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Diastereoselective 1,3-Dipolar Cycloaddition Reactions between Azomethine Ylides and Chiral Acrylates Derived from Methyl (*S*)- and (*R*)-Lactate – Synthesis of Hepatitis C Virus RNA-Dependent RNA Polymerase Inhibitors

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Dedicated to Prof. Vicente Gotor on the occasion of his 60th birthday

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Highly *endo*-diastereoselective 1,3-dipolar cycloadditions between acrylates derived from methyl (*R*)- and (*S*)-lactate, as chiral dipolarophiles, and azomethine ylides derived from glycine and α-substituted amino acids are described. The origins of the observed excellent stereocontrol are interpreted on the basis of computational studies on model systems. This methodology was successfully employed for the first asymmetric synthesis of both enantiomers, as well as of its racemic form, of a biologically active pyrrolidine (hepatitis C virus inhibitor) incorporating a leucine residue and a 2-thienyl group.

Introduction

The general increasing demand for pure chiral substrates is continuously encouraging chemists to develop new methodologies in asymmetric synthesis.[1] Recently, a series of pyrrolidine derivatives **1** (Figure 1) have been discovered to be versatile, nonstructural 5B protein (NS5B) inhibitors offering great potential as effective antiviral agents; in particular, molecules **2** (Figure 1) proved to be the most promising potential drugs.[2] In fact, it was demonstrated that the activity of the *endo*-(+)-**2** enantiomer (IC_{50} = 190 nM) is higher than that exhibited by its *endo*-(–)-**2** form (IC_{50} = 18000 nM, Figure 1). Significantly, though, the relatively low concentration required by the racemic *endo*-(±)-**2** form (IC_{50} = 300 nM, Figure 1) was not negligible. The NS5B protein is a NS-protein product possessing RNA-dependent RNA polymerase (RdRp) activity, crucial for general viral replication[3] and, particularly, for the hepatitis C virus (HCV). Chronic HCV infection causes significant liver diseases and can eventually lead to the development of hepatocellular carcinoma. In spite of the effectiveness of the interferon-ribavirin and pegylated interferon against HCU, improvements in sustained response rate are still needed and new attempts to identify alternative treatments are ongoing.

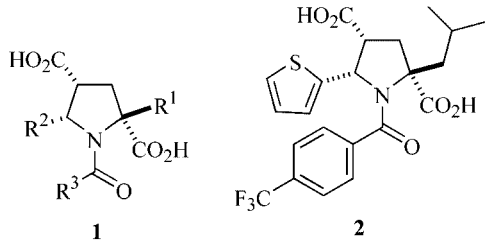

Figure 1. Biologically active pyrrolidines and activity of each enantiomer of *endo*-**2**, together with that of the racemic form.

The preparation of *N*-acylpyrrolidines **2** in their racemic forms was accomplished by means of thermal 1,3-dipolar cycloaddition reactions[4] between supported (Wang resin) azomethine ylides and *tert*-butyl acrylate (Scheme 1), the pure enantiomers being separated by preparative chiral HPLC.[2] However, no direct asymmetric synthesis of these type of pyrrolidine derivatives **2** has yet been described, so an asymmetric synthesis of the title compounds **2** would

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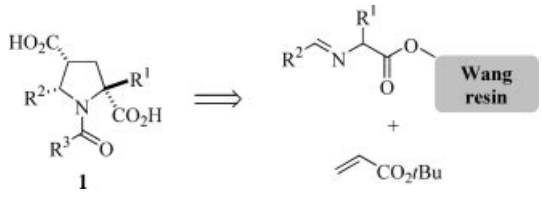
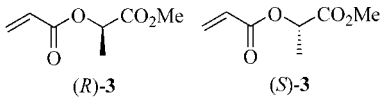
be desirable. At this moment, diastereoselective 1,3-dipolar cycloaddition reactions[4a,4d–h,5] employing metallo-azomethine ylides seem to be procedures more tolerant towards structural modifications of the reagents (dipole and dipolarophile) than enantioselective 1,3-dipolar cycloaddition reactions.[4b,4c,6] Thus, many interesting products have been obtained by using chiral acrylamides or acrylates,[7] chiral enones,[8,9] chiral Fischer alkenyl carbenes,[10] and chiral nitroalkenes.[11]



Scheme 1. Retrosynthetic analysis of bioactive molecules **1** and **2**.

In this context, we envisaged that the enantiomerically enriched acrylates (*R*)- and (*S*)-**3**[12,13] could be good candidates to carry out these 1,3-dipolar cycloaddition reactions. They are known compounds that have been employed in diastereoselective Diels–Alder reactions using in situ thermal generation of α-hydroxy-*o*-quinodimethane,[13a,13b] in the preparation of optically active podophyllotoxin analogues,[13c] in the preparation of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN),[13d] and in the 1,3-dipolar cycloaddition reaction between the alkene (*S*)-**3** and *N*-benzyl-3-hydroxypyridinium chloride for the synthesis of the alkaloid Bao Gong Teng A.[13e]

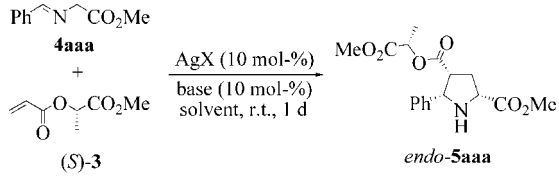


In this work we present a full account[12] of the diastereoselective 1,3-dipolar cycloaddition reactions between imino esters **4**, as azomethine ylide precursors, and chiral acrylates **3**,[13] derived from the very easily accessible (*S*)- and (*R*)-lactate. A direct application of this asymmetric transformation is used as key step for the preparation of the biologically active molecules (+)- and (–)-**2**. The driving force responsible for the high diastereoselection exhibited by this small source of chirality is studied by computational analysis.

Results and Discussion

The enantiomerically pure acrylates (*R*)- and (*S*)-**3** were easily obtained in 86% isolated yield, starting from acryloyl chloride and the corresponding methyl (*R*)- or (*S*)-lactate and using triethylamine and a small amount of *N*,*N*-dimethylaminopyridine (DMAP) as bases in dichloromethane for 2 d at room temperature.[12] This process represents an advantageous alternative to the previously reported synthesis employing acryloyl chloride and the corresponding methyl lactates at reflux in carbon tetrachloride (very toxic and no longer commercially available) for 4 d.[13a]

Following our precedent work on the 1,3-dipolar cycloaddition reactions,[14] involving PTC agents under different reaction conditions, we surveyed some parameters such as solvent, silver salt, and base for running the diastereoselective cycloaddition reaction between the enantiomerically pure alkene (*S*)-**3** and the benzaldehyde methyl glycinate **4aaa** (Scheme 2 and Table 1). The reaction, carried out in the presence of a silver salt (10 mol-%) at room temperature for 1 day, gave product *endo*-**5aaa** with the same yield and *de* with either triethylamine or potassium hydroxide (10 mol-%) as base.[15] However, the crude reaction product obtained using KOH was cleaner (96% purity as revealed by ^{1}H NMR spectroscopy) than its counterpart obtained with triethylamine (90% purity; Table 1, Entries 1 and 2). With regard to the solvent, toluene gave the purest compound, rather than other solvents such as THF or DCM (Table 1; compare Entries 2–4).[14] The silver salt does not appear to have a dramatic effect on the reaction yield and diastereoselectivity, so silver acetate was chosen as metal catalyst (Table 1, compare Entry 2 with Entries 5–7) as it is inexpensive and easier to handle. When this reaction was performed with the acrylate (*R*)-**3** the enantiomer of the compound *endo*-**5aaa** was obtained in 98% yield and with 93% *de* (Table 1, Entry 8). The reaction became slower (1.5 d to completion) if 5 mol-% of silver acetate was used, though it furnished the cycloadduct with identical purity to that previously obtained with 10 mol-% catalyst.



Scheme 2. Diastereoselective synthesis of substituted pyrrolidine **5aaa**.

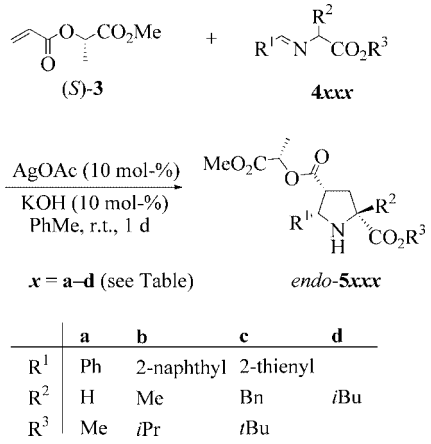
Table 1. Effects of the solvent, silver salt, and the base in the 1,3-dipolar cycloaddition reaction between (*S*)-**3** and methyl *N*-benzylideneglycinate (**4aaa**).

				Product **4aaa**	
Entry	Base[a]	AgX[a]	Solvent	Yield [%][b]	*de* [%][c]
1	Et_3N	AgOAc	PhMe	98 (90)	93
2	KOH	AgOAc	PhMe	98 (96)	93
3	KOH	AgOAc	THF	95 (85)	90
4	KOH	AgOAc	DCM	94 (85)	89
5	KOH	AgOTf	PhMe	95 (93)	90
6	KOH	$AgClO_4$	PhMe	98 (87)	92
7	KOH	AgF	PhMe	94 (88)	93
8	KOH	AgOAc	PhMe	98 (96)	93[d]

[a] 10 mol-%. [b] Pure crude yield (purity according to ^{1}H NMR spectroscopy using an internal standard in parentheses). [c] Determined by chiral HPLC (see Experimental Section). [d] The reaction was performed with acrylate (*R*)-**3** and the resulting product **5aaa** was obtained with the opposite absolute configuration.

Under the reaction conditions established in Entry 2 of Table 1, different substituents on the imino ester **4** (R^1, R^2, and R^3) were evaluated in the reaction with acrylate (*S*)-**3**

in the presence of silver acetate (10 mol-%) in toluene with KOH (10 mol-%) for 1 d (Scheme 3 and Table 2). The corresponding *endo*-**5** products were mainly obtained as practically pure crude compounds, though in most examples the *exo* adducts were detectable in very low proportions (<3%) by ^{1}H NMR spectroscopy.



	a	b	c	d
R^1	Ph	2-naphthyl	2-thienyl	
R^2	H	Me	Bn	*i*Bu
R^3	Me	*i*Pr	*t*Bu	

Scheme 3. Diastereoselective synthesis of substituted pyrrolidines **5**.

