ni mechanism was more favorable than the substitution with a poor nucleophile like methanol by 3.2 kcal mol^{-1}. It is worth mentioning that no transition structure for the ring-expansion of this aziridinium cation, by means of attack of the carbonyl group at the less-hindered β-position could be located, which means that this process could only have taken place at the more substituted α-position. This preference of the incoming nucleophile to react at the most-hindered carbon atom could be a consequence of the well-known ability of quaternary carbon atoms to stabilize the partial positive charge generated in the transition structures.

A point to note is that the formation of a "naked" planar carbocation (**c$^+$**) through a barrierless S_N1 process was also detected in this region of the PES, although this structure was found to be much less stable (27.1 kcal mol^{-1} higher in energy) than the oxazolinium cation, which appeared to be exceedingly stable in the calculations. The final nucleophilic attack of methanol at the 5-position of this derivative, by means of a S_N2 mechanism (**tsS$_N$2o**, $\Delta G^{\neq}=35.1$ kcal mol^{-1}) led to the final product (*S*)-**3b** as a single regioisomer and with inversion of configuration at the quaternary carbon atom.

In summary, the theoretical calculations carried out in this work suggest a multistep mechanism for the ring opening of sulfamidate (*R*)-**1b** with methanol as the nucleophile. Hence, the minimum-energy pathway of this process involves the ring contraction of sulfamidate into an aziridine–SO_3 complex as the rate-determining step (highest activation energy), followed by the fast (lower activation barriers) release of SO_3 to form an aziridinium cation, its subsequent ring-expansion into an oxazolinium cation, and, finally, the regio- and stereoselective opening of this derivative at the quaternary position with inversion of configuration. In this mechanism, the SO_3 moiety of sulfamidate acts as an "acid reservoir" in the presence of methanol, producing increasing amounts of sulfonic acid(s) at the sulfamidate–aziridine interconversion step and promoting the ring-opening reaction. These computational results are in good agreement with the aforementioned experimental observations.

Conclusions

The thorough study on the reactions of hindered ester or amide-derived sulfamidates with O nucleophiles in acidic and neutral media has given us a greater insight into the reactivity of these systems. Thus, it is possible to fully direct the chemoselectivity of the reactions towards ring opening, amide–ester exchange, or carbamate deprotection depending on the experimental conditions. The most important outcome of this study is the development of a conceptually new, simple, and self-promoted practical method for the

ring-opening reaction of hindered sulfamidates by using alcohols as O nucleophiles, allowing the synthesis of interesting enantiopure $\beta^{2,2}$-amino acids. This methodology overcomes one of the most reported drawbacks in the chemistry of cyclic sulfamidates: the ring-opening reaction of these substrates with alcohols. In addition, this is carried out in the absence of external activators and under mild conditions, at a quaternary carbon atom and with inversion of configuration. Moreover, the cleavage of sulfamic acid derived intermediates is totally suppressed within this protocol, which allows a greater compatibility with other functional groups present on the molecule. This observed reactivity has been explained by means of a multistep mechanism involving aziridinium and oxazolinium intermediates as found by theoretical calculations. We think that this new strategy broadens the chemistry of sulfamidates and will be useful for a number of synthetic organic chemists in the future.

Experimental Section

General procedures: All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere by using standard Schlenk techniques. Solvents were purified according to standard procedures. The chemical reagents were purchased from Aldrich Chemical Co. Analytical TLC was performed by using Polychrom SI F254 plates. Column chromatography was performed by using Kieselgel 60 (230–400 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, concentrated under reduced pressure by using a rotary evaporator. NMR spectra were recorded on Bruker ARX 300 and Bruker Avance 400 spectrometers 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 Hz. Mass spectra were obtained by electrospray ionization (ESI). Melting points were determined on a Büchi B-545 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in a 1 dm cell of 1 mL capacity. Microanalyses were carried out on a CE Instruments EA-1110 analyzer and are in good agreement with the calculated values.

(*R*)-5-Methyl-5-(*N*-methoxy-*N*-methylcarbamoyl)-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine ((*R*)-2a): $Sm(TfO)_3$ (238 mg, 0.39 mmol) was added to a solution of sulfamidate (*R*)-**1a** (110 mg, 0.39 mmol) in MeOH (10 mL), and the mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in a mixture of CH_2Cl_2 (15 mL) and an aqueous 2 M HCl solution (10 mL). Then, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and the residue was purified by silica-gel column chromatography (hexane/AcOEt 7:3) to give compound (*R*)-**2a** (82 mg, 94%) as a colorless oil. $[\alpha]_D^{25}=-46.3$ ($c=1.04$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.77$ (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 ppm (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=21.8$ (CH_3), 33.7 (NCH_3), 52.5 (CH_2N), 61.7 ($NOCH_3$), 90.7 (CCH_3), 167.8 ppm (CON); elemental analysis 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; ESI+: m/z: 225.2.

Methyl (*R*)-5-methyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-5-carboxylate ((*R*)-2b): $Sm(TfO)_3$ (232 mg, 0.38 mmol) was added to a solution of sulfamidate (*R*)-**1b** (97 mg, 0.38 mmol) in MeOH (10 mL) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in a mixture of CH_2Cl_2 (15 mL) and an aqueous 2 M HCl solution (10 mL). Then, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and the residue was purified by silica-gel column chromatography (hexane/AcOEt 7:3) to give compound (*R*)-**4b** (74 mg, 99%) as a colorless oil. $[\alpha]_D^{25}=-24.4$ ($c=1.30$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.75$ (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 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=22.5$ (CH_3), 52.1 (CH_2N), 53.7 (CO_2CH_3), 88.0 (CCH_3), 169.8 ppm (CO_2); elemental analysis 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; ESI+: m/z: 196.2.

General procedure for amide–ester exchange in cyclic sulfamidates (conditions A in Table 1): Sulfamidate (*R*)-**1a** (1.0 equiv) was dissolved in the corresponding alcohol (20 mL) (see Table 1) and the solution was cooled to 0 °C, then TfOH (1.5 equiv) was added dropwise. The temperature of the reaction was slowly increased to 40 °C and the mixture was stirred for 24 h (48 h and 80 °C in the case of *i*PrOH). The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (30 mL). The acid was then neutralized by addition of a saturated solution of $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and the residue was purified by flash silica-gel column chromatography, to give the corresponding sulfamidates (*R*)-**1b–j**.

