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# Stereocontrolled Ring-Opening of a Hindered Sulfamidate with Nitrogen-Containing Aromatic Heterocycles: Synthesis of Chiral Quaternary Imidazole Derivatives

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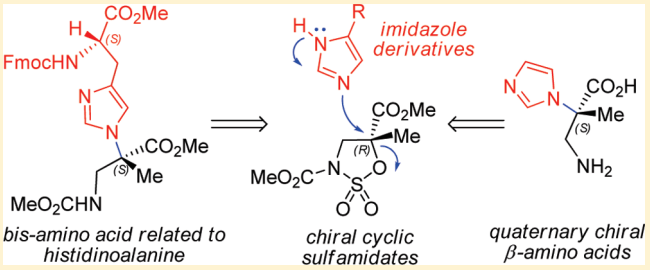
Supporting Information

**ABSTRACT:** This paper explores the role of a hindered cyclic sulfamidate derived from α-methylisoserine as an electrophile in a nucleophilic displacement reaction with nitrogen-containing aromatic heterocycles. Several imidazoles and pyrazole were tested as nucleophiles in the absence of an additional base to give the corresponding ring-opening compounds. We show that the process takes place by inversion of the configuration of the quaternary electrophilic center, retaining the enantiomeric excess of the starting sulfamidate. This reaction opens the way to obtain important quaternary imidazole derivatives such as an innovative type of bis-amino acid related to histidinoalanine and a novel α,α-disubstituted β-amino acid ($\beta^{2,2}$-amino acid).




## INTRODUCTION

The main roles that cyclic sulfamidates have played in organic synthesis, as well as the recent developments in their chemistry, have profusely been described in the recent literature.[1] These systems can compete with epoxides and aziridines in terms of reactivity and selectivity in ring-opening reactions with nucleophiles.

Recently, we focused our interest on five-membered cyclic α-methylisoserine-derived sulfamidates as excellent chiral building blocks for the synthesis of several β-amino acids by nucleophilic ring-opening reactions (Figure 1).[2] In this context, a thorough study has been carried out using *S*-nucleophiles,[2a−f] demonstrating in all cases the inversion of configuration at the electrophilic center by a $S_N2$ mechanism. Later, we studied their behaviors toward *O*-nucleophiles in acidic and neutral media. The most important outcome of this last study was the development of a simple and practical method for the ring-opening reaction of hindered sulfamidates using alcohols as *O*-nucleophiles[2g,h] under mild conditions, at a quaternary carbon and with total inversion of the configuration.

However, the only *N*-nucleophile introduced in these systems was the sodium azide through the corresponding $S_N2$ mechanism.[2a] In this context, the incorporation of nitrogen aromatic heterocycles such as the imidazole or pyrazole systems into certain chiral molecules could provide new chiral ligands, since the potential utility of imidazoles and pyrazoles as efficient coordinating ligands is well-established in chemistry (Figure 1).

The ring-opening reactions of epoxides,[3] aziridines,[4] and sulfamidates[5] with imidazoles and pyrazoles as nucleophiles have been used to prepare new diazole derivatives. These compounds

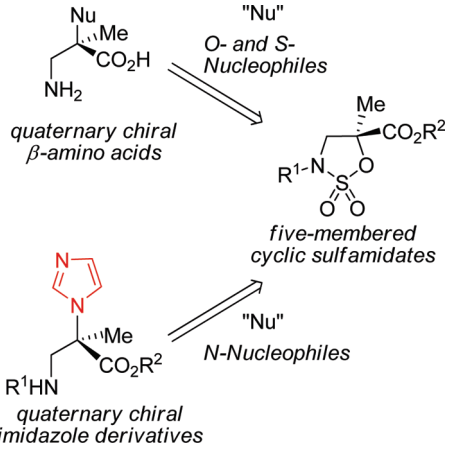



**Figure 1.** Cyclic sulfamidates and hindered chiral imidazole derivatives.

in their chiral version have been employed in the synthesis of imidazolium-based chiral ionic liquids[6] and chiral *N*-heterocyclic carbene−transition metal complexes.[7] On the other hand, the 1*H*-imidazol-1-yl moiety incorporated in quaternary systems shows good oral bioavailability and increased GH secretion.[8]

## RESULTS AND DISCUSSION

Sulfamidate (*R*)-**1** (scheme of Table 1) was obtained in a gram scale using a methodology previously published by us.[2a] We first

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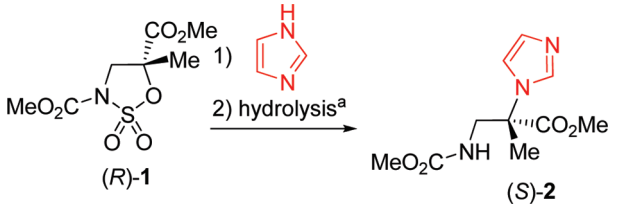
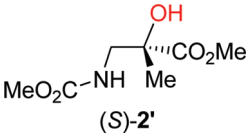
**Table 1. Reaction of Sulfamidate (*R*)-1 with Imidazole**




| entry | equiv | solvent | *T* (°C) | time (h) | (*S*)-**2**[b] |
|---|---|---|---|---|---|
| 1 | 2 | $CH_3CN$ | rt | 48 | 52% |
| 2 | 2 | $CH_3CN$ | 50 | 48 | 24% |
| 3 | 3 | $CH_3CN$ | reflux | 24 | 67% |
| 4 | 2 | DMSO | rt | 8 | 33% |
| 5 | 2 | DMF | rt | 36 | 79%[c] |

[a] Hydrolysis conditions: 20% $H_2SO_4$ (aq)/CH2Cl2 (1:1). [b] Yields after column chromatography purification. [c] Yield of product (*S*)-**2** after separation from the side product (S)-**2′** (10%).

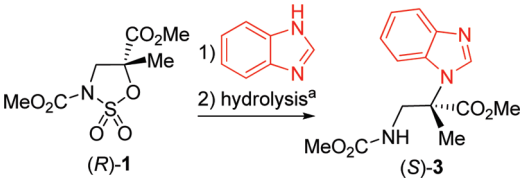



explored the reactivity of this sulfamidate (*R*)-**1** with imidazole as a nucleophile using basic conditions. We observed that the nucleophilic opening reaction did not progress satisfactorily in any tested conditions [DBU in DMF or acetonitrile, and $Cs_2CO_3$ in DMF] yielding decomposition products, principally carbamate cleavage product, but not elimination product.

However, when the reaction was carried out in the absence of a base, we could obtain some positive results. As a consequence, mixing both reagents, sulfamidate and imidazole, in acetonitrile ($CH_3CN$) as a solvent at room temperature for 48 h, we obtained the sulfamate ring-opening product, which provided compound (*S*)-**2** (Table 1, entry 1) after acid hydrolysis with 20% $H_2SO_4$ (aq)/$CH_2Cl_2$ (1:1). The best conditions using $CH_3CN$ were found at reflux with 3 equiv of imidazole to give 67% of (*S*)-**2** (Table 1, entry 3). The change to other more polar solvents such as DMSO provided lower yields (Table 1, entry 4). When we used DMF as a solvent at room temperature, the yield increased to 79%, but unexpectedly, the required opening product (*S*)-**2** was accompanied with side products (Table 1, entry 5). The possible attack of the DMF carbonyl oxygen as a nucleophile has been considered. After hydrolysis, we could isolate the corresponding alcohol (*S*)-**2′** in a 10% yield, after column chromatography. To confirm the structure and the configuration of this new product, we carried out an alternative synthesis from (*S*)-α-methylisoserine, previously obtained following the procedure described in the literature[2a] (see Experimental Section). The optical rotation for this compound was $[\alpha]^{20}_D = +45$, identical to that obtained as a side product in the ring-opening reaction with imidazol in DMF.

