Asymmetric Control of 1,3-Dipolar Cycloaddition Reactions with Azomethine Ylides by Means of Proline Esters as Chiral Auxiliary Groups

Herbert Waldmann,* Edwin Bläser, Martin Jansen, and Hans-Peter Letschert

Abstract: Upon treatment with triethylamine or DBU in the presence of LiBr, aromatic and aliphatic imines of amino acid esters are converted to *N*-metalated azomethine ylides. These 1,3-dipoles undergo highly stereoselective cycloadditions with *N*-acryloyl-(*S*)-proline esters in THF at −78 to −40 °C to afford highly substituted pyrrolidines with complete regiocontrol and good to excellent diastereomeric ratios. The chiral auxiliary groups can readily be removed from the cycloadducts by simple acid hydrolysis. To rationalize the observed stereoselectivity a transition-state model is proposed in which the lithium cation is coordinated to both the 1,3-dipole and the dipolarophile.

Keywords: asymmetric syntheses · azomethine ylides · chiral auxiliaries · cycloadditions · pyrrolidines

Introduction

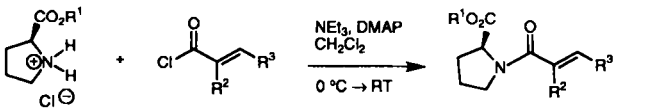
1,3-Dipolar cycloadditions belong to the most efficient tools available for the synthesis of carbo- and heterocycles. In particular, the reaction of azomethine ylides with olefins, which allows the simultaneous construction of up to four stereocenters, has proven to be a powerful method for the construction of highly substituted pyrrolidines.[1] These nitrogen heterocycles are widely found as integral parts of numerous biologically relevant alkaloids[1] and are of considerable interest in the field of medicinal chemistry, for example, as glycosidase inhibitors[2] and antagonists of excitatory amino acids.[3] Thus, cycloadditions of azomethine ylides are increasingly becoming important as key steps in the synthesis of complex natural products and pharmaceuticals.[4]

Following the pioneering work of Padwa et al.[5] two general approaches to the asymmetric control of the steric course of 1,3-dipolar cycloadditions with azomethine ylides were developed, involving the use of either chiral, nonracemic dipolarophiles[6, 7] or dipoles[8] as stereodirecting reagents. In addition, an enantioselective transformation was recently described.[9] Although high diastereomeric ratios were detected in some cases, in general the results obtained have been mixed. In the course of studies directed at the use of the readily available amino acid esters as chiral auxiliaries for the asymmetric synthesis of carbo- and heterocycles,[10] we found that proline esters can advantageously be applied as efficient mediators of stereoselectivity in 1,3-dipolar cycloadditions with azomethine ylides.[11]

[*] Prof. Dr. H. Waldmann, Dipl. Chem. E. Bläser
Institut für Organische Chemie der Universität Karlsruhe
Richard-Willstätter-Allee 2, D-76128 Karlsruhe (Germany)
Telefax: Int. code + (721)608-4825
Prof. Dr. M. Jansen, Dipl. Chem. H. Letschert
Institut für Anorganische Chemie der Universität Bonn

Results and Discussion

To direct the steric course of the planned 1,3-dipolar cycloadditons, α,β-unsaturated amides **3** of proline esters were chosen as chiral dipolarophiles, since they had already proven to be efficient reagents in asymmetric carbo Diels–Alder cycloadditions.[10, 12] These compounds are readily prepared in high yields by *N*-acylation of the respective proline esters **1** with the appropriate acid chloride **2** in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (Scheme 1).



1a: R^1 = Bzl
b: R^1 = CH_3

2 a: R^2 = R^3 = H
b: R^2 = CH_3, R^3 = H
c: R^2 = H, R^3 = CH_3

3 a: R^1 = Bzl, R^2 = R^3 = H
b: R^1 = Bzl, R^2 = CH_3, R^3 = H
c: R^1 = Bzl, R^2 = H, R^3 = CH_3
d: R^1 = CH_3, R^2 = R^3 = H

Scheme 1. *N*-Acylation of proline esters **2** to give α,β-unsaturated proline ester amides **3**.

The azomethine ylides were generated in situ by deprotonation of the imines **5** of amino acid esters **4**. The Schiff bases **5** were obtained in a straightforward manner by condensation of aliphatic or aromatic aldehydes and amino acid esters **4** in dichloromethane in the presence of $MgSO_4$ or molecular sieves as dehydrating agents (Scheme 2).[13] Upon treatment of the amino acid ester imines **5** with a nitrogen base in the presence of anhydrous LiBr the metalated 1,3-dipoles **6** were formed. The lithium cation serves as a Lewis acid, which, by association with the carbonyl oxygen and/or the imine nitrogen, enhances the acidity of the amino acid α-H and enables the formation of stable chelates as intermediates.[14] However, the *N*-metalated

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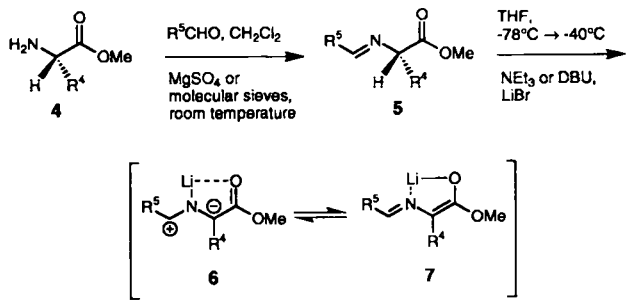
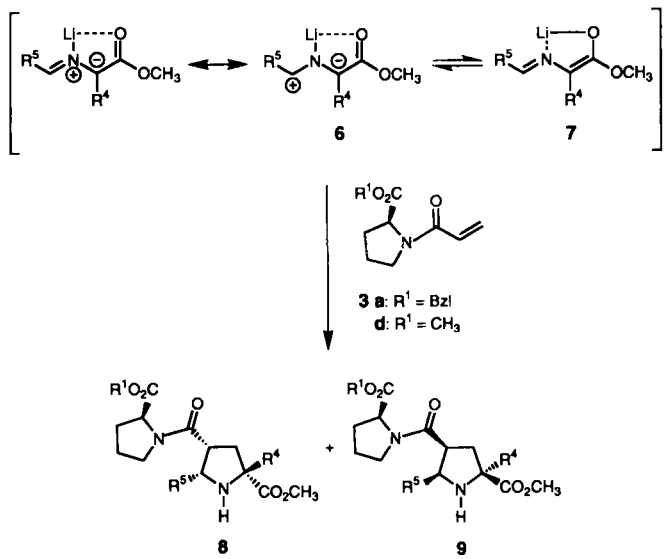


Scheme 2. Azomethine ylides **6** generated by deprotonation of amino acid ester imines **5**.

azomethine ylides **6** may also be in equilibrium with the respective ester enolates **7**[15] (Scheme 2), and either may be the reactive species in the subsequent cycloadditions.