Methyl (*R*)-5-ethoxycarbonyl-5-methyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1c): Compound (*R*)-**1c** (120 mg, 94%) was obtained as a white solid, starting from sulfamidate (*R*)-**1a** (135 mg, 0.48 mmol), after purification by column chromatography (hexane/AcOEt 8:2). M.p. 72–74 °C; $[\alpha]_D^{25}=-59.1$ ($c=1.33$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.35$ (t, 3H, $J=7.2$ Hz; CH_2CH_3), 1.82 (s, 3H; CCH_3), 3.88–3.97 (m, 4H; $CH_2N+CO_2CH_3$), 4.27–4.42 (m, 2H; CH_2CH_3), 4.59 ppm (d, 1H, $J=10.4$ Hz; CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=13.9$ (CH_2CH_3), 22.7 (CCH_3), 53.0 (CH_2N), 54.8 (CO_2CH_3), 63.3 (CH_2CH_3), 83.4 (CCH_3), 150.0 (NCO), 167.7 ppm (CO_2); elemental analysis calcd (%) for ($C_8H_{13}NO_7S$): C 35.95, H 4.90, N 5.24, S 12.00; found: C 35.81, H 4.92, N 5.26, S 12.04; ESI+: m/z: 268.3.

Methyl (*R*)-5-methyl-5-(*n*-propoxy)carbonyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1d): Compound (*R*)-**1d** (135 mg, 93%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1a** (145 mg, 0.51 mmol), after purification by column chromatography (hexane/AcOEt 8:2). $[\alpha]_D^{25}=-59.1$ ($c=1.64$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.98$ (t, 3H, $J=7.4$ Hz; $CH_2CH_2CH_3$), 1.67–1.79 (m, 2H; $CH_2CH_2CH_3$), 1.83 (s, 3H; CCH_3), 3.89–3.96 (m, 4H; $CH_2N+CO_2CH_3$), 4.16–4.31 (m, 2H; $CH_2CH_2CH_3$), 4.59 ppm (d, 1H, $J=10.4$ Hz; CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=10.1$ ($CH_2CH_2CH_3$), 21.7 ($CH_2CH_2CH_3$), 22.8 (CCH_3), 53.0 (CH_2N), 54.8 (CO_2CH_3), 68.8 ($CH_2CH_2CH_3$), 83.5 (CCH_3), 150.0 (NCO), 167.8 ppm (CO_2); elemental analysis calcd (%) for ($C_9H_{15}NO_7S$): C 38.43, H 5.38, N 4.98, S 11.40; found: C 38.31, H 5.36, N 5.00, S 11.43; ESI+: m/z: 282.3.

Methyl (*R*)-5-(*n*-butoxycarbonyl)-5-methyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1e): Compound (*R*)-**1e** (118 mg, 89%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1a** (127 mg, 0.45 mmol), after purification by column chromatography (hexane/AcOEt 8:2). $[\alpha]_D^{25}=-58.7$ ($c=1.62$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.95$ (t, 3H, $J=7.4$ Hz; $CH_2CH_2CH_2CH_3$), 1.33–1.50 (m, 2H; $CH_2CH_2CH_2CH_3$), 1.62–1.78 (m, 2H; $CH_2CH_2CH_2CH_3$), 1.82 (s, 3H; CCH_3), 3.87–3.97 (m, 4H; $CH_2N+CO_2CH_3$), 4.19–4.34 (m, 2H; $CH_2CH_2CH_2CH_3$), 4.58 ppm (d, 1H, $J=10.4$ Hz; CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=13.5$ ($CH_2CH_2CH_2CH_3$), 18.8 ($CH_2CH_2CH_2CH_3$), 22.7 (CCH_3), 30.2 ($CH_2CH_2CH_2CH_3$), 53.0 (CH_2N), 54.8 (CO_2CH_3), 67.1 ($CH_2CH_2CH_2CH_3$), 83.5 (CCH_3), 150.0 (NCO), 167.8 ppm (CO_2); elemental analysis calcd (%) for ($C_{10}H_{17}NO_7S$): C 40.67, H 5.80, N 4.74, S 10.86; found: C 40.81, H 5.82, N 4.72, S 10.82; ESI+: m/z: 296.3.

Methyl (*R*)-5-methyl-5-(*n*-pentyloxy)carbonyl-2,2-dioxo-2λ^6-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1f): Compound (*R*)-**1f** (130 mg, 90%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1a** (132 mg, 0.47 mmol), after purification by column chromatography (hexane/AcOEt 8:2). $[\alpha]_D^{25}=-54.5$ ($c=2.43$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.82$–1.03 (m, 3H; $CH_2CH_2CH_2CH_2CH_3$), 1.24–1.45 (m, 4H; $CH_2CH_2CH_2CH_2CH_3$), 1.61–1.79 (m, 2H; $CH_2CH_2CH_2CH_2CH_3$), 1.82 (s, 3H; CCH_3), 3.83–4.02 (m, 4H; $CH_2N+CO_2CH_3$), 4.17–4.36 (m, 2H; $CH_2CH_2CH_2CH_2CH_3$), 4.58 ppm (d, 1H, $J=$

10.4 Hz; CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ ($CH_2CH_2CH_2CH_2CH_3$), 22.1 ($CH_2CH_2CH_2CH_2CH_3$), 22.7 (CCH_3), 27.6, 27.8 ($CH_2CH_2CH_2CH_2CH_3$), 53.0 (CH_2N), 54.7 (CO_2CH_3), 67.3 ($CH_2CH_2CH_2CH_2CH_3$), 83.5 (CCH_3), 149.9 (NCO), 167.7 ppm (CO_2); elemental analysis calcd (%) for ($C_{11}H_{19}NO_7S$): C 42.71, H 6.19, N 4.53, S 10.37; found: C 42.59, H 6.16, N 4.56, S 10.41; ESI+: *m/z*: 310.3.

Methyl (*R*)-5-allyloxycarbonyl-5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1g): Compound (*R*)-**1g** (101 mg, 86%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1a** (119 mg, 0.42 mmol), after purification by column chromatography (hexane/AcOEt 8:2). $[\alpha]_D^{25} = -54.7$ ($c = 2.52$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.84$ (s, 3H; CCH_3), 3.87–4.00 (m, 4H; $CH_2N + CO_2CH_3$), 4.59 (d, 1H, $J = 10.4$ Hz; CH_2N), 4.76 (ddd, 2H, $J = 6.2$, 2.6, 1.3 Hz; $CH_2CH{=}CH_2$), 5.29–5.47 (m, 2H; $CH_2CH{=}CH_2$), 5.94 ppm (tdd, 1H, $J =$ 17.6, 10.5, 5.9 Hz; $CH_2CH{=}CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.7$ (CCH_3), 52.9 (CH_2N), 54.7 (CO_2CH_3), 67.5 ($CH_2CH{=}CH_2$), 83.4 (CCH_3), 119.9 ($CH_2CH{=}CH_2$), 130.4 ($CH_2CH{=}CH_2$), 149.9 (NCO), 167.4 ppm (CO_2); elemental analysis calcd (%) for ($C_9H_{13}NO_7S$): C 38.71, H 4.69, N 5.02, S 11.48; found: C 38.55, H 4.67, N 5.04, S 11.52; ESI+: *m/z*: 280.3.

