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Synthesis of Prolines by Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides and Alkenes Catalyzed by Chiral Phosphoramidite-Silver(I) Complexes

Carmen Nájera,*[a] María de Gracia Retamosa,[a] María Martín-Rodríguez,[a] José M. Sansano,*[a] Abel de Cózar,[b] and Fernando P. Cossío[b][‡]

Dedicated to Professor Peter Stanetty on the occasion of his 65th birthday

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The *endo*-diastereo- and enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes is efficiently catalysed by chiral phosphoramidite–silver(I) perchlorate complexes. The reaction allows the presence of different types of substituents in the 1,3-dipole and can be applied to the synthesis of enantiomerically enriched, highly substituted prolines. This methodology was applied to the total synthesis of the inhibitors of the hepatitis C virus (HCV). Computational studies support a two-step mechanism predicting exactly the experimental results and the origin of both the diastereo- and enantioselections, as well as a reasonable explanation concerning the different reaction rates observed for some substrates.

Introduction

The catalytic enantioselective 1,3-dipolar cycloaddition (1,3-DC),[1] involving azomethine ylides and electrophilic alkenes, constitutes a straightforward transformation[2] in the generation of up to four stereogenic centres in only one step. The highly diastereo- and enantioselective nature of the reaction allows enantiomerically substituted proline derivatives to be obtained;[3] these compounds are important structures in scientific areas such as biology (peptide design),[3,4] medicine (antiviral,[5] neuroexcitatory[6] and insecticide agents[7]) and organic chemistry (organocatalysts).[8]

Grigg et al. pioneered the catalytic enantioselective 1,3-DC by employing large amounts of chiral cobalt complexes.[9] In 2002, the enantioselective synthesis of enantiomerically pure prolines through the 1,3-DC of azomethine ylides and electron-deficient alkenes was successfully achieved by employing a chiral bisphosphane–silver(I) complex in substoichiometric amounts.[10] Later on, many other contributions regarding the employment of the chiral complexes formed by silver(I),[10,11] copper(I),[12] zinc(II),[13] nickel(II)[14] and calcium(II)[15] were reported. Recently, organocatalyzed processes[16] have been employed but with notable structural restrictions; for instance, highly activated iminomalonates are needed as 1,3-dipole precursors in addition to α,β-unsaturated aldehydes or ketones as dipolarophiles.

Silver and copper complexes are the most employed catalysts generating excellent enantioselections in the resulting proline derivatives. Whilst a chiral copper(I)-catalyzed process occurs with high *exo*-diastereoselection, the silver(I)-catalyzed reaction yields the corresponding *endo* adducts. In general, chiral bidentate ligands such as bisphosphanes, aminophosphanes, sulfur-containing phosphanes, bisoxazolines and diimines are used as chiral ligands. A common problem in these reactions is their sensitivity to the presence of very bulky substituents in the 1,3-dipole and in the dipolarophile as well.

In a previous communication[11c] we reported the first enantioselective 1,3-DC of azomethine ylides and alkenes by using monodentate ligands such as chiral phosphoramidites together with $AgClO_4$. The main advantages of this type of catalyst are its availability, the easy modulation of the two stereogenic elements of the chiral ligand and the use of α-branched imino esters. All these aspects are combined to obtain high enantioselectivities of the resulting

[a] Departmento de Química Orgánica (Facultad de Ciencias) and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Ctra. Alicante-San Vicente s/n, 03080 Alicante, Spain
Fax: +34-96-590-3549
E-mail: cnajera@ua.es
jmsansano@ua.es
[b] Department of Organic Chemistry I, University of the País Vasco-Euskal Herriko Unibertsitatea, P. K. 1072, 20018 San Sebastián-Donostia, Spain
[‡] For correspondence on computational studies, E-mail: fpcossio@ehu.es

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pyrrolidines. In this work, we describe the full account of this reaction and a DFT-based study focused on the elucidation of the origin of the diastereo- and enantioselectivity observed in the process.[17]

Results and Discussion

Although chiral phosphoramidites **1**, **2** and **3**[18] (Figure 1) have been extensively used in asymmetric hydrogenations[19] and many other transformations such as allylations, Michael-type additions and carbonyl addition reactions,[19b] they were not previously used as ligands in the 1,3-DC of azomethine ylides and dipolarophiles.

Initially, the optimization of the reaction was carried out at room temperature employing *tert*-butyl acrylate and methyl or isopropyl *N*-benzylideneiminoglycinates **4aa** or **4ab**, respectively. Employing 5 mol-% of catalyst, formed by in situ addition of a 1:1 mixture of phosphoramidite and the silver salt (Scheme 1, Table 1) was employed in the presence of an organic base (5 mol-%). The catalysts formed by $AgClO_4$ (5 mol-%) and ligands (S_a)-**1** or **2** (5 mol-%) and triethylamine as base (5 mol-%) gave a lower *er* value of cycloadduct **5aa** than with the catalyst system consisting of a 1:1 mixture of $AgClO_4$ (5 mol-%) and (S_a,*R*,*R*)-**3** (5 mol-%; Table 1, Entries 1–3). When a 2:1 mixture of $AgClO_4$/(S_a,*R*,*R*)-**3** (5 mol-%) was used instead, the *er* value was also lower than the result described for the 1:1 mixture (Table 1, Entry 4). Other silver salts like acetate, triflate, fluoride or tetrafluoroborate did not improve the enantiomeric ratio generated by $AgClO_4$ (Table 1, Entries 5–8).

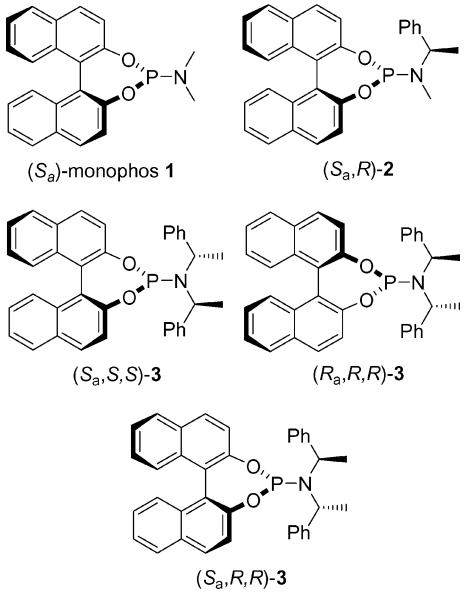
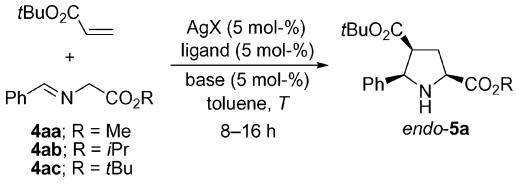


Figure 1. Phosphoramidites **1**–**3**.



Scheme 1.

Table 1. Optimization of the 1,3-DC of imino esters **4** (1 equiv.) and *tert*-butyl acrylate (1 equiv.) in toluene catalyzed by the chiral ligand (5 mol-%) and the Ag^I salt (5 mol-%) with the use of a base (5 mol-%).

Entry	R	Imino ester	AgX	Ligand	Base	*T* [°C]	*t* [h]	Cycloadduct	Conv. [%]	*er*[a]
1	Me	**4aa**	$AgClO_4$	(S_a)-**1**	Et_3N	20	8	**5aa**	98	76:24
2	Me	**4aa**	$AgClO_4$	(S_a,*R*)-**2**	Et_3N	20	8	**5aa**	98	69:31
3	Me	**4aa**	$AgClO_4$	(S_a,*R*,*R*)-**3**	Et_3N	20	8	**5aa**	98	85:15
4	Me	**4aa**	$AgClO_4$[b]	(S_a,*R*,*R*)-**3**	Et_3N	20	8	**5aa**	95	74:26
5	Me	**4aa**	AgOAc	(S_a,*R*,*R*)-**3**	Et_3N	20	8	**5aa**	98	80:20
6	Me	**4aa**	AgOTf	(S_a,*R*,*R*)-**3**	Et_3N	20	8	**5aa**	98	84:16
7	Me	**4aa**	AgF	(S_a,*R*,*R*)-**3**	Et_3N	20	8	**5aa**	90	76:24
8	Me	**4aa**	$AgBF_4$	(S_a,*R*,*R*)-**3**	Et_3N	20	8	**5aa**	95	60:40
9	Me	**4aa**	$AgClO_4$	(S_a,*R*,*R*)-**3**	Et_3N	0	16	**5aa**	96	87:17
10	Me	**4aa**	$AgClO_4$	(S_a,*R*,*R*)-**3**	Et_3N	–20	16	**5aa**	98	90:10
11	Me	**4aa**	$AgClO_4$	(S_a)-**1**	Et_3N	–20	17	**5aa**	97	79:21
12	Me	**4aa**	$AgClO_4$	(S_a,*R*,*R*)-**3**	DIPEA[c]	–20	16	**5aa**	97	89:11
13	Me	**4aa**	$AgClO_4$	(S_a,*R*,*R*)-**3**	DABCO[d]	–20	17	**5aa**	96	94:6
14	Me	**4aa**	$AgClO_4$	(R_a,*S*,*S*)-**3**	DABCO	–20	17	*ent*-**5aa**	>98	6:94
15	*i*Pr	**4ab**	$AgClO_4$	(S_a,*R*,*R*)-**3**	Et_3N	0	16	**5ab**	>98	93:7
16	*i*Pr	**4ab**	$AgClO_4$	(S_a,*R*,*R*)-**3**	Et_3N	–20	16	**5ab**	>98	>99:1
17	*i*Pr	**4ab**	$AgClO_4$	(S_a,*R*,*R*)-**3**	DABCO	–20	16	**5ab**	97	>99:1
18	*i*Pr	**4ab**	$AgClO_4$	(S_a)-**1**	Et_3N	–20	17	**5ab**	94	53:47
19	*i*Pr	**4ab**	$AgClO_4$	(R_a,*S*,*S*)-**3**	Et_3N	–20	16	*ent*-**5ab**	97	<1:99
20	*i*Pr	**4ab**	$AgClO_4$	(S_a,*R*,*R*)-**3**	Et_3N	–20	16	*ent*-**5ab**	95	28:72
21	*i*Pr	**4ab**	$AgClO_4$	(S_a,*S*,*S*)-**3**	Et_3N	–20	16	*ent*-**5ab**	95	28:72
22	*i*Pr	**4ab**	$AgClO_4$[e]	(S_a,*R*,*R*)-**3**	Et_3N	–20	16	**5ab**	76	98:2

[a] Determined by chiral HPLC analysis (Daicel, Chiralpak AS) of the crude product. More than 98:2 *endo*/*exo* ratio by ^1H NMR spectroscopy. [b] Reaction performed with ligand **3** (2 equiv.) and silver perchlorate (1 equiv.). [c] DIPEA = diisopropylethylamine. [d] DABCO = 1,4-diazabicyclo[2.2.2]octane. [e] 3 mol-% of the catalyst was employed.