The metalated azomethine ylides **6**, which were derived from aliphatic or aromatic aldehydes and the methyl esters of glycine or aliphatic or aromatic amino acids, underwent highly stereoselective 1,3-dipolar cycloadditions with the acrylamide **3a** of proline benzyl ester (Scheme 3, Table 1). The best results were obtained when triethylamine or 1,8-diazabicylo[5.4.0]undec-7-ene (DBU) was employed as deprotonating base and when the reactions were carried out at −40 to −78 °C in THF as solvent. Under these conditions the pyrrolidines **8** and **9** were formed in yields of 22–70%. When both substituents R^4 and R^5 on the 1,3-dipole were aromatic, the yield was generally 60–70% (Table 1, entries 5–7 and 11). When either R^4 or R^5 was aliphatic or H, the cycloaddition did not go to completion and by-products were formed, which were not further identified. In these cases the yield varied between 22 and 48% (Table 1, entries 1–4 and 8–10). Imines derived from esters of aliphatic amino acids and aliphatic aldehydes did not undergo the desired cycloadditions in the presence of triethylamine or diisopropylethylamine. This trend can be rationalized by the decrease in the C–H acidity of the amino acid α-H on switching from an aromatic to an aliphatic side chain, and by the better stabilization of the 1,3-dipoles by neighboring aromatic substituents than by aliphatic groups in the imine and/or amino acid.



Scheme 3. Asymmetric 1,3-dipolar cycloadditions of *N*-acryloyl-(*S*)-proline esters **3** with *N*-metalated azomethine ylides **6**.

Table 1. Results of the asymmetric 1,3-dipolar cycloadditions between the azomethine ylides **6** and *N*-acryloyl-(*S*)-proline esters **3a** and **3d** to give the pyrrolidines **8** und **9**.

entry	8	R^1	R^4 [a]	R^5	*T* [°C]	reaction time [h]	yield [%]	*endo*/*exo* ratio	8:9
1	**a**	Bzl	H	Ph	−78 → 25	72	43	>99:1	93:7
2	**b**	Bzl	CH_3	Ph	−40	72	48	>99:1	91:9
3	**c**	Bzl	*i*Pr	Ph	−40 → 25	72	30	>99:1	>99:1
4	**d**	Bzl	*i*Bu	Ph	−40	72	30	>99:1	>99:1
5	**e**	Bzl	Ph	Ph	−78 → 25	48	67	>99:1	>99:1
6	**f**	Bzl	Ph	4-NO_2-C_6H_4	−40	48	60	93:7	97:3
7	**g**	Bzl	Ph	4-H_3CO-C_6H_4	−40	48	65	>99:1	95:5
8	**h**	Bzl	Ph	*i*Pr	−40 → 25	96	35	>99:1	90:10
9	**i**	Bzl	Ph	*t*Bu	−50	96	22	>99:1	90:10
10	**j**	Bzl	Ph	*n*Pr	−50	96	33	>99:1	80:20
11	**k**	CH_3	Ph	Ph	−78 → 25	48	70	>99:1	85:15

[a] In entries 3 and 4, DBU was used as base; in all other cases triethylamine was employed.

In all cycloadditions only four of the eight possible diastereomers could be detected, and one stereoisomer was always formed in large excess. The absolute configuration of the major diastereomer was established unambiguously by crystal structure analysis of the pyrrolidine **8e** (Fig. 1). In nearly all cases the cycloadducts were formed with an *endo*/*exo* selectivity >99:1; only for **8f** could the corresponding *exo* adducts be detected. The diastereomeric excess determined for the *endo* isomers is influenced by several factors: Firstly, with increasing steric demand of the side chains of the amino acids in the 1,3-dipoles, the stereoselectivity increases. For instance, **8a** and **8b**, which were derived from the benzaldimine of glycine and alanine methyl ester, respectively, were formed with diastereomeric ratios of 93:7 and 91:9 (Table 1, entries 1 and 2). However, when aromatic Schiff bases of valine, isoleucine, or phenylglycine methyl ester were employed as precursors to the metalated dipoles, isomer ratios of >95:5 to >99:1 were observed (Table 1, entries 3–7). In the case of pyrrolidines **8c**, **8d**, and **8e**, the corresponding *endo* isomer **9** could not be detected at all. Secondly, imines derived from aromatic aldehydes, in general, gave the cycloadducts with substantially higher selectivity than those formed from aliphatic carbonyl compounds. For instance, the pyrrolidines **8e**–**8g** were obtained from benzaldehyde derivatives with isomer ratios of 95:5 to >99:1 (Table 1, entries 5–7); however, the nitrogen heterocycles **8h**–**8j**, which ultimately were built up from an aliphatic aldehyde, were formed with isomer ratios of 80:20 to 90:10 (Table 1, entries 8–10). Thirdly, the diastereoselectivity observed for the dipolar cycloaddition is strongly influenced by the size of the ester group in the dipolarophile. Thus, in the reaction of *N*-acryloyl proline benzyl ester **3a** with the imine **5** ($R^4 = R^5 = Ph$) the *endo* isomer **8e** was formed with a diastereomeric ratio of >99:1, whereas the analogous reaction employing proline methyl ester as chiral auxiliary yielded the *endo* cycloadduct **8k** with an isomeric ratio of only 85:15 (Table 1, entries 5 and 11). Deprotonation of the Schiff bases **5** with lithium diisopropylamide (LDA) resulted in the formation of complex product mixtures, which were not analyzed in detail. Also, the recommended[15] use of acetonitrile as solvent was not advantageous, since undesired side reactions