Methyl (*R*)-5-isobutoxycarbonyl-5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1h): Compound (*R*)-**1h** (142 mg, 91%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1a** (149 mg, 0.53 mmol), after purification by column chromatography (hexane/AcOEt 8:2). $[\alpha]_D^{25} = -56.6$ ($c = 2.24$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.79$–1.00 (m, 6H; $CH_2CH(CH_3)_2$), 1.75 (s, 3H; CCH_3), 1.87–2.03 (m, 1H; $CH_2CH(CH_3)_2$), 3.76–3.91 (m, 4H; $CH_2N + CO_2CH_3$), 3.91–4.05 (m, 2H; $CH_2CH(CH_3)_2$), 4.51 ppm (d, 1H, $J = 10.4$ Hz; CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$ ($CH_2CH(CH_3)_2$), 22.8 (CCH_3), 27.5 ($CH_2CH(CH_3)_2$), 53.0 (CH_2N), 54.7 (CO_2CH_3), 73.0 ($CH_2CH(CH_3)_2$), 83.5 (CCH_3), 149.9 (NCO), 167.7 ppm (CO_2); elemental analysis calcd (%) for ($C_{10}H_{17}NO_7S$): C 40.67, H 5.80, N 4.74, S 10.86; found: C 40.82, H 5.78, N 4.76, S 10.90; ESI+: *m/z*: 296.3.

Methyl (*R*)-5-isopentoxycarbonyl-5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1i): Compound (*R*)-**1i** (135 mg, 93%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1a** (132 mg, 0.47 mmol), after purification by column chromatography (hexane/AcOEt 8:2). $[\alpha]_D^{25} = -56.6$ ($c = 1.90$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.77$–1.07 (m, 7H; $CH_2CH_2CH(CH_3)_2$), 1.50–1.93 (m, 5H; $CCH_3 + CH_2CH_2CH(CH_3)_2$), 3.80–4.01 (m, 4H; $CH_2N + CO_2CH_3$), 4.02–4.38 (m, 2H; $CH_2CH_2CH(CH_3)_2$), 4.56 ppm (d, 1H, $J =$ 10.4 Hz; CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.1$, 16.1 ($CH_2CH_2CH(CH_3)_2$), 22.2 ($CH_2CH_2CH(CH_3)_2$), 22.7 (CCH_3), 24.9, 25.8, 33.9, 36.8 ($CH_2CH_2CH(CH_3)_2$), 53.0 (CH_2N), 54.8 (CO_2CH_3), 66.0, 71.7 ($CH_2CH_2CH(CH_3)_2$), 83.5 (CCH_3), 150.0 (NCO), 167.8 ppm (CO_2); elemental analysis calcd (%) for ($C_{11}H_{19}NO_7S$): C 42.71, H 6.19, N 4.53, S 10.37; found: C 42.58, H 6.23, N 4.55, S 10.40; ESI+: *m/z*: 310.3.

Methyl (*R*)-5-isopropoxycarbonyl-5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1j): Compound (*R*)-**1j** (122 mg, 79%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1a** (155 mg, 0.55 mmol), after purification by column chromatography (hexane/AcOEt 8:2); $[\alpha]_D^{25} = -59.2$ ($c = 1.09$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$–1.48 (m, 6H; $CH(CH_3)_2$), 1.79 (s, 3H; CCH_3), 3.80–4.02 (m, 4H; $CH_2N + CO_2CH_3$), 4.57 (d, 1H, $J = 10.2$ Hz; CH_2N), 5.01–5.25 ppm (m, 1H; $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$ ($CH(CH_3)_2$), 22.7 (CCH_3), 53.0 (CH_2N), 54.8 (CO_2CH_3), 71.7 ($CH(CH_3)_2$), 83.4 (CCH_3), 150.0 (NCO), 167.2 ppm (CO_2); elemental analysis calcd (%) for ($C_9H_{15}NO_7S$): C 38.43, H 5.38, N 4.98, S 11.40; found: C 38.52, H 5.36, N 4.96, S 11.44; ESI+: *m/z*: 282.3.

Methyl (*R*)-5-benzyloxycarbonyl-5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-1k): TsOH·H_2O (141 mg, 0.74 mmol) and benzylic alcohol (159 mg, 1.47 mmol) were added to a solution of sulfamidate (*R*)-**1a** (139 mg, 0.49 mmol) in toluene (10 mL) and the mixture was stirred at reflux for 24 h. After evaporating the solvent, the residue was dissolved in CH_2Cl_2 (30 mL) and the acid was neutralized by addition of an aqueous saturated solution of $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3× 30 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and the residue purified by silica-gel column chromatography (hexane/AcOEt 8:2), to give compound (*R*)-**1k** (144 mg, 89%) as a colorless oil. $[\alpha]_D^{25} = -42.3$ ($c = 1.11$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.80$ (s, 3H; CH_3), 3.80–4.00 (m, 4H; $CH_2N + CO_2CH_3$), 4.57 (d, 1H, $J = 10.5$ Hz; CH_2N), 5.27 (s, 2H; CH_2Ph), 7.31–7.49 ppm (m, 5H; Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.6$ (CH_3), 52.9 (CH_2N), 54.8 (CO_2CH_3), 68.8 (CH_2Ph), 83.4 (CCH_3), 128.3, 128.7, 128.8, 134.1 (Ph), 149.9 (NCO), 167.6 ppm (CO_2); elemental analysis calcd (%) for ($C_{13}H_{15}NO_7S$): C 47.41, H 4.59, N 4.25, S 9.74; found: C 47.52; H 4.61, N 4.27, S 9.71; ESI+: *m/z*: 330.3.

General procedure for the ring opening of cyclic sulfamidates with alcohols (conditions B in Table 1): The corresponding sulfamidate (*R*)-**1b–j** was dissolved in the corresponding alcohol (see Table 1) and the solution was heated at 70–80°C for 48 h (120 h in the case of *i*PrOH). The reactions were monitored by TLC. After evaporating the solvent, the corresponding ring-opening products (*S*)-**3b–j** were cleanly obtained as colorless oils. Moreover, the products were purified by flash silica-gel column chromatography.