To further improve the enantioselectivity of the process, the temperature, the base and the nature of the ester group were studied. When the reaction of **4aa** was run at 0 or –20 °C with Et_3N the enantioselection was improved (Table 1, compare Entries 3, 9 and 10). Other bases such as DIPEA or DABCO (5 mol-%) were also used at –20 °C, resulting in even better enantioselections (96:4 *er*) with DABCO (Table 1, compare Entries 10, 12 and 13). Under these conditions, monophos ligand (S_a)-**1** was also employed but with lower chiral induction than for the reaction with ligand **3** (Table 1, compare Entries 10 and 11). In contrast, the substitution of the methyl group by an isopropyl group at the imino ester (Table 1, Entries 15–22) was very satisfactory in terms of enantioselection (>99:1) and conversions of product **5ab** when the reaction was performed at –20 °C independently of the base used (Table 1, compare Entries 10 with 16 and 13 with 17). The best reaction conditions were employed in the reaction of imino ester **4ab** with the chiral complex generated from ligand (S_a)-**1**, but disappointing results were again achieved (Table 1, compare Entries 17 and 18). It was also noticeable that *tert*-butyl imino ester **4ac** (R = *t*Bu) was not appropriate as a substrate for this particular transformation, because the yields, conversions and enantioselectivities were extremely low.

When enantiomeric ligand (R_a,*S*,*S*)-**3** was employed, both imino esters (**4aa** and **4ab**) afforded at –20 °C the corresponding enantiomer of **5aa** and **5ab** (Table 1, Entries 14 and 19). By contrast, complexes formed by phosphoramidites (R_a,*R*,*R*)-**3** or (S_a,*S*,*S*)-**3** and $AgClO_4$ demonstrated to be mismatched combinations, because the reaction of **4ab** and *tert*-butyl acrylate afforded, in each case, compound *ent*-**5ab** with a 28:72 *er* (Table 1, Entries 20 and 21). A lower catalyst loading (3 mol-%) in the reaction at –20 °C gave a lower yield but similar enantioselectivity of **5ab** (Table 1, Entry 22).

Other solvents such as THF, dichloromethane, diethyl ether, acetonitrile and methanol gave both lower conversions and *er* values. In all of the examples shown in the tables, the *endo* adduct[20] was obtained as the major stereoisomer with a *dr* value higher than 98:2 (^{1}H NMR). All of the *er* data were determined by chiral HPLC analysis, and the absolute configuration was assigned by comparison of the optical rotations between the newly generated products and the reported data for the same compounds.[11]

The new 1:1 and 2:1 complexes of $AgClO_4$ and phosphoramidite (S_a,*R*,*R*)-**3** were characterised by X-ray crystallographic diffraction of the monocrystals.[11c] Whilst the 1:1 (S_a,*R*,*R*)-**3**/$AgClO_4$ complex formed cross-linked sheets, the 2:1 mixture afforded well-defined crystals. The formation of these polymeric assemblies are typical of silver(I) complexes, independent of the mono- or bidentate character of the corresponding ligand.[21] These complexes are soluble in toluene and could not be recovered from the reaction mixture as in the case of the complex formed by binap and $AgClO_4$.[11b,11d]

The MS (ESI) experiments of the 1:1 and 2:1 (S_a,*R*,*R*)-**3**/$AgClO_4$ complexes revealed $[M+1]^+$ peaks at *m*/*z* = 646 and 1187, respectively. When an equimolar amount of 1,3-dipole precursor **4aa** and triethylamine and a 1:1 mixture of (S_a,*R*,*R*)-**3**/$AgClO_4$ complex were put together, the ESI experiment revealed a very abundant species with *m*/*z* = 824, which is due to the formation of chiral silver complex–dipole adduct **I** (Figure 2) and a tiny peak at *m*/*z* = 1000 as a result of the combination of two molecules of dipole to the chiral silver complex. Intermediate complex **I** can also explain the high diastereo- and enantioselection offered by the matched combination of the stereochemical elements of ligand (S_a,*R*,*R*)-**3**.

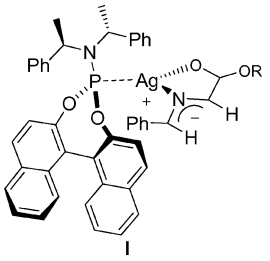


Figure 2. Suggested structure of intermediate complex **I**.

Analogous ^{31}P NMR ($CDCl_3$, 10 mol-% aq. polyphosphoric acid as internal reference) spectroscopic experiments also revealed interesting aspects. Only a wide band centred at δ = 126.9 ppm was observed when a 1:1 mixture of (S_a,*R*,*R*)-**3**/$AgClO_4$ was formed in solution, which corresponded to its polymeric character detected by X-ray diffraction analysis. However, two separated bands were observed at δ = 124.9 and 132.0 ppm in the case of a 2:1 mixture as a consequence of partial disaggregation. The almost-complete disaggregation of the polymeric sheets of the 1:1 complex was achieved with the addition of 1 equivalent of the 1,3-dipole generated from **4aa** and triethylamine. The result was the transformation of the original ^{31}P NMR band into two perfectly defined doublets at δ = 125.1 ($J_{P,^{109}Ag}$ = 76 Hz) and 133.61 ppm ($J_{P,^{107}Ag}$ = 73 Hz), which seems to correspond to the phosphorus atom of complex **I**.

Because perchlorates are classified as low-order explosives, the thermal stability of the 1:1 mixture of (S_a,*R*,*R*)-**3**/$AgClO_4$ was studied. The thermogravimetric (TG) and differential thermal analysis (DTA) of this complex (Figure 3) revealed that the loss of water occurred from 50 to 150 °C without any variation in the heat of the system. The exothermic decomposition of the complex started at 200 °C approximately, continuing till 600 °C with a noticeable heat liberation.

Then, the general scope of the enantioselective 1,3-DC of azomethine ylides, generated from imino esters, with electrophilic alkenes, catalyzed by a 5 mol-% of a 1:1 complex of (S_a,*R*,*R*)-**3**/$AgClO_4$ in toluene and in the presence of a base was studied. Firstly, glycine-derived imino esters **4** were allowed to react with *tert*-butyl acrylate under the previously described conditions by using triethylamine or DABCO (5 mol-%) at several temperatures (Scheme 2, Table 2). The presence of an isopropyl ester in molecule **4ab**, rather than the methyl ester, was very important because the reaction performed at –20 °C, independently of

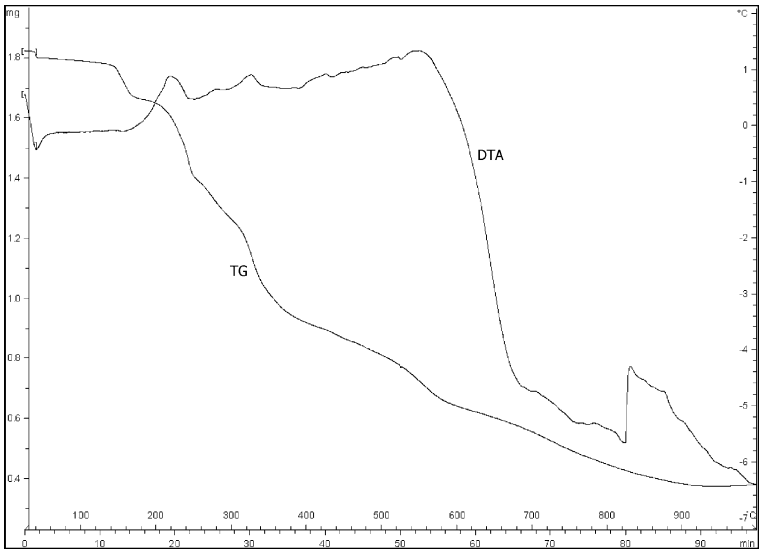
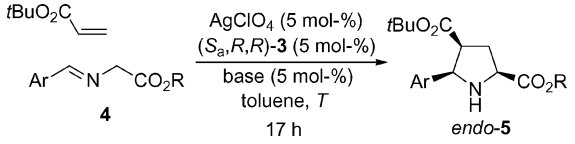


Figure 3. TG and DTA plots of the (S_a,*R*,*R*)-**3**/$AgClO_4$ complex.

the used base, afforded *endo*-cycloadduct **5ab** in good yield (81%) with >99:1 *er* (Table 2, Entries 1–4). *ortho*-Substituted aryl imines **4ba** and **4ca** gave satisfactory results by employing DABCO as base at –20 °C. The *er* value of both cycloadducts **5ba** and **5ca** was very high after purification (>99:1; Table 2, Entries 5–8). In these last examples, the presence of an isopropyl group was not so advantageous as before.



Scheme 2.