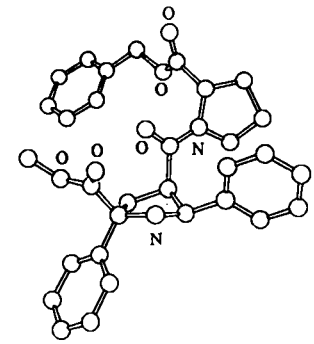


Fig. 1. Structure of the 1,3-dipolar cycloadduct **8e** determined by X-ray analysis (see the Experimental Procedure for details).

occurred under these conditions, and the stereoselectivity of the cycloaddition was lowered dramatically (for instance **8e** was formed in 77% yield with a diastereomeric ratio of 75:25 in acetonitrile at −40 °C, compared with a ratio of >99:1 in THF; Table 1, entry 5). When the less electrophilic *N*-methacroyl amide **3b** or the *N*-crotonoyl amide **3c** were employed as chiral dipolarophiles instead of the acrylamides **3a**, no cycloadducts could be detected.

In order to rationalize the almost total *endo/exo* selectivity and the excellent diastereofacial differentiation observed for the 1,3-dipolar cycloadditions of the α,β-unsaturated proline ester amides **3** with the metalated azomethine ylides **6**, we assume that the reaction proceeds preferentially via the highly ordered *endo* transition states **A** and **B** (Fig. 2). In both these transition states,

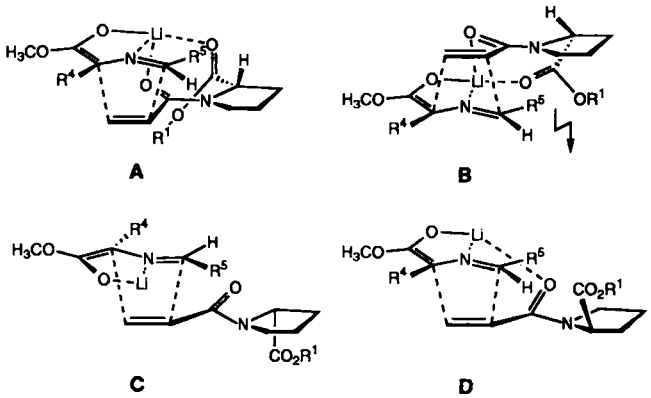
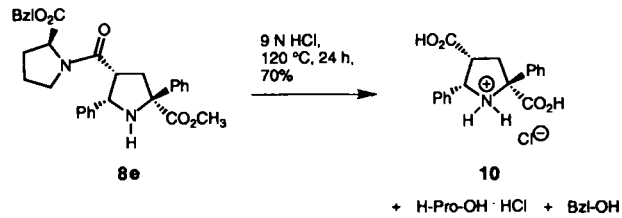


Fig. 2. Possible transition states in the 1,3-dipolar cycloadditions of *N*-acryloyl-(*S*)-proline esters **3** with *N*-metalated azomethine ylides **6**.

the lithium cation is coordinated to the ester enolate and the dipolarophile in such a way that a compact and efficient arrangement of the reaction partners results. If the 1,3-dipole had an *exo* orientation, like in transition state **C**, such double coordination would not be possible. To achieve a complexation of the lithium cation by the amide and the ester carbonyl group of the dipolarophile, the acrylamide must adopt the proposed *cis–anti* conformation depicted in **A**.[1,2] In the corresponding *cis–syn* conformation depicted in **D**, the dipoles of these two carbonyl groups would be oriented in an antiparallel and, consequently, electrostatically more favorable arrangement. However, the ester carbonyl function would then not be accessible to the cation for additional complexation.

The *endo* transition state **A** is energetically more favorable than **B**. In **B** the group R^5 of the dipole lies close to the ester function R^1 of the chiral auxiliary, whereas in **A** only interactions with the sterically less demanding α-hydrogen of the proline have to be considered. This mechanistic rationale explains the observation that the proline benzyl ester is a more efficient mediator of selectivity in the dipolar cycloadditions than the corresponding methyl ester. The methyl group is clearly sterically much less demanding than the benzyl group, so that the discriminating interaction is much more pronounced in the latter case, and a better differentiation between the two competing transition states **A** and **B** results. The model also accounts for the higher selectivity observed for aromatic (i.e., R^5 = aromatic) than for aliphatic imines (i.e., R^5 = aliphatic). Whereas the "rod-like" aromatic substituents must point directly towards the ester groups, aliphatic substituents have a higher flexibility and can adopt conformations in which the unfavorable steric interaction with the ester is less disturbing. However, this mechanistic picture does not explain the increase in the stereoselectivity with increasing steric demand of the amino acid side chain R^4.

The chiral auxiliary group could be removed from the cycloadducts **8** by simple acid hydrolysis. Thus, treatment of the pyrrolidine **8e** with 9 N HCl at elevated temperatures resulted in the simultaneous hydrolysis of the amide and the two ester groups (Scheme 4). The resulting proline could be recovered quantitatively, for instance, by chromatography. Attempts to cleave the amide bond to the proline by O-alkylation with an oxonium salt and subsequent hydrolysis of the resulting imidoester[1,2] or by enzymatic hydrolysis remained unsuccessful.



Scheme 4. Removal of the chiral auxiliary from the cycloadduct **8e**.

Enantiomerically pure pyrrolidine-2,4-dicarboxylic acids like **10** are not only attractive as congeners for the construction of more complex alkaloids,[1,2] they are also of great interest as candidates for pharmacological studies, since they may function as antagonists of the excitatory glutamic acid and also may be employed as tools for studying the glutamic acid receptor.[3]

Experimental Procedure

General: All melting points were recorded on a Büchi melting point apparatus and are uncorrected. Infrared spectra were measured with a Bruker IFS 88 spectrometer. Proton and carbon NMR spectra were measured on a Bruker AC-250 and a Bruker AM-400 spectrometer. Chemical shifts are expressed relative to tetramethylsilane as an internal standard. Specific optical rotation values were determined on a Perkin-Elmer polarimeter 241. Elemental analyses were performed on an Elementar CHN-Rapid analyzer. HPLC was performed on a Merck Hitachi instrument equipped with a L-3000 diode array detector, using a LiChrospher 100 RP 18 250 × 4 mm column, a LiChrospher 60 RP-select B 125 × 4 mm column, various mixtures of methanol/water (v/v), and a solvent flow-rate of 0.6 mL min^{-1}.