Methyl (*S*)-2-methoxy-2-methoxycarbonylaminomethylpropanoate ((*S*)-3b)

Method 1 (conditions B in Table 1): Following the general procedure described for the ring opening of sulfamidates with alcohols, compound (*S*)-**3b** (97 mg, 93%) was obtained by starting from sulfamidate (*R*)-**1b** (145 mg, 0.51 mmol), after purification by flash silica-gel column chromatography (hexane/AcOEt 7:3).

Method 2 (one-pot): TfOH (0.2 mL, 1.74 mmol) was added dropwise t o a precooled (0°C) solution of sulfamidate (*R*)-**1a** (327 mg, 1.16 mmol) in MeOH (10 mL). The temperature of the reaction was slowly increased to 70–80°C and the mixture was stirred for 48 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (30 mL). The acid was then neutralized by addition of a saturated solution of $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and the residue was purified by flash silica-gel column chromatography (hexane/AcOEt 7:3) to give compound (*S*)-**3b** as a colorless oil (232 mg, 98%). $[\alpha]_D^{25} = -4.6$ ($c = 1.33$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 3H; CCH_3), 3.28 (s, 3H; $COCH_3$), 3.38 (dd, 1H, $J = 13.9$, 5.9 Hz; CH_2N), 3.52 (dd, 1H, $J = 13.8$, 6.5 Hz; CH_2N), 3.63 (s, 3H; CO_2CH_3), 3.72 (s, 3H; CO_2CH_3), 4.87–5.27 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.6$ (CCH_3), 47.1 (CH_2N), 52.1, 52.2, 52.3, ($COCH_3 + CO_2CH_3 + CO_2CH_3$), 79.5 ($CCH_3$), 157.0 (NCO), 172.8 ($CO_2$); elemental analysis calcd (%) for ($C_8H_{15}NO_5$): C 46.82, H 7.37, N 6.83; found: C 47.00, H 7.39, N 6.81; ESI+: *m/z*: 206.2.

Ethyl (*S*)-2-ethoxy-2-methoxycarbonylaminomethylpropanoate ((*S*)-3c): Compound (*S*)-**3c** (96 mg, 94%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1c** (117 mg, 0.44 mmol), after purification by column chromatography (hexane/AcOEt 9:1). $[\alpha]_D^{25} = 0.0$ ($c = 1.03$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (t, 3H, $J = 7.0$ Hz; CH_2CH_3), 1.26 (t, 3H, $J = 7.2$ Hz; CH_2CH_3), 1.38 (s, 3H; CCH_3), 3.33–3.58 (m, 4H; $COCH_2 + CH_2N$), 3.64 (s, 3H; CO_2CH_3), 4.12–4.24 (m, 2H; CO_2CH_2), 4.82–5.22 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 14.1 (CH_2CH_3), 15.6 (CH_2CH_3), 19.3 (CCH_3), 47.5 (CH_2N), 52.1 (CO_2CH_3), 60.1 ($COCH_2$), 61.2 (CO_2CH_2), 79.2 (CCH_3), 157.0 (NCO), 172.7 ppm (CO_2); elemental analysis calcd (%) for ($C_{10}H_{19}NO_5$): C 51.49, H 8.21, N 6.00; found: C 51.62, H 8.18, N 6.02; ESI+: *m/z*: 234.3.

***n*-Propyl (*S*)-2-methoxycarbonylaminomethyl-2-(*n*-propoxy)propanoate ((*S*)-3d)**: Compound (*S*)-**3d** (109 mg, 91%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1d** (129 mg, 0.46 mmol), after purification by column chromatography (hexane/AcOEt 9:1). $[\alpha]_D^{25} = -2.3$ ($c =$ 1.19 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$–0.99 (m, 6H; $CH_2CH_2CH_3 + CH_2CH_2CH_3$), 1.39 (s, 3H; CCH_3), 1.50–1.76 (m, 4H; $CH_2CH_2CH_3 + CH_2CH_2CH_2CH_3$), 3.30–3.46 (m, 3H; $COCH_2 + CH_2N$), 3.53 (dd, 1H, $J = 13.7$, 6.2 Hz; CH_2N), 3.65 (s, 3H; CO_2CH_3), 4.08 (t, 2H, $J =$ 6.7 Hz; CO_2CH_2), 4.81–5.17 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.3$, 10.5 ($CH_2CH_2CH_3 + CH_2CH_2CH_3$), 19.3 ($CCH_3$), 21.9, 23.3 ($CH_2CH_2CH_3 + CH_2CH_2CH_3$), 47.6 ($CH_2N$), 52.1 ($CO_2CH_3$), 66.2 ($COCH_2$), 66.8 ($CO_2CH_2$), 79.0 ($CCH_3$), 157.0 (NCO), 172.8 ppm (CO_2); elemental analysis calcd (%) for ($C_{12}H_{23}NO_5$): C 55.16, H 8.87, N 5.36; found: C 55.31, H 8.90, N 5.34; ESI+: *m/z*: 262.3.

***n*-Butyl (*S*)-2-(*n*-butoxy)-2-methoxycarbonylaminomethylpropanoate ((*S*)-3e)**: Compound (*S*)-**3e** (104 mg, 93%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1e** (114 mg, 0.39 mmol), after purification by column chromatography (hexane/AcOEt 9:1). $[\alpha]_D^{25}=-1.7$ ($c=1.04$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.84$–0.96 (m, 6H; $CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_3$), 1.27–1.44 (m, 7H; $CCH_3+CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_3$), 1.46–1.67 (m, 4H; $CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_3$), 3.30–3.44 (m, 3H; $COCH_2+CH_2N$), 3.51 (dd, 1H, $J=13.6$, 6.2 Hz; CH_2N), 3.64 (s, 3H; CO_2CH_3), 4.10 (t, 2H, $J=6.6$ Hz; CO_2CH_2), 4.80–5.15 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=13.6$, 13.9 ($CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_3$), 19.1, 19.2, 19.3 ($CCH_3+CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_3$), 30.5, 32.2 ($CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_3$), 47.6 ($CH_2N$), 52.1 ($CO_2CH_3$), 64.3 ($COCH_2$), 65.0 ($CO_2CH_2$), 79.1 ($CCH_3$), 157.0 (NCO), 172.8 ppm (CO_2); elemental analysis calcd (%) for ($C_{14}H_{27}NO_5$): C 58.11, H 9.40, N 4.84; found: C 58.29, H 9.43, N 4.82; ESI+: *m*/*z*: 290.4.