For *para*-substituted aryl imimes, the best results were achieved by using Et_3N as base at –20 °C and isopropyl rather than methyl esters of *N*-arylideneimino glycinates **4**. The increment in the enantiomeric ratio was very small for *endo*-cycloadducts **5da**, **5db** and **5fa**, **5fb** (Table 2, Entries 9–13 and 18–21, respectively), but was significant for *endo*-**5eb** (99:1 *er*; Table 2, Entries 14–17). 2-Naphthyl derivative **4ga** furnished better yields and enantioselectivities for the methyl esters than the analogous isopropyl esters (not shown in Table 2) by using Et_3N as base at –20 °C. The corresponding *endo*-product **5ga** was obtained in 84% yield and 96:4 *er* after flash chromatography (Table 2, Entries 22–24).

Different dipolarophiles were allowed to react with several imino esters (Scheme 3, Table 3). Glycine-derived imino esters reacted in very good yields with maleimides at higher temperatures (r.t. or 0 °C) to afford excellent enantioselectivities of the corresponding cycloadducts **9aa** and **10aa** (Table 3, Entries 1 and 2). Fumarates, chalcone and cyclopent-2-enone were very suitable dipolarophiles by employing triethylamine as base at –20 °C. The yields were in the 72–81% range and the enantioselections were very important, especially in the examples run with chalcone (>99:1 *er*; Table 3, Entries 3–8).

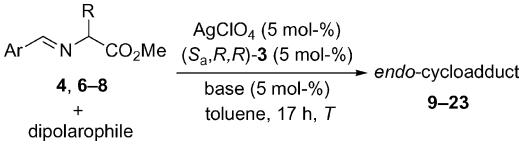
α-Substituted imino esters derived from alanine, phenylalanine and leucine reacted with *tert*-butyl acrylate to give *endo*-cycloadducts **16**–**19** in good purified yields and very high enantioselectivities (Table 3, Entries 9–15). The best results were always achieved by using Et_3N as base at –20 °C rather than by employing DABCO (Table 3, Entries 9–15). *N*-Methylmaleimide (NMM) furnished good yields of cycloadducts **20** and **21** and high enantiomeric ratios under the analogous reaction conditions; phenylalanine derivative **7aa** was the less reactive system (Table 3, Entries 16–19). Chalcone and (*E*)-pent-3-enone also reacted with alanine dipole precursors **6aa** and **6ga** to give good yields of proline derivatives **22aa** and **23ga**, with 90:10 and 84:16 *er*, respectively (Table 3, Entries 20 and 21). In all of these examples the presence of isopropyl or *tert*-buyl esters produced lower enantioselectivities and very long reaction times. Many of these cycloadducts are known compounds and comparison of their physical and spectroscopic data with the reported data confirm the absolute configuration represented on each structure.

It has been demonstrated that enantiomerically pure proline derivative **19ha** is the key precursor to a series of antiviral agents inhibitors of the hepatitis C virus (HCV) polymerase[15a,16b,22] such as prolinamide **26**.[5a,23] Intermediate prolinamide **25** was synthesized in 88% yield (estimated by ^1H NMR) from enantiomerically pure **19ha** by simple amidation with 4-(trifluoromethyl)benzoyl chloride in refluxing dichloromethane over 19 h. The crude product was submitted, in a second step, to hydrolysis of the *tert*-butyl ester with trifluoroacetic acid followed by methyl ester hydrolysis by using an aqueous solution of KOH in meth-

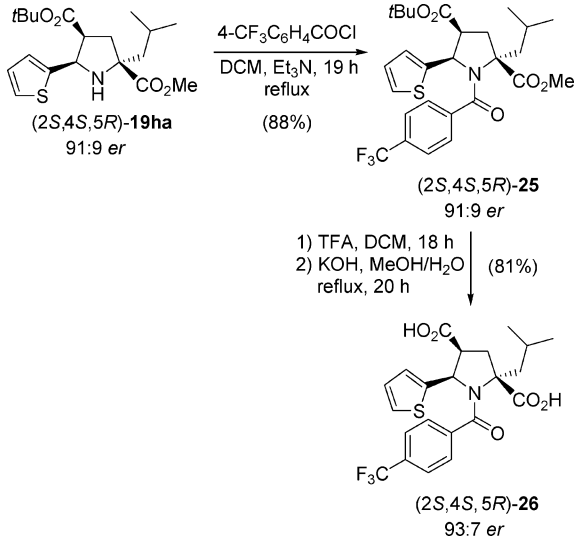
Table 2. 1,3-DC of glycine derived imino esters **4** and *tert*-butyl acrylate catalyzed by (S_a,*R*,*R*)-**3**/$AgClO_4$ complex (5 mol-%).

Entry	Ar	R	**4**	Base	*T* [°C]	Cycloadduct	Yield [%][a]	er_{endo}[b]
1	Ph	Me	**4aa**	Et_3N	–20	**5aa**	80	90:10 (90:10)
2	Ph	Me	**4aa**	DABCO	–20	**5aa**	80	94:6 (94:6)
3	Ph	*i*Pr	**4ab**	Et_3N	–20	**5ab**	83	>99:1 (>91:1)
4	Ph	*i*Pr	**4ab**	DABCO	–20	**5ab**	81	>99:1 (>91:1)
5	2-MeC_6H_4	Me	**4ba**	DABCO	0	**5ba**	78	95:5 (95:5)
6	2-MeC_6H_4	Me	**4ba**	DABCO	–20	**5ba**	83	99:1 (>99:1)
7	2-ClC_6H_4	Me	**4ca**	DABCO	0	**5ca**	79	94:6 (95:5)
8	2-ClC_6H_4	Me	**4ca**	DABCO	–20	**5ca**	80	98:2 (>99:1)
9	4-MeC_6H_4	Me	**4da**	Et_3N	–20	**5da**	78	90:10 (90:10)
10	4-MeC_6H_4	Me	**4da**	DABCO	0	**5da**	77	90:10 (91:9)
11	4-MeC_6H_4	Me	**4da**	DABCO	–20	**5da**	77	91:9 (92:8)
12	4-MeC_6H_4	*i*Pr	**4db**	Et_3N	–20	**5db**	80	95:5 (96:4)
13	4-MeC_6H_4	*i*Pr	**4db**	DABCO	–20	**5db**	78	94:6 (95:5)
14	4-$MeOC_6H_4$	Me	**4ea**	DABCO	0	**5ea**	77	94:6 (94:6)
15	4-$MeOC_6H_4$	Me	**4ea**	DABCO	–20	**5ea**	79	95:5 (96:4)
16	4-$MeOC_6H_4$	*i*Pr	**4eb**	Et_3N	–20	**5eb**	80	99:1 (99:1)
17	4-$MeOC_6H_4$	*i*Pr	**4eb**	DABCO	–20	**5eb**	76	94:6 (95:5)
18	4-ClC_6H_4	Me	**4fa**	DABCO	0	**5fa**	77	92:8 (93:7)
19	4-ClC_6H_4	Me	**4fa**	DABCO	–20	**5fa**	76	94:6 (95:5)
20	4-ClC_6H_4	*i*Pr	**4fb**	Et_3N	–20	**5fb**	77	95:5 (97:3)
21	4-ClC_6H_4	*i*Pr	**4fb**	DABCO	0	**5fb**	77	92:8 (94:6)
22	2-naphthyl	Me	**4ga**	Et_3N	–20	**5ga**	84	95:5 (96:4)
23	2-naphthyl	Me	**4ga**	DABCO	0	**5ga**	78	90:10 (90:10)
24	2-naphthyl	Me	**4ga**	DABCO	–20	**5ga**	76	92:8 (94:6)

[a] Yield obtained after flash chromatography of the *endo* product. [b] Determined by chiral HPLC analysis (Daicel, Chiralpak AS) of the crude product. More than 98:2 *endo*/*exo* ratio by ^1H NMR spectroscopy. The *er* values of purified product **5** are given in parentheses.



Scheme 3.



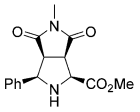
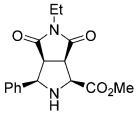
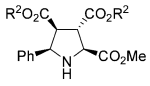
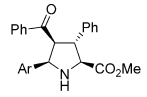
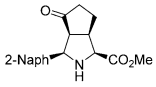
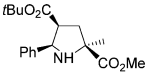
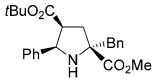
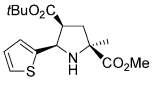
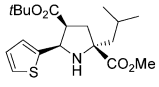
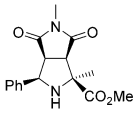
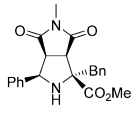
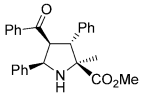
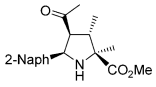
Scheme 4.

anol for 16 h. Resulting dicarboxylic acid **26** was finally obtained in 81% yield from compound **25** (50% overall yield from imino ester **8ha**; Scheme 4). The purity of the antiviral agent was >98% and only 0.7 ppm of silver were present in this sample according to inductively coupled plasma mass spectrometry (ICP-MS) analysis. On the basis of this instrumental technique, purified samples of compound **19ha** only contained around 4 ppm of silver.