To explore the scope of this reaction, other imidazole derivatives were tested as nucleophiles. Therefore, the reaction with the less nucleophilic benzimidazole was carried out under the best conditions described above (Table 2, entry 1). However, we had to try other conditions because of the low conversion and the

**Table 2. Reaction of Sulfamidate (*R*)-1 with Benzimidazole**




| entry | equiv | solvent | *T* (°C) | time (h) | (*S*)-**3**[b] |
|---|---|---|---|---|---|
| 1 | 2 | DMF | rt | 48 | 30%[c] |
| 2 | 2 | DMF | 50 | 24 | 9%[c] |
| 3 | 2 | $CH_3CN$ | 50 | 24 | 38% |
| 4 | 2 | $CH_3CN$ | reflux | 48 | 47% |
| 5 | 3 | $CH_3CN$ | reflux | 48 | 60% |

[a] Hydrolysis conditions: 20% $H_2SO_4$ (aq)/$CH_2Cl_2$ (1:1). [b] Yields after column chromatography purification. [c] Yield of product (*S*)-**3** after separation from the side products.

presence of side products. Taking into account that the increase of temperature in DMF did not give good results (Table 2, entry 2), the solvent was changed to $CH_3CN$, the best yield being obtained when 3 equiv of benzimidazole at reflux for 48 h was used (Table 2, entry 5).

Taking into account the previous experiments, we carried out the ring-opening reaction with different substituted imidazoles using 3 equiv of nucleophile at reflux of $CH_3CN$ for 48 h. As a result, 2-methyl-1*H*-imidazole, 2-ethyl-1*H*-imidazole and 2-isopropyl-1*H*-imidazole were found to operate as nucleophiles with moderate yields in the same conditions (Table 3, entries 1, 2, and 3). The structures for compounds (*S*)-**4** and (*S*)-**5** were unambiguously determined by X-ray diffraction analyses (see Supporting Information).

To extend this methodology to other nitrogen heteroaromatic nucleophiles, we attempted the ring-opening reaction with pyrazole, obtaining in standard conditions a good yield (69%) for compound (*S*)-**9** (Table 3, entry 6). To test that these reactions take place by the conventional $S_N2$-type mechanism similar to the cases of *S*-nucleophiles,[2a−f] with inversion of the configuration at the stereogenic center, we carried out the reaction with 2-bromo-1*H*-imidazole. The reaction (Table 3, entry 7) proceeded with a low yield of compound (*S*)-**10**, but we were able to obtain a single crystal suitable to be analyzed by X-ray diffraction (see Supporting Information) with refinement of the Flack parameter,[9] by which it was possible to determine an absolute *S*-configuration.

When the alkyl substituent of imidazole derivatives is located at position 5, two isomers are possible in the nucleophilic starting material due to the tautomerism,[10] and they could give two different reaction compounds (Scheme 1). In this context, two imidazole derivatives, 4(5)-methyl-1*H*-imidazole (Table 3, entry 4) and 2,4(5)-dimethyl-1*H*-imidazole (Table 3, entry 5), were tested. In the first case, only one ring-opening compound (*S*)-**7a** was obtained, which corresponded to the nucleophilic attack of the 4-methyl-1*H*-imidazole isomer, which has a less hindered nucleophilic nitrogen. When the reaction with 2,4(5)-dimethyl-1*H*-imidazole was carried out, two compounds (*S*)-**8a** and (*S*)-**8b** in a 2:1 ratio were obtained. Again, the attack is favored for the isomer in which the nitrogen electron density is more accessible to give mainly the isomer (*S*)-**8a**. This compound was isolated and characterized by NMR experiments (COSY, HSQC, and HMBC).


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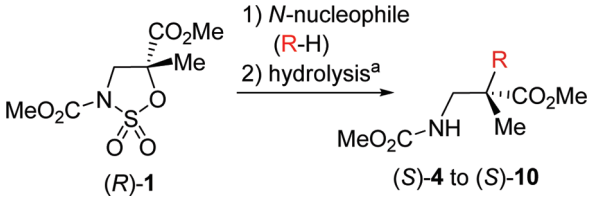
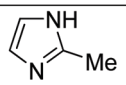
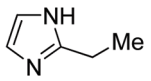
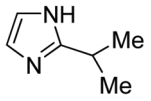
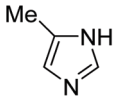
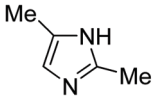
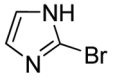
**Table 3. Reaction of Sulfamidate (*R*)-1 with Nitrogen Aromatic Heterocycles**



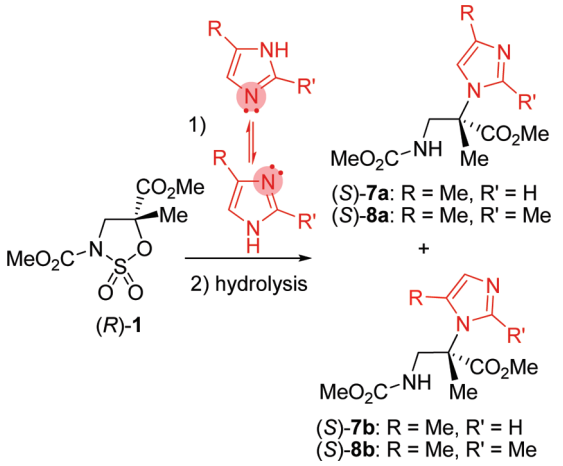

| entry | *N*-nucleophile (R-H) | product | yield[b] |
|---|---|---|---|
| 1 |  | (*S*)-**4** | 62% |
| 2 |  | (*S*)-**5** | 42% |
| 3 |  | (*S*)-**6** | 48% |
| 4 |  | (*S*)-**7a** | 66% |
| 5 |  | (*S*)-**8a** and (*S*)-**8b** | 52%[c] |
| 6 |  | (*S*)-**9** | 69% |
| 7 |  | (*S*)-**10** | 29%[d] |

[a] Hydrolysis conditions: 20% $H_2SO_4$ (aq)/$CH_2Cl_2$ (1:1). [b] Yields after column chromatography purification. [c] Yield for both isomers. Yield for compound (*S*)-**8a** was 36%. [d] Yield obtained by using 6 equiv of nucleophile for 4 days of reaction time.

To gain insight into the reactivity and selectivity of these processes, we have carried out theoretical calculations. First, genuine $S_N2$ transition states (TS), in which a total inversion of configuration takes place at the quaternary carbon atom, were located and characterized at the B3LYP/6-31G+(d,p) level starting from sulfamidate (*R*)-**1** and neutral imidazole. Every structure (for example **ts2**) comprised several carbonyl rotamers (for both the ester and carbamate groups) and sulfamidate ring conformers, as well as distinct imidazole approximations. Overall, up to 18 TS were calculated with the simplest imidazole (see Supporting. Information). Counterpoise-corrected gas-phase energy barriers were recalculated in solution through single-point energy calculations with implicit continuous solvation in acetonitrile (see Computational Details).