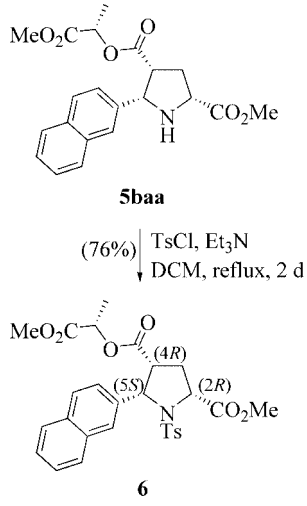
For glycine-derived 1,3-dipoles, the influence of the ester group in the reaction could be deduced when benzaldehyde iminoglycinates **4aaa**, **4aab**, and **4aac** (methyl, isopropyl, and *tert*-butyl esters, respectively) were allowed to react with chiral alkene (*S*)-**3** (Table 2, Entries 1–3). The cycloadditions proceeded almost quantitatively to afford the corresponding crude cycloadducts *endo*-**5aaa**, *endo*-**5aab**, and *endo*-**5aac**, with very similar *de* values. However, the *tert*-butyl ester was the most appropriate, because **5aac** was isolated after purification with a 99% *de*. This effect is independent of the aryl substituent bonded to the imine derived from glycine, as was also observed in the analogous reaction performed with 2-naphthalene iminoglycinates **4baa** and **4bac** (Table 2, Entries 4 and 5).

Next, several α-substituted amino acids such as alanine, phenylalanine, and leucine were used for the elaboration of the 1,3-dipole precursors **4**. Alanine derivatives **4aba**, **4abc**, and **4bba** gave clean reaction crude products *endo*-**5aba**, *endo*-**5abc**, and *endo*-**5bba**, respectively, in excellent yields and with high diastereoselectivities (Table 2, Entries 6–8). For this type of α-substituted imino esters, compound **4aba**, bearing a phenyl substituent on the imino group and a methyl ester, displayed higher diastereoselection than the *tert*-butyl phenylimino ester **4abc**. The phenylalanine-derived imino esters **4aca**, **4bca**, and **4cca**, were subjected to these reaction conditions with acrylate (*S*)-**3** and afforded good yields but lower diastereoselectivities of *endo*-**5aca**, *endo*-**5bca**, and *endo*-**5cca** than those achieved with alanine derivatives (Table 2, Entries 9–11).

At this point alanine was replaced by leucine and the phenyl group of the imine moiety by the 2-thienyl group in order to access the antiviral target compounds **2**. A first attempt was carried out with imino ester **4ada**, which gave a very low yield (45%) of *endo*-**5ada** after 2 d, though with high diastereoselection (90% *de*, Table 2, Entry 12). Fortunately, when the 2-thienyl derivatives **4cda**, **4cdb**, and **4cdc** were allowed to react with (*S*)-**3** the processes were complete after 2 d (Table 2, Entries 13–15). Focusing our efforts on this transformation we obtained better diastereoselection when using a methyl ester instead of isopropyl or *tert*-butyl esters (Table 2, compare Entries 13–15).

As a partial conclusion we can surmise that the yields and conversions obtained using α-branched azomethine ylide precursors were similar to those obtained for the examples described with glycine, although with slightly lower diastereoselection (from 88–93% to 80–92% *de*). In all of the examples described, partial decomposition of the cycloadducts was observed during the flash chromatography purification and significant drops in the isolated yields consequently occurred, but cycloadducts **5** were obtained in higher *de* values than the crude products.

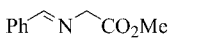
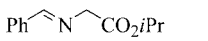
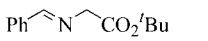
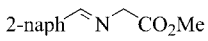
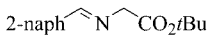
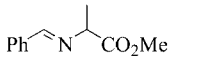
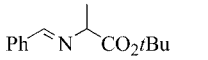
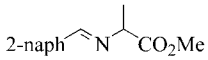
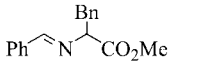
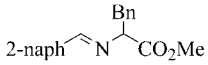
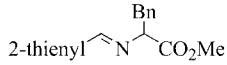
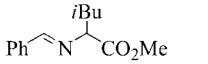
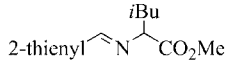
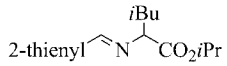
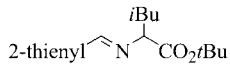
The absolute configurations of these three newly created stereogenic centers were determined by X-ray diffraction analysis of the *N*-(*p*-tolylsulfonyl) derivative **6**,[12] obtained from the corresponding compound **5baa** by treatment with *p*-toluenesulfonyl chloride and triethylamine in DCM at reflux for 2 d (Scheme 4). It can be deduced that (*S*)-lactate acrylate gave (2*R*,4*R*,5*S*)-prolinates and that the enantiomeric (*R*)-lactate acrylate yielded (2*S*,4*S*,5*R*)-prolinates.



Scheme 4. Derivatization of pyrrolidine **5baa**.

In order to understand the origins of the excellent regio- and stereocontrol observed in these reactions, we performed several DFT calculations[16] relating to the reaction between (*S*)-**3** and the azomethine ylides **7a**–**c** depicted in Scheme 5. These model reactions include the main features of the transformations studied experimentally. Previous computational work[17] has shown that these 1,3-dipolar cycloadditions are not concerted but stepwise (Scheme 5). The first step consists of a Michael-type nucleophilic attack on the α,β-unsaturated carboxy derivative to yield the intermediates **INT** depicted in Scheme 5. The intramolecular Mannich-like ring closure of these ionic intermediates leads to the stereocontrolled formation of the pyrrolidine derivatives

Table 2. Diastereoselective 1,3-dipolar cycloaddition reactions between compounds **4** and chiral acrylate (*S*)-**3**.

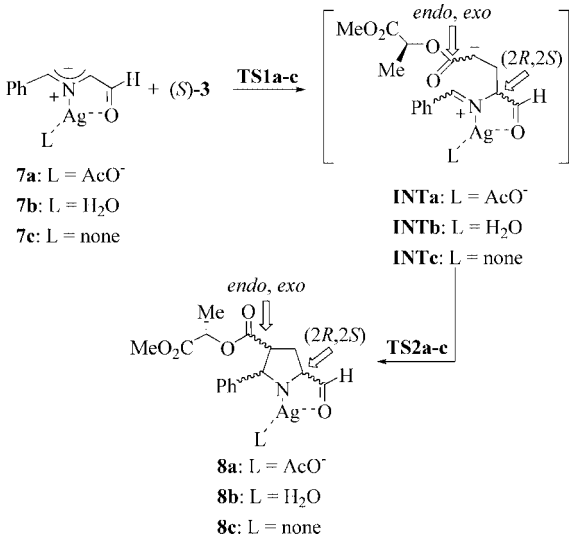
	Imino ester **4**		Product *endo*-**5**							
Entry		Structure		R^1	R^2	R^3	Yield [%][a]	*de* [%][b]	Yield [%][c]	*de* [%][d]
1	**4aaa**		**5aaa**	Ph	H	Me	98	93	64	94
2	**4aab**		**5aab**	Ph	H	*i*Pr	98	92	63	92
3	**4aac**		**5aac**	Ph	H	*t*Bu	99	95	73	99
4	**4baa**		**5baa**	2-naphthyl	H	Me	99	88	60	90
5	**4bac**		**5bac**	2-naphthyl	H	*t*Bu	98	90	70	99
6	**4aba**		**5aba**	Ph	Me	Me	99	90-92	65	88-90
7	**4abc**		**5abc**	Ph	Me	*t*Bu	97	88	70	92
8	**4bba**		**5bba**	2-naphthyl	Me	Me	99	88	67	85
9	**4aca**		**5aca**	Ph	Bn	Me	97-98	83	67	86
10	**4bca**		**5bca**	2-naphthyl	Bn	Me	97	80	65	84
11	**4cca**		**5cca**	2-thienyl	Bn	Me	90	84	64	95
12	**4ada**		**5ada**	Ph	*i*Bu	Me	45[e]	90	32	90
13	**4cda**		**5cda**	2-thienyl	*i*Bu	Me	99[e]	92	77	96
14	**4cdb**		**5cdb**	2-thienyl	*i*Bu	*i*Pr	99[e]	80	82	82
15	**4cdc**		**5cdc**	2-thienyl	*i*Bu	*t*Bu	99[e]	86	83	87

[a] Isolated crude yield after workup. [b] Determined by chiral HPLC (Chiralcel OD-H). [c] Isolated yield after purification by flash chromatography. [d] For purified products. [e] After a reaction time of 2 d.

8. In this mechanistic scheme, it is interesting to note that both the regiochemistry and the *endo* diastereoselectivity of the reaction are determined by the step leading to the formation of the C2–C3 bond.[11]

The four possible transition structures **TS1a** were studied first (Scheme 5). These saddle points are generated from the interaction between (*S*)-**3** and the model azomethine ylide **7a**, which incorporates an acetate ligand. The chief geometric features of these transition structures are collected in Figure 2. According to our results, (2*R*)-*endo*-**TS1a** is ca. 3 kcal mol^{-1} lower in energy than (2*S*)-*endo*-**TS1a** because of the *inside* orientation of the methyl group of the (*S*)-lactate moiety in (2*S*)-*endo*-**TS1a**, which results in a destabilizing steric interaction with the 5-phenyl group. This orientation in turn stems from the non-coplanar conformation of the two C=O bonds. In contrast, the alternative *endo* saddle point (2*R*)-*endo*-**TS1a** bears this methyl group in a less sterically demanding outside orientation (Figure 2).

Our calculations also indicate that the two possible *exo* transition structures are of lower energy than the *endo* ones (Figure 2). According to this result, almost exclusive formation of (2*R*,4*S*,5*S*) cycloadducts should have occurred, an outcome not observed in the experimental studies (vide supra). Analysis of the saddle points depicted in Figure 2 shows that the relative stabilization of the *exo* transition structures stems from the Coulombic repulsion between the acetate anion and the weakly coordinated carboxylate moieties in the *endo* transition structures.



Scheme 5.

Since silver acetate and potassium hydroxide had been used as metal source and base, respectively, in most of the experimental studies, we mixed these two components in deuterated water, at which point a black colloidal precipitate appeared. After filtration, the resulting solution did not contain any silver traces as revealed by ^{1}H and ^{13}C NMR experiments, which demonstrated the very fast formation of insoluble AgOH and soluble KOAc. We therefore also computed the four possible transition structures resulting from the interaction between (*S*)-**3** and model H_2O/silver azomethine ylide complex **7b** (Scheme 5). The main geometric and energetic features of these **TS1b** transition structures are shown in Figure 3. In this case, the water ligand favors *endo* transition structures in which the interactions between the carboxylate moieties and the silver atom are stronger than those computed for the *endo*-**TS1a** series. As far as the (2*S*)-*endo*-**TS1b** and (2*R*)-*endo*-**TS1b** saddle points are concerned, in the former there is steric congestion generated by the methyl and the phenyl groups, a destabilizing interaction similar to that observed in (2*S*)-*endo*-**TS1a**. However, the lack of bonding between the silver atom and the carboxy group in the *exo*-**TS1b** saddle points results in a destabilization as there is now no noticeable electrostatic repulsion between the neutral ligand and the carboxy groups in the two alternative *endo*-**TS1b** stationary points (Figure 3). As a consequence, this series of transition structures leads to the exclusive formation of the (2*R*,4*R*,5*S*) cycloadducts, in good agreement with the experimental results.