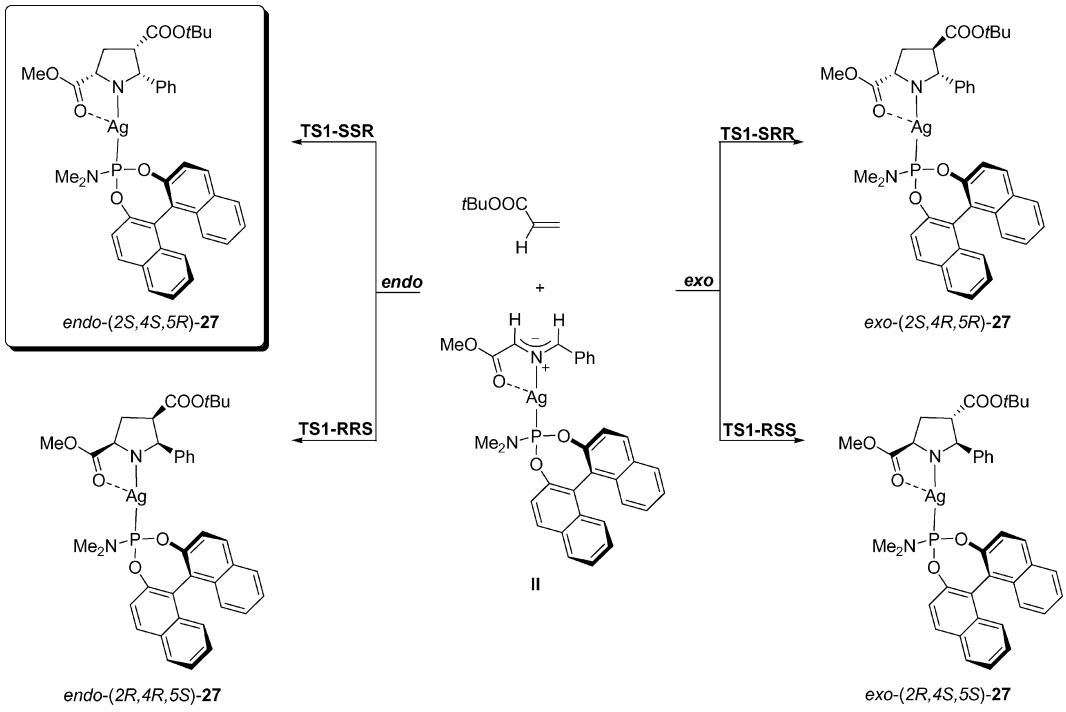
With the aim to better understand the origin of the observed stereocontrol, we carried out different calculations (see below for technical details) on the interaction modes between *tert*-butyl acrylate and complex **II** formed by 1,3-dipole precursor **4aa** and (S_a)-monophos (**1**). Because we determined that nonlinear effects are not observed in these reactions, only monomeric species were considered along the different reaction paths. Our results indicate that the formal [3+2] cycloaddition is actually a stepwise process,[24] in which the first step consists of a Michael addition of **II** on *tert*-butyl acrylate. This step determines the stereochemical outcome of the whole reaction. Possible cycloadducts **27** and corresponding transition structures TS1 that lead to them are depicted in Scheme 5.

Calculations located and characterized the four possible transition structures and their main organic features are gathered in Figure 4. The less energetic saddle points are those that exhibit the *tert*-butoxycarboxyl group in an *endo* relationship with respect to the phenyl group of **4aa**. Both TS1-SRR and TS1-RSS lack the highly stabilizing bonding interaction between the *tert*-butoxycarbonyl moiety and the metallic centre. As a consequence, these transition structures are ca. 10 kcal/mol less stable than their *endo* analogues.

Table 3. 1,3-DC of glycine methyl imino esters **4** and α-substituted methyl imino esters **6**–**8** with assorted dipolarophiles, catalyzed by (S_a,*R*,*R*)-**3**/$AgClO_4$ complex (5 mol-%).

Entry	Ar	R	Imino ester	Base	Dipolarophile	*T* [°C]	Structure	Cycloadduct	Yield [%] [a]	er_{endo} [b] [c]
1	Ph	H	**4aa**	DABCO	NMM[d]	20		**9aa**	80	>99:1 (>99:1)
2	Ph	H	**4aa**	Et_3N	NEM[d]	0		**10aa**	78	94:6 (94:6)
3	Ph	H	**4aa**	Et_3N	diisopropyl fumarate	–20		**11aa**	81	91:9 (91:9)
4	Ph	H	**4aa**	DABCO	diisobutyl maleate	0		**12aa**	79	91:9 (91:9)
5	Ph	H	**4aa**	Et_3N	chalcone	–20		**13aa**	80	>99:1 (>91:1)
6	2-Me-C_6H_4	H	**4ba**	Et_3N	chalcone	–20		**14ba**	70	90:10 (99:1)[e]
7	4-Me-C_6H_4	H	**4da**	Et_3N	chalcone	–20		**14da**	75	97:3 (97:3)
8	2-naphthyl	H	**4ga**	Et_3N	cyclopent-2-enone	–20		**15ga**	72	96:4 (97:3)
9	Ph	Me	**6aa**	Et_3N	*tert*-butyl acrylate	–20		**16aa**	78	97:3 (97:3)
10	Ph	Me	**6aa**	DABCO	*tert*-butyl acrylate	0		**16aa**	77	94:6 (94:6)
11	Ph	Bn	**7aa**	Et_3N	*tert*-butyl acrylate	–20[f]		**17aa**	77	99:1 (99:1)
12	2-thienyl	Me	**6ha**	Et_3N	*tert*-butyl acrylate	–20		**18ha**	78	96:4 (96:4)
13	2-thienyl	Me	**6ha**	DABCO	*tert*-butyl acrylate	–20		**18ha**	79	94:6 (94:6)
14	2-thienyl	*i*Bu	**8ha**	Et_3N	*tert*-butyl acrylate	–20[f]		**19ha**	70	91:9 (91:9)
15	2-thienyl	*i*Bu	**8ha**	DABCO	*tert*-butyl acrylate	–20[f]		**19ha**	68	78:22 (78:22)
16	Ph	Me	**6aa**	Et_3N	NMM	0[e]		**20aa**	80	78:22 (78:22)
17	Ph	Me	**6aa**	Et_3N	NMM	–20[f]		**20aa**	74	86:14 (86:14)
18	Ph	Bn	**7aa**	Et_3N	NMM	0		**21aa**	71	88:12 (95:5)
19	Ph	Bn	**7aa**	Et_3N	NMM	–20[f]		**21aa**	80	75:25 (75:25)
20	Ph	Me	**6aa**	Et_3N	chalcone	–20		**22aa**	81	90:10 (90:10)
21	2-naphthyl	Me	**6ga**	Et_3N	pent-3-enone	–20		**23ga**	71	84:16 (84:16)

[a] Yield obtained after flash chromatography of the *endo* product. [b] Determined by chiral HPLC analysis (see the Experimental Section) of the crude product. More than 98:2 *endo*/*exo* ratio by ^{1}H NMR spectroscopy. [c] The *er* values of the purified *endo* cycloadduct are given in parentheses. [d] The reaction required 6 h. [e] A 70:30 *endo*/*exo* mixture was obtained in the crude product. [f] The reaction required 48 h.



Scheme 5.

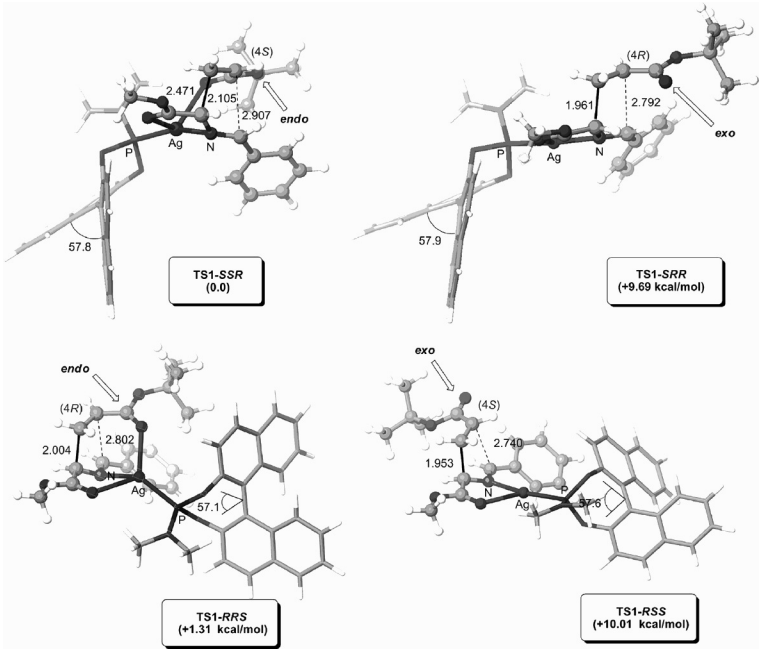


Figure 4. Chief geometric features saddle relative energies [kcal/mol] of the four transition structures associated with the first step in the reaction between *tert*-butyl acrylate and complex **II** formed by (S_a)-monophos (**1**) and imine **4aa**. Bond lengths [Å] and angles are given [°]. These fully optimized structures were computed at the B3LYP/LanL2DZ&6-31G* level. The energies were computed at the B3LYP/LanL2DZ &6-31G*+ΔZPVE level of theory.

The two possible *endo*-TS1 saddle points were much closer in energy (Figure 4). However, TS1-SSR was calculated to be 1.31 kcal/mol lower in energy than TS1-RRS. It is observed that the dihedral angle formed by the two naphthyl groups is ca. 57–58°. In the case of TS1-SSR, this leads to the blockage of the *Re-Si* face of the dipole. Because there is a stronger steric congestion between one naphthyl group and the *tert*-butyl group of the dipolarophile in TS1-

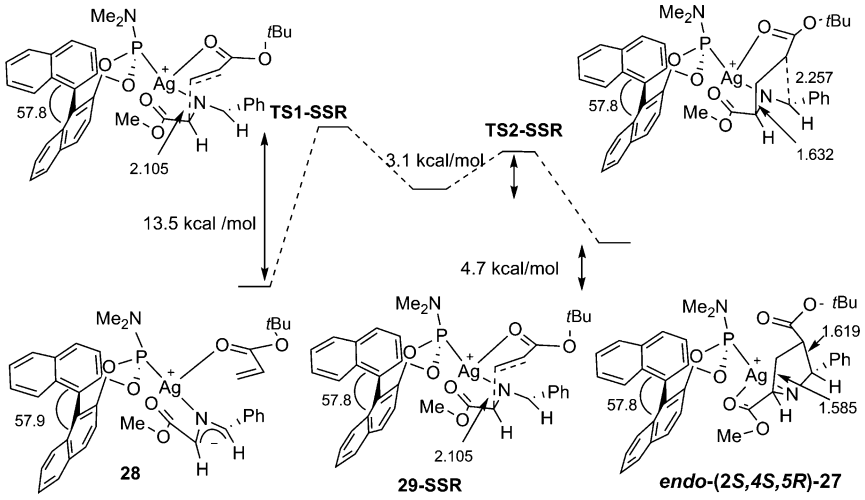


Figure 5. Reaction coordinate associated with the reaction between *tert*-butyl acrylate and complex **II**. Bond lengths [Å] and angles [°] are given. The relative energies were computed at the B3LYP/LanL2DZ&6-31G*+ΔZPVE level of theory.