Once the concerted nature of the nucleophilic ring-opening reaction was demonstrated, the high site selectivity exhibited by nonsymmetric substituted imidazoles was tested theoretically. To this aim, both tautomeric forms of 4(5)-methyl-1*H*-imidazole and 2,4(5)-dimethyl-1*H*-imidazole approximating to sulfamidate

**Scheme 1. Tautomerism of Substituted Imidazoles and Reactivity as Nucleophiles**




(*R*)-**1** in different orientations were considered. In sum, up to 40 and 34 different reaction pathways were calculated for the mono- and disubstituted imidazoles, respectively (see Supporting Information). The minimum energy structures of these calculated reaction pathways are depicted in Figure 2. As can be seen on this plot, a very similar activation barrier ($\Delta G^{\ddagger}$) was observed when one methyl group was appended to the heterocyclic nucleophile; on the contrary, the presence of a second methyl group increases the energy barrier by *ca.* 2−3 kcal mol$^{-1}$. These computational kinetic data agree quite well with the slight decrease in reactivity observed experimentally when we shifted from unsubstituted and monomethylated to dimethylated imidazole. Moreover, and as experimentally demonstrated, complete selectivity toward the nucleophilic attack of the less sterically hindered N atom was obtained as a result of the great difference between the lowest energies of activation calculated for both reaction pathways, labeled as **ts9** and **ts10** (4.2 kcal mol$^{-1}$).[11] As can be seen in **ts10** (Figure 2), steric interactions occurring between methyl group of imidazole and methylene, methyl ester, and methyl groups of sulfamidate at the most crowded TS are most likely at the origin of this high site selectivity. The same tendency, although somewhat overestimated, was observed with dimethylated imidazole. In this case, the lowest activation barriers leading to both site isomers (**ts11** and **ts12**) differ by 5.5 kcal mol$^{-1}$, the attack of the most accessible nitrogenated position being favored again. This energy gap is too big to account for the experimental decrease of selectivity to a 2:1 mixture of isomers when carrying out the $S_N2$ reaction with dimethylated imidazole; the major reaction product is predicted correctly. Again, steric repulsions between the methyl groups of the incoming nucleophile and the substituents located at the quaternary position of the electrophile determine the energy distribution of all calculated TS.

The aforementioned results encouraged us to discover synthetic applications of the ring-opening reaction of sulfamidates with nitrogen aromatic heterocycles described above. In this way, we wanted to explore the utility of this methodology for the synthesis of both the $\beta$-amino acids and the bis-amino acids, also named cross-linking amino acids. Thus, although bis-amino acids are non-natural amino acids, they appear naturally as protein linkers in certain proteins and antibiotic peptides. Moreover, they can be formed on exposure of proteins to certain processing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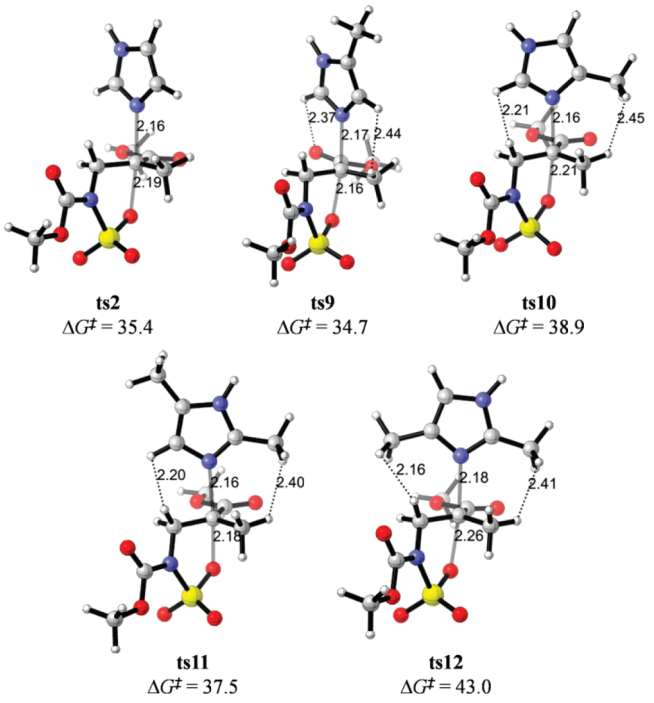


**Figure 2.** Minimum energy TS calculated at the B3LYP/6-31G+(d,p) level for all the proposed pathways starting from sulfamidate (*R*)-**1** and mono-, di-, and unsubstituted imidazoles. Distances are given in Å and activation energies ($\Delta G^{\ddagger}$) in kcal mol$^{-1}$.

conditions, resulting in adverse effects especially in nutritional proteins related to food science.[12] In this sense, lanthionine (LAN) and histidinoalanine (HAL) are two of the most relevant bis-amino acids. Lanthionine consists of two alanines (Ala) covalently linked by a sulfur atom (Ala-S-Ala), which is considered a thioether analogue of cystine (Ala−S−S−Ala). LAN is found in an important class of antibiotic peptides known as lantibiotics.[13] Because of this, several synthetic efforts[14] have been made to develop both lanthionine and their mimetics, methyllanthionine (MeLAN), norlanthionine (*nor*LAN), and methylnorlanthionine (Me*nor*LAN), whose structures can be seen in Figure 3.[14]

HAL is derived from a covalent linkage of nitrogen of the imidazol of a histidine (His) to $\beta$-carbon of an Ala.[15] Depending on which nitrogen of the imidazole is linked to the Ala, two regioisomers can appear ($\tau$-HAL and $\pi$-HAL). Both regioisomers have been detected in different sources: (1) protein-containing foods that have been treated with alkali, (2) tissue proteins such as bone, dentin, and eye cataracts, where their formation may be related to the aging process, (3) phosphoproteins of bivalve mollusks, and (4) the theonellamides, which are a family of bicyclic dodecapeptides characterized by a bridging $\tau$-HAL (Figure 3). A number of biological activities have been described for theonellamides, but the role of HAL is unclear, and several authors suggest that they are the histidine analogues of the lantibiotics.

Taking into account the importance of cross-linking amino acids, the development of synthetic methods that allow the preparation of bis-amino acids has attracted significant interest. Nevertheless, while several derivatives of LAN have been described,[13,14] the synthesis of HAL and derivatives has been scarcely explored because of the problem of regioisomers and the low yield. To the best of our knowledge, four syntheses of HAL