Finally, we calculated the transition structures (2*R*)-*endo*-**TS1c** and (2*S*)-*endo*-**TS1c**, resulting from the interaction between (*S*)-**3** and **7c** (Scheme 5). In this case, the two possible *exo* transition structures **TS1c** could not be located as the starting geometries converged to the *endo* ones upon optimization. In addition, the absence of the additional ligand promotes the coordination between the silver atom and the *two* carboxylate groups of (*S*)-**3**. These results gen-

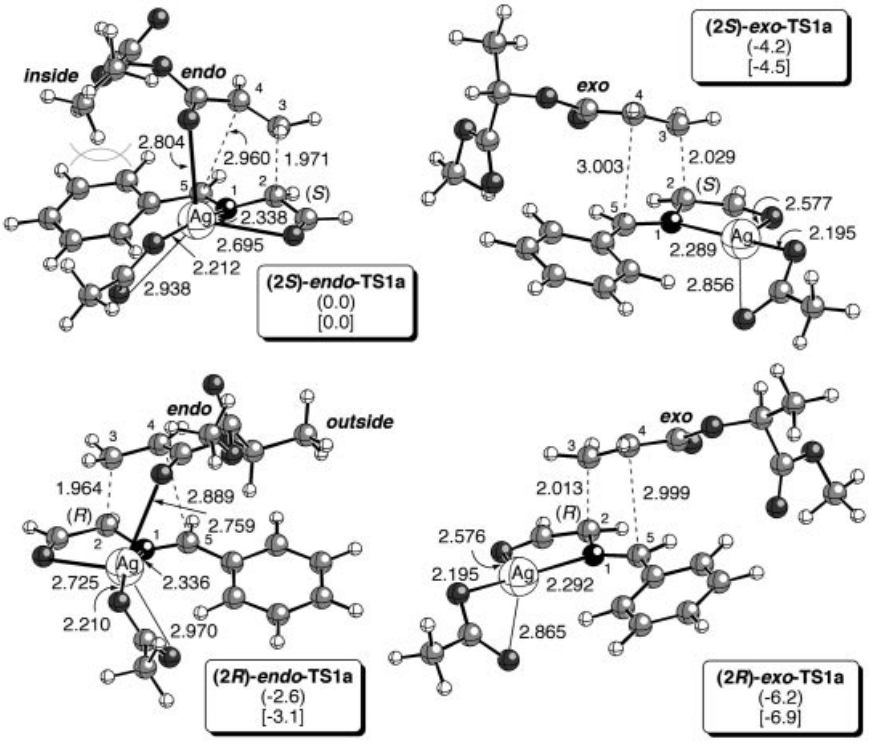


Figure 2. Chief geometric features (B3LYP/6-31G&LANL2DZ level of theory) of transition structures associated with the reaction between (*S*)-**3** and azomethine ylide **7a** to yield cycloadducts **8a** (Scheme 5). Bond lengths are in Å. Numbers in parentheses and square brackets correspond to the relative energies and Gibbs free energies (at 298 K), respectively, in kcal mol^{-1}.

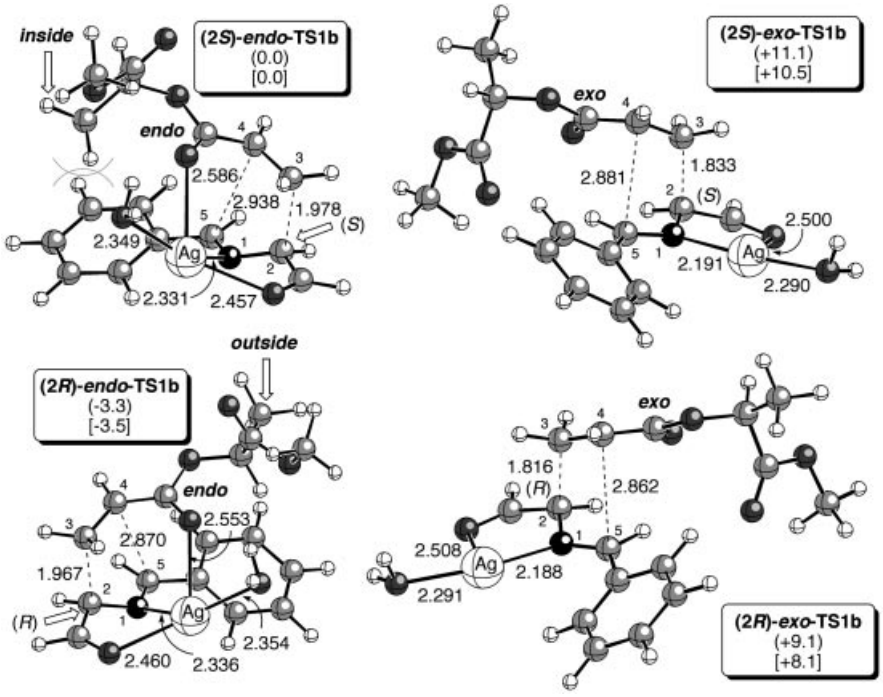


Figure 3. Chief geometric features (B3LYP/6-31G&LANL2DZ level of theory) of transition structures involved in the reaction between (*S*)-**3** and azomethine ylide **7b** to yield cycloadducts **8b** (Scheme 5). Bond lengths are in Å. Numbers in parentheses and square brackets correspond to the relative energies and Gibbs free energies (at 298 K), respectively, in kcal mol^{-1}.

erate a destabilizing pseudoaxial orientation of the methyl group in (2*R*)-*endo*-**TS1c**, as shown in Figure 4. Under these conditions, the reverse stereochemical outcome – namely, formation of the (2*S*,4*S*,5*R*) cycloadduct – was predicted, in sharp contrast with the experimental results.

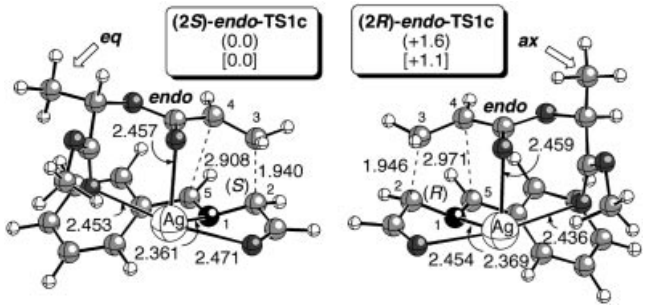
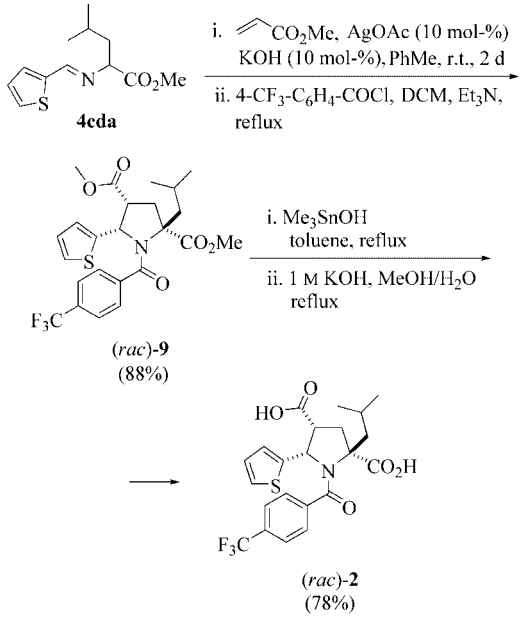


Figure 4. Chief geometric and energetic features of transition structures (2*R*)-*endo*-**TS1c** and (2*S*)-*endo*-**TS1c** (Scheme 5). Numbers in parentheses and square brackets correspond to the relative energies and Gibbs free energies, respectively, in kcal mol^{-1}.

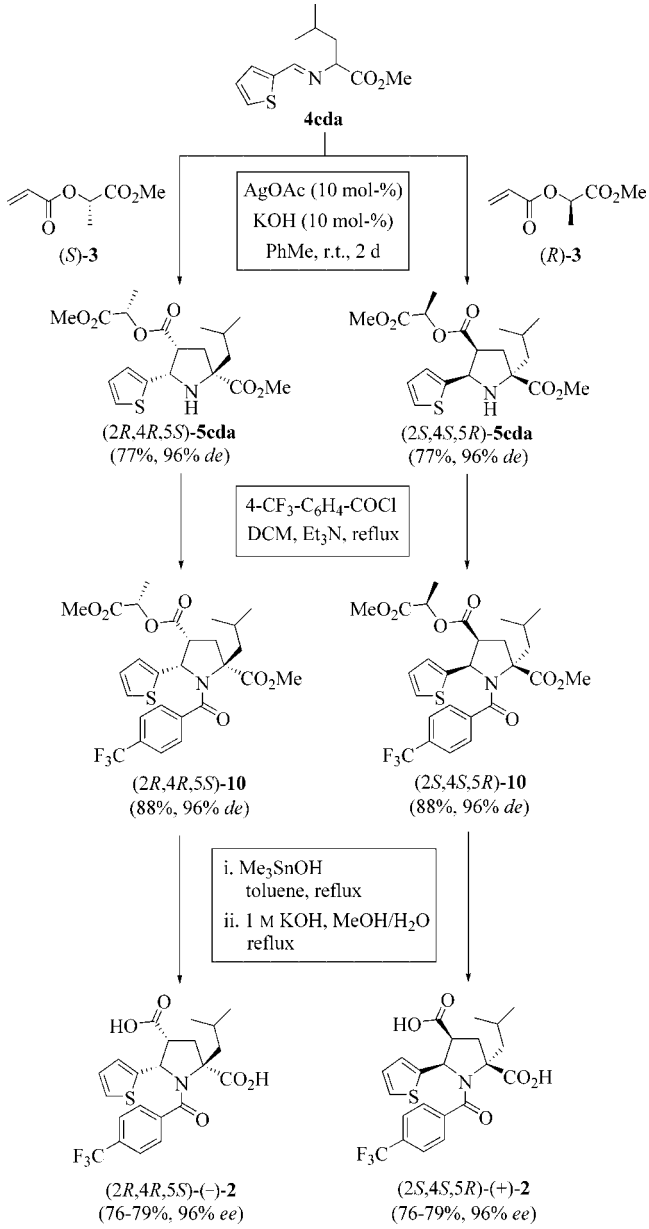
From our computational studies we conclude that the formation of the observed (2*R*,4*R*,5*S*)-pyrrolidines depends critically on the coordination pattern around the metallic center of the azomethine ylide produced in situ. If the acetate anion is considered, preferential formation of *exo* cycloadducts is predicted. If a neutral ligand such as water is included in the evaluation of the relative energies of the respective transition structures, the exclusive formation of the corresponding *endo* cycloadducts with the correct stereochemistry is obtained [(2*R*)-*endo*-**TS1b**, Figure 3]. Finally, coordination of only the azomethine ylide and acrylate moieties to the silver atom results in the formation of *endo* cycloadducts, but with the reverse absolute configuration.