***n*-Pentyl (*S*)-2-methoxycarbonylaminomethyl-2-(*n*-pentoxy)propanoate ((*S*)-3f)**: Compound (*S*)-**3f** (113 mg, 88%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1f** (125 mg, 0.40 mmol), after purification by column chromatography (hexane/AcOEt 9:1). $[\alpha]_D^{25}=-1.8$ ($c=1.10$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=0.75$–1.02 (m, 6H; $CH_2CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_2CH_3$), 1.16–1.45 (m, 11H; $CCH_3+CH_2CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_2CH_3$), 1.46–1.74 (m, 4H; $CH_2CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_2CH_3$), 3.26–3.43 (m, 3H; $COCH_2+CH_2N$), 3.50 (dd, 1H, $J=13.6$, 6.2 Hz; CH_2N), 3.63 (s, 3H; CO_2CH_3), 4.09 (t, 2H, $J=6.7$ Hz; CO_2CH_2), 4.80–5.13 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=13.6$, 14.0 ($CH_2CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_2CH_3$), 19.3 ($CCH_3$), 22.2, 22.5 ($CH_2CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_2CH_3$), 28.0, 28.2 ($CH_2CH_2CH_2CH_2CH_3+CH_2CH_2CH_2CH_2CH_3$), 29.8 ($CH_2CH_2CH_2CH_2CH_3$), 47.5 ($CH_2N$), 52.1 ($CO_2CH_3$), 64.6 ($COCH_2$), 65.3 ($CO_2CH_2$), 79.1 ($CCH_3$), 157.0 (NCO), 172.8 ppm (CO_2); elemental analysis calcd (%) for ($C_{16}H_{31}NO_5$): C 60.54, H 9.84, N 4.41; found: C 60.71, H 9.87, N 4.39; ESI+: *m*/*z*: 318.4.

Allyl (*S*)-2-allyloxy-2-methoxycarbonylaminomethylpropanoate ((*S*)-3g): Compound (*S*)-**3g** (66 mg, 84%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1g** (85 mg, 0.30 mmol), after purification by column chromatography (hexane/AcOEt 9:1). $[\alpha]_D^{25}=+4.9$ ($c=1.01$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.38$ (s, 3H; CCH_3), 3.38 (dd, 1H, $J=13.7$, 5.6 Hz; CH_2N), 3.52 (dd, 1H, $J=13.7$, 6.3 Hz; CH_2N), 3.59 (s, 3H; CO_2CH_3), 3.81–4.04 (m, 2H; $COCH_2$), 4.46–4.67 (m, 2H; CO_2CH_2), 4.94–5.35, (m, 5H; $CH_2CH=CH_2+CH_2CH=CH_2+NH$), 5.72–5.97 ppm (m, 2H; $CH_2CH=CH_2+CH_2CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.3$ (CCH_3), 47.6 (CH_2N), 52.2 (CO_2CH_3), 65.8 ($COCH_2$), 66.0 (CO_2CH_2), 79.6 (CCH_3), 116.8, 118.8 ($CH_2CH=CH_2+CH_2CH=CH_2$), 131.6, 134.5 ($CH_2CH=CH_2+CH_2CH=CH_2$), 157.0 (NCO), 172.2 ppm (CO_2); elemental analysis calcd (%) for ($C_{12}H_{19}NO_5$): C 56.02, H 7.44, N 5.44; found: C 56.20, H 7.42, N 5.46; ESI+: *m*/*z*: 258.3.

Isobutyl (*S*)-2-isobutoxy-2-methoxycarbonylaminomethylpropanoate ((*S*)-3h): Compound (*S*)-**3h** (116 mg, 90%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1h** (131 mg, 0.44 mmol), after purification by column chromatography (hexane/AcOEt 9:1). $[\alpha]_D^{25}=-5.0$ ($c=1.18$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.72$–0.99 (m, 12H; $CH_2CH(CH_3)_2+CH_2CH(CH_3)_2$), 1.32 (s, 3H; CCH_3), 1.67–1.97 (m, 2H; $CH_2CH(CH_3)_2+CH_2CH(CH_3)_2$), 3.02–3.21 (m, 2H; $COCH_2$), 3.45 (dd, 1H, $J=13.6$, 5.8 Hz; CH_2N), 3.47 (dd, 1H, $J=13.6$, 6.2 Hz; CH_2N), 3.59 (s, 3H; CO_2CH_3), 3.84 (d, 2H, $J=6.6$ Hz; CO_2CH_2), 4.76–5.11 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=19.0$ ($CH_2CH(CH_3)_2+CH_2CH(CH_3)_2$), 19.3 ($CCH_3$), 27.6, 28.8 ($CH_2CH(CH_3)_2+CH_2CH(CH_3)_2$), 47.7 ($CH_2N$), 52.1 ($CO_2CH_3$), 70.9 ($COCH_2$), 71.2 ($CO_2CH_2$), 79.0 ($CCH_3$), 157.0 (NCO), 172.7 ppm (CO_2); elemental analysis calcd (%) for ($C_{14}H_{27}NO_5$): C 58.11, H 9.40, N 4.84; found: C 58.02, H 9.43, N 4.82; ESI+: *m*/*z*: 290.4.

Isopentyl (*S*)-2-isopentoxy-2-methoxycarbonylaminomethylpropanoate ((*S*)-3i): Compound (*S*)-**3i** (121 mg, 92%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1i** (128 mg, 0.41 mmol), after purification by column chromatography (hexane/AcOEt 9:1). $[\alpha]_D^{25}=-0.6$ ($c=1.23$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.72$–0.98 (m, 12H; $CH_2CH_2CH(CH_3)_2+CH_2CH_2CH(CH_3)_2$), 1.29–1.71 (m, 9H; $CCH_3+CH_2CH_2CH(CH_3)_2+CH_2CH_2CH(CH_3)_2$), 3.04–3.52 (m, 4H; $CH_2N+COCH_2$), 3.59 (s, 3H; CO_2CH_3), 3.79–4.19 (m, 2H; CO_2CH_2), 4.73–5.13 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.1$, 11.3, 16.3, 16.5 ($CH_2CH_2CH(CH_3)_2+CH_2CH_2CH(CH_3)_2$), 19.2 ($CCH_3$), 22.3, 22.5, 22.6, ($CH_2CH_2CH(CH_3)_2+CH_2CH_2CH(CH_3)_2$), 24.9, 25.9, 26.1 ($CH_2CH_2CH(CH_3)_2+CH_2CH_2CH(CH_3)_2$), 34.0, 35.3, 37.1, 38.9 ($CH_2CH_2CH(CH_3)_2+CH_2CH_2CH(CH_3)_2$), 47.6 ($CH_2N$), 52.1 ($CO_2CH_3$), 62.9, 69.3 ($COCH_2$), 63.8, 69.7 ($CO_2CH_2$), 79.0 ($CCH_3$), 157.0 (NCO), 172.7 ppm (CO_2); elemental analysis calcd (%) for ($C_{16}H_{31}NO_5$): C, 60.54; H, 9.84; N, 4.41; found: C 60.71, H 9.87, N 4.39; ESI+: *m*/*z*: 318.4.