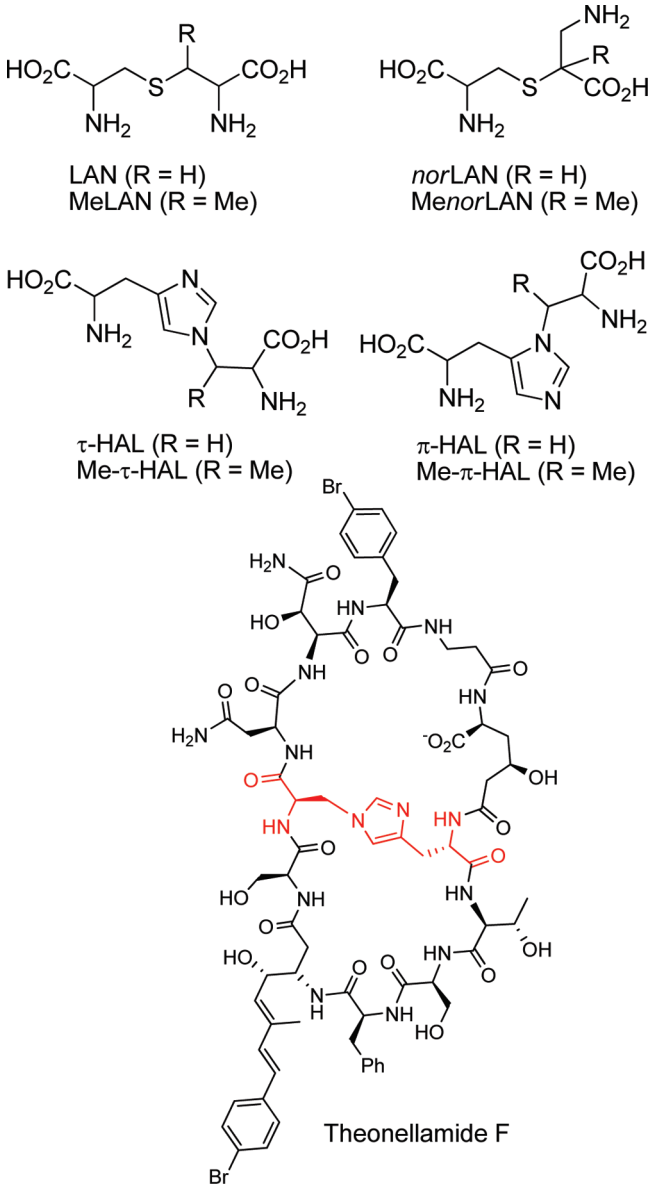


**Figure 3.** Structures of several bis-amino acids and Theonellamide F.

have been reported.[16] The first three syntheses[16a−c,f] give a mixture of $\tau$-HAL and $\pi$-HAL regioisomers, both as distereomeric mixtures arising from the conjugate addition of the nucleophilic side chain (nitrogens of imidazole) of His to dehydroamino acid derivatives (2-acetamidoacrylic acid or methyl 2-acetamidoacrylate). There is only one methodology[16d,e] described in which the configurations of both stereocenters are controlled, and it involves the nucleophilic attack of the His on a $\beta$-lactone derived from D-serine. Although a mixture of regioisomers again appeared, they could be separated, giving 40% of $\tau$-HAL derivative and 21% $\pi$-HAL derivative. During the preparation of this manuscript, we became aware of related work on the synthesis of $\tau$-HAL via a cyclic sulfamidate.[16g]

Therefore, we decided to carry out the ring-opening reaction of cyclic sulfamidate (*R*)-**1** using as a nucleophile the imidazole heterocycle incorporated in the adequately protected amino acid His. Thus, the Fmoc-L-His-OMe was prepared from commercial Fmoc-L-His-OH using acetyl chloride (AcCl) in MeOH. The ring-opening reaction was carried out with 3 equiv of Fmoc-L-His-OMe


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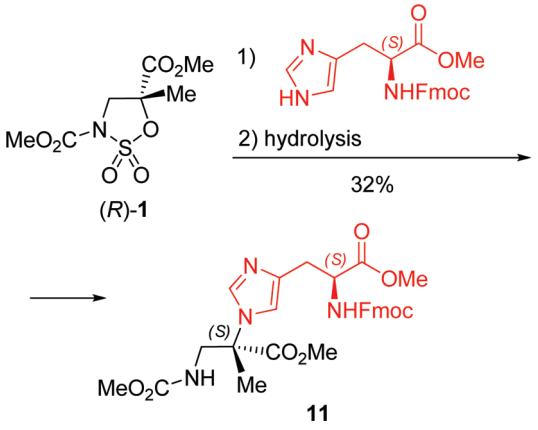
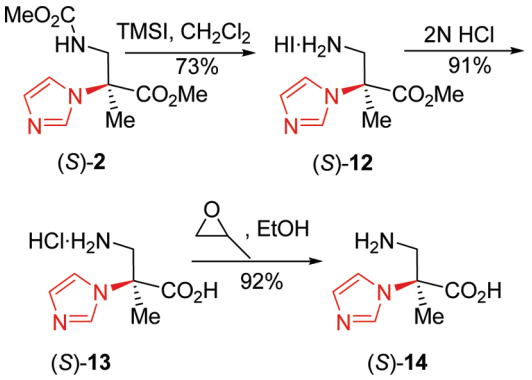
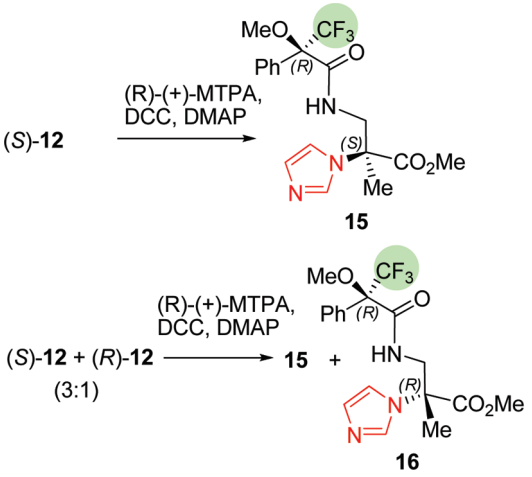
**Scheme 2. Synthesis of Protected Me*nor*-$\tau$-HAL**




**Scheme 3. Synthesis of a Novel $\beta^{2,2}$-Amino Acid**




**Scheme 4. Synthesis of Mosher Derivatives**




in acetonitrile at reflux and proceeded with moderate yield, but we could isolate, after column chromatography, compound **11** in a 32% yield as a sole regioisomer (Scheme 2), recovering some quantities of unreacted starting material and affording some traces of a new product corresponding to the cleavage of the carbamate group. This compound **11** can be regarded as a protected derivative of $\tau$-HAL that involves the covalent linking of nitrogen of the imidazole of the α-amino acid His with the α-carbon of the $\beta$-amino acid $\beta$-alanine ($\beta$-Ala), with the peculiarity of bearing a quaternary stereocenter, whose configuration is controlled in the nucleophilic substitution. Therefore, this derivative can be named as Me*nor*-$\tau$-HAL compared with their lanthionine partner (Me*nor*LAN).[14d] Taking into account that, from a conformational viewpoint, the role of $\tau$-HAL in theonellamides is not clear,[17] probably the future inclusion of other derivatives like Me*nor*-$\tau$-HAL will allow the exploration of conformational space that is not available with the bis-amino acids that appear naturally as protein linkers.

The field of the $\beta$-amino acids is a matter of continuous interest due to the remarkable structures displayed by the corresponding $\beta$-peptides that they can generate.[18] Particularly attractive are the chiral $\beta^{2,2}$-amino acids,[19] since they bear a quaternary stereocenter at the α-position. In this context, with the aim of exploring the synthetic utility of this reaction, we carried out the synthesis of a new $\beta^{2,2}$-amino acid from methyl ester (*S*)-**2** (Scheme 3). The first step involved the deprotection of methyl carbamate from amino group. When we attempted the hydrolysis under several acids conditions, we could not release the amino group and a rather complex mixture of compounds was obtained. However, the more specific deprotection method for methyl carbamates, using trimethylsilyl iodide (TMSI) in $CH_2Cl_2$,[20] allowed us to obtain hydroiodide (*S*)-**12** in a 73% yield. In the next step, the hydrolysis of methyl ester in an aqueous solution of 2 N HCl gave the $\beta^{2,2}$-amino acid hydrochloride (*S*)-**13** in an excellent yield. An aliquot of this compound was treated with propylene oxide to obtain the free amino acid (*S*)-**14** in a 92% yield.