Before the preparation of the enantiomerically enriched compounds (+)- and (–)-**2**, and also in view of the high inhibitory activity of its racemic form, we first studied the elaboration of (±)-**2**. The cycloaddition reaction between



Scheme 6. Synthesis of (*rac*)-**2**.

the imino ester **4cda** and methyl acrylate under the described reaction conditions (see above) gave a racemic crude pure *endo*-**5cda** product in almost quantitative yield, and this was *N*-acylated in the presence of excess of triethylamine and 4-trifluoromethylbenzoyl chloride in DCM at reflux (Scheme 6). Several attempts directed towards the hydrolysis of both methyl esters of (*rac*)-**9** in only one step failed. In basic media, undesired epimerizations and some decomposition occurred, while in acidic media, incomplete hydrolysis and some decomposition products were observed. Finally, the synthesis of (*rac*)-**2** was accomplished through two combined steps involving an initial hydrolysis of the less hindered methyl ester at the 4-position with trimethyltin hydroxide[22] in toluene at reflux, followed by hydrolysis of the less accessible methyl ester, at the 2-position, in a 1 M solution of KOH in methanol/H_2O at reflux



Scheme 7. Synthesis of the biologically active pyrrolidines **2**.

(Scheme 6). The overall yield of (±)-**2** (68% from the starting leucine derivative **4cda**) was relatively high because the purification of intermediate cycloadduct *endo*-**5cda** could be avoided (Scheme 6).

The synthesis of the enantiomerically enriched molecules (–)- and (+)-**2** was achieved from purified cycloadducts (2*R*,4*R*,5*S*)-**5cda** [bearing a unit derived from (*S*)-lactate] and (2*S*,4*S*,5*R*)-**5cda** [bonded to (*R*)-lactate], respectively. Each enantiomer was transformed into its corresponding amide **10** by treatment with 4-trifluoromethylbenzoyl chloride in DCM at reflux in 88% yield and 96% *de* (Scheme 7). The synthesis of (+)- and (–)-**2** was accomplished through the two combined steps described previously for the racemic form, and the trimethyltin hydroxide was able to remove the methyl lactate unit completely while the methyl ester remained unaltered. The enantiomeric excesses of both (–)- and the more active (+)-**2** (96%) demonstrated that no epimerization occurred during this sequence, and the isolated overall yield remained in the 76–79% range (Scheme 7). The presumed absolute configuration of (–)-**2**, which was fully characterized, was confirmed by the HPLC data for each enantiomer, according to the X-ray diffraction analysis and HPLC data described by Burton's group[2,23] (see Experimental Section). This reaction sequence was scaled up to 2–5 g, with the observation that the diastereoselectivity decreased in the first step to 89–90% *de*, the target products **2** finally being obtained in 95% *ee*. On both large and small scales, the overall yield achieved ranged between 51 to 54% from pure imino ester **4cda**.

Conclusions

Chiral acrylates derived from methyl (*R*)- and (*S*)-lactate are excellent dipolarophiles for diastereoselective 1,3-dipolar cycloadditions with amino esters azomethine ylides. Toluene, room temperature, silver acetate, and KOH (both in substoichiometric amounts) are the most appropriate parameters for running these cycloaddition processes. In particular, methyl (*S*)-lactate generated a (2*R*,4*R*,5*S*) configuration in the *endo*-**5** adducts with very good diastereoselectivities. As well as glycine Schiff bases, this procedure was also successfully applied to imino esters derived from α-substituted amino acids, generating the three new stereogenic centers, one of them a quaternary carbon atom. These products were cleanly obtained with use of potassium hydroxide rather than triethylamine. We can conclude that chiral molecules (+)- and (–)-**2** can be prepared by this methodology in 51–54% overall yields and in 96% *ee*s, using as key step the diastereoselective 1,3-dipolar cycloaddition reactions between azomethine ylides derived from amino esters and acrylates derived from methyl (*R*)- and (*S*)-lactate, easily obtained in one-step processes from inexpensive starting materials. Computational studies show that inclusion of a neutral ligand in the coordination sphere of the metal is crucial to obtain the experimentally observed stereochemistry. Under these conditions, the small methyl group of (*S*)-lactate interacts with the aromatic system of

the imine, causing destabilization in an inside orientation of a possible TS whilst the other possible *endo*-TS bears the methyl group in a more stable outside orientation.

Experimental Section

Computational Methods: All the calculations reported in this paper were performed by Density Functional Theory,[16] using the hybrid three-parameter functional customarily denoted as B3LYP.[18] The standard 6-31G* basis set[19] as implemented in the GAUSSIAN 03[20] suite of programs was used to describe hydrogen, carbon, nitrogen and oxygen atoms. Silver atoms were described by the Hay–Wadt effective core potential.[21] This computational treatment is denoted as B3LYP/6-31G*&LANL2DZ. Harmonic analysis on transition structures showed that all the saddle points had only one imaginary frequency, associated with nuclear motion along the reaction coordinate associated with formation of the C–C bonds under study. The reported differences in energy include zero-point vibration energy corrections, denoted as ⊗ZPVE. The Gibbs free energies were computed at 298 K.

General Remarks: All reactions were carried out in the absence of light. Anhydrous solvents were freshly distilled under argon. Aldehydes were also distilled prior to use for the elaboration of the imino esters. Melting points were determined with a Reichert Thermovar hot-plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded on a Nicolet 510 P-FT) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC 300 with $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. HPLC analyses were performed on a JASCO 2000-series equipped with a chiral column (detailed for each compound in the main text), using mixtures of *n*-hexane/isopropyl alcohol as mobile phase, at 25 °C. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 and high-resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed on a Perkin–Elmer 2400 and a Carlo Erba EA1108. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized under UV light (λ = 254 nm). For flash chromatography we employed Merck silica gel 60 (0.040–0.063 mm).

General Method for the Synthesis of Cycloadducts 5: Potassium hydroxide (0.025 mmol, 2 mg) or triethylamine (0.025 mmol, 7 μL) was added to a suspension of the iminoester **4** (0.25 mmol), chiral alkene **3** (0.3 mmol, 47 mg), and silver acetate (0.025 mmol, 4 mg) in toluene (3 mL), and the resulting mixture was vigorously stirred for 1 d at room temperature. The solvent was evaporated under vacuo (15 Torr), ethyl acetate was added, and the mixture was percolated through celite with elution with ethyl acetate. Solvent was evaporated (15 Torr) to provide the prolinates **5** in the yields and with the *de* values given in Table 2 and Schemes 2, 3, 6, and 7. The crude product was next purified by flash chromatography with elution with mixtures of hexanes and ethyl acetate.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*R*,4*R*,5*S*)-5-Phenylpyrrolidine-2,4-dicarboxylate (5aaa): Colorless plates, m.p. 63–65 °C (*n*-hexane/Et_2O), 53 mg (64%). $[\alpha]_D^{20}$ = –82.6 (*c* = 1, $CHCl_3$). 94% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 90:10, λ = 214 nm), t_{Rmaj} = 29.94 min, t_{Rmin} = 18.23 min. R_f = 0.09 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.92 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 2.44–2.49 (m, 2 H, CH_2), 2.74 (br. s, 1 H, NH), 3.37–3.44 (m, 1 H, PhCHC*H*), 3.65 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.93–4.02 (m, 1 H, NHC*H*CH$_2$), 4.50 (q, *J* = 7.0 Hz, 1 H, C*H*CH$_3$), 4.55 (d, *J* = 7.8 Hz, 1 H, PhCH), 7.24–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.3 (CH*C*H$_3$), 33.4 (CH_2), 49.0 (PhCH*C*H), 52.2 (OCH_3), 52.3 (OCH_3), 59.7 (NH*C*CH$_2$), 66.0 (PhCH), 68.2 (*C*HCH$_3$), 126.9, 127.7, 128.2 (ArCH), 138.7 (ArC), 171.0, 172.1, 173.6 (C*C*OO) ppm. IR (KBr): $\tilde{\nu}$ = 1731, 1735, 3421 cm^{-1}. MS (EI): *m*/*z* (%) = 335 (3) [M]$^+$, 277 (19), 276 (100), 248 (11), 232 (21), 177 (71), 170 (12), 146 (25), 145 (34), 144 (78), 143 (11), 118 (15), 117 (77). HRMS calcd. for $C_{17}H_{21}NO_6$: 335.1369; found 335.1366. $C_{17}H_{21}NO_6$ (335.1): calcd. C 60.9, H 6.3, N 4.2; found C 60.9, H 6.5, N 4.3.

2-Isopropyl 4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] (2*R*,4*R*,5*S*)-5-Phenylpyrrolidine-2,4-dicarboxylate (5aab): Pale yellow oil, 57 mg (63%). $[\alpha]_D^{20}$ = –63 (*c* = 1, $CHCl_3$). 92% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 90:10, λ = 220 nm), t_{Rmaj} = 15.00 min, t_{Rmin} = 10.53 min. R_f = 0.38 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.94 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.29 [d, *J* = 6.3 Hz, 6 H, CH(C*H*$_3$)$_2$], 2.38–2.50 (m, 2 H, CH_2), 2.82 (br. s, 1 H, NH), 3.38–3.43 (m, 1 H, PhCHC*H*), 3.63 (s, 3 H, OCH_3), 3.90–3.94 (m, 1 H, NHC*H*CH$_2$), 4.49 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 4.55 (d, *J* = 7.8 Hz, 1 H, PhCH), 5.14 [sep, *J* = 6.3 Hz, 1 H, C*H*(CH$_3$)$_2$], 7.23–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.2 (CH*C*H$_3$), 21.7 [CH(*C*H$_3$)$_2$], 33.5 (CH_2), 49.0 (PhCH*C*H), 52.0 (OCH_3), 60.0 (NH*C*CH$_2$), 66.0 (PhCH), 68.1 (*C*HCH$_3$), 68.6 [*C*H(CH$_3$)$_2$], 126.8, 127.5, 128.1 (ArCH), 138.8 (ArC), 170.9, 172.0, 172.5 (C*C*OO) ppm. IR (neat): $\tilde{\nu}$ = 1740, 3358 cm^{-1}. MS (EI): *m*/*z* (%) = 363 (0.8) [M]$^+$, 277 (18), 276 (100), 205 (14), 172 (24), 145 (15), 144 (44), 117 (19). HRMS calcd. for $C_{19}H_{25}NO_6$: 363.1682; found 363.1690.