Isopropyl (*S*)-2-isopropoxy-2-methoxycarbonylaminomethylpropanoate ((*S*)-3j): Compound (*S*)-**3j** (71 mg, 65%) was obtained as a colorless oil, by starting from sulfamidate (*R*)-**1j** (119 mg, 0.42 mmol), after purification by column chromatography (hexane/AcOEt 9:1); $[\alpha]_D^{25}=+2.6$ ($c=1.13$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.08$ (d, 3H, $J=6.1$ Hz; $CH(CH_3)_2$), 1.13 (d, 3H, $J=6.1$ Hz; $CH(CH_3)_2$), 1.19 (d, 6H, $J=6.2$ Hz; $CH(CH_3)_2$), 1.33 (s, 3H; CCH_3), 3.28 (dd, 1H, $J=13.5$, 5.4 Hz; CH_2N), 3.42 (dd, 1H, $J=13.5$, 6.4 Hz; CH_2N), 3.59 (s, 3H; CO_2CH_3), 3.69 (sept, 1H, $J=12.2$, 6.1 Hz; COCH), 4.75–5.09 ppm (m, 2H; CO_2CH+NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.0$ (CCH_3), 21.6, 21.7, 23.9, 24.7 ($CH(CH_3)_2+CH(CH_3)_2$), 48.4 (CH_2N), 52.1 (CO_2CH_3), 68.0 ($COCH$), 68.8 (CO_2CH), 79.6 (CCH_3), 157.0 (NCO), 172.7 ppm (CO_2); elemental analysis calcd (%) for ($C_{12}H_{23}NO_5$): C 55.16, H 8.87, N 5.36; found: C 55.05, H 8.84, N 5.38; ESI+: *m*/*z*: 262.3.

(*S*)-*N*-(Tosyl)phenylalaninyl-(*S*)-*O*-methyl-α-methylisoserine methyl ester ((*S*,*S*)-6) and (*S*)-*N*-(tosyl)phenylalaninyl-(*S*)-α-methylisoserine methyl ester ((*S*,*S*)-7): Compound (*S*)-**3b** (202 mg, 0.98 mmol) was suspended in aqueous 9 M HCl (5 mL) and the mixture was heated at reflux for 12 h. After evaporation of the solvent, the residue was dissolved in water (2 mL) and was eluted through a C_{18} reverse-phase Sep-pak cartridge to give, after evaporation, the corresponding mixture of β-amino acids (*S*)-*O*-methyl-α-methylisoserine and (*S*)-α-methylisoserine as hydrochloride derivatives (*S*)-**4** and (*S*)-**5**, respectively, as white solids. This residue was dissolved in a mixture of MeOH/HCl, previously prepared by 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 (*S*)-*N*-(*p*-tosyl)phenylalaninyl chloride (432 mg, 1.26 mmol) and ethyldiisopropylamine (DIEA) (508 μL, 2.91 mmol) were added. The resulting solution was stirred at room temperature for 14 h. The reaction was quenched by 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 (Na_2SO_4), concentrated, and the crude reaction was purified by silica-gel column chromatography (hexane/AcOEt 6:4) to give dipeptides (*S*,*S*)-**6** (268 mg, 61%) and (*S*,*S*)-**7** (156 mg, 32%) as oils.

Compound (S,S)-**6**: $[\alpha]_D^{25}=-31.5$ ($c=1.12$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.24$ (s, 3H; CCH_3), 2.33 (s, 3H; $PhCH_3$), 2.69–2.94 (m, 2H; CH_2Ph), 3.19 (s, 3H; $COCH_3$), 3.28–3.50 (m, 2H; CH_2N), 3.64 (s, 3H; CO_2CH_3), 3.67–3.83 (m, 1H; CH), 4.95–5.11 (m, 1H; $NHSO_2$), 6.59 (br s, 1H; NHCO), 6.78–6.92 (m, 2H; $PhCH_3$), 6.95–7.15 (m, 5H; Ph), 7.35–7.52 ppm (m, 2H; $PhCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=18.5$ (CCH_3), 21.5 ($PhCH_3$), 38.4 (CH_2Ph), 45.4 (CH_2N), 52.1 ($COCH_3$), 52.3 (CO_2CH_3), 58.0 (CH), 79.2 (CCH_3), 127.0, 127.1, 128.8, 129.0, 129.7, 135.3, 135.7, 143.6 (Ph), 170.3 (CON), 172.7 ppm (CO2); elemental analysis calcd for ($C_{22}H_{28}N_2O_6S$): C 58.91, H 6.29, N, 6.25, S 7.15; found: C 58.74, H 6.27, N 6.23, S 7.17; ESI+: *m*/*z*: 449.5.

Compound (S,S)-**7**: $[\alpha]_D^{25}=-23.4$ ($c=1.12$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.39$ (s, 3H; CCH_3), 2.41 (s, 3H; $PhCH_3$), 2.79 (dd, 1H, $J=14.1$, 8.6 Hz; CH_2Ph), 3.01 (dd, 1H, $J=14.1$, 5.4 Hz; CH_2Ph), 3.36 (dd, 1H, $J=13.7$, 5.8 Hz; CH_2N), 3.62–3.95 (m, 5H; $CH_2N+CO_2CH_3+CH$), 5.28 (d, 1H, $J=6.3$ Hz; $NHSO_2$), 6.83–7.03 (m, 3H; $PhCH_3+NHCO$), 7.06–7.22 (m, 5H; Ph), 7.38–7.55 ppm (m, 2H; $PhCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=21.5$ ($PhCH_3$), 23.2 (CCH_3), 38.2 (CH_2Ph), 47.2 (CH_2N), 53.1 (CO_2CH_3), 58.1 (CH), 74.5 (CCH_3), 127.0, 128.8, 129.0, 129.1, 129.7, 135.2, 135.3, 143.7 (Ph), 171.1 (CON), 175.6 ppm (CO_2); elemental analysis calcd (%) for ($C_{21}H_{26}N_2O_6S$): C 58.05, H 6.03, N 6.45, S 7.38; found: C 58.22, H 6.05, N 6.47, S 7.36; ESI+: *m*/*z*: 435.5.