To confirm that the enantiomeric excess (93%) of sulfamidate (*R*)-**1** is kept in the nucleophilic ring-opening process, we repeated the reaction starting from sulfamidate (*S*)-**1** and with imidazole as a nucleophile to give compound (*R*)-**2**. The deprotection of methyl carbamate with TMSI allowed us to obtain hydroiodide (*R*)-**12**. With compounds (*S*)-**12** and (*R*)-**12** in our hands, we synthesized the corresponding Mosher amides, first from hydroiodide (*S*)-**12** and second with a known ratio of both enantiomers. In accordance with the protocol described in the literature,[21] amine (*S*)-**12** was coupled with (*R*)-(+)-methoxytrifluorophenylacetic acid [(*R*)-(+)-MTPA], in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP), to give the Mosher amide **15**. The mixture of (*S*)-**12** and (*R*)-**12** (3:1) was treated in the same way to obtain amides **15** and **16** (Scheme 4). Analysis of the $^1$H NMR and $^{19}$F NMR spectra of amides in both reactions (see Supporting Information) showed that the enantiomeric excess of starting sulfamidate (previously established by us in several works[2b,22] as 93% ee) was maintained in the ring-opening reaction, and racemization has not been observed in these new reactions.

## CONCLUSION

We have obtained a new family of imidazole and pyrazole-derived quaternary systems. Interestingly, the starting material sulfamidate (*R*)-**1** shows a tertiary electrophilic center with high reactivity able to react with nitrogen-containing aromatic heterocycles in the absence of additional base through a ring-opening process and with simple experimental conditions. Starting from nucleophilic ring-opening products, we have gained in a good yield a novel $\beta^{2,2}$-amino acid, and we could access an interesting bis-amino acid derived from histidine.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## EXPERIMENTAL SECTION

**General Procedures.** Solvents were purified according to standard procedures. Column chromatography was performed using silica gel 60 (230−400 mesh). $^1$H and $^{13}$C NMR spectra were recorded on a 400 MHz spectrometer, using $CDCl_3$ as a deuterated solvent with TMS as an internal reference (chemical shifts are reported in ppm on the $\delta$ scale, and coupling constants are in Hz). Assignment of all separate signals in the $^1$H NMR spectra was made on the basis of coupling constants and gradient enhanced $^1$H−$^1$H COSY and $^1$H−$^{13}$C HSQC 2D NMR experiments recorded on a 400 MHz spectrometer. Melting points were determined on a melting point apparatus and are uncorrected. Optical rotations were measured on a polarimeter in 1.0 dm cells of 1.0 and 0.3 mL capacity, respectively. Electrospray mass spectra were recorded on a spectrometer; accurate mass measurements were achieved using sodium formate as an external reference.

*General Procedure for Ring-Opening Reactions of Cyclic Sulfamidates.* Sulfamidate (*R*)-**1** or (*S*)-**1** (1 equiv) and the corresponding nitrogen-containing aromatic heterocycle (3 equiv) were dissolved in DMF at rt or $CH_3CN$ under reflux, and the mixture was stirred for 48 h. After evaporation of the solvent, the residue was dissolved in a mixture of aqueous 20% $H_2SO_4/CH_2Cl_2$ (1:1), and the mixture was stirred at room temperature for 12 h. Sodium hydrogen carbonate was added to the biphasic system (until effervescence ceased). Once the phases were separated, the aqueous layer was extracted with EtOAc. The combined organic phases were dried over $Na_2SO_4$ and evaporated to give a residue, which was purified by a silica gel column chromatography ($CH_2Cl_2$/MeOH, 9:1).

*(S)-Methyl 2-(1H-Imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**2***. Starting from (*R*)-**1** using DMF as a solvent, compound (*S*)-**2** was isolated in a 79% yield as a white solid. Mp: 67−69 °C. $[\alpha]^{20}_D$ (*c* 1.02, $CHCl_3$): −53.9. $^1$H NMR ($CDCl_3$) $\delta$ 1.85 (s, 3H, $CH_3$), 3.66 (s, 3H, $NCO_2CH_3$), 3.72 (dd, 1H, *J* = 14.4 Hz, *J* = 6.2 Hz, C*H*$_2$NH), 3.78 (s, 3H, $CO_2CH_3$), 3.91 (dd, 1H, *J* = 14.4 Hz, *J* = 7.3 Hz, C*H*$_2$NH), 5.05 (s, 1H, NH), 7.00 (s, 1H, arom), 7.11 (s, 1H, arom), 7.61 (s, 1H, arom). $^{13}$C NMR ($CDCl_3$) $\delta$ 20.8 ($CH_3$), 48.0 ($CH_2$NH), 52.5 ($NCO_2CH_3$), 53.3 ($CO_2CH_3$), 64.0 (*C*$CH_3$), 117.0, 129.7, 135.4 (arom), 157.1 ($NCO_2CH_3$), 171.2 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{10}H_{16}N_3O_4$ (M + H) 242.1135, found (M + H) 242.1131.

*(R)-Methyl 2-(1H-Imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (R)-**2***. Starting from (*S*)-**1** using DMF as a solvent, compound (*R*)-**2** was isolated in a 79% yield as a white solid. $[\alpha]^{20}_D$ (*c* 1.03, $CHCl_3$): +54.4. HRMS (ESI+): calcd for $C_{10}H_{16}N_3O_4$ (M + H) 242.1135, found (M + H) 242.1141.

*(S)-Methyl 2-Hydroxy-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**2′***. This experimental procedure describes an alternative synthesis for the side product (*S*)-**2′**, which was obtained when sulfamidate (*R*)-**1** was opened with imidazole, using DMF as a solvent (Table 1, entry 5). (*S*)-α-Methylisoserine (119 mg, 1.00 mmol), previously obtained following the method described in the literature,[2a] was suspended 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 hydrochloride derivative was dissolved in water (5 mL), and $Na_2CO_3 \cdot 10H_2O$ (0.57 g, 2.00 mmol) was added. A solution of dimethyl dicarbonate (174 mg, 1.3 mmol) in THF (20 mL) was added to the mixture. The mixture was vigorously stirred at rt for 15 h, and a saturated aqueous NaCl solution (40 mL) was then added. The resulting mixture was extracted with EtOAc (3 × 20 mL). The organic layer was dried, filtered, and evaporated to give a residue, which was purified by column chromatography, eluting with hexane/EtOAc (1:1), to give (*S*)-**2′** (76 mg, 40%) as an oil. $[\alpha]^{20}_D$ (*c* 0.99, $CHCl_3$): +45.0. $^1$H NMR ($CDCl_3$) $\delta$ 1.39 (s, 3H, $CH_3$), 3.26 (dd, 1H, *J* = 13.9, *J* = 5.0 Hz, C*H*$_2$NH), 3.57−3.65 (m, 4H, $NCO_2CH_3$, C*H*$_2$NH), 3.79 (s, 3H, $CO_2CH_3$), 5.10 (s, 1H, NH). $^{13}$C NMR ($CDCl_3$) $\delta$ 23.2 ($CH_3$), 48.7 ($CH_2$NH), 52.3 ($NCO_2CH_3$), 53.1 ($CO_2CH_3$), 74.5 (*C*$CH_3$), 157.3 ($NCO_2CH_3$), 175.9 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_7H_{14}NO_5$ (M + H) 192.0866, found (M + H) 192.0862.

*(S)-Methyl 2-(1H-Benzo[d]imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**3***. Starting from (*R*)-**1** and using $CH_3CN$ as a solvent, compound (*S*)-**3** was isolated in a 60% yield as a white solid. Mp: 126−128 °C. $[\alpha]^{26}_D$ (*c* 0.96, $CHCl_3$): −95.1. $^1$H NMR ($CDCl_3$) $\delta$ 1.94 (s, 3H, $CH_3$), 3.56 (s, 3H, $NCO_2CH_3$), 3.65 (s, 3H, $CO_2CH_3$), 3.79 (dd, 1H, *J* = 14.5 Hz, *J* = 6.1 Hz, C*H*$_2$NH), 4.08 (dd, 1H, *J* = 14.5 Hz, *J* = 7.3 Hz, C*H*$_2$NH), 4.94 (s, 1H, NH), 7.09−7.24 (m, 3H, arom), 7.67−7.77 (m, 1H, arom), 7.98 (m, 1H, arom). $^{13}$C NMR ($CDCl_3$) $\delta$ 21.2 ($CH_3$), 45.4 ($CH_2$NH), 52.5 ($NCO_2CH_3$), 53.2 ($CO_2CH_3$), 64.0 (*C*$CH_3$), 110.6, 120.9, 122.7, 123.4, (arom), 157.4 ($NCO_2CH_3$), 171.6 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{14}H_{18}N_3O_4$ (M + H) 292.1292, found (M + H) 292.1296.