2-*tert*-Butyl 4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] (2*R*,4*R*,5*S*)-5-Phenylpyrrolidine-2,4-dicarboxylate (5aac): Colorless plates, m.p. 87–89 °C (*n*-hexane/diethyl ether), 62 mg (73%). $[\alpha]_D^{20}$ = –59.8 (*c* = 1, $CHCl_3$). 99% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 90:10, λ = 220 nm), t_{Rmaj} = 10.72 min, t_{Rmin} = 9.37 min. R_f = 0.21 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.95 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.52 (s, 9 H, 3 × CH$_3$), 2.34–2.48 (m, 2 H, CH_2), 2.81 (br. s, 1 H, NH), 3.39–3.44 (m, 1 H, PhCHC*H*), 3.65 (s, 3 H, OCH_3), 3.84–3.88 (m, 1 H, NHC*H*CH$_2$), 4.48–4.55 (m, 2 H, C*H*CH$_3$ and PhC*H*), 7.25–7.34 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.3 (CH*C*H$_3$), 28.1 [C(*C*H$_3$)$_3$] 33.9 (CH_2), 49.2 (PhCH*C*H), 52.2 (OCH_3), 60.6 (NH*C*CH$_2$), 66.0 (PhCH), 68.2 (*C*HCH$_3$), 81.6 [O*C*(CH$_3$)$_3$], 127.0, 127.6, 128.2 (ArCH), 139.0 (ArC), 171.1, 172.1, 172.3 (C*C*OO) ppm. IR (KBr): $\tilde{\nu}$ = 1731, 1759, 3437 cm^{-1}. MS (EI): *m*/*z* (%) = 377 (0.13) [M]$^+$, 277 (18), 276 (100), 172 (20), 145 (10), 144 (37), 117 (12). $C_{20}H_{27}NO_6$ (377.4): calcd. C 63.6, H 7.2, N 3.7; found C 63.9, H 7.3, N 3.7.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*R*,4*R*,5*S*)-5-(2-Naphthyl)pyrrolidine-2,4-dicarboxylate (5baa): Pale yellow oil, 58 mg (60%). $[\alpha]_D^{20}$ = –63.9 (*c* = 1.2, $CHCl_3$). 90% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 80:20, λ = 220 nm), t_{Rmaj} = 33.72 min, t_{Rmin} = 23.05 min. R_f = 0.12 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.70 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 2.50–2.54 (m, 2 H, CH_2), 2.70 (br. s, 1 H, NH), 3.47–3.52 (m, 1 H, NaphCHC*H*), 3.57 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.03–4.07 (m, 1 H, NHC*H*CH$_2$), 4.40 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 4.71 (d, *J* = 7.6 Hz, 1 H, NaphCH), 7.43–7.49 (m, 3 H, ArH), 7.78–7.84 (m, 4 H, ArH) ppm. ^{13}C NMR: δ = 16.1 (CH*C*H$_3$), 33.5 (CH_2), 49.0 (NaphCH*C*H), 52.1 (OCH_3), 52.3 (OCH_3), 59.7 (NH*C*CH$_2$), 66.10 (NaphCH), 68.2 (*C*HCH$_3$), 125.2, 125.4, 125.9, 126.2, 127.5, 127.7, 127.9 (ArCH), 132.8, 133.0, 136.0 (ArC), 170.9, 172.1, 173.6

(C*C*OO) ppm. IR (neat): ṽ = 1743, 3358 cm^{-1}. MS (EI): *m*/*z* (%) = 385 (25) [M]$^+$, 327 (11), 326 (45), 298 (13), 282 (21), 228 (10), 227 (60), 222 (21), 196 (46), 195 (19), 194 (48), 193 (11), 167 (100), 166 (12), 165 (15), 152 (13), 140 (11). HRMS calcd. for $C_{21}H_{23}NO_6$: 385.1525; found 385.1529.

2-*tert*-Butyl 4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] (2*R*,4*R*,5*S*)-5-(2-Naphthyl)pyrrolidine-2,4-dicarboxylate (5bac): Colorless prisms, m.p. 102–104 °C (*n*-hexane/diethyl ether), 75 mg (70%). $[\alpha]_D^{20}$ = –57 (*c* = 1, $CHCl_3$). 99% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 90:10, λ = 214 nm), t_{Rmaj} = 30.06 min, t_{Rmin} = 20.13 min. R_f = 0.21 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.75 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.54 (s, 9 H, 3 × CH_3), 2.38–2.55 (m, 2 H, CH_2), 2.98 (br. s, 1 H, NH), 3.47–3.54 (m, 1 H, NaphCHC*H*), 3.57 (s, 3 H, OCH_3), 3.90–3.95 (m, 1 H, NHC*H*CH$_2$), 4.41 (q, *J* = 7.0 Hz, 1 H, C*H*CH$_3$), 4.70 (d, *J* = 7.7 Hz, 1 H, NaphCH) 7.42–7.49 (m, 3 H, ArH), 7.77–7.81 (m, 4 H, ArH) ppm. ^{13}C NMR: δ = 16.2 (CH*C*H$_3$), 28.1 [C(*C*H$_3$)$_3$] 33.9 (CH_2), 49.2 (NaphCH*C*H), 52.1 (OCH_3), 60.6 (NH*C*CH$_2$), 66.1 (NaphCH), 68.1 (*C*HCH$_3$), 81.6 [O*C*(CH$_3$)$_3$], 125.3, 125.5, 125.9, 126.2, 127.5, 127.7, 127.9 (ArCH), 133.0, 136.3 (ArC), 171.0, 172.0, 173.6 (C*C*OO) ppm. IR (KBr): ṽ = 1731, 1764, 3440 cm^{-1}. MS (EI): *m*/*z* (%) = 427 (2) [M]$^+$, 327 (23), 326 (100), 325 (12), 222 (28), 219 (27), 213 (15), 207 (17), 195 (19), 194 (67), 193 (21), 168 (17), 167 (42), 166 (10), 165 (16), 152 (11), 139 (10), 56 (13), 55 (10). HRMS calcd. for $C_{24}H_{29}NO_6$ – CO_2tBu: 326.1329; found 326.1327. $C_{24}H_{29}NO_6$ (427.5): calcd. C 67.4, H 6.8, N 3.3; found C 67.3, H 7.0, N 3.4.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*R*,4*R*,5*S*)-2-Methyl-5-phenylpyrrolidine-2,4-dicarboxylate (5aba): Colorless oil. $[\alpha]_D^{20}$ = –66.3 (*c* = 1.2, $CHCl_3$), 57 mg (65%). 90% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 90:10, λ = 214 nm), t_{Rmaj} = 14.61 min, t_{Rmin} = 11.17 min. R_f = 0.29 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.89 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.51 (s, 3 H, CCH$_3$), 2.10 (dd, *J* = 13.6, 7.6 Hz, 1 H, CH_2), 2.76 (dd, *J* = 13.6, 4.8 Hz, 1 H, CH_2), 3.06 (br. s, 1 H, NH), 3.43–3.48 (m, 1 H, PhCHC*H*), 3.65 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.51 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 4.69 (d, *J* = 7.6 Hz, 1 H, PhCH), 7.23–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.4 (CH*C*H$_3$), 27.3 (C*C*H$_3$), 40.5 (CH_2), 50.1 (PhCH*C*H), 52.1 (OCH_3), 52.5 (OCH_3), 64.9 (PhCH), 65.6 (NH*C*CH$_2$), 68.1 (*C*HCH$_3$), 126.8, 127.6, 128.2 (ArCH), 138.7 (ArC), 171.0, 172.0, 176.4 (C*C*OO) ppm. IR (neat): ṽ = 1743, 3358 cm^{-1}. MS (EI): *m*/*z* (%) = 349 (0.15) [M]$^+$, 291 (22), 290 (100), 191 (24), 186 (17), 159 (10), 158 (33), 131 (28). HRMS calcd. for $C_{18}H_{23}NO_6$: 349.1525; found 349.1526.