RRS (Figure 4), this results in the preferential formation of *endo*-(2*S*,4*S*,5*R*)-**27**, which is in good agreement with the experimental results.

The reaction coordinate associated with the 1,3-DC between *tert*-butyl acrylate and complex **II** to form cycloadduct *endo*-(2*S*,4*S*,5*R*)-**27** is gathered in Figure 5. Reaction between the dipolarophile and complex **II** results in the formation of complex **28**. The computed reaction barrier to form zwiterionic intermediate **29**-SSR via TS1-SSR is ca. 13 kcal/mol. In this first step, complex **II** and *tert*-butyl acrylate behave as a silver enolate and a Michael acceptor, respectively. Intermediate **29**-SSR cyclises to *endo*-(2*S*,4*S*,5*R*)-**27** via an intramolecular Mannich-like reaction through TS2-SSR with a reaction barrier of ca. 3 kcal/mol. Therefore, the Michael addition reaction determines the stereoselectivity of the stepwise 1,3-DC and it is also the limiting step.

It is interesting to note that *endo*-(2*S*,4*S*,5*R*)-**27** is ca. 5 kcal/mol less stable than **28** because of the strain induced by the coordination pattern around the metallic centre after the complete cyclisation. This ensures the catalyst recovery and the delivery of *endo*-NH-cycloadduct **5aa**.

The simulation of the geometry of intermediate complex **II** also revealed that a torsion dihedral angle (ca. 23°) exists between the imaginary dipole-containing plane and the plane defined by the imine aromatic ring (Figure 6, top; see also Figure 4). This detail, a priori insignificant, can seriously affect the reaction rate. It was experimentally observed that the optimised enantioselective reaction of imino ester **8ha** (methyl 2-thienyliminoleucinate) and *tert*-butyl acrylate was completed in 48 h, but the analogous reaction attempted with imino ester **8aa** (methyl phenyliminoleucinate) did not proceed at all after 48 h. In fact, 2-thienyliminoglycinate could not be used as starting material because it reacted with itself (forming the presumed imidazolidine according to ^{1}H NMR) rather than add to the dipolarophile, unlike methyl phenyliminoglycinate (**4aa**) did. This different reactivity, presumably, originated from better hyperconjugation of the enolate in the presence of the thienyl substituent as a result of the existence of a more planar conformation of complexes **III** than in complex **IV**. This hypothes is supported by NOESY experiments performed on complexes **III** and **IV**, whose results are depicted in Figure 6 (bottom). The phenyl ring has to rotate in intermediate complex **IV**, such as it was observed for complex **II**, to ensure the interaction of the aromatic π-electronic current with the silver cation.[25]

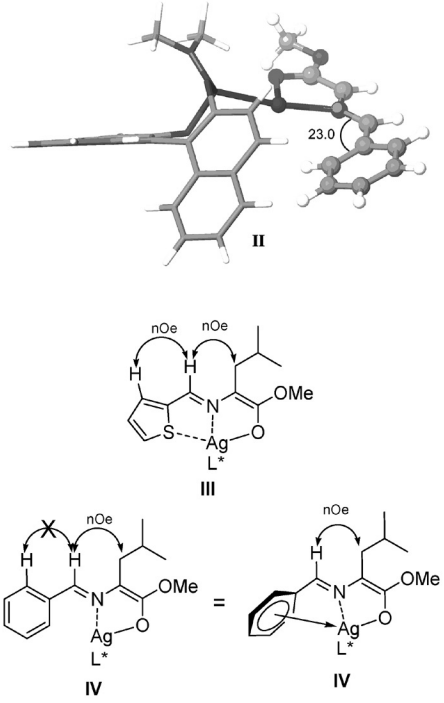


Figure 6. Geometrical features of complex **II** (angle given in °; top); nOe effects observed in intermediate complexes **III** and **IV** (bottom).

Conclusions

The novel equimolar monodentate phosphoramidite (S_a,*R*,*R*)-**3**-silver perchlorate complex is a very efficient chiral catalyst for a wide range of 1,3-dipolar cycloaddition reactions between azomethine ylides and dipolarophiles. This type of monodentate complex opens new perspectives in this and other reactions, as it can promote cycloadditions involving sterically hindered components; finetuning of the complex can be achieved by modifying the temperature, base and ester substituent. A direct application of this methodology is the direct synthesis of dicarboxylic acid **26**, a very effective agent inhibitor of the HCV polymerase. It was isolated in 50% overall yield (four steps) with 93:7 *er*. The overall cyclisation process occurred through a nonconcerted reaction; a Michael-type addition was the determinant step of the stereochemical outcome of the cyclisation reaction.

Experimental Section

General: All reactions were carried out in the absence of light. Anhydrous solvents were freshly distilled under an argon atmosphere. 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 with a Nicolet 510 P-FT) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained with a Bruker AC-300 by using $CDCl_3$ as the solvent and TMS as the internal standard, unless otherwise stated. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. HPLC analyses were performed with a JASCO 2000-series equipped with a chiral column (detailed for each compound in the main text) by using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase at 25 °C. Thermal analysis studies were done with a TG-DTA Mettler Toledo TGA/SDTA851e/SF/1100. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV with a Shimadzu QP-5000, and high-resolution mass spectra were obtained with a Finnigan VG Platform or a Finnigan MAT 95S. Microanalyses were performed with a Perkin–Elmer 2400 and a Carlo–Erba EA1108 instrument. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized under UV light (λ = 254 nm). Merck silica gel 60 (0.040–0.063 mm) was used for flash chromatography.

Computational Methods: All the calculations were obtained with the GAUSSIAN03 suite of programs.[26] Electron correlation was partially taken into account by using the hybrid functional B3LYP[27] and the standard 6-31G* basis set[28] for hydrogen, carbon, oxygen, phosphorus and nitrogen, and the Hay–Wadt small core effective potential (ECP)[29] including double-ξ valence basis set[30] for silver atoms (LanL2DZ keyword). Zero-point vibrational energy (ZPVE) corrections were computed at the B3LYP/LanL2DZ&6-31G* level and were not scaled. All stationary points were characterized by harmonic analysis. Reactants intermediates and cycloadducts have positive definite Hessian matrices. Transition structures show only one negative eigenvalue in their diagonalysed force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration (for more details see the Supporting Information).

General Procedure for the 1,3-Dipolar Cycloaddition of Imino Esters and Dipolarophiles: A solution of the imino ester (1 mmol) and dipolarophile (1 mmol) in toluene (5 mL) was added to a suspension containing the phosphoramidite (0.05 mmol) and $AgClO_4$ (0.05 mmol, 10 mg) in toluene (5 mL). To the resulting suspension was added triethylamine (0.05 mmol, 7 μL), and the mixture was stirred at the temperature indicated in the text in the absence of the light for 16–48 h. The precipitate was filtered, and the organic phase was directly evaporated. The residue was purified by recrystallisation or by flash chromatography to yield the pure *endo*-cycloadducts (see Tables 2 and 3 for details).

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-5-Phenyl-2,4-pyrrolidinedicarboxylate (5aa):[11j] Yield: 254 mg (80%).

4-*tert*-Butyl 2-Isopropyl (2*S*,4*S*,5*R*)-5-Phenyl-2,4-pyrrolidinedicarboxylate (5ab): Sticky oil (276 mg, 83%); $[\alpha]_D^{20}$ = +20.1 (*c* = 0.9, $CHCl_3$, 99% *ee* by HPLC); R_f = 0.46 (*n*-hexane/ethyl acetate, 3:2). IR (KBr): $\tilde{\nu}$ = 1727, 1705, 2977 cm^{-1}. ^{1}H NMR: δ = 1.03 [s, 9 H, $CO_2C(CH_3)_3$], 1.30 [d, *J* = 6.3 Hz, 3 H, $CO_2CH(CH_3)_2$], 2.26 (m, 1 H, CH_2), 2.44 (m, 1 H, CH_2), 2.69 (br. s, 1 H, NH), 3.26 (m, 1 H, $CHCO_2tBu$), 3.89 (dd, *J* = 8.4, 8.4 Hz, 1 H, $CHCO_2iPr$), 4.48 (d, *J* = 7.9 Hz, 1 H, CHPh), 5.15 [sept, *J* = 6.3 Hz, 1 H, $CO_2CH(CH_3)_2$], 7.21–7.38 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 21.8 [$CO_2CH(CH_3)_2$], 27.4 [$CO_2C(CH_3)_3$], 34.3 (CH_2), 50.3 ($CHCO_2tBu$), 60.2 ($CHCO_2iPr$), 65.6 [$CO_2CH(CH_3)_2$], 68.6 (PhCH), 80.5 [$CO_2C(CH_3)_3$], 127.2, 127.3, 128.1 (ArCH), 139.5 (ArC), 171.8, 172.8 (CO_2iPr, CO_2tBu) ppm. MS (EI): *m*/*z* (%) = 333 (0.78) [M$^+$], 246 (47), 205 (12), 191 (13), 190 (100), 172 (13), 163 (11), 145 (12), 144 (31), 117 (22). HRMS: calcd. for $C_{19}H_{27}NO_4$ 333.1940; found 333.1929. HPLC (Chiralpak AS; 1 mL/min; *n*-hexane/*i*PrOH, 99:1; λ = 220 nm): t_R = 15.3 (major), 58.5 (minor) min.