Materials: The preparation of α,β-unsaturated proline ester amides **3** is described in an earlier paper [12]. Triethylamine (dried over KOH pellets), diazabicyclo-[5.4.0]undec-7-ene (DBU, dried over molecular sieves) and lithium bromide are commercially available and were used without further purification. Tetrahydrofuran (THF) was distilled over potasssium immediately prior to use.

General Procedure for the Preparation of Imines 5 [13]: The aldehyde (1 mmol) was added to a solution of amino acid ester **4** (1 mmol) in CH_2Cl_2 (50 mL). The solution was stirred until water separated. After addition of $MgSO_4$ or molecular sieves stirring was continued for another 12 h. Filtration and washing of the dehydrating agent with CH_2Cl_2, followed by evaporation of the solvent in vacuo, afforded the imines as yellowish oils, which in the cases of aromatic aldehydes frequently crystallized. The Schiff bases were used directly in the 1,3-dipolar cycloaddition reactions without further purification.

General Procedure for the Preparation of Pyrrolidines 8a–8k: Triethylamine (4.8 mmol, 1.2 equiv) was slowly added at the temperature given in Table 1 to a solution of the imine **5** (4 mmol) and anhydrous LiBr (6 mmol, 1.5 equiv) in dry THF (100 mL). After 10 min *N*-acryloyl-(*S*)-proline ester **3** (4 mmol, 1 equiv) was added, and the solution was stirred under nitrogen (checked by TLC) for the time given in Table 1. The solvent was then evaporated. The residue was treated with a saturated aqueous solution of ammonium chloride (20 mL) and extracted with methylene chloride (3 × 50 mL). The combined extracts were dried with magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel with mixtures of EtOAc/*n*-hexane as eluent to give the pure diastereomers **8a–8k**. The diastereomeric ratios of the products were determined by HPLC for samples that were taken directly from the crude product mixtures. The reaction conditions as well as the results are listed in Table 1.