2-*tert*-Butyl 4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] (2*R*,4*R*,5*S*)-2-Methyl-5-phenylpyrrolidine-2,4-dicarboxylate (5abc): Colorless oil, 68 mg (70%). $[\alpha]_D^{20}$ = –57.4 (*c* = 1, $CHCl_3$). 91.5% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 95:5, λ = 214 nm), t_{Rmaj} = 8.92 min, t_{Rmin} = 7.56 min. R_f = 0.40 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.93 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.47 (s, 3 H, CCH$_3$), 1.52 [s, 9 H, C(CH$_3$)$_3$], 2.05 (dd, *J* = 13.64, 7.8 Hz, 1 H, CH_2), 2.68 (dd, *J* = 13.6, 5.6 Hz, 1 H, CH_2), 3.05 (br. s, 1 H, NH), 3.44–3.49 (m, 1 H, PhCHC*H*), 3.64 (s, 3 H, OCH_3), 4.51 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 4.66 (d, *J* = 7.6 Hz, 1 H, PhCH), 7.22–7.30 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.22 (CH*C*H$_3$), 27.1 (C*C*H$_3$), 27.8 [C(*C*H$_3$)$_3$], 40.5 (CH_2), 49.9 (PhCH*C*H), 52.0 (OCH_3), 64.8 (PhCH), 65.9 (NH*C*CH$_2$), 68.0 (*C*HCH$_3$), 81.3 [O*C*(CH$_3$)$_3$], 126.8, 127.5, 128.1 (ArCH), 139.0 (ArC), 171.0, 171.9, 174.8 (C*C*OO) ppm. IR (neat): ṽ = 1737, 3369 cm^{-1}. MS (EI): *m*/*z* (%) = 391 (0.06) [M$^+$], 291 (19), 290 (100), 186 (12), 158 (22). HRMS calcd. for $C_{21}H_{29}NO_6$ – CO_2Bu^t: 290.1392; found 290.1396.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*R*,4*R*,5*S*)-2-Methyl-5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate (5bba): Pale yellow oil, 67 mg (67%). $[\alpha]_D^{20}$ = –61.7 (*c* = 1, $CHCl_3$). 84% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 95:5, λ = 214 nm), t_{Rmaj} = 27.6 min, t_{Rmin} = 30.6 min. R_f = 0.27 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.67 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.55 (s, 3 H, CCH$_3$), 2.14 (dd, *J* = 13.7, 7.6 Hz, 1 H, CH_2), 2.82 (dd, *J* = 13.7, 4.5 Hz, 1 H, CH_2), 3.25 (br. s, 1 H, NH), 3.44–3.49 (m, 1 H, NaphCHC*H*), 3.56 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.42 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 4.69 (d, *J* = 7.6 Hz, 1 H, NaphCH), 7.41–7.46 (m, 3 H, ArH), 7.76–7.81 (m, 4 H, ArH) ppm. ^{13}C NMR: δ = 16.0 (CH*C*H$_3$), 27.4 (C*C*H$_3$), 40.5 (CH_2), 49.9 (NaphCH*C*H), 52.0 (OCH_3), 52.5 (OCH_3), 64.8 (NaphCH), 65.5 (NH*C*CH$_2$), 68.0 (*C*HCH$_3$), 125.2, 125.8, 126.1, 127.4, 127.7, 127.8 (ArCH), 132.7, 133.0, 136.1 (ArC), 170.1, 171.9, 176.3 (C*C*OO) ppm. IR (neat): ṽ = 1740, 3358 cm^{-1}. MS (EI): *m*/*z* (%) = 399 (3.82) [M]$^+$, 341 (23), 340 (100), 241 (53), 236 (20), 210 (11), 208 (33), 193 (11), 182 (16), 181 (63), 180 (13), 165 (10), 140 (10). HRMS calcd. for $C_{22}H_{25}NO_6$: 399.1682; found 399.1681.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*S*,4*R*,5*S*)-2-Benzyl-5-phenylpyrrolidine-2,4-dicarboxylate (5aca): Colorless oil, 71 mg (67%). $[\alpha]_D^{20}$ = –45.3 (*c* = 1, $CHCl_3$). 86% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 95:5, λ = 214 nm), t_{Rmaj} = 15.66 min, t_{Rmin} = 12.88 min. R_f = 0.40 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.86 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 2.23 (dd, *J* = 13.6, 7.6 Hz, 1 H, CH_2), 2.80 (dd, *J* = 13.6, 4.3 Hz, 1 H, CH_2), 2.95 (d, *J* = 13.1 Hz, 1 H, PhCH_2), 3.13 (d, *J* = 13.1 Hz, 1 H, PhCH_2), 3.30–3.35 (m, 1 H, PhCHC*H*), 3.62 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.48 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 4.56 (d, *J* = 7.6 Hz, 1 H, PhCH), 7.19–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.2 (CH*C*H$_3$), 38.9 (CH_2), 45.7 (PhCH_2), 49.6 (PhCH*C*H), 52.0 (OCH_3), 52.1 (OCH_3), 64.9 (PhCH), 68.0 (*C*HCH$_3$), 70.2 (NH*C*CH$_2$), 126.7, 126.9, 127.5, 128.0, 128.1, 130.0 (ArCH), 136.8, 139.3 (ArC), 171.0, 171.9, 175.4 (C*C*OO) ppm. IR (neat): ṽ = 1739, 3366 cm^{-1}. MS (EI): *m*/*z* (%) = 425 (0.04) [M]$^+$, 366 (12), 335 (20), 334 (100), 202 (21), 170 (13), 91 (17). HRMS calcd. for $C_{24}H_{27}NO_6$: 425.1838; found 425.1843.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*S*,4*R*,5*S*)-2-Benzyl-5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate (5bca): Colorless oil. $[\alpha]_D^{20}$ = –47.9 (*c* = 1, $CHCl_3$), 77 mg (65%). 84% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 98:2, λ = 220 nm), t_{Rmaj} = 17.35 min, t_{Rmin} = 15.14 min. R_f = 0.37 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.63 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 2.29 (dd, *J* = 13.6, 7.6 Hz, 1 H, CH_2), 2.87 (dd, *J* = 13.6, 4.3 Hz, 1 H, CH_2), 3.00 (d, *J* = 13.1 Hz, 1 H, PhCH_2), 3.02 (br. s, 1 H, NH), 3.17 (d, *J* = 13.1 Hz, 1 H, PhCH_2), 3.40–3.45 (m, 1 H, NaphCHC*H*), 3.55 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.39 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 4.72 (d, *J* = 7.3 Hz, 1 H, PhCH), 7.21–7.25 (m, 5 H, ArH), 7.39–7.45 (m, 3 H, ArH), 7.74–7.80 (m, 4 H, ArH) ppm. ^{13}C NMR: δ = 16.0 (CH*C*H$_3$), 39.0 (CH_2), 45.7 (PhCH_2), 49.6 (NaphCH*C*H), 52.0 (OCH_3), 52.2 (OCH_3), 65.0 (NaphCH), 68.0 (*C*HCH$_3$), 70.2 (NH*C*CH$_2$), 125.3, 125.4, 125.8, 126.1, 126.8, 127.4, 127.7, 127.8, 128.1, 130.1 (ArCH), 132.8, 133.0, 136.6, 136.8 (ArC), 170.9, 171.9, 175.4 (C*C*OO) ppm. IR (neat): ṽ = 1740, 3372 cm^{-1}. MS (EI): *m*/*z* (%) = 457 (27), 456 (100), 285 (14), 284 (14), 280 (10), 277 (24), 252 (20), 220 (14), 193 (17), 91 (18). HRMS calcd. for $C_{28}H_{29}NO_6$: 475.1996; found 475.2000.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*S*,4*R*,5*S*)-2-Benzyl-5-(2-thienyl)pyrrolidine-2,4-dicarboxylate (5cca): Colorless plates, m.p. 86–88 °C (*n*-hexane/diethyl ether), 69 mg (64%). $[\alpha]_D^{20}$ = –29.1 (*c* = 1, $CHCl_3$). 95% *de* from HPLC (Chiralcel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 95:5, λ = 235 nm), t_{Rmaj} = 17.78 min, t_{Rmin} = 14.44 min. R_f = 0.37 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 1.13 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 2.24 (dd, *J* = 13.6, 7.6 Hz, 1 H,

CH_2), 2.81 (dd, J = 13.6, 6.6 Hz, 1 H, CH_2), 2.91 (d, J = 13.1 Hz, 1 H, $PhCH_2$), 2.97 (br. s, 1 H, NH), 3.08 (d, J = 13.1 Hz, 1 H, $PhCH_2$), 3.29–3.34 (m, 1 H, ThieCHC*H*), 3.67 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.71 (q, J = 7.1 Hz, 1 H, C*H*CH_3), 4.56 (d, J = 7.6 Hz, 1 H, ThieCH), 6.89–6.93 (m, 2 H, ThieH), 7.15–7.17 (m, 1 H, ThieH), 7.22–7.26 (m, 5 H, PhH) ppm. ^{13}C NMR: δ = 16.5 (CH*C*H_3), 37.4 (CH_2), 46.2 ($PhCH_2$), 49.4 (ThieCH*C*H), 52.2 (OCH_3), 52.3 (OCH_3), 60.4 (ThieCH), 68.4 (*C*HCH_3), 69.6 (NH*C*CH_2), 124.4, 124.6, 126.5, 126.9, 128.1, 130.2 (ArCH), 136.6, 143.6 (ArC), 171.1, 171.3, 175.4 (C*C*OO) ppm. IR (KBr): $\tilde{\nu}$ = 1724, 1749, 3466 cm^{-1}. MS (EI): *m*/*z* (%) = 431 (0.09) $[M]^+$, 372 (14), 341 (18), 340 (100), 236 (33), 208 (19), 204 (33), 176 (11), 149 (10), 91 (20). $C_{22}H_{25}NO_6S$ (431.2): C 61.2, H 5.8, N 3.3, S 7.4; found C 61.4, H 5.9, N 3.3, S 7.4.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*R*,4*R*,5*S*)-2-(2-Methylpropyl)-5-phenylpyrrolidine-2,4-dicarboxylate (5ada): Pale yellow oil, 32 mg (32%). $[\alpha]_D^{20}$ = –44.0 (c = 1, $CHCl_3$). 90% *de* from HPLC (Chiralcel OD-H, 0.5 mL min^{-1}, *n*-hexane/*i*PrOH, 93:7, λ = 214 nm), t_{Rmaj} = 11.40 min, t_{Rmin} = 14.36 min. R_f = 0.41 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.82–0.88 [m, 6 H, CH(CH_3)$_2$], 0.95 (d, J = 6.6 Hz, 3 H, OCHCH_3), 1.61 [dd, J = 13.0, 4.5 Hz, 1 H, HC*H*CH(CH_3)$_2$], 1.70–1.87 [m, 2 H, HC*H*C*H*(CH_3)$_2$], 2.07 (dd, J = 13.6, 7.6 Hz, 1 H, PhCHCH_2), 2.68 (dd, J = 13.6, 4.5 Hz, 1 H, PhCHCH_2), 3.05 (br. s, 1 H, NH), 3.35–3.42 (m, 1 H, PhCHC*H*), 3.64 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.49 (q, J = 7.0 Hz, 1 H, C*H*CH_3), 4.61 (d, J = 7.5 Hz, 1 H, PhCH), 7.22–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.3 (CH*C*H_3), 22.7, 24.3 [CH(*C*H_3)$_2$], 25.3 [*C*H(CH_3)$_2$], 41.4 (CH_2), 48.6 [*C*H_2CH(CH_3)$_2$], 49.7 (PhCH*C*H), 52.2 (OCH_3), 52.3 (OCH_3), 65.3 (PhCH), 68.1 (*C*HCH_3), 69.0 (NH*C*CH_2), 126.9, 127.7, 128.3 (ArCH), 138.8 (ArC), 171.1, 172.2, 176.5 (C*C*OO) ppm. IR (neat): $\tilde{\nu}$ = 1739, 3365 cm^{-1}. MS (EI): *m*/*z* (%) = 391 (0.08) $[M]^+$, 334 (14), 333 (22), 332 (100), 190 (19). HRMS calcd. for $C_{21}H_{29}NO_6$: 391.1995; found 391.1996.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*R*,4*R*,5*S*)-2-(2-Methylpropyl)-5-(2-thienyl)pyrrolidine-2,4-dicarboxylate [(2*R*,4*R*,5*S*)-5cda]: Pale yellow oil. $[\alpha]_D^{20}$ = –40.5 (c = 1, $CHCl_3$), 76 mg (77%). 95% *de* from HPLC (Chiracel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 90:10, λ = 220 nm), t_{Rmaj} = 6.48 min, t_{Rmin} = 7.61 min. R_f = 0.41 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.81 (d, J = 6.2 Hz, 3 H, CH_3), 0.93 (d, J = 6.4 Hz, 3 H, CH_3), 1.13 (d, J = 7.2 Hz, 3 H, OCHCH_3), 1.52–1.60 [m, 1 H, HC*H*CH(CH_3)$_2$], 1.67–1.81 [m, 2 H, HC*H*C*H*(CH_3)$_2$], 2.06 (dd, J = 13.6, 7.3 Hz, 1 H, ThieCHCH_2), 2.69 (dd, J = 13.6, 6.6 Hz, 1 H, ThieCHCH_2), 3.05 (br. s, 1 H, NH), 3.39–3.46 (m, 1 H, ThieCHC*H*), 3.66 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.70 (q, J = 7.2 Hz, 1 H, C*H*CH_3), 4.84 (d, J = 7.5 Hz, 1 H, ThieCH), 6.90–6.96 (m, 2 H, ArH), 7.17 (d, J = 4.8 Hz, 1 H, ArH) ppm. ^{13}C NMR: δ = 16.5 (CH*C*H_3), 22.7, 24.3 [CH(*C*H_3)$_2$], 25.0 [*C*H(CH_3)$_2$], 39.9 (CH_2), 49.2 [*C*H_2CH(CH_3)$_2$], 49.5 (ThieCH*C*H), 52.2 (OCH_3), 52.2 (OCH_3), 60.6 (ThieCH), 68.3 (*C*HCH_3), 68.3 (NH*C*CH_2), 124.3, 124.6, 126.6 (ArCH), 143.1 (ArC), 171.1, 171.5, 176.3 (C*C*OO) ppm. IR (neat): $\tilde{\nu}$ = 1741, 3372 cm^{-1}. MS (EI): *m*/*z* (%) = 397 (0.62) $[M]^+$, 340 (13), 339 (21), 338 (100), 239 (11), 234 (11), 206 (13), 196 (24). HRMS calcd. for $C_{19}H_{27}NO_6S$: 397.1559; found 397.1562.