(*S*)-*N*-(Tosyl)phenylalaninyl-(*S*)-α-methylisoserine methyl ester ((*S*,*S*)-7): (*S*)-α-Methylisoserine hydrochloride (*S*)-**5**[12c,14,16] (78 mg, 0.34 mmol) was dissolved in a mixture of MeOH/HCl, previously prepared by 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 (*S*)-*N*-(*p*-tosyl)phenylalaninyl 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 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 (Na_2SO_4), concentrated, and the crude reaction was purified by silica-gel column chromatography (hexane/AcOEt 6:4), to give dipeptide (*S*,*S*)-**7** (134 mg, 91 %) as an oil. $[\alpha]_D^{25} = -24.2$ ($c = 1.15$ in $CHCl_3$); NMR spectroscopic data agree with those described above; elemental analysis calcd (%) for ($C_{21}H_{26}N_2O_6S$): C 58.05, H 6.03, N 6.45, S 7.38; found: C 58.43, H 6.11, N 6.51, S 7.40; ESI+: *m*/*z*: 435.5.

(*S*)-*N*-(Tosyl)phenylalaninyl-(*R*)-α-methylisoserine methyl ester ((*S*,*R*)-7): Following the same protocol described for diastereomer (*S*,*S*)-**7**, dipeptide (*S*,*R*)-**7** was prepared from (*R*)-α-methylisoserine hydrochloride (*R*)-**5**[12c,16] (54 mg, 0.24 mmol) as an oil (91 mg, 87 %). $[\alpha]_D^{25} = -32.2$ ($c =$ 1.23 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (s, 3H; CCH_3), 2.40 (s, 3H; PhCH_3), 2.80 (ddd, 1H, $J = 8.4$, 14.2, 17.3 Hz; CH_2Ph), 2.98 (ddd, 1H, $J = 5.7$, 9.7, 13.8 Hz; CH_2Ph), 3.32 (ddd, 1H, $J = 5.4$, 13.7, 17.0 Hz; CH_2N), 3.67 (dd, 1H, $J = 6.9$, 13.7 Hz; CH_2N), 3.73–3.93 (m, 4H; CO_2CH_3 + CH), 5.29 (d, 1H, $J = 6.6$ Hz; $NHSO_2$), 6.84–7.03 (m, 3H; *Ph*CH_3 + NHCO), 7.05–7.24 (m; 5H; Ph), 7.39–7.62 ppm (m, 2H; *Ph*CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.5$ (Ph*C*H_3), 23.2, 23.3 (*C*CH_3), 38.2 (CH_2Ph), 47.2, 47.4 (CH_2N), 53.1 (CO_2CH_3), 57.9, 58.1 (CH), 74.3, 74.5 (*C*CH_3), 127.0, 127.1, 128.4, 128.8, 129.0, 129.5, 129.6, 129.7, 135.2, 135.3, 135.4, 143.7 (Ph), 171.2, 171.3 (CON), 175.4, 175.5 ppm (CO_2); elemental analysis calcd (%) for ($C_{21}H_{26}N_2O_6S$): C 58.05, H 6.03, N 6.45, S 7.38; found: C 58.61, H 6.13, N 6.53, S 7.40; ESI+: *m*/*z*: 435.5.

Methyl (*S*)-2-methoxycarbonylaminomethyl-2-(*n*-propoxy)propanoate ((*S*)-8): Sulfamidate (*R*)-**1b** (116 mg, 0.46 mmol) was dissolved in *n*PrOH and the solution was heated at 55 °C for 96 h at which point total consumption of starting material was observed by TLC. After evaporating the solvent, the residue was purified by silica-gel column chromatography (hexane/AcOEt 9:1) to give the ring-opening product (*S*)-**8** (88 mg, 82 %) as a colorless oil. $[\alpha]_D^{25} = -11.8$ ($c = 0.90$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, 3H, $J = 7.4$ Hz; $CH_2CH_2CH_3$), 1.34 (s, 3H; CCH_3), 1.44–1.58 (m, 2H; $CH_2CH_2CH_3$), 3.23–3.40 (m, 3H; $COCH_2 + CH_2N$), 3.47 (dd, 1H, $J = 13.7$, 6.5 Hz; CH_2N), 3.54–3.71 (m, 6H; CO_2CH_3 + CO_2CH_3), 4.73–5.07 ppm (m, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 10.5 ($CH_2CH_2CH_3$), 19.3 (*C*CH_3), 23.3 ($CH_2CH_2CH_3$), 47.6 (CH_2N), 52.2 (CO_2CH_3 + CO_2CH_3), 66.2 ($COCH_2$), 79.1 (*C*CH_3), 157.1 (NCO), 173.2 ppm (CO_2); elemental analysis calcd (%) for ($C_{10}H_{19}NO_5$): C 51.49, H 8.21, N 6.00; found: C 51.61, H 8.23, N 6.02; ESI+: *m*/*z*: 234.3.

(*S*)-2-Aminomethyl-2-(*n*-propoxy)propanoic acid hydrochloride ((*S*)-9): Compound (*S*)-**8** (71 mg, 0.30 mmol) was suspended in aqueous 6 M HCl (5 mL) and the mixture was heated at 90 °C for 48 h. After evaporation of the solvent, the residue was dissolved in water (2 mL) and was eluted through a C_{18} reverse-phase Sep-pak cartridge to give, after evaporation, the corresponding hydrochloride (*S*)-**9** as a white solid (57 mg, 95 %). $[\alpha]_D^{25} = -4.8$ ($c = 1.01$ in H_2O); ^{1}H NMR (300 MHz, D_2O): $\delta = 0.87$ (t, 3H, $J = 7.4$ Hz; $CH_2CH_2CH_3$), 1.49 (s, 3H; CH_3), 1.51–1.66 (m, 2H; $CH_2CH_2CH_3$), 3.11–3.54 ppm (m, 4H; $COCH_3 + CH_2N$); ^{13}C NMR (75 MHz, D_2O): $\delta = 12.0$ ($CH_2CH_2CH_3$), 21.3 (CH_3), 25.0 ($CH_2CH_2CH_3$), 46.7 (CH_2N), 69.1 ($COCH_2$), 79.1 (*C*CH_3), 177.2 ppm (CO_2); elemental analysis calcd (%) for ($C_7H_{16}ClNO_3$): C 42.54, H 8.16, N 7.09; found: C 42.71, H 8.19, N 7.11; ESI+: *m*/*z*: 162.2.

