Synthetic Studies on L-Proline and (4*R*)-Hydroxy-L-proline Derivatives

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Abstract: The preparation of a number of L-proline and (4*R*)-hydroxy-L-proline derivatives to assess their enantioselectivity when applied to several techniques and experimental conditions is described. All the derivatives prepared incorporated at least one 3,5-disubstituted aromatic ring that contained nitro, chloro or methyl groups and were obtained by classical methods. In spite of the difficulties that arise from the presence of rotational isomers in most cases, the compounds studied are fully described by their ^{1}H and ^{13}C NMR spectra.

Key words: amino acids, enantiomeric resolution, chirality, L-proline derivatives, chiral selectors

Introduction

Natural and synthetic enantiomerically pure α-amino acids have been extensively used as chiral moieties in the preparation of chiral selectors for the separation of enantiomers. In particular, multiple interaction chiral stationary phases (CSPs) for HPLC, also known as brush-type phases or 'Pirkle phases', have chiral selectors of this kind.[1,2] The structural simplicity of these chiral selectors facilitates their modification in order to assess the effect of structural changes on enantioselectivity.

L-Proline derivatives have been mostly used as chiral moiety in the so-called 'ligand-exchange' CSPs.[3] However, their applications as multiple interaction CSPs in chiral liquid chromatography are few,[4–9] although high enantioselectivity is sometimes attained for certain enantiomeric mixtures.[7] L-Proline derivatives have also been used as chiral selectors for chiral gas chromatography,[10] chiral countercurrent chromatography (CCC),[11] capillary electrophoresis[12] or as chiral ligands for enantioselective catalytic reactions.[13] In this context, in our laboratory, the preparation of chiral selectors derived from L-proline to be used not only in CSPs for HPLC but also in CCC, enantioselective liquid membranes or as chiral solvating agents in NMR has been undertaken.

Structural modifications on the chiral selectors have been proposed either to adapt them to the intrinsic characteristics of the technique or to improve enantioselectivity. Thus, on the one hand, to tune lipophilicity while simultaneously maintaining the same chiral structure, several selectors have been prepared from the same chiral entity. On the other hand, the establishment of a second π-π interaction was considered to reinforce the association between chiral selector and enantiomers. Thus, two aromatic rings were introduced in a number of selectors (Figure 1). The presence of aromatic rings of distinct character (π-donor/π-acceptor) in the same selector was also considered in order to enlarge their application domain.

A third reacting point is required on the chiral selector to fix it on the chromatographic matrix and to test its enantioselectivity in CSPs for HPLC. (4*R*)-Hydroxy-L-proline was then used as the basic scaffold. The three functions of this hydroxy amino acid allow the introduction of the two aromatic rings previously mentioned and the fixation of the selector through the third function (Figure 2).

The enantioselectivity of doubly derivatized chiral selectors can also be studied in solution (CCC[14] or NMR). Some selectors derivatized in the three functions have also been prepared for this purpose. Here we address the synthesis and spectroscopic characterization of these L-proline derivatives (Figure 1).

Results and Discussion

N-Acyl Derivatives of L-Proline and (4R)-Hydroxy-L-proline

General methods were applied to prepare the L-proline and (4*R*)-hydroxy-L-proline derivatives. The acylation of the amino group of amino acids with the corresponding acyl chloride in basic aqueous media was first described by Saunders[15,16] for the preparation of 3,5-dinitrobenzoyl derivatives of amino acids. The same method has been used as a general procedure for the preparation of *N*-acyl derivatives of L-proline[3,9] and other amino acids.[17,18] The *N*-acyl derivatives of L-proline and (4*R*)-hydroxy-L-proline were obtained in moderate yields by this method (Scheme 1). The use of an excess of the acyl chloride in the reaction with (4*R*)-hydroxy-L-proline to obtain *N*,*O*-diacylated derivatives yielded only the corresponding *N*-acyl derivative. The formation of the *O*-acyl derivative was not observed in any case.