4-[(1′*R*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*S*,4*S*,5*R*)-2-(2-Methylpropyl)-5-(2-thienyl)pyrrolidine-2,4-dicarboxylate [(2*S*,4*S*,5*R*)-5cda]: Pale yellow oil, 76 mg (77%). $[\alpha]_D^{20}$ = 40.8 (c = 1, $CHCl_3$). 95% *de* from HPLC (Chiracel OD-H, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 90:10, λ = 220 nm), t_{Rmin} = 6.48 min, t_{Rmaj} = 7.61 min.

2-Isopropyl 4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] (2*R*,4*R*,5*S*)-2-(2-Methylpropyl)-5-(2-thienyl)pyrrolidine-2,4-dicarboxylate (5cdb): Pale yellow oil, 87 mg (82%). $[\alpha]_D^{20}$ = –28.8 (c = 1, $CHCl_3$). 82% *de* from HPLC (Chiralcel OD-H, 0.5 mL min^{-1}, *n*-hexane/*i*PrOH, 95:5, λ = 250 nm), t_{Rmaj} = 11.63 min, t_{Rmin} = 14.36 min. R_f = 0.44 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.85 (d, J = 6.4 Hz, 3 H, CH_3), 0.95 (d, J = 6.4 Hz, 3 H, CH_3), 1.16 (d, J = 7.2 Hz, 3 H, OCHCH_3), 1.28 [d, J = 6.2 Hz, 3 H, OCH(CH_3)$_2$], 1.29 [d, J = 6.2 Hz, 3 H, OCH(CH_3)$_2$], 1.50–1.61 [m, 1 H, HC*H*CH(CH_3)$_2$], 1.69–1.85 [m, 2 H, HC*H*C*H*(CH_3)$_2$], 2.06 (dd, J = 13.6, 7.4 Hz, 1 H, ThieCHCH_2), 2.65 (dd, J = 13.6, 7.4 Hz, 1 H, ThieCHCH_2), 3.07 (br. s, 1 H, NH), 3.42–3.49 (m, 1 H, ThieCHC*H*), 3.67 (s, 3 H, OCH_3), 4.71 (q, J = 7.2 Hz, 1 H, C*H*CH_3), 4.86 (d, J = 7.5 Hz, 1 H, ThieCH), 5.04–5.16 [m, 1 H, OC*H*(CH_3)$_2$], 6.90–6.96 (m, 2 H, ArH), 7.17 (dd, J = 4.9, 1.1 Hz, 1 H, ArH) ppm. ^{13}C NMR: δ = 16.5 (CH*C*H_3), 21.6, 21.8 [OCH(*C*H_3)$_2$], 23.0, 24.3 [CH_2CH(*C*H_3)$_2$], 25.1 [*C*H(CH_3)$_2$], 39.8 (CH_2), 48.8 [CH_2CH(CH_3)$_2$], 49.4 (ThieCH*C*H), 52.2 (OCH_3), 60.5 (ThieCH), 68.3 (NH*C*CH_2), 68.4 (*C*HCH_3), 68.8 [*C*H(CH_3)$_2$], 124.3, 124.7, 126.6 (ArCH), 143.5 (ArC), 171.2, 171.5, 175.3 (C*C*OO) ppm. IR (neat): $\tilde{\nu}$ = 1747, 3365 cm^{-1}. MS (EI): *m*/*z* (%) = 425 (0.09) $[M]^+$, 339 (21), 338 (100), 206 (11). HRMS calcd. for $C_{21}H_{31}NO_6S$: 425.1872; found 425.1871.

2-*tert*-Butyl 4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] (2*R*,4*R*,5*S*)-2-(2-Methylpropyl)-5-(2-thienyl)pyrrolidine-2,4-dicarboxylate (5cdc): Pale yellow oil. $[\alpha]_D^{20}$ = –26.4 (c = 1, $CHCl_3$), 97 mg (83%). 86.5% *de* from HPLC (Chiracel OD-H, 0.5 mL min^{-1}, *n*-hexane/*i*PrOH, 98:2, λ = 235 nm), t_{Rmaj} = 10.22 min, t_{Rmin} = 11.07 min. R_f = 0.47 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 0.88 (d, J = 6.2 Hz, 3 H, CH_3), 0.96 (d, J = 6.4 Hz, 3 H, CH_3), 1.18 (d, J = 7.0 Hz, 3 H, OCHCH_3), 1.5 [s, 9 H, OC(CH_3)$_3$], 1.46–1.54 [m, 1 H, HC*H*CH(CH_3)$_2$], 1.71–1.82 [m, 2 H, HC*H*C*H*(CH_3)$_2$], 2.03 (dd, J = 13.4, 7.3 Hz, 1 H, ThieCHCH_2), 2.60 (dd, J = 13.4, 8.0 Hz, 1 H, ThieCHCH_2), 3.03 (br. s, 1 H, NH), 3.43–3.51 (m, 1 H, ThieCHC*H*), 3.68 (s, 3 H, OCH_3), 4.71 (q, J = 7.0 Hz, 1 H, C*H*CH_3), 4.84 (d, J = 7.7 Hz, 1 H, ThieCH), 6.89–6.95 (m, 2 H, ArH), 7.16 (dd, J = 5.0, 1.3 Hz, 1 H, ArH) ppm. ^{13}C NMR: δ = 16.5 (CH*C*H_3), 23.2, 24.3 [CH(*C*H_3)$_2$], 25.2 [*C*H(CH_3)$_2$], 27.9 [C(*C*H_3)$_3$], 39.8 (CH_2), 48.6 [*C*H_2CH(CH_3)$_2$], 49.3 (ThieCH*C*H), 52.2 (OCH_3), 60.6 (ThieCH), 68.4 (*C*HCH_3), 68.6 (NH*C*CH_2), 81.5 [*C*(CH_3)$_3$], 124.3, 124.7, 126.5 (ArCH), 143.7 (ArC), 171.2, 171.4, 174.7 (C*C*OO) ppm. IR (neat): $\tilde{\nu}$ = 1742, 3365 cm^{-1}. MS (EI): *m*/*z* (%) = 439 (0.03) $[M]^+$, 339 (21), 338 (100), 206 (10). HRMS calcd. for $C_{22}H_{33}NO_6S$: 439.2029; found 439.2023.

Synthesis of 2-*tert*-Butyl 4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] (2*R*,4*R*,5*S*)-1-[(4-Methylphenyl)sulfonyl]-5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate (6): A solution of compound **5baa** (1 mmol, 385 mg), *p*-toluenesulfonyl chloride (1.5 mmol, 285 mg), and triethylamine (2 mmol, 279 μL) in DCM (10 mL) was heated at reflux for 2 d. The organic phase was washed with aqueous K_2CO_3 (1 M, 10 mL) dried with $MgSO_4$, and evaporated to yield the crude product, which was recrystallized from a mixture of *n*-hexane/diethyl ether. Compound **6** (409 mg, 76% yield) was isolated as colorless prisms, m.p. 142–144 °C (*n*-hexane/diethyl ether). $[\alpha]_D^{20}$ = –112 (c = 1.2, $CHCl_3$). 99% *de* from HPLC (Chiralpak AD, 1 mL min^{-1}, *n*-hexane/*i*PrOH, 80:20, λ = 225 nm), t_{Rmaj} = 32.65 min, t_{Rmin} = 20.76 min. R_f = 0.24 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 1.10 (d, J = 7.2 Hz, 3 H, CHCH_3), 2.16 (s, 3 H, $PhCH_3$), 2.43–2.54 (m, 1 H, CH_2), 2.65–2.76 (m, 1 H, CH_2), 3.45–3.52 (m, 1 H, NaphCHC*H*), 3.55 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.40 (q, J = 7.0 Hz, 1 H, C*H*CH_3), 4.59 (dd, J = 9.7, 7.0 Hz, 1 H, NHC*H*CH_2), 5.36 (d, J = 9.1 Hz, 1 H, NaphCH), 6.98 (d, J = 8.0 Hz, 2 H, ArH), 7.41–7.48 (m, 3 H, ArH), 7.55–7.73 (m, 6 H, ArH) ppm. ^{13}C NMR: δ = 16.5 (CH*C*H_3), 21.3 ($PhCH_3$), 30.9 (CH_2), 48.9 (NaphCH*C*H), 52.2 (OCH_3), 52.7 (OCH_3), 60.9 (NH*C*CH_2), 64.7 (PhCH), 68.8 (*C*HCH_3), 125.3, 125.9, 126.0, 127.4, 127.7, 128.0, 129.0 (ArCH), 132.7, 132.9, 134.8, 143.8 (ArC), 168.3, 170.6, 172.0 (C*C*OO) ppm.

IR (KBr): $\tilde{\nu}$ = 1740 cm^{-1}. MS (EI): *m*/*z* (%) = 539 (33) [M]$^+$, 482 (10), 481 (30), 480 (100), 385 (14), 384 (60), 383 (10), 376 (14), 348 (30), 325 (15), 222 (10), 221 (34), 220 (41), 205 (18), 195 (13), 194 (74), 193 (38), 192 (11), 167 (44), 166 (24), 165 (20), 155 (31), 154 (10), 140 (14), 139 (13), 91 (53). HRMS calcd. for $C_{28}H_{29}NO_8S$: 539.1614; found 539.1618. $C_{28}H_{29}NO_8S$ (539.1): calcd. C 62.3, H 5.4, N 2.6, S 5.9; found C 62.6, H 5.5, N 2.7, S 5.9.