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***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-5-phenyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8a)**: M.p. 87 °C, $[\alpha]_D^{22} = -99.3$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.37-7.23$ (m, 10H; Ph), 5.07 (dd, $^2J(H,H) = 12.60$ Hz, 2H; CH_2-Ph), 4.38 (d, $^3J(H,H) = 7.20$ Hz, 1H; C*H*-NH), 4.03 (dd, $^3J(H,H) = 8.40$ Hz, $^3J(H,H) = 8.10$ Hz, 1H; CO_2Bzl-CH-N), 3.92 (dd, $^3J(H,H) = 9.36$ Hz, $^3J(H,H) = 9.12$ Hz, 1H; HN-C*H*-CO_2CH_3), 3.81 (s, 3H; OCH_3), 3.80 (s, 1H; NH), 3.37–3.30 (m, 2H; NCH_2), 2.82–2.74 (m, 1H; NCO-CH), 2.61–2.53 (m, 1H; NCO-CH-CH_2), 2.41–2.35 (m, 1H; NCO-CH-CH_2), 1.72–1.51 (m, 3H; CH-CH_2-CH_2), 1.24–1.15 (m, 1H; CH-CH_2-CH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 173.46$ (C=O), 171.87 (C=O), 171.01 (C=O), 137.99, 135.58, 128.31, 128.03, 127.98, 127.83, 127.03 (Ph), 67.08 (N-*C*-CO_2CH_3), 66.40 (CH_2-Ph), 60.12 (N-*C*H-CO_2Bzl), 58.25 (CH-NH), 52.04 (NCO-*C*H), 47.63 (OCH_3), 46.56 (NCH_2), 34.09 (NCO-CH-*C*H_2), 28.61 (CO_2Bzl-CH-*C*H_2), 24.03 (CH_2-CH_2-N). IR (KBr): $\tilde{\nu} = 3282$ (NH), 1740 (C=O), 1631 cm^{-1} (Ph); $C_{25}H_{28}N_2O_5$ (436.3): calcd C 68.79, H 6.47, N 6.42; found C 68.32, H 6.49, N 6.47.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-methyl-5-phenyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8b)**: Oil, $[\alpha]_D^{22} = -251.0$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.36-7.19$ (m, 10H; Ph), 5.07 (dd, $^2J(H,H) = 12.60$ Hz, 2H; CH_2-Ph), 4.52 (d, $^3J(H,H) = 6.60$ Hz, 1H; C*H*-NH), 4.07 (dd, $^3J(H,H) = 7.90$ Hz, $^3J(H,H) = 4.00$ Hz, 1H; CO_2Bzl-CH-N), 3.81 (s, 3H; OCH_3), 3.40–3.25 (m, 2H; NCH_2), 2.87 (dd, $^3J(H,H) = 1.90$ Hz, $^2J(H,H) = 13.80$ Hz, 1H; NCO-CH-CH_2), 2.73–2.66 (m, 1H; NCO-CH), 2.00 (dd, $^3J(H,H) = 7.30$ Hz, $^2J(H,H) = 13.80$ Hz, 1H; NCO-CH-CH_2), 1.69–1.54 (m, 3H; CH-CH_2-CH_2), 1.49 (s, 3H; HN-C-CH_3), 1.20–1.12 (m, 1H; CH-CH_2-CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 176.59$ (C=O), 171.90 (C=O), 170.95 (C=O), 135.74, 128.59, 128.38, 128.22, 128.10, 128.02, 127.92, 127.81, 127.11 (Ph), 66.33 (CH_2-Ph), 65.91 (N-*C*-CO_2CH_3), 65.79 (N-*C*H-CO_2Bzl), 58.30 (CH-NH), 52.34 (OCH_3), 49.13 (NCO-*C*H), 46.63 (NCH_2), 41.63 (NCO-CH-*C*H_2), 28.69 (CO_2Bzl-CH-*C*H_2), 27.77 (HN-C-*C*H_3), 24.09 (CH_2-CH_2-N). IR (KBr): $\tilde{\nu} = 3340$ (NH), 1739 (C=O), 1636 cm^{-1} (Ph); $C_{26}H_{30}N_2O_5$ (450.5): calcd C 69.32, H 6.71, N 6.22; found C 69.12, H 6.74, N 6.18.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-isopropyl-5-phenyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8c)**: M.p. 95° C, $[\alpha]_D^{22} = -128.0$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.39-7.19$ (m, 10H; Ph), 5.08 (dd, $^2J(H,H) = 12.60$ Hz, 2H; CH_2-Ph), 4.42 (d, $^3J(H,H) = 6.60$ Hz, 1H; C*H*-NH), 4.13 (dd, $^3J(H,H) = 8.10$ Hz, $^3J(H,H) = 4.10$ Hz, 1H; CO_2Bzl-CH-N), 3.80 (s, 3H; OCH_3), 3.27–3.21 (m, 2H; NCH_2), 2.79 (dd, $^3J(H,H) = 1.80$ Hz, $^2J(H,H) = 13.80$ Hz, 1H; NCO-CH-CH_2), 2.61–2.54 (m, 1H; NCO-CH), 2.16 (dd, $^3J(H,H) = 7.50$ Hz, $^2J(H,H) = 13.80$ Hz, 1H; NCO-CH-CH_2), 1.94 (sept, $^3J(H,H) = 6.60$ Hz, 1H; C*H*-$(CH_3)_2$), 1.66–1.49 (m, 3H; CH-CH_2-CH_2), 1.15–1.05 (m, 1H; CH-CH_2-CH_2), 1.02 (d, $^3J(H,H) = 6.60$ Hz, 