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-5-(2-Methylphenyl)-2,4-pyrrolidinedicarboxylate (5ba):[11j] Yield: 276 mg (83%).

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-5-(2-Chlorophenyl)-2,4-pyrrolidinedicarboxylate (5ca):[11j] Yield: 283 mg (80%).

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-5-(4-Methylphenyl)-2,4-pyrrolidinedicarboxylate (5da):[11j] Yield: 260 mg (78%).

4-*tert*-Butyl 2-Isopropyl (2*S*,4*S*,5*R*)-5-(4-Methylphenyl)-2,4-pyrrolidinedicarboxylate (5 db): Sticky oil (278 mg, 80%); $[\alpha]_D^{20}$ = +44.1 (*c* = 1, $CHCl_3$, 99% *ee* by HPLC); R_f = 0.43 (*n*-hexane/ethyl acetate, 3:2). IR (liq.): $\tilde{\nu}$ = 1727, 3018 cm^{-1}. ^{1}H NMR: δ = 1.07 [s, 9 H, $CO_2C(CH_3)_3$], 1.30 [d, *J* = 6.2 Hz, 3 H, $CO_2CH(CH_3)_2$], 2.32 (s, 3 H, $PhCH_3$), 2.50 (m, 1 H, CH_2), 2.44 (m, 1 H, CH_2), 3.31 (dd, *J* = 13.9, 7.7 Hz, 1 H, $CHCO_2tBu$), 4.07 (dd, *J* = 8.4, 8.2 Hz, 1 H, $CHCO_2iPr$), 4.59 (d, *J* = 7.8 Hz, 1 H, CHPh), 5.15 [m, 1 H, $CO_2CH(CH_3)_2$], 7.13 (d, *J* = 8.0 Hz, 2 H, ArH), 7.23 (d, *J* = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR: δ = 21.0 ($ArCH_3$), 21.7 [$CO_2CH(CH_3)_2$], 27.5 [$CO_2C(CH_3)_3$], 33.6 (CH_2), 51.0 ($CHCO_2tBu$), 59.7 ($CHCO_2iPr$), 65.2 [$CO_2CH(CH_3)_2$], 69.6 (ArCH), 81.2 [$CO_2C(CH_3)_3$], 127.0, 129.1 (ArCH), 137.5, 137.6 (*Ar*C), 171.4, 171.6 (CO_2iPr, CO_2tBu) ppm. MS (EI): *m*/*z* (%) = 347 (1.35) [M]$^+$, 290 (16), 274 (12), 260 (46), 219 (25), 205 (14), 204 (100), 186 (25), 177 (12), 160 (13), 159 (21), 158 (42), 143 (17), 131 (46), 57 (12), 56 (14). HRMS: calcd. for $C_{20}H_{29}NO_4$ 347.2097; found 347.2102. HPLC (Chiralpak AS; 1 mL/min; *n*-hexane/*i*PrOH, 95:5; λ = 220 nm): t_R = 6.8 (major), 18.6 (minor) min.

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-5-(4-Methoxyphenyl)-2,4-pyrrolidinedicarboxylate (5ea):[11j] Yield: 275 mg (79%).

4-*tert*-Butyl 2-Isopropyl (2*S*,4*S*,5*R*)-5-(4-Methoxyphenyl)-2,4-pyrrolidinedicarboxylate (5eb): Sticky oil (290 mg, 80%); $[\alpha]_D^{20}$ = +26.6 (*c* = 0.9, $CHCl_3$, 98% *ee* by HPLC); R_f = 0.37 (*n*-hexane/ethyl ace-

tate, 3:2). IR (liq.): $\tilde{\nu}$ = 1730, 1727, 2978 cm^{-1}. ^{1}H NMR: δ = 1.07 [s, 9 H, $CO_2C(CH_3)_3$], 1.30 [d, J = 6.3 Hz, 6 H, $CO_2CH(CH_3)_2$], 2.25 (m, 1 H, CH_2), 2.41 (m, 1 H, CH_2), 3.24 (dd, J = 14.7, 7.7 Hz, 1 H, C*H*CO_2tBu), 3.79 (s, 3 H, OCH_3), 3.86 (m, 1 H, C*H*CO_2iPr), 4.43 (d, J = 7.9 Hz, 1 H, C*H*Ar), 5.14 [sept, J = 6.3 Hz, 1 H, $CO_2CH(CH_3)_2$], 6.85 (d, J = 8.8 Hz, 2 H, Ar*H*), 7.28 (d, J = 8.7 Hz, 2 H, Ar*H*) ppm. ^{13}C NMR: δ = 21.8 [$CO_2CH(CH_3)_2$], 27.5 [$CO_2C(CH_3)_3$], 34.2 (CH_2), 50.4 (*C*HCO_2tBu), 55.3 (OCH_3), 60.1 (*C*HCO_2iPr), 65.0 [$CO_2CH(CH_3)_2$], 68.7 (PhC*H*), 80.5 [$CO_2C(CH_3)_3$], 113.5, 128.3 (ArCH), 131.8, 158.8 (ArC), 171.9, 172.9 (CO_2iPr, CO_2tBu) ppm. MS (EI): m/z (%) = 363 (2.9) [M]$^+$, 306 (41), 290 (23), 276 (43), 235 (61), 221 (10), 220 (70), 202 (32), 193 (14), 176 (27), 175 (39), 174 (30), 159 (19), 148 (18), 147 (100), 135 (11), 132 (16), 57 (14), 56 (41), 55 (18). HRMS: calcd. for $C_{20}H_{29}NO_5$ 363.2046; found 363.2029. HPLC (Chiralpak AS; 1 mL/min; *n*-hexane/*i*PrOH, 95:5; λ = 220 nm): t_R = 9.5 (major), 24.9 (minor) min.

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-5-(4-Chlorophenyl)-2,4-pyrrolidinedicarboxylate (5fa):[11j] Yield: 269 mg (76%).

4-*tert*-Butyl 2-Isopropyl (2*S*,4*S*,5*R*)-5-(4-Chlorophenyl)-2,4-pyrrolidinedicarboxylate (5fb): Colourless prisms (283 mg, 77%); m.p. 88–90 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ = +23.6 (c = 0.8, $CHCl_3$, 94%*ee* by HPLC); R_f = 0.46 (*n*-hexane/ethyl acetate, 3:2). IR (liq.): $\tilde{\nu}$ = 1737, 1709, 2978 cm^{-1}. ^{1}H NMR: δ = 1.06 [s, 9 H, $CO_2C(CH_3)_3$], 1.29 [d, J = 6.3 Hz, 3 H, $CO_2CH(CH_3)_2$], 1.30 [d, J = 6.3 Hz, 3 H, $CO_2CH(CH_3)_2$], 2.26 (m, 1 H, CH_2), 2.44 (m, 1 H, CH_2), 3.26 (dd, J = 14.7, 7.8 Hz, 1 H, C*H*CO_2tBu), 3.89 (dd, J = 8.4, 8.4 Hz, 1 H, C*H*CO_2iPr), 4.43 (d, J = 7.8 Hz, 1 H, C*H*Ph), 5.15 [sept, J = 6.2 Hz, 1 H, $CO_2CH(CH_3)_2$], 7.25–7.31 (m, 4 H, Ar*H*) ppm. ^{13}C NMR: δ = 21.8 [$CO_2CH(CH_3)_2$], 27.5 [$CO_2C(CH_3)_3$], 33.9 (CH_2), 50.1 (*C*HCO_2tBu), 60.0 (*C*HCO_2iPr), 64.8 [$CO_2CH(CH_3)_2$], 68.8 (Ar*C*H), 80.8 [$CO_2C(CH_3)_3$], 128.2, 128.6, 133.1, 138.3 (Ar*C*), 171.5, 172.9 (CO_2iPr, CO_2tBu) ppm. MS (EI): m/z (%) = 367 (0.66) [M]$^+$, 282 (14), 280 (40), 239 (10), 226 (33), 225 (13), 224 (100), 206 (15), 197 (12), 180 (12), 179 (13), 178 (18), 151 (19), 57 (11). HRMS: calcd. for $C_{19}H_{26}ClNO_4$ 367.1550; found 367.1547. HPLC (Chiralpak AS; 1 mL/min; *n*-hexane/*i*PrOH, 95:5; λ = 220 nm), t_R = 6.7 (major), 16.5 (minor) min.

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-5-(2-naphthyl)-2,4-pyrrolidinedicarboxylate (5ga):[11j] Yield: 299 mg (78%).

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-Methyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9aa):[11b] Yield: 230 mg (80%).

Methyl (1*S*,3*R*3a*S*,6a*R*)-5-Ethyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (10aa):[11b] Yield: 236 mg (78%).