Synthesis of *rac*-9: Potassium hydroxide (0.1 mmol, 8 mg) was added to a suspension of the iminoester **4cda** (1 mmol, 239 mg), methyl acrylate (1.5 mmol, 135 μL), and silver acetate (0.1 mmol, 16 mg) in toluene (10 mL), and the resulting mixture was vigorously stirred for 2 d at room temperature. The solvent was evaporated under vacuo (15 Torr), ethyl acetate was added, and the mixture was percolated through celite, with elution with ethyl acetate. Solvent was evaporated (15 Torr) to provide the intermediate prolinate **5cda**, which was immediately dissolved in DCM (25 mL), and triethylamine (1.2 mmol, 166 μL) and 4-(trifluoromethyl)benzoyl chloride (1.2 mmol, 182 μL) were successively added. The mixture was heated at reflux overnight and the solvent was evaporated under vacuum. The residue was chromatographed (flash silica) to afford pure compound **9** (437 mg, 88%), which was recrystallized from mixtures of hexanes and ethyl acetate: Pale yellow solid, m.p. 155–157 °C. R_f = 0.41 (ethyl acetate). ^{1}H NMR: δ = 1.09 [d, *J* = 6.6 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.88–1.96 [m, 1 H, CH$_2$C*H*(CH$_3$)$_2$], 2.11–2.18 [m, 1 H, C*H*$_2$CH(CH$_3$)$_2$], 2.25–2.35 [m, 2 H, C*H*$_2$CH(CH$_3$)$_2$ and ThieCHCHC*H*$_2$], 2.92 (dd, *J* = 13.5, 13.5 Hz, 1 H, ThieCHCHC*H*$_2$), 3.36 (s, 1 H, OCH$_3$), 3.71 (ddd, *J* = 13.5, 6.5, 8.67 Hz, 1 H, ThieCHC*H*), 3.90 (s, 1 H, OCH$_3$), 5.38 (d, *J* = 8.9 Hz, 1 H, ThieCH), 6.74 (dd, *J* = 5.0, 3.6 Hz, 1 H, ThieSCHC*H*), 6.89 (d, *J* = 3.1 Hz, 1 H, ThieSCCH), 7.07–7.11 (m, 3 H, ThieSCH and ArCOCCH), 7.43 (d, *J* = 8.0 Hz, 2 H, ArCF$_3$CCH) ppm. ^{13}C NMR: δ = 24.4, 25.0 [CH(*C*H$_3$)$_2$], 25.3 [*C*H(CH$_3$)$_2$], 34.6 (CH$_2$), 42.3 [*C*H$_2$CH(CH$_3$)$_2$], 48.4 (ThieCH*C*H), 51.8 (OCH$_3$), 52.5 (OCH$_3$), 61.1 (ThieCH), 69.6 (N*C*CH$_2$), 124.9, 125.9, 126.0, 126.3, 127.8 (ArCH), 130.8 (m, CF$_3$), 140.2, 140.3, 140.7 (ArC), 1.68.6, 169.0, 173.0 (*C*O) ppm. IR (KBr): $\tilde{\nu}$ = 1628, 1739 cm^{-1}. MS (EI): *m*/*z* (%) = 497 (0.42) [M$^+$], 438 (15), 355 (17), 324 (20), 296 (45), 173 (100), 145 (31). HRMS calcd. for $C_{24}H_{26}F_3NO_5S$: 497,1484; found 497.1487.

Synthesis of Racemic 2-Isobutyl-5-(2-thienyl)-1-[4-(trifluoromethyl)-benzoyl]pyrrolidine-2,4-dicarboxylic Acid [(±)-2]: A suspension of compound **9** (1 mmol, 497 mg) and trimethyltin hydroxide (4 mmol, 738 mg) in toluene (35 mL) was heated at reflux for 19 h (the reaction in toluene at reflux was much faster than the analogous transformation in 1,2-dichloroethane at reflux).[22] The mixture was acidified with aqueous HCl (0.5 M) until a white precipitate appeared. Ethyl acetate was added (2 × 15 mL) and the organic phase was dried (MgSO$_4$) and evaporated to afford a residue, which was treated with a solution of KOH (1 M) in a MeOH/H$_2$O mixture (4–1, 45 mL). The mixture was then heated at reflux for an additional 16 h and methanol was evaporated. The resulting solution was acidified with aqueous HCl (0.5 M) and a precipitate was observed. Ethyl acetate (2 × 20 mL) was added and the organic phases were collected, dried (MgSO$_4$), and evaporated to afford crude compound **2**, which was recrystallized from an acetone/chloroform mixture. Colorless prisms, m.p. 126–127 °C (dec.), 231 mg (78%). R_f = 0.41 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR (400 MHz, CD$_3$COCD$_3$): δ = 1.08 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 1.09 [d, *J* = 6.5 Hz, 3 H, CH(C*H*$_3$)$_2$], 2.01–2.10 [m, 1 H, C*H*$_2$CH(CH$_3$)$_2$], 2.11–2.16 [m, 1 H, C*H*$_2$CH(CH$_3$)$_2$], 2.36–2.42 [m, 2 H, CH$_2$C*H*(CH$_3$)$_2$ and ThieCHCHC*H*$_2$], 2.91 (dd, *J* = 13.5, 13.5 Hz 1 H, ThieCHC*H*$_2$), 3.87 (ddd, *J* = 13.6, 8.6, 6.4 Hz, 1 H, ThieCHC*H*), 5.63 (d, *J* = 8.6 Hz, 1 H, ThieCH), 6.76 (dd, *J* = 5.1, 3.6 Hz, 1 H, ThieSCHC*H*), 6.97 (d, *J* = 3.6 Hz, 1 H, ThieSCCH), 7.20 (dd, *J* = 5.1, 1.2 Hz, 1 H, ThieSCH), 7.34 (d, *J* = 8.7 Hz, 2 H, ArCOCCH), 7.58 (d, *J* = 8.7 Hz, 2 H, ArCF$_3$CCH) ppm. ^{13}C NMR: δ = 25.1, 25.3 [CH(*C*H$_3$)$_2$], 25.6 [*C*H(CH$_3$)$_2$], 35.5 (CH$_2$), 43.1 [*C*H$_2$CH(CH$_3$)$_2$], 48.2 (ThieCH*C*H), 62.0 (ThieCH), 71.1 (N*C*CH$_2$), 125.8 (q, *J* = 16.0 Hz, CF$_3$), 126.5, 127.0, 127.3, 128.4, 131.2 (ArCH), 141.9, 142.0, 142.3 (ArC), 169.9, 170.1, 173.7 (*C*O) ppm. IR (KBr): $\tilde{\nu}$ = 1593, 1723 cm^{-1}. MS (EI): *m*/*z* (%) = 469 (0.19) [M]$^+$, 296 (24), 271 (24), 229 (15), 228 (13), 173 (100), 145 (43). HRMS calcd. for $C_{22}H_{22}F_3NO_5S$ – $C_8H_4F_3O$: 296.0957; found 296.0949. $C_{22}H_{22}F_3NO_5S$ (469.5): calcd. C 56.3, H 4.7, N 3.0, S 6.8; found C 56.6, H 4.8, N 3.3, S 7.0.

4-[(1′*R*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*S*,4*S*,5*R*)-2-Isobutyl-5-(2-thienyl)-1-[4-(trifluoromethyl)benzoyl]pyrrolidine-2,4-dicarboxylate [(2*S*,4*S*,5*R*)-10]: This compound was obtained from (2*S*,4*S*,5*R*)-**5cda** as described for compound **9**, as colorless prisms, m.p. 51–53 °C (*n*-hexane/diethyl ether), 500 mg (88%). $[\alpha]_D^{20}$ = +94 (*c* = 1, CHCl$_3$). 95% *de* from HPLC (Chiracel OD-H, 0.7 mL min^{-1}, *n*-hexane/*i*PrOH, 95:5, λ = 254 nm), t_{Rmaj} = 14.95 min, t_{Rmin} = 19.74 min. R_f = 0.38 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ = 1.08–1.20 [m, 6 H, CH(CH$_3$)$_2$], 1.21 (d, *J* = 7.0 Hz, 3 H, OCHCH$_3$), 1.88–2.00 [m, 1 H, CH$_2$CH(CH$_3$)$_2$], 2.17–2.23 [m, 2 H, CH$_2$CH-(CH$_3$)$_2$], 2.35 (dd, *J* = 13.4, 6.7 Hz, 1 H, ThieCHCHC*H*$_2$), 2.87–2.96 (m, 1 H, ThieCHCHC*H*$_2$), 3.68 (s, 3 H, OCH$_3$), 3.78–3.85 (m, 1 H, ThieCHC*H*), 3.88 (s, 3 H, OCH$_3$), 4.61 (q, *J* = 7.0 Hz, 1 H, CHCH$_3$), 5.44 (d, *J* = 9.0 Hz, 1 H, ThieCH), 6.70–6.72 (m, 1 H, ArH), 6.78–6.79 (m, 1 H, ArH), 7.06–7.11 (m, 3 H, ArH), 7.45 (d, *J* = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR: δ = 16.6 (CHCH$_3$), 24.4, 24.9 [CH(CH$_3$)$_2$], 25.3 [CH(CH$_3$)$_2$], 35.0 (CH$_2$), 42.5 [CH$_2$CH(CH$_3$)$_2$], 47.8 (ThieCHCH), 52.4 (OCH$_3$), 52.5 (OCH$_3$), 60.7 (ThieCH), 69.0 (CHCH$_3$), 69.4 (NCCH$_2$), 125.0, 125.0, 125.9, 126.1, 126.2 (ArCH), 129.4 (q, *J* = 32.3 Hz, CF$_3$), 140.4 (ArC), 168.0, 168.5, 170.8, 173.0 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1648, 1747 cm^{-1}. MS (EI): *m*/*z* (%) = 569 (0.36) [M]$^+$, 296 (33), 173 (100), 145 (24). HRMS calcd. for $C_{27}H_{30}F_3NO_7S$: 569.1695; found 569.1696. $C_{27}H_{30}F_3NO_7S$ (569.1): calcd. C 56.9, H 5.3, N 2.5, S 5.6; found C 57.1, H 5.4, N 2.6, S 5.8.

4-[(1′*S*)-1-(Methoxycarbonyl)ethyl] 2-Methyl (2*R*,4*R*,5*S*)-2-Isobutyl-5-(2-thienyl)-1-[4-(trifluoromethyl)benzoyl]pyrrolidine-2,4-dicarboxylate [(2*R*,4*R*,5*S*)-10]: Colorless plates, m.p. 52–53 °C (*n*-hexane/diethyl ether), 500 mg (88%). $[\alpha]_D^{20}$ = –94 (*c* = 1, CHCl$_3$). 95% *de* from HPLC.

(2*S*,4*S*,5*R*)-2-Isobutyl-5-(2-thienyl)-1-[4-(trifluoromethyl)benzoyl]-pyrrolidine-2,4-dicarboxylic Acid [(2*S*,4*S*,5*R*)-(+)-2]: Colorless plates, m.p. 126–127 °C (dec.), 225 mg (76%). $[\alpha]_D^{20}$ = +95 (*c* = 1, MeOH), 96% *ee* from HPLC (Chiralpak AD, 2 mL min^{-1}, *n*-hexane/*i*PrOH/trifluoroacetic acid, 85:15:0.1, λ = 250 nm), t_{Rmin} = 4.2 min, t_{Rmaj} = 5.4 min.[23]

(2*R*,4*R*,5*S*)-2-Isobutyl-5-(2-thienyl)-1-[4-(trifluoromethyl)benzoyl]-pyrrolidine-2,4-dicarboxylic Acid [(2*R*,4*R*,5*S*)-(–)-2]: Colorless plates, m.p. 126–127 °C (dec.), 234 mg (79%). $[\alpha]_D^{20}$ = –95 (*c* = 1, MeOH). 96% *ee* from HPLC.

Supporting Information (see also the footnote on the first page of this article): Total electronic energies, zero-point correction of energies, thermal corrections to Gibbs free energies and number of imaginary frequencies (NIMAG) of all stationary points discussed in this article.

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