3H; CH-$(CH_3)_2$), 0.92 (d, $^3J(H,H) = 6.60$ Hz, 3H; CH-$(CH_3)_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 176.60$ (C=O), 172.02 (C=O), 171.07 (C=O), 138.51, 135.69, 128.33, 128.12, 127.96, 127.93, 127.80, 127.09 (Ph), 73.43 (N-*C*-CO_2CH_3), 67.73 (N-*C*H-CO_2Bzl), 66.31 (CH_2-Ph), 58.11 (CH-NH), 52.09 (OCH_3), 49.39 (NCO-*C*H), 46.58 (NCH_2), 38.27 (NCO-CH-*C*H_2), 37.14 (*C*H-$(CH_3)_2$), 28.66 (CO_2Bzl-CH-*C*H_2), 23.99 (CH_2-CH_2-N), 18.38 (CH-*C*H_3), 17.37 (CH-*C*H_3). IR (KBr): $\tilde{\nu} = 3362$ (NH), 1733 (C=O), 1640 cm^{-1} (Ph); $C_{28}H_{34}N_2O_5$ (478.6): calcd C 70.27, H 7.16, N 5.85; found C 70.23, H 7.09, N 5.83.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-isobutyl-5-phenyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8d)**: M.p. 119 °C, $[\alpha]_D^{22} = -153.3$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.37-7.23$ (m, 10H; Ph), 5.09 (dd, $^2J(H,H) = 12.60$ Hz, 2H; CH_2-Ph), 4.45 (d, $^3J(H,H) = 6.60$ Hz, 1H; C*H*-NH), 4.12 (dd, $^3J(H,H) = 7.50$ Hz, $^3J(H,H) = 4.50$ Hz, 1H; CO_2Bzl-C*H*-N), 3.80 (s, 3H; OCH_3), 3.27–3.18 (m, 2H; NCH_2), 2.83 (dd, $^3J(H,H) = 1.60$ Hz, $^2J(H,H) = 13.80$ Hz, 1H; NCO-CH-CH_2), 2.63–2.55 (m, 1H; NCO-CH), 2.17 (dd, $^3J(H,H) = 7.50$ Hz, $^2J(H,H) = 13.80$ Hz, 1H; NCO-CH-CH_2), 1.71–1.54 (m, 3H; CH-CH_2-CH_2), 1.53–1.48 (m, 1H; C*H*-CH_2-CH_3), 1.47–1.40 (m, 1H; CH-CH_2-CH_3), 1.22–1.15 (m, 1H; CH-CH_2-CH_3), 1.14–1.05 (m, 1H; CH-CH_2-CH_2), 1.00 (d, $^3J(H,H) = 6.70$ Hz, 3H; CH-CH_3), 0.90 (t, $^3J(H,H) = 7.40$ Hz, 3H; CH_2-CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 187.53$ (C=O), 182.97 (C=O), 181.98 (C=O), 149.52, 146.65, 139.22, 139.05, 138.90, 138.84, 138.75, 138.06 (Ph), 84.78 (N-*C*-CO_2CH_3), 78.52 (N-CH-CO_2Bzl), 77.26 (CH_2-Ph), 69.07 (CH-NH), 62.98 (OCH_3), 60.29 (NCO-*C*H), 57.52 (NCH_2), 55.55 (*C*H-CH_3), 49.49 (NCO-CH-*C*H_2), 39.59 (CO_2Bzl-CH-*C*H_2), 35.93 (CH_2-CH_2-N), 34.95 (CH_2-CH_3), 24.59 (CH-*C*H_3), 23.53 (CH_2-*C*H_3). IR (KBr): $\tilde{\nu} = 3350$ (NH), 1734 (C=O), 1639 cm^{-1} (Ph); $C_{29}H_{36}N_2O_5$ (492.6): calcd C 70.71, H 7.37, N 5.69; found C 70.91, H 7.36, N 5.70.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2,5-diphenyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8e)**: M.p. 115 °C, $[\alpha]_D^{22} = -74.8$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.79-7.75$ (m, 2H; Ph), 7.38–7.23 (m, 13H; Ph), 5.10 (dd, $^2J(H,H) = 12.60$ Hz, 2H; CH_2-Ph), 4.36 (d, $^3J(H,H) = 7.02$ Hz, 1H; C*H*-NH), 4.05 (dd, $^3J(H,H) = 8.20$ Hz, $^3J(H,H) = 7.80$ Hz, 1H; CO_2Bzl-CH-N), 3.73 (s, 3H, OCH_3), 3.61 (s, 1H; NH), 3.33–3.25 (m, 3H; NCH_2, NCO-CH), 2.77–2.72 (m, 1H; NCO-CH-CH_2), 2.64–2.58 (m, 1H, NCO-CH-CH_2), 1.71–1.53 (m, 3H; CH-CH_2-CH_2), 1.25–1.14 (m, 1H; CH-CH_2-CH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 174.42$ (C=O), 171.96 (C=O), 170.89 (C=O), 143.43, 138.23, 135.68, 128.38, 128.14, 128.03, 127.95, 127.87, 127.21, 127.11, 126.63 (Ph), 72.08 (N-*C*-CO_2CH_3), 66.42 (CH_2-Ph), 65.60 (N-*C*H-CO_2Bzl), 58.31 (CH-NH), 52.71 (NCO-*C*H), 49.22 (OCH_3), 46.58 (NCH_2), 42.09 (NCO-CH-*C*H_2), 28.68 (CO_2Bzl-CH-*C*H_2), 24.09 (*C*H_2-CH_2-N). IR (KBr): $\tilde{\nu} = 3340$ (NH), 1734 (C=O), 1627 cm^{-1} (Ph); $C_{31}H_{32}N_2O_5$ (512.6): calcd C 72.64, H 6.29, N 5.46; found C 72.74, H 6.34, N 5.62.