3,4-Diisopropyl 2-Methyl (2*S*,3*S*,4*S*,5*R*)-5-Phenyl-2,3,4-pyrrolidinetricarboxylate (11aa): Sticky oil (305 mg, 81%); $[\alpha]_D^{20}$ = 32.1 (c = 0.5, $CHCl_3$, 82%*ee* by HPLC); R_f = 0.37 (*n*-hexane/ethyl acetate, 3:2). IR (liq.): $\tilde{\nu}$ = 1741, 1731, 2982 cm^{-1}. ^{1}H NMR: δ = 0.65 [d, J = 6.2 Hz, 3 H, $CH(CH_3)_2$], 0.94 [d, J = 6.2 Hz, 3 H, $CH(CH_3)_2$], 1.27 [d, J = 6.2 Hz, 3 H, $CH(CH_3)_2$], 1.28 [d, J = 6.2 Hz, 3 H, $CH(CH_3)_2$], 2.86 (br. s, 1 H, NH), 3.55 (m, 2 H, 2 × C*H*CO_2iPr), 3.83 (s, 3 H, CO_2CH_3), 4.14 (d, J = 7.3 Hz, 1 H, $CHCO_2Me$), 4.56 [sept, J = 6.2 Hz, 1 H, C*H*$(CH_3)_2$], 4.65 (d, J = 7.3 Hz, 1 H, C*H*Ph), 5.08 [sept, J = 6.2 Hz, 1 H, C*H*$(CH_3)_2$], 7.22–7.34 (m, 5 H, Ar*H*) ppm. ^{13}C NMR: δ = 20.8, 21.4, 21.6 [$CH(CH_3)_2$], 51.4, 52.4 (*C*HCO_2iPr), 53.8 (CO_2CH_3), 63.4 [*C*HCO_2Me], 65.2 (Ph*C*H), 68.2, 68.8 [*C*H$(CH_3)_2$], 127.0, 127.7, 128.2, 138.4 (Ar*C*), 170.5, 171.5, 171.6 (CO_2Me, CO_2iPr) ppm. MS (EI): m/z (%) = 377 (14) [M]$^+$, 318 (33), 317 (23), 316 (23), 290 (20), 276 (17), 274 (12), 258 (38), 248 (15), 230 (43), 228 (17), 216 (10), 205 (25), 202 (50), 188 (47), 187 (23), 177 (67), 170 (34), 149 (12), 146 (29), 145 (46), 144 (100), 143 (29), 119 (22), 118 (19), 117 (96), 116 (14), 115 (28), 106 (11), 104 (10), 91 (12), 90 (10). HRMS: calcd. for $C_{20}H_{27}NO_6$ 377.1838; found 377.1843. HPLC (Chiralpak OD-H; 1 mL/min; *n*-hexane/*i*PrOH, 80:20; λ = 220 nm): t_R = 6.6 (major), 13.5 (minor) min.

3,4-Diisobutyl 2-Methyl (2*S*,3*S*,4*S*,5*R*)-5-Phenyl-2,3,4-pyrrolidinetricarboxylate (12aa): Sticky oil (320 mg, 79%); $[\alpha]_D^{20}$ = 47.1 (c = 0.5, $CHCl_3$, 82%*ee* by HPLC); R_f = 0.56 (*n*-hexane/ethyl acetate, 1:5). IR (liq.): $\tilde{\nu}$ = 1737 1730, 2958 cm^{-1}. ^{1}H NMR: δ = 0.66 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$], 0.68 [d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$], 0.95 [d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.51 [d, J = 6.7 Hz, 1 H, C*H*$(CH_3)_2$], 1.63 (br. s, 1 H, NH), 1.97 [d, J = 6.7 Hz, 1 H, C*H*$(CH_3)_2$], 3.25 [dd, J = 10.5, 6.6 Hz, 1 H, $CH_2CH(CH_3)_2$], 3.50 [dd, J = 10.6, 6.6 Hz, 1 H, $CH_2CH(CH_3)_2$], 3.63 (m, 2 H, 2 × C*H*CO_2iBu), 3.83 (s, 3 H, CO_2CH_3), 3.96 [m, 2 H, $CH_2CH(CH_3)_2$], 4.19 (d, J = 7.3 Hz, 1 H, $CHCO_2Me$), 4.66 (d, J = 7.5 Hz, 1 H, C*H*Ph), 7.25–7.32 (m, 5 H, Ar*H*) ppm. ^{13}C NMR: δ = 18.8, 18.9, 19.0 [$CH(CH_3)_2$], 27.2, 27.7 [*C*H$(CH_3)_2$], 51.3 (*C*HCO_2iBu), 52.5 (CO_2CH_3), 54.0 (*C*HCO_2iBu), 63.4 [*C*HCO_2Me], 65.5 (Ph*C*H), 71.1, 71.5 (2 × CH_2), 126.9, 127.8, 128.3, 138.1 (ArC), 171.4, 172.1, 172.2 (CO_2Me, 2 × CO_2iBu) ppm. MS (EI): m/z (%) = 405 (11) [M]$^+$, 346 (11), 345 (22), 332 (20), 304 (20), 272 (36), 245 (11), 244 (54), 219 (11), 202 (38), 188 (38), 178 (11), 177 (90), 170 (26), 164 (46), 155 (12),149 (14), 146 (54), 145 (46), 144 (82), 143 (24), 119 (12), 118 (19), 117 (100), 116 (13), 115 (21), 106 (11), 105 (11), 90 (11), 57 (46), 56 (21), 55 (12). HRMS: calcd. for $C_{22}H_{31}NO_6$ 405.2151; found 405.2151. HPLC (Chiralpak OD-H; 1 mL/min; *n*-hexane/*i*PrOH, 80:20; λ = 220 nm): t_R = 8.5 (major), 16.7 (minor) min.

2-Methyl (2*S*,3*R*,4*S*,5*R*)-4-Benzoyl-3,5-diphenyl-2-pyrrolidinecarboxylate (13aa): Colourless needles (262 mg, 80%); m.p. 152 °C (hexane/ethyl acetate). $[\alpha]_D^{20}$ = –20 (c = 1, CH_2Cl_2, 99%*ee* by HPLC). IR (KBr): $\tilde{\nu}$ = 1673, 1741, 3435 cm^{-1}. ^{1}H NMR: δ = 2.65 (s, 1 H, NH), 3.74 (s, 3 H, CO_2Me), 4.21–4.09 (m, 2 H, CHCOPh and $CHCO_2$Me), 4.52 (t, J = 7.5 Hz, 1 H, C*H*Ph), 5.00 (d, J = 8.6 Hz, 1 H, C*H*Ar), 7.13–7.04 (m, 5 H, Ar*H*), 7.26–7.21 (m, 3 H, Ar*H*), 7.41–7.31 (m, 5 H, Ar*H*), 7.54–7.51 (m, 2 H, Ar*H*) ppm. ^{13}C NMR: δ = 52.30 (CH_3CO_2), 52.65 (C*H*Ph), 60.56 (C*H*COPh), 66.62 (C*H*CO_2Me), 67.63 (PhC*H*NH), 127.11, 1.27.34, 127.72, 128.01, 128.10, 128.18, 128.76, 132.75, 137.35, 138.90, 140.68 (Ar*C*), 173.30 and 198.61 (2 × CO) ppm. MS (EI): m/z (%) = 326 (12) [M]$^+$. HRMS (EI): calcd. for $C_{23}H_{21}NO$ [M – $C_2H_3O_2$]$^+$ 327.1623; found 327.1622. HPLC (Chiralpak OD-H; 1 mL/min; *n*-hexane/*i*PrOH, 90:10; λ = 220 nm): t_R = 18.4 (major), 33.2 (minor) min.

2-Methyl (2*S*,3*R*,4*S*,5*R*)-4-Benzoyl-5-(2-methylphenyl)-3-phenyl-2-pyrrolidinecarboxylate (14ba): Colourless prisms (141, 70%); m.p. 128 °C; $[\alpha]_D^{20}$ = –9 (c = 1.15, CH_2Cl_2, 99%*ee* by HPLC). IR (KBr): $\tilde{\nu}$ = 1672, 1746, 3373 cm^{-1}. ^{1}H NMR: δ = 2.14 (s, 3 H, CH_3Ph), 3.77 (s, 3 H, CO_2CH_3), 4.12–410 (m, 2 H, *CH*COPh and *CH*CO_2Me), 4.52–4.43 (m, 1 H, *CH*Ph), 5.11 (d, J = 8.3 Hz, 1 H, *CH*Ar), 6.75 (d, J = 7.7 Hz, 1 H), 6.92 (t, J = 6.4 Hz, 1 H, Ar*H*), 7.17–7.05 (m, 3 H, Ar*H*), 7.41–7.24 (m, 9 H, Ar*H*) ppm. ^{13}C NMR: δ = 19.9 (CH_3Ph), 52.7 (CH_3CO_2), 54.4 (*C*HPh), 59.7 (*CH*CO_2Me), 63.3 (*CH*COPh), 68.5 (*CH*Ar), 126.5, 126.6, 127.5, 127.7, 127.9, 127.9, 128.3, 129.3, 130.3, 132.8, 135.2, 136.2, 138.1, 142.1 (Ar*C*), 173.22 (CO_2Me), 200.93 (*C*OPh) ppm. MS (EI): m/z (%) = 340 (15) [M]$^+$. HRMS (EI): calcd. for $C_{24}H_{22}NO$ [M – $C_2H_3O_2$]$^+$ 341.1780; found 340.1685. HPLC (Chiralpak OD-H; 1 mL/min; *n*-hexane/*i*PrOH, 90:10; λ = 220 nm): t_R = 19.7 (major), 24.8 (minor) min.

2-Methyl (2*S*,3*R*,4*S*,5*R*)-4-Benzoyl-5-(4-methylphenyl)-3-phenyl-2-pyrrolidinecarboxylate (14da): Colourless prisms (256 mg, 75%);

m.p. 154 °C; $[\alpha]_D^{20}$ = –25 (*c* = 1.06, CH_2Cl_2, 90%*ee* by HPLC). IR (KBr): $\tilde{\nu}$ = 1675, 1741, 3374 cm^{-1}. ^1H NMR: δ = 2.17 (s, 3 H, CH_3Ph), 3.73 (s, 3 H, CO_2Me), 4.18–4.07 (m, 2 H, *CH*COPh and *CH*CO_2Me), 4.50 (t, *J* = 7.8 Hz, 1 H, *CH*Ph), 4.97 (d, *J* = 8.6 Hz, 1 H, *CH*Ar), 6.9 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.99 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 7.39–7.42 (m, 9 H, Ar*H*), 7.55 (d, *J* = 6.4 Hz, 2 H, Ar*H*) ppm. ^{13}C NMR: δ = 20.9 (*C*H_3Ph), 52.2 (CO_2CH_3), 52.6 (*C*HPh), 60.6 (*C*HCO_2Me), 66.4 (*C*HCOPh), 67.6 (*C*HAr), 127.2, 128.0, 128.7, 128.7, 132.7, 136.0, 137.2, 137.4, 140.7 (Ar*C*), 173.4 (*C*O_2Me), 198.6 (*C*OPh) ppm. MS (EI): *m*/*z* (%) = 340 (45) $[M]^+$. HRMS (EI): calcd. for $C_{24}H_{22}NO$ $[M - C_2H_3O_2]^+$ 341.1780; found 340.1705. HPLC (Chiralpak OD-H; 1 mL/min; *n*-hexane/*i*PrOH, 90:10; λ = 220 nm): t_R = 19.7 (major), 24.8 (minor) min.