*(S)-Methyl 3-(Methoxycarbonylamino)-2-methyl-2-(2-methyl-1H-imidazol-1-yl)propanoate (S)-**4***. Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound (*S*)-**4** was isolated in a 62% yield as a white solid. Mp: 122−124 °C. $[\alpha]^{26}_D$ (*c* 1.07, $CHCl_3$): −62.2. $^1$H NMR ($CDCl_3$) $\delta$ 1.81 (s, 3H, $CH_3$), 2.25 (s, 3H, $CH_{3imi}$), 3.65−3.70 (m, 4H, $CO_2CH_3$, C*H*$_2$NH), 3.79 (s, 3H, $CO_2CH_3$), 3.92 (dd, 1H, *J* = 14.3 Hz, *J* = 6.8 Hz, C*H*$_2$NH), 5.70−5.74 (s, 1H, NH), 6.87 (s, 1H, arom), 6.95 (s, 1H, arom). $^{13}$C NMR ($CDCl_3$) $\delta$ 15.0 ($CH_{3imi}$), 22.7 ($CH_3$), 46.6 ($CH_2$NH), 52.5 ($NCO_2CH_3$), 53.2 ($CO_2CH_3$), 63.7 (*C*$CH_3$), 117.4, 126.8, 144.3 (arom), 157.6 ($NCO_2CH_3$), 172.3 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{11}H_{18}N_3O_4$ (M + H) 256.1292, found (M + H) 256.1294.

*(S)-Methyl 2-(2-Ethyl-1H-imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**5***. Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound (*S*)-**5** was isolated in a 42% yield as white solid. Mp: 123−125 °C. $[\alpha]^{20}_D$ (*c* 1.17, $CHCl_3$): −63.3. $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (t, 3H, *J* = 7.38 Hz, $CH_{3imi}$), 1.81 (s, 3H, $CH_3$), 2.35−2.55 (m, 2H, $CH_{2imi}$), 3.56−3.75 (m, 4H, C*H*$_2$NH, $CO_2CH_3$), 3.79 (s, 3H, $CO_2CH_3$), 3.87−3.92 (m, 1H, C*H*$_2$NH), 5.13 (s, 1H, NH), 6.95 (s, 1H, arom), 7.00 (s, 1H, arom). $^{13}$C NMR ($CDCl_3$) $\delta$ 12.2 ($CH_{3imi}$), 21.5 ($CH_{2imi}$), 22.9 ($CH_3$), 41.7 ($CH_2$NH), 52.6 ($NCO_2CH_3$), 53.3 ($CO_2CH_3$), 63.6 (*C*$CH_3$), 116.9, 126.8, 149.3 (arom), 157.4 ($NCO_2CH_3$), 172.6 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{12}H_{20}N_3O_4$ (M + H) 270.1448, found (M + H) 270.1449.

*(S)-Methyl 2-(2-Isopropyl-1H-imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**6***. Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound (*S*)-**6** was isolated in a 48% yield as colorless oil. $[\alpha]^{20}_D$ (*c* 0.99, $CHCl_3$): −39.8. $^1$H NMR ($CDCl_3$) $\delta$ 1.24 (d, 3H, *J* = 6.62 Hz, $CH_{3imi}$), 1.27 (d, 3H, *J* = 6.62 Hz, $CH_{3imi}$), 1.82 (s, 3H, $CH_3$), 2.55−2.63 (m, 1H, $CH_{imi}$), 3.59−3.66 (m, 4H, C*H*$_2$NH, $CO_2CH_3$), 3.79 (s, 3H, $CO_2CH_3$), 3.92−3.97 (m, 1H, C*H*$_2$NH), 5.01−5.04 (m, 1H, NH), 6.89 (s, 1H, arom), 7.01 (s, 1H, arom). $^{13}$C NMR ($CDCl_3$) $\delta$ 22.3 ($CH_{3imi}$), 22.8 ($CH_3$), 22.9 ($CH_3$), 27.5 ($CH_{imi}$), 47.5 ($CH_2$NH), 52.5 ($NCO_2CH_3$), 53.1 ($CO_2CH_3$), 63.1 (*C*$CH_3$), 115.6, 127.2, 153.5 (arom), 157.2 ($NCO_2CH_3$), 172.8 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{13}H_{22}N_3O_4$ (M + H) 284.1610, found (M + H) 284.1599.

*(S)-Methyl 3-(Methoxycarbonylamino)-2-methyl-2-(4-methyl-1H-imidazol-1-yl)propanoate (S)-**7a***. Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound (*S*)-**7a** was isolated in a 66% yield as colorless oil. $[\alpha]^{20}_D$ (*c* 1.15, $CHCl_3$): −50.5. $^1$H NMR ($CDCl_3$) $\delta$ 1.74 (s, 3H, $CH_3$), 2.11 (s, 3H, $CH_{3imi}$), 3.59−3.64 (m, 4H, $NCO_2CH_3$, C*H*$_2$NH), 3.69 (s, 3H, $CO_2CH_3$), 3.82−3.87 (m, 1H, C*H*$_2$NH), 5.77 (s, 1H, NH), 6.62 (s, 1H, arom), 7.42 (s, 1H, arom). $^{13}$C NMR ($CDCl_3$) $\delta$ 13.1 ($CH_{3imi}$), 20.1 ($CH_3$), 47.4 ($CH_2$NH), 51.9 ($NCO_2CH_3$), 52.7 ($CO_2CH_3$), 63.4 (*C*$CH_3$), 113.1, 134.0, 137.9 (arom), 157.0 ($NCO_2CH_3$), 170.8 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{11}H_{18}N_3O_4$ (M + H) 256.1292, found (M + H) 256.1290.

*(S)-Methyl 2-(2,4-Dimethyl-1H-imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**8a** and (S)-Methyl 2-(2,5-Dimethyl-1H-imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**8b***. (*S*)-**8a**: Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound


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(*S*)-**8a** was isolated in a 36% yield as colorless oil. $[\alpha]^{26}_D$ (*c* 0.94, $CHCl_3$): −40.3. $^1H$ NMR ($CDCl_3$) $\delta$ 1.78 (s, 3H, $CH_3$), 2.16 (s, 3H, $CH_{3imi}$), 2.23 (s, 3H, $CH_{3imi}$), 3.62−3.71 (m, 4H, $NCO_2CH_3$, $CH_2NH$), 3.79 (s, 3H, $CO_2CH_3$), 3.86−3.91 (m, 1H, $CH_2NH$), 5.41 (s, 1H, NH), 6.66 (s, 1H, arom). $^{13}C$ NMR ($CDCl_3$) $\delta$ 12.9 ($CH_{3imi}$), 14.3 ($CH_{3imi}$), 22.1 ($CH_3$), 46.3 ($CH_2NH$), 52.1 ($NCO_2CH_3$), 52.8 ($CO_2CH_3$), 63.2 ($CCH_3$), 113.3, 134.8, 143.0 (arom), 157.0 ($NCO_2CH_3$), 171.9 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{12}H_{20}N_3O_4$ (M + H) 270.1448, found (M + H) 270.1451.