Crystal data: $C_{31}H_{32}N_2O_5$, orthorhombic crystals, space group $P2_1/m$ (no. 11), with $a = 8.473(5)$, $b = 17.736(3)$, $c = 8.927(2)$ Å, $Z = 2$, $\beta = 95.32(1)$. 2807 reflections were measured (quadropole diffractometer Enraf-Nonius CAD4, $Mo_{K\alpha}$ radiation, graphite monochromator), of which 2717 were independent with $I > 2\sigma(I)$. The structure determination was carried out with direct methods (SHELX-76 and SHELX-93). $R = 0.0547$, $R_w = 0.0838$, $w = 1/(\sigma^2 F) + 0.0001\,F^2$. All C, N, and O atoms were anisotropically refined. The hydrogen atoms are found in the calculated sites with the appropriate isotropic temperature factors for CH, CH_2, CH_3, and phenyl H [16].

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-phenyl-5-*p*-nitrophenyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8f)**: M.p. 160 °C, $[\alpha]_D^{22} = -77.5$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.18-8.15$ (m, 2H; Ph), 7.73–7.69 (m, 2H; Ph), 7.53–7.49 (m, 2H; Ph), 7.39–7.27 (m, 8H; Ph), 5.09 (dd, $^2J(H,H) = 12.60$ Hz, 2H; CH_2-Ph), 4.48 (d, $^3J(H,H) = 7.27$ Hz, 1H; C*H*-NH), 4.02 (dd, $^3J(H,H) = 8.20$ Hz, $^3J(H,H) = 7.80$ Hz, 1H; CO_2Bzl-CH-N), 3.72 (s, 3H; OCH_3), 3.66 (s, 1H; NH), 3.48–3.36 (m, 2H; NCH_2), 3.30–3.26 (m, 1H; NCO-CH), 2.98–2.91 (m, 1H; NCO-CH-CH_2), 2.71–2.65 (m, 1H; NCO-CH-CH_2), 1.88–1.67 (m, 3H; CH-CH_2-CH_2), 1.47–1.40 (m, 1H; CH-CH_2-CH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 174.08$ (C=O), 171.54 (C=O), 170.22 (C=O), 147.25, 146.82, 142.64, 135.52, 128.41, 128.34, 127.89, 127.51, 126.30, 123.21 (Ph), 71.97 (N-*C*-CO_2CH_3), 66.57 (CH_2-Ph), 64.13 (N-*C*H-CO_2Bzl), 58.38 (CH-NH), 52.78 (NCO-*C*H), 48.44 (OCH_3), 46.80 (NCH_2), 41.51 (NCO-CH-*C*H_2), 28.74 (CO_2Bzl-CH-*C*H_2), 24.29 (CH_2-CH_2-N). IR (KBr): $\tilde{\nu} = 3346$ (NH), 1735 (C=O), 1635 (Ph), 1511, 1347 cm^{-1} (NO_2); $C_{31}H_{31}N_3O_7$ (557.6): calcd C 66.78, H 5.60, N 7.53; found C 66.91, H 5.63, N 7.46.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-phenyl-5-*p*-methoxyphenyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8g)**: M.p. 53 °C, $[\alpha]_D^{22} = -79.8$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.77-7.73$ (m, 2H; Ph), 7.38–7.22 (m, 10H; Ph), 6.84–6.81 (m, 2H; Ph), 5.11 (dd, $^2J(H,H) = 12.60$ Hz, 2H; CH_2-Ph), 4.32 (d, $^3J(H,H) = 7.00$ Hz, 1H; C*H*-NH), 4.08 (dd, $^3J(H,H) = 8.20$ Hz, $^3J(H,H) = 7.80$ Hz, 1H; CO_2Bzl-CH-N), 3.78 (s, 3H; OCH_3), 3.73 (s, 3H; OCH_3), 3.52 (s, 1H; NH), 3.33–3.25 (m, 3H; NCH_2, NCO-CH), 2.79–2.74 (m, 1H; NCO-CH-CH_2), 2.63–2.58 (m, 1H; NCO-CH-CH_2), 1.75–1.60 (m, 3H; CH-CH_2-CH_2), 1.30–1.22 (m, 1H; CH-CH_2-CH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 174.74$ (C=O), 172.23 (C=O), 171.19 (C=O), 159.43, 143.46, 135.86, 130.61, 128.59, 128.53, 128.32, 128.26, 128.13, 127.40, 126.85, 113.69 (Ph), 72.06 (N-*C*-CO_2CH_3), 66.71 (CH_2-Ph), 65.07 (N-*C*H-CO_2Bzl), 58.57 (CH-NH), 55.42 (NCO-*C*H), 52.93 (OCH_3), 49.31 (OCH_3), 46.78 (NCH_2), 42.07 (NCO-CH-*C*H_2), 28.97 (CO_2Bzl-CH-*C*H_2), 24.38 (CH_2-CH_2-N). IR (KBr): $\tilde{\nu} = 3330$ (NH), 1736 (C=O), 1636 cm^{-1} (Ph); $C_{32}H_{34}N_2O_6$ (542.6): calcd C 70.83, H 6.32, N 5.16; found C 70.40, H 6.51, N 4.98.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-phenyl-5-isopropyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8h)**: Oil, $[\alpha]_D^{22} = -50.6$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.74-7.70$ (m, 2H; Ph), 7.38–7.22 (m, 8H; Ph), 5.17 (s, 2H; CH_2-Ph), 4.52 (dd, $^3J(H,H) = 8.47$ Hz, $^3J(H,H) = 3.28$ Hz, 1H; CO_2Bzl-CH-N), 3.67–3.62 (m, 2H; NCH_2), 3.63 (s, 3H; OCH_3), 3.23 (s, 1H; NH), 3.08 (dd, $^3J(H,H) = 2.90$ Hz, $^2J(H,H) = 13.60$ Hz, 1H; NCO-CH-CH_2), 3.02–2.98 (m, 1H; NCO-CH), 2.76 (dd, $^3J(H,H) = 9.40$ Hz, $^3J(H,H) = 5.50$ Hz, 1H; C*H*-NH), 2.46 (dd, $^3J(H,H) = 7.70$ Hz, $^2J(H,H) = 13.40$ Hz, NCO-CH-CH_2), 2.17–2.14 (m, 1H; C*H*-$(CH_3)_2$), 2.06–1.93 (m, 4H; CH-CH_2-CH_2), 1.15 (d, $^3J(H,H) = 6.56$ Hz, 1H; CH-$(CH_3)_2$), 0.84 (d, $^3J(H,H) = 6.56$ Hz, 1H; CH-$(CH_3)_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 174.94$ (C=O), 173.54 (C=O), 172.44 (C=O), 144.96, 136.36, 129.20, 129.06, 128.90, 128.70, 128.64, 127.83, 127.57, 126.86 (Ph), 67.14 (N-*C*-CO_2CH_3), 59.12 (CH_2-Ph), 53.06 (CH-NH), 47.71 (NCH_2), 45.45 (NCO-CH-*C*H_2), 44.37 (NCO-*C*H), 29.90 (CO_2Bzl-CH-*C*H_2), 29.47 (CH-$(CH_3)_2$), 25.21 (CH_2-CH_2-N), 21.92 (CH-$(CH_3)_2$), 21.62 (CH-$(CH_3)_2$). IR (KBr): $\tilde{\nu} = 3325$ (NH), 1740 (C=O), 1636 cm^{-1} (Ph); $C_{28}H_{34}N_2O_5$ (478.6): calcd C 70.27, H 7.16, N 5.85; found C 70.14, H 7.13, N 5.93.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-phenyl-5-*t*-butyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8i)**: Oil, $[\alpha]_D^{22} = -42.5$ ($c = 2$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.76-7.73$ (m, 2H; Ph), 7.40–7.21 (m, 8H; Ph), 5.16 (dd, $^2J(H,H) = 12.30$ Hz, 2H; CH_2-Ph), 4.46 (dd, $^3J(H,H) = 8.77$ Hz, $^3J(H,H) = 3.59$ Hz, 1H; CO_2Bzl-CH-N), 3.63 (s, 3H; OCH_3), 3.62–3.59 (m, 2H; NCH_2), 3.10 (dd, $^3J(H,H) = 2.64$ Hz, $^2J(H,H) = 13.27$ Hz, 1H; NCO-CH-CH_2), 2.97–2.93 (m, 1H; NCO-CH), 2.83 (d, $^3J(H,H) = 2.64$ Hz, 1H; C*H*-NH), 2.29 (dd, $^3J(H,H) = 7.07$ Hz, $^2J(H,H) = 13.27$ Hz, 1H; NCO-CH-CH_2), 2.20–2.16 (m, 1H; CH-CH_2-CH_2), 2.07–1.94 (m, 3H; CH-CH_2-CH_2), 1.03 (s, 9H; CH-$(CH_3)_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 174.57$ (C=O), 173.69 (C=O), 171.90 (C=O), 145.01, 135.79, 128.93, 128.49, 128.18, 127.63, 126.98, 126.55, 126.19 (Ph), 72.63 (CO_2Bzl-*C*H-N), 71.62 (N-*C*-CO_2CH_3), 66.67 (CH_2-Ph), 58.90 (CH-NH), 52.56 (OCH_3), 47.26 (NCH_2), 44.90 (NCO-CH-CH_2), 43.96 (NCO-*C*H), 33.03