Methyl (1*S*,3*R*,3a*S*,6a*R*)-Octahydro-3-(naphthalen-2-yl)-4-oxocyclopenta[*c*]pyrrole-1-carboxylate (15ga):[12b] Yield: 222 mg (72%).

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-2-Methyl-5-phenyl-2,4-pyrrolidinedicarboxylate (16aa):[11j] Yield: 238 mg (78%).

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-2-Benzyl-5-phenyl-2,4-pyrrolidinedicarboxylate (17aa):[11j] Yield: 293 mg (77%).

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-2-Methyl-5-(2-thienyl)-2,4-pyrrolidinedicarboxylate (18ha): Sticky oil (257 mg, 79%); $[\alpha]_D^{20}$ = +46.3 (*c* = 1, $CHCl_3$, 92%*ee* by HPLC); R_f = 0.30 (*n*-hexane/ethyl acetate, 3:2). IR (liq.): $\tilde{\nu}$ = 1728, 1725, 2977 cm^{-1}. ^1H NMR: δ = 1.15 [s, 9 H, $CO_2C(CH_3)_3$], 1.46 (s, 1 H, CCH_3), 2.07 (dd, *J* = 13.7, 7.7 Hz, 1 H, CH_2), 2.70 (dd, *J* = 13.7, 7.7 Hz, 1 H, CH_2), 3.35 (dd, *J* = 15.2, 7.7 Hz, 1 H, C*H*CO_2tBu), 3.79 (s, 3 H, CO_2CH_3), 4.81 (d, *J* = 7.5 Hz, 1 H, C*H*Ar), 6.91–6.95 (m, 2 H, Ar*H*), 7.17 (dd, *J* = 4.9, 0.9 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR: δ = 27.6 (C*C*H_3), 27.8 (C*C*H_3), 39.4 (CH_2), 50.6 (*C*HCO_2tBu), 52.5 [$CO_2C(CH_3)_3$], 60.3 (Ar*C*H), 80.8 [$CO_2C(CH_3)_3$], 124.1, 124.8, 126.5, 143.5 (Ar*C*), 171.0, 176.3 (CO_2Me, CO_2tBu) ppm. MS (EI): *m*/*z* (%) = 325 (3.4) $[M]^+$, 268 (22), 267 (10), 266 (65), 252 (26), 211 (12), 210 (100), 197 (56), 166 (15), 165 (15), 164 (18), 137 (67), 96 (11), 57 (18), 53 (10). HRMS: calcd. for $C_{16}H_{23}NO_4S$ 325.1348; found 325.1347. HPLC (Chiralpak OD-H; 1 mL/min; *n*-hexane/*i*PrOH, 99:1; λ = 220 nm): t_R = 13.4 (major), 14.8 (minor) min.

4-*tert*-Butyl 2-Methyl (2*S*,4*S*,5*R*)-2-Isobutyl-5-(2-thienyl)-2,4-pyrrolidinedicarboxylate (19ha): Viscous oil (257 mg, 70%); $[\alpha]_D^{20}$ = +38.6 (*c* = 1, $CHCl_3$, 84%*ee* by HPLC); R_f = 0.49 (*n*-hexane/ethyl acetate, 3:2). IR (liq.): $\tilde{\nu}$ = 1735, 1728, 2952 cm^{-1}. ^1H NMR: δ = 0.82 [d, *J* = 6.1 Hz, 3 H, $CH(CH_3)_2$], 0.93 [d, *J* = 6.4 Hz, 3 H, $CH(CH_3)_2$], 1.14 [s, 9 H, $CO_2C(CH_3)_3$], 1.58 [m, 1 H, $CH_2CH(CH_3)_2$], 1.75 [m, 2 H, $CH_2CH(CH_3)_2$], 2.06 (dd, *J* = 13.6, 7.6 Hz, 1 H, CCH_2), 2.61 (dd, *J* = 13.7, 8.0 Hz, 1 H, CCH_2), 3.05 (br. s, 1 H, NH), 3.29 (dd, *J* = 15.4, 7.8, 7.6 Hz, 1 H, $CHCO_2t$Bu), 3.77 (s, 3 H, CO_2CH_3), 4.76 (d, *J* = 7.5 Hz, 1 H, C*H*Ar), 6.90–6.94 (m, 2 H, Ar*H*), 7.16 (dd, *J* = 4.8, 1.4 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR: δ = 22.7 [$CH(CH_3)_2$], 24.3 [$CH(CH_3)_2$], 25.0 [$CH(CH_3)_2$], 27.6 [$CO_2C(CH_3)_3$], 39.9 (CH_2CHCO_2tBu), 49.0 [$CH_2CH(CH_3)_2$], 50.3 (*C*HCO_2tBu), 52.2 (CO_2CH_3), 60.3 (Ar*C*H), 68.1 (*C*CO_2Me), 80.7 [$CO_2C(CH_3)_3$], 124.1, 124.9, 126.4, 143.9 (ArC), 171.1, 176.4 (CO_2Me, CO_2tBu) ppm. MS (EI): *m*/*z* (%) = 367 (0.9) $[M]^+$, 310 (14), 309 (13), 308 (65), 254 (18), 253 (16), 252 (100), 208 (11), 196 (41), 179 (14), 57 (12). HRMS: calcd. for $C_{19}H_{29}NO_4S$ 367.1817; found 367.1821. HPLC (Chiralpak AD; 1 mL/min; *n*-hexane/*i*PrOH, 99:1; λ = 220 nm): t_R = 11.1 (major), 13.7 (minor) min.

Methyl (1*S*,3*R*3a*S*,6a*R*)-1,5-Dimethyl-3-phenyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20aa):[11b] Yield: 242 mg (80%).

Methyl (1*S*,3*R*3a*S*,6a*R*)-1-Benzyl-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (21aa):[11b] Yield: 302 mg (80%).

Methyl (2*S*,3*R*,4*S*,5*R*)-4-Benzoyl-2-methyl-3,5-diphenyl-2-pyrrolidinecarboxylate (22aa):[12b,31] Yield: 324 mg (81%).

Methyl (2*S*,3*R*,4*S*,5*R*)-4-Acetyl-2,3-dimethyl-5-(2-naphthyl)-2-pyrrolidinecarboxylate (23ga): Pale-yellow oil (189 mg, 71%); $[\alpha]_D^{20}$ = 20 (*c* = 1.02, CH_2Cl_2, 65%*ee* by HPLC). IR (NaCl): $\tilde{\nu}$ = 1689, 1722, 2958, 3312 cm^{-1}. ^1H NMR: δ = 1.19 (d, *J* = 6.2 Hz, 3 H, CH_3CH), 1.38 (s, 3 H, CH_3CN), 1.61 (s, 3 H, CH_3CO), 2.99–3.04 (m, 1 H, C*H*CH_3), 3.29 (t, *J* = 10.3 Hz, 1 H, CHCO), 3.82 (s, 3 H, OCH_3), 4.90 (d, *J* = 9.5 Hz, 1 H, CHN), 7.37–7.34 (m, 2 H, Ar*H*), 7.48–7.43 (m, 3 H, Ar*H*) ppm. ^{13}C NMR: δ = 19.77 (*C*H_3CH), 24.99 (CH_3CO), 30.60 (*C*HCH_3), 42.58 (CHCO), 52.17 (CH_3O), 62.23 (CHCO), 64.47 (CHN), 125.05, 125.88, 126.38, 127.31 127.60 128.18, 132.72, 137.67 (Ar*C*), 175.57 (CO_2), 206.59 (*C*OCH_3) ppm. MS (EI): *m*/*z* = 266 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{20}NO$ $[M - C_2H_3O_2]^+$ 266.1555; found 266.1552. HPLC (Chiralpak OD-H; 1 mL/min; *n*-hexane/*i*PrOH, 90:10; λ = 220 nm): t_R = 10.5 (major), 12.2 (minor) min.

Synthesis of Antiviral Compound (2*S*,4*S*,5*R*)-26: To a solution of (2*S*,4*S*,5*R*)-**8ha** (1.2 mmol, 441 mg) dissolved in dichloromethane (25 mL) was slowly added triethylamine (1.2 mmol, 166 μL) and 4-(trifluoromethyl)benzoyl chloride (1.2 mmol, 182 μL) at 0 °C. The resulting mixture was heated at reflux overnight, and the solvent was removed in vacuo (15 Torr). Crude compound (2*S*,4*S*,5*R*)-**25** was allowed to react with trifluoroacetic acid/dichloromethane mixture (9.6 mL:18 mL). The resulting mixture was stirred at room temperature overnight, and the solvent was evaporated in vacuo. The residue was dissolved in a solution of KOH (1 M in MeOH/H_2O, 4:1; 50 mL). This reaction was heated at reflux for 16 h. Methanol was evaporated and aqueous HCl (0.5 M, 20 mL) and ethyl acetate were added (2 × 20 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to yield the crude (2*S*,4*S*,5*R*)-**26**, which was recrystallised from acetone/chloroform.

(2*S*,4*S*,5*R*)-2-Isobutyl-5-(2-thienyl)-1-[4-(trifluoromethyl)benzoyl]-2,4-pyrrolidinedicarboxylic Acid [(2*S*,4*S*,5*R*)-(+)-26]:[5a] Yield: 395 mg (71% from **19ha**).

Supporting Information (see also the footnote on the first page of this article): The main geometrical features of the stationary points found along the reaction coordinate depicted in Figure 5; total electronic energies, zero-point correction of energies, thermal corrections to Gibbs free energies and number of imaginary frequencies of all stationary points discussed in this article; Cartesian coordinates of all the stationary points discussed.

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