NMR data of (*S*)-**8b** extracted from a mixture of regioisomers: $^1H$ NMR ($CDCl_3$) $\delta$ 1.81 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_{3imi}$), 2.21 (s, 3H, $CH_{3imi}$), 3.60−3.63 (m, 1H, $CH_2NH$), 3.77 (s, 3H, $NCO_2CH_3$), 3.74 (s, 3H, $CO_2CH_3$), 4.08−4.14 (m, 1H, $CH_2NH$), 5.19 (s, 1H, NH), 6.69 (s, 1H, arom). $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.6 ($CH_{3imi}$), 14.7 ($CH_{3imi}$), 22.5 ($CH_3$), 46.6 ($CH_2NH$), 52.4 ($NCO_2CH_3$), 53.2 ($CO_2CH_3$), 63.8 ($CCH_3$), 113.3, 134.8, 143.0 (arom), 157.2 ($NCO_2CH_3$), 171.3 ($CO_2CH_3$).

*(S)-Methyl 3-(Methoxycarbonylamino)-2-methyl-2-(1H-pyrazol-1-yl)propanoate (S)-**9***. Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound (*S*)-**9** was isolated in a 69% yield as colorless oil. $[\alpha]^{20}_D$ (*c* 1.15, $CHCl_3$): −46.9. $^1H$ NMR ($CDCl_3$) $\delta$ 1.75 (s, 3H, $CH_3$), 3.57 (s, 3H, $CO_2CH_3$), 3.66 (s, 3H, $CO_2CH_3$), 3.93−4.05 (m, 2H, $CH_2NH$), 5.35 (s, 1H, NH), 6.25 (s, 1H, arom), 7.48 (s, 2H, arom). $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.2 ($CH_3$), 47.2 ($CH_2NH$), 52.2 ($NCO_2CH_3$), 52.9 ($CO_2CH_3$), 67.3 ($CCH_3$), 105.9, 128.1, 139.7 (arom), 157.1 ($NCO_2CH_3$), 171.4 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{10}H_{15}N_3O_4Na$ (M + Na) 264.0955, found (M + Na) 264.0962.

*(S)-Methyl 2-(2-Bromo-1H-imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate (S)-**10***. Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound (*S*)-**10** was isolated in a 29% yield as a white solid. Mp: 136−138 °C. $[\alpha]^{20}_D$ (*c* 1.01, $CHCl_3$): −69.1. $^1H$ NMR ($CDCl_3$) $\delta$ 1.92 (s, 3H, $CH_3$), 3.67 (s, 3H, $CO_2CH_3$), 3.78−3.84 (m, 4H, $CO_2CH_3$, $CH_2NH$), 4.04 (dd, 1H, *J* = 14.5 Hz, *J* = 6.9 Hz, $CH_2NH$), 5.04 (s, 1H, NH), 7.03 (s, 1H, arom), 7.11 (s, 1H, arom). $^{13}C$ NMR ($CDCl_3$) $\delta$ 22.7 ($CH_3$), 46.6 ($CH_2NH$), 52.8 ($NCO_2CH_3$), 53.5 ($CO_2CH_3$), 65.1 ($CCH_3$), 117.9, 120.5, 129.6 (arom), 157.5 ($NCO_2CH_3$), 171.7 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{10}H_{15}BrN_3O_4$ (M + H) 320.0240, found (M + H) 320.0238.

*(S)-Methyl 2-(4-((S)-2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-methoxy-3-oxopropyl)-1H-imidazol-1-yl)-3-(methoxycarbonylamino)-2-methylpropanoate **11***

Synthesis of Nucleophile: Fmoc-His-OH (218 mg, 0.57 mmol) was dissolved in a mixture of MeOH/HCl, previously prepared by the addition of AcCl (0.12 mL) over MeOH (4 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. After evaporation of the solvent, the crude product was treated with saturated $NaHCO_3$ solution (5 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried over $Na_2SO_4$, concentrated, and the residue was purified by a silica gel column chromatography ($CH_2Cl_2$/MeOH, 95:5) to give compound Fmoc-His-OMe (174 mg, 77%) as a white solid. Mp: 113−115 °C. $[\alpha]^{20}_D$ (*c* 1.00, $CHCl_3$): +12.1. $^1H$ NMR ($CDCl_3$) $\delta$ 3.15 (s, 2H, $CH_2$), 3.71 (s, 3H, $CO_2CH_3$), 4.23 (t, 1H, *J* = 7.09 Hz, CH), 4.37−4.39 (m, 2H, $CH_2$), 4.62−4.64 (m, 1H, CH), 6.19−6.23 (m, 1H, NH), 6.79 (s, 1H, arom), 7.31 (t, 2H, *J* = 7.45 Hz, arom), 7.39 (t, 2H, *J* = 7.40 Hz, arom), 7.57−7.62 (m, 3H, arom), 7.76 (d, 2H, *J* = 7.54 Hz, arom). $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.6 ($CH_2$), 47.2 (CH), 52.5 ($CO_2CH_3$), 54.1 (CH), 67.1 ($CH_2$), 120.0, 125.2, 127.1, 127.7, 135.1, 141.3, 143.9, 144.0 (arom), 156.2 ($NCO_2CH_2$), 172.2 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{22}H_{22}N_3O_4$ (M + H) 392.1605, found (M + H) 392.1617.

Compound **11**: Starting from (*R*)-**1** using $CH_3CN$ as a solvent, compound **11** was isolated in a 32% yield as a white solid. Mp: 61−63 °C. $[\alpha]^{20}_D$ (*c* 1.00, $CH_3OH$): −15.9. $^1H$ NMR ($CDCl_3$) $\delta$ 1.79 (s, 3H, $CH_3$), 3.08−3.09 (m, 2H,$CH_{2His}$), 3.57−3.68 (m, 4H, $CO_2CH_3$, $CH_2NH$), 3.73 (s, 3H, $CO_2CH_3$), 3.75 (s, 3H, $CO_2CH_3$), 3.79−3.87 (m, 1H, $CH_2NH$), 4.21−4.30 (m, 2H, $CH_{2Fmoc}$), 4.35−4.39 (m, 1H, $CH_{Fmoc}$), 4.62−4.67 (m, 1H, $CH_{His}$), 5.10−5.14 (m, 1H, NH), 6.34−6.36 (m, 1H, NH), 6.79 (s, 1H, arom), 7.30 (t, 2H, *J* = 7.43 Hz, arom), 7.39 (t, 2H, *J* = 7.43 Hz, arom), 7.52 (s, 1H, arom), 7.60−7.64 (m, 2H, arom), 7.75 (d, 2H, *J* = 7.52 Hz, arom). $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.9 ($CH_3$), 30.7 ($CH_{2His}$), 47.3 ($CH_{Fmoc}$), 48.2 ($CH_2$), 52.5 ($CO_2CH_3$), 52.7 ($CO_2CH_3$), 53.5 ($CO_2CH_3$), 54.3 ($CH_{His}$), 64.4 ($CCH_3$), 67.3 ($CH_{2Fmoc}$), 115.3, 120.1, 125.4, 125.5, 127.1, 127.2, 127.8, 135.6, 137.9, 141.4, 144.0, 144.2 (arom), 156.4, 157.3 ($NCO_2$), 171.2, 172.4 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{29}H_{33}N_4O_8$ (M + H) 565.2293, found (M + H) 565.2298.