***tert*-Butyl (*R*)-5-methoxycarbonyl-5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidine-3-carboxylate ((*R*)-10)**: Boc_2O (123 mg, 0.56 mmol) and Et_3N (71 μL, 0.52 mmol) were added to a solution of sulfamidate (*R*)-**2b** (91 mg, 0.47 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at 25 °C for 16 h. A second portion of Boc_2O (123 mg, 0.56 mmol) and Et_3N (71 μL, 0.52 mmol) was added and the mixture was stirred at 25 °C for another 16 h. The solvent was evaporated and the residue was purified directly by silica-gel column chromatography (hexane/AcOEt 8:2) to give compound (*R*)-**10** as a colorless oil (104 mg, 76 %). $[\alpha]_D^{25} = -35.2$ ($c = 1.34$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.54$ (s, 9H; $C(CH_3)_3$), 1.80 (s, 3H; CCH_3), 3.82–3.93 (m, 4H; $CH_2N + CO_2CH_3$), 4.48 ppm (d, 1H, $J = 10.2$ Hz; CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.0$ (*C*CH_3), 27.9, 29.7 ($C(CH_3)_3$), 52.8 (CH_2N), 53.8 (CO_2CH_3), 82.7, 86.0 (*C*CH_3, $C(CH_3)_3$), 148.2 (NCO), 168.6 ppm (CO_2); elemental analysis calcd (%) for ($C_{10}H_{17}NO_7S$): C 40.67, H 5.80, N 4.74, S 10.86; found: C 40.95, H 5.84, N 4.77, S 10.94; ESI+: *m*/*z*: 296.3.

Methyl (*S*)-2-bromo-3-methoxycarbonylamino-2-methylpropanoate ((*S*)-11): Et_4NBr (404 mg, 1.25 mmol) was added to a solution of sulfamidate (*R*)-**1b** (289 mg, 1.14 mmol) in CH_3CN (20 mL) and the mixture was stirred at 25 °C for 20 h. The solvent was evaporated and the residue dissolved into a mixture of 20 % H_2SO_4/CH_2Cl_2 1:1 and stirred for 8 h to hydrolize the sulfamic acid intermediate. The organic phase was separated and the aqueous phase was extracted with AcOEt (3×15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and the residue was purified by silica-gel column chromatography (hexane/AcOEt 8:2), to give compound (*S*)-**11** as a colorless oil (194 mg, 76 %). $[\alpha]_D^{25} = -11.0$ ($c = 1.65$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.86$ (s, 3H; CCH_3), 3.54–3.87 (m, 8H; $COCH_3 + CH_2N + COCH_3$), 5.10–5.46 ppm (m, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.5$ (*C*CH_3), 49.8 (CH_2N), 52.3, 53.3, (CO*C*$H_3 + CO_2$*C*H_3), 58.4 (*C*CH_3), 157.0 (NCO), 171.0 ppm (CO_2); elemental analysis calcd (%) for ($C_7H_{12}BrNO_4$): C 33.09, H 4.76, N 25.19; found: C 33.32, H 4.79, N 25.37; ESI+: *m*/*z*: 255.1.

(*R*)-Dimethyl 2-methylaziridine-1,2-dicarboxylate ((*R*)-12): Potassium *tert*-butoxide (1 M in THF, 0.2 mL, 0.22 mmol) was added dropwise to a solution of compound (*S*)-**11** (62 mg, 0.24 mmol) in THF (5 mL) under an argon atmosphere at 0 °C. The mixture was stirred at 0 °C for 12 h and the resulting white suspension was filtered and washed with cold THF and AcOEt to obtain aziridine (*R*)-**12** as a white solid (18 mg, 43 %). The spectroscopic data obtained for this compound are in accordance with those reported in the literature.[25]

Computational details: All calculations were carried out with the B3LYP hybrid functional[28] and 6-31+G(d,p) basis set. Full geometry optimizations and transition structure searches were carried out with the Gaussian 03 package.[29] The possibility of different conformations was taken into account for all structures. Basis set superposition errors (BSSE) were corrected by the Boys–Bernardi counterpoise method.[30] Frequency analyses were carried out at the same level used in the geometry optimizations, and the nature of the stationary points was determined in each case according to the appropriate number of negative eigenvalues of the Hessian matrix. Scaled frequencies were not considered since significant errors in the calculated thermodynamic properties are not found at this theoretical level.[31] Where necessary, mass-weighted intrinsic reaction coordinate (IRC) calculations were carried out by using the Gonzalez and Schlegel scheme[32] to ensure that the TSs indeed connected the appropriate reactants and products. Solvent effects were taken into account through the polarized continuum model (IEF-PCM)[33] by using UAHF radii, as implemented in Gaussian 03. The internally stored parameters for methanol were used to calculate solvation free energies (ΔG_{solv}). Gibbs free energies (ΔG) were used for the discussion on the relative stabilities of the considered structures. Cartesian coordinates, electronic energies, entropies, enthalpies, Gibbs free energies, and lowest frequencies of the different conformations of all structures considered are available as Supporting Information.

X-ray diffraction analysis

Crystal data for (R)-***1c***: $C_8H_{13}NO_7S$; $M_w = 267.25$; colorless prism of 0.40×0.20×0.05 mm; $T = 100$ K; orthorhombic; space group; $P2_12_12_1$; $Z = 4$; $a = 8.2030(5)$, $b = 9.3790(7)$, $c = 14.9320(10)$ Å; $\alpha = \beta = \gamma = 90°$; $V = 1148.81(13)$ Å^3; $\rho_{calcd} = 1.545$ g cm^{-3}; $F(000) = 560$; $\lambda = 0.71073$ Å ($Mo_{K\alpha}$); $\mu = 0.306$ mm^{-1}; Nonius kappa CCD diffractometer; θ range = 3.30–27.46°; 14787 collected reflections, 2620 unique; full-matrix least-squares (SHELXL97[34]), $R_1 = 0.0825$, $\omega R_2 = 0.0752$ ($R_1 = 0.0731$, $\omega R_2 = 0.0830$ all data); goodness-of-fit = 1.084; residual electron density = 0.272-(−0.320) e Å^{-3}; absolute structure parameter (Flack) = 0.04(10); hydrogen atoms

were located by mixed methods (electron-density maps and theoretical positions).

CCDC-691617 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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