(*C*H-(CH$_3$)$_3$), 29.66 (CO$_2$Bzl-CH-*C*H$_2$), 28.04 (CH-(*C*H$_3$)$_3$), 24.67 (*C*H$_2$-CH$_2$-N). IR (KBr): $\tilde{\nu}$ = 3451 (NH), 1739 (C=O), 1634 (Ph), 1449 cm^{-1} (CH-(CH$_3$)$_3$); $C_{29}H_{36}N_2O_5$ (492.6): calcd C 70.72, H 7.37, N 5.69; found C 70.79, H 7.36, N 5.76.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2-phenyl-5-*n*-propyl-4-pyrrolidinoyl]-(*S*)-proline benzyl ester (8j)**: Oil, $[\alpha]_D^{22} = -25.6$ (c = 2, in CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 7.70–7.66 (m, 2H; Ph), 7.39–7.22 (m, 8H; Ph), 5.17 (dd, ^2J(H,H) = 12.36 Hz, 2H; CH$_2$-Ph), 4.54 (dd, ^3J(H,H) = 8.48 Hz, ^3J(H,H) = 3.69 Hz, 1H; CO$_2$Bzl-CH-N), 3.66 (s, 3H; OCH$_3$), 3.46–3.41 (m, 1H; C*H*-NH), 3.29–3.24 (m, 1H; NCO-CH), 3.08–3.02 (m, 2H; NCH$_2$), 2.51 (dd, ^3J(H,H) = 9.23 Hz, ^2J(H,H) = 15.12 Hz, 1H; NCO-CH-C*H*$_2$), 2.23–2.13 (m, 2H; NCO-C*H*-CH$_2$, CO$_2$Bzl-CH-C*H*$_2$), 2.07–1.91 (m, 3H; CO$_2$Bzl-CH-C*H*$_2$-C*H*$_2$), 1.61–1.48 (m, 2H; C*H*$_2$-CH$_2$-CH$_3$), 1.46–1.33 (m, 2H; CH$_2$-C*H*$_2$ CH$_3$), 0.93 (t, ^3J(H,H) = 7.08 Hz, 3H; CH$_2$-CH$_2$-C*H*$_3$). ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 174.75 (C=O), 172.07 (C=O), 172.01 (C=O), 143.54, 135.77, 128.70, 128.53, 128.19, 128.10, 127.17, 126.48, 126.35, 126.18 (Ph), 71.56 (N-*C*-CO$_2$CH$_3$), 66.74 (CH$_2$-Ph), 60.73 (CO$_2$Bzl-*C*H-N), 58.70 (CH-NH), 52.68 (OCH$_3$), 47.26 (NCH$_2$), 46.34 (NCO-*C*H), 41.97 (NCO-CH-*C*H$_2$), 33.52 (CH$_2$-CH$_2$-CH$_3$), 29.15 (CO$_2$Bzl-CH-*C*H$_2$), 24.76 (*C*H$_2$-CH$_2$-N), 20.62 (CH$_2$-*C*H$_2$-CH$_3$), 14.18 (CH$_2$-CH$_2$-*C*H$_3$). IR (KBr): $\tilde{\nu}$ = 3324 (NH), 1739 (C=O), 1639 cm^{-1} (Ph); $C_{28}H_{34}N_2O_5$ (478.6): calcd C 70.27, H 7.16, N 5.86; found C 70.62, H 7.13, N 5.93.

***N*-[(2*S*,4*R*,5*S*)-2-Carboxymethyl-2,5-diphenyl-4-pyrrolidinoyl]-(*S*)-proline methyl ester (8k)**: M.p. 49 °C, $[\alpha]_D^{22} = -70.3$ (c = 2, in CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 7.77–7.75 (m, 2H; Ph), 7.38–7.26 (m, 8H; Ph), 4.36 (d, ^3J(H,H) = 7.05 Hz, 1H; C*H*-NH), 3.96 (dd, ^3J(H,H) = 8.20 Hz, ^3J(H,H) = 4.70 Hz, 1H; CO$_2$CH$_3$-C*H*-N), 3.73 (s, 3H, OCH$_3$), 3.68 (s, 1H, OCH$_3$), 3.33–3.26 (m, 3H; NCH$_2$, NCO-CH), 2.79–2.75 (m, 1H; NCO-CH-C*H*$_2$), 2.67–2.61 (m, 1H, NCO-CH-C*H*$_2$), 1.71–1.57 (m, 3H; CH-C*H*$_2$-C*H*$_2$), 1.28–1.20 (m, 1H; CH-CH$_2$-C*H*$_2$). ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 175.05 (C=O), 173.95 (C=O), 171.54 (C=O), 143.87, 138.93, 129.03, 128.80, 128.59, 127.88, 127.79, 127.44, 127.29 (Ph), 72.66 (HN-*C*-CO$_2$CH$_3$), 66.12 (CO$_2$CH$_3$-*C*H-CH$_2$), 58.83 (CH-NH), 53.35 (OCH$_3$), 52.60 (NCO-*C*H), 49.81 (OCH$_3$), 47.22 (NCH$_2$), 42.64 (NCO-CH-*C*H$_2$), 29.36 (CO$_2$CH$_3$-CH-*C*H$_2$), 24.78 (*C*H$_2$-CH$_2$-N). IR (KBr): $\tilde{\nu}$ = 3350 (NH), 1739 (C=O), 1636 cm^{-1} (Ph); $C_{25}H_{28}N_2O_5$ (512.6): calcd C 68.79, H 6.47, N 6.42; found C 68.38, H 6.59, N 6.49.

General Procedure for the Removal of the Chiral Auxiliary: A solution of the cycloadduct **8e** (512 mg, 1.0 mmol) in 9 N HCl (30 mL) was heated at 120 °C for 24 h. After cooling to room temperature, the excess solvent was removed in vacuo, and the mixture was separated by flash chromatography (CH$_2$Cl$_2$/MeOH 15/1) to yield 243.6 mg (70%) of enantiomerically pure pyrrolidine-2,4-dicarboxylic acid **10**.

(2*S*,4*R*,5*S*)-2,4-Dicarboxy-2,5-diphenylpyrrolidine hydrochloride (10): M.p 280 °C, $[\alpha]_D^{22} = +32.4$ (c = 1, in CH$_3$OH); ^{1}H NMR (400 MHz, D$_2$O, 25 °C, TMS): δ = 7.62–7.38 (m, 10H; Ph), 4.96 (d, ^3J(H,H) = 7.50 Hz, 1H; C*H*-NH), 3.68–3.62 (m, 1H, C*H*-CH$_2$), 3.29 (dd, ^3J(H,H) = 8.70 Hz, ^2J(H,H) = 11.40 Hz, 1H; CH-C*H*$_2$), 2.97 (dd, ^3J(H,H) = 6.00 Hz, ^2J(H,H) = 11.40 Hz, 1H; CH-C*H*$_2$). ^{13}C NMR (100.6 MHz, D$_2$O, 25 °C, TMS): δ = 179.15 (C=O), 176.43 (C=O), 137.58, 133.78, 130.76, 130.50, 130.13, 129.62, 129.05, 127.64, 127.17 (Ph), 75.95 (N-*C*-CO$_2$H) 64.25 (HN-CH), 50.85 (*C*H-CH$_2$), 39.92 (CH-*C*H$_2$). IR (KBr): $\tilde{\nu}$ = 1734 (C=O), 1645 cm^{-1} (Ph); $C_{18}H_{18}NO_4Cl$ (347.8): calcd C 62.16, H 5.22, N 4.03; found C 62.38, H 5.27, N 4.09.

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[16] Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (Germany) on quoting the depository number CSD-58112.