*(S)-Methyl 3-Amino-2-(1H-imidazol-1-yl)-2-methylpropanoate Hydroiodide (S)-**12***. To a solution of (*S*)-**2** (35 mg, 0.07 mmol) in dry $CH_2Cl_2$ (3 mL) under argon was added TMSI (17 $\mu$L, 0.14 mmol). The reaction mixture was stirred at room temperature for 12 h, then it was quenched with MeOH (5 mL), and the solvent was evaporated in vacuo. The residue was dissolved in $H_2O$ (5 mL) and was extracted with $CHCl_3$/$^i$PrOH (3:1) (2 × 5 mL). The combined aqueous phases were concentrated, and the residue was dissolved in $H_2O$ (2 mL) and eluted through a reverse-phase Sep-pak C18 cartridge to obtain, after evaporation of the $H_2O$, compound (*S*)-**12** as a yellow oil (33 mg, 73%). $[\alpha]^{20}_D$ (*c* 1.02, $CH_3OH$): +2.7. $^1H$ NMR ($CD_3OD$) $\delta$ 2.19 (s, 3H, $CH_3$), 3.91 (s, 3H, $CO_2CH_3$), 4.03 (s, 2H, $CH_2NH$), 7.75 (s, 1H, arom), 8.00 (s, 1H, arom), 9.38 (s, 1H, arom). $^{13}C$ NMR ($CD_3OD$) $\delta$ 21.9 ($CH_3$), 46.0 ($CH_2NH$), 55.6 ($CO_2CH_3$), 66.1 ($CCH_3$), 122.5, 122.6, 137.4 (arom), 169.6 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_8H_{14}N_3O_2$ (M + H) 184.1081, found (M + H) 184.1071.

*(R)-Methyl 3-Amino-2-(1H-imidazol-1-yl)-2-methylpropanoate Hydroiodide (R)-**12***. Following the same procedure described above for compound (*S*)-**12**, but starting from (*R*)-**2**, the enantiomer (*R*)-**12** was obtained. $[\alpha]^{20}_D$ (*c* 1.01, $CH_3OH$): −2.9. HRMS (ESI+): calcd for $C_8H_{14}N_3O_2$ (M + H) 184.1081, found (M + H) 184.1074.

*(S)-3-Amino-2-(1H-imidazol-1-yl)-2-methylpropanoic Acid Hydrochloride (S)-**13***. Compound (*S*)-**12** (55 mg) was suspended in aqueous 2 N HCl (4 mL), and the mixture was heated at 50 °C for 48 h. After that, the solvent was evaporated, and the residue was dissolved in $H_2O$ (2 mL) and then eluted through a reverse-phase Sep-pak C18 cartridge to obtain, after evaporation of the $H_2O$, the corresponding compound (*S*)-**13** as a colorless oil (39 mg, 91%). $[\alpha]^{20}_D$ (*c* 1.06, $H_2O$): +15.7. $^1H$ NMR ($D_2O$) $\delta$ 2.01 (s, 3H, $CH_3$), 3.52−3.58 (m, 1H, $CH_2NH$), 3.62−3.73 (m, 1H, $CH_2NH$), 7.60 (s, 1H, arom), 7.70 (s, 1H, arom), 9.01 (s, 1H, arom). $^{13}C$ NMR ($D_2O$) $\delta$ 20.8 ($CH_3$), 45.4 0 ($CH_2NH$), 65.3 ($CCH_3$), 120.4, 120.7, 134.8 (arom), 175.0 ($CO_2H$). HRMS (ESI+): calcd for $C_7H_{12}N_3O_2$ (M + H) 170.0924, found (M + H) 170.0928.

*(S)-3-Amino-2-(1H-imidazol-1-yl)-2-methylpropanoic Acid (S)-**14***. Compound (*S*)-**13** (39 mg) was dissolved in ethanol/propylene oxide (3:1, 4 mL), and the solution was refluxed for 1 h. After that, (*S*)-**14** precipitated as a white solid (25 mg, 92%). $[\alpha]^{20}_D$ (*c* 1.08, $H_2O$): +16.5. $^1H$ NMR ($D_2O$) $\delta$ 1.89 (s, 3H, $CH_3$), 3.46 (q, 2H, *J* = 13.62 Hz, $CH_2NH$), 7.24 (s, 1H, arom), 7.35 (s, 1H, arom). $^{13}C$ NMR ($D_2O$) $\delta$ 21.2 ($CH_3$), 46.4 0 ($CH_2NH$), 63.8 ($CCH_3$), 126.1 (arom), 175.0 ($CO_2H$). HRMS (ESI+): calcd for $C_7H_{12}N_3O_2$ (M + H) 170.0924, found (M + H) 170.0920.

*(S)-Methyl 2-(1H-Imidazol-1-yl)-2-methyl-3-((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)propanoate **15***. A solution of (*R*)-(+)-MTPA (24 mg, 0.10 mmol) in $CH_3CN$ (1 mL) was added to a solution of (*S*)-**12** (29 mg, 0.09 mmol), DCC (21 mg, 0.10 mmol), and DMAP (12 mg, 0.10 mmol) in $CH_3CN$ (1.0 mL), under an inert atmosphere. The mixture was stirred at room temperature for 24 h. The resulting white suspension was filtered to remove the *N*,*N*′-dicyclohexylurea and then concentrated to give the crude product, which was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH, 95:5) to give compound **15** (9 mg, 25%), as a yellow oil. $[\alpha]^{20}_D$ (*c* 0.96, $CHCl_3$): −4.1. $^1H$ NMR

($CDCl_3$) $\delta$ 1.82 (s, 3H, $CH_3$), 3.31 (s, 3H, $CH_3O$), 3.77 (s, 3H, $CO_2CH_3$), 3.88 (dd, 1H, $J$ = 14.2 Hz, $J$ = 6.2 Hz, $CH_2NH$), 4.08 (dd, 1H, $J$ = 14.2 Hz, $J$ = 7.2 Hz, $CH_2NH$), 7.02 (s, 2H, arom), 7.15 (s, 1H, arom), 7.40 (s, 5H, arom), 7.71 (s, 1H, arom). $^{13}C$ NMR ($CDCl_3$) 20.6 ($CH_3$), 46.1 ($CH_2NH$), 53.7 ($CO_2CH_3$), 63.8 ($CCH_3$), 127.7, 128.9, 128.9, 132.1 (arom + $CF_3$), 167.1 ($NCO_2C$), 169.4 ($CO_2CH_3$). HRMS (ESI+): calcd for $C_{18}H_{21}F_3N_3O_4$ (M + H) 400.1479, found (M + H) 400.1460.

*Computational Details.* All calculations were carried out with the B3LYP hybrid functional[23] and 6-31G+(d,p) basis set. Full geometry optimizations and transition structure (TS) searches were carried out with the Gaussian 03 package.[24] The possibility of different conformations and nucleophile approximations was taken into account for all structures. Basis set superposition errors (BSSE) were corrected by the Boys−Bernardi counterpoise method.[25] 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.[26] Mass-weighted intrinsic reaction coordinate (IRC) calculations were carried out by using the Gonzalez and Schlegel scheme[27] in order 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)[28] using UAHF radii, as implemented in Gaussian 03. The internally stored parameters for acetonitrile ($\epsilon$ = 35.7) were used to calculate solvation free energies ($\Delta G_{solv}$). Gibbs free energies ($\Delta G$) were used for the discussion on the relative stabilities of the considered structures. Cartesian coordinates, electronic energies, entropies, enthalpies, Gibbs free energies, lowest frequencies of the different conformations of all structures considered are available as Supporting Information.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Spectroscopic characterization of all new compounds, crystal structure data, computational data, and complete ref 24 (Gaussian). This material is available free of charge via the Internet at http://pubs.acs.org.

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