The reaction of *N*-acyl-L-proline derivatives with the appropriate amine in the presence of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) as a coupling agent[19] yielded the corresponding *N*-acyl-L-prolinamides (Scheme 1). The standard procedure (Method A) was used in most cases. However, the characteristics of some

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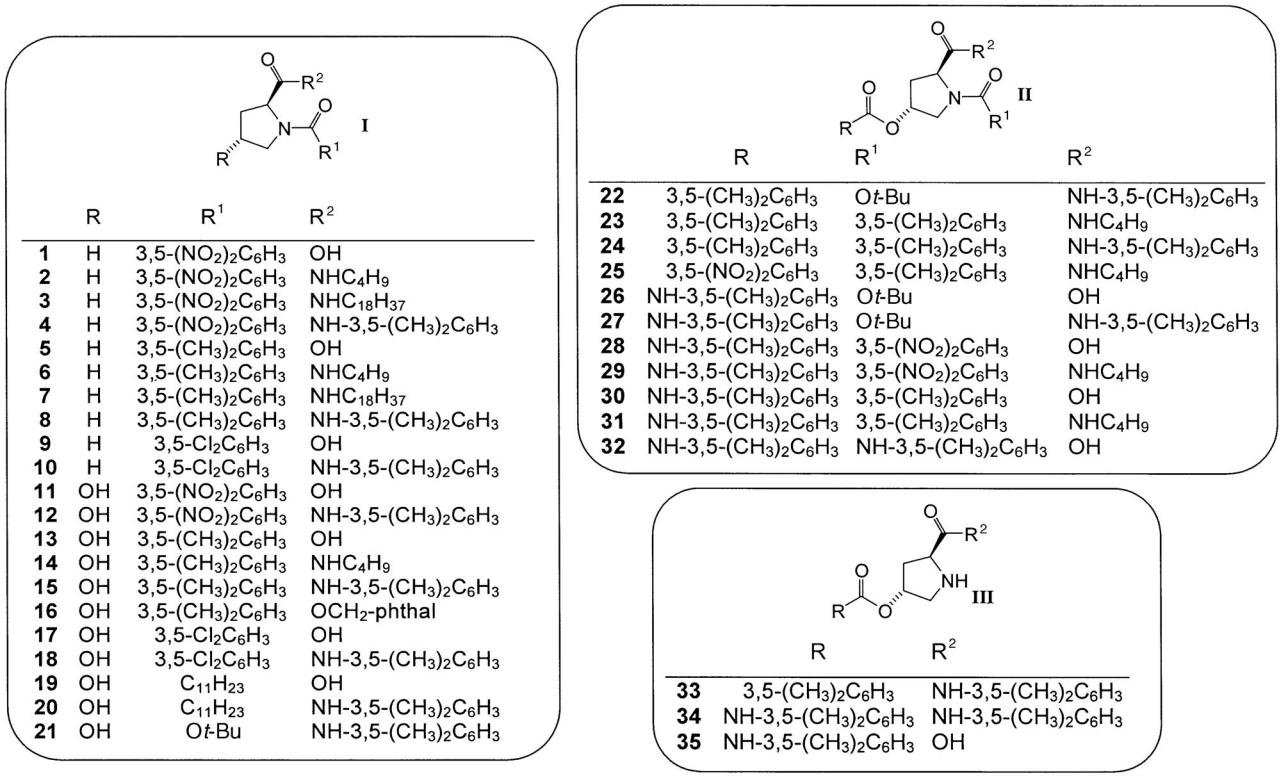


	R	R^1	R^2
1	H	3,5-$(NO_2)_2C_6H_3$	OH
2	H	3,5-$(NO_2)_2C_6H_3$	NHC_4H_9
3	H	3,5-$(NO_2)_2C_6H_3$	$NHC_{18}H_{37}$
4	H	3,5-$(NO_2)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
5	H	3,5-$(CH_3)_2C_6H_3$	OH
6	H	3,5-$(CH_3)_2C_6H_3$	NHC_4H_9
7	H	3,5-$(CH_3)_2C_6H_3$	$NHC_{18}H_{37}$
8	H	3,5-$(CH_3)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
9	H	3,5-$Cl_2C_6H_3$	OH
10	H	3,5-$Cl_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
11	OH	3,5-$(NO_2)_2C_6H_3$	OH
12	OH	3,5-$(NO_2)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
13	OH	3,5-$(CH_3)_2C_6H_3$	OH
14	OH	3,5-$(CH_3)_2C_6H_3$	NHC_4H_9
15	OH	3,5-$(CH_3)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
16	OH	3,5-$(CH_3)_2C_6H_3$	OCH_2-phthal
17	OH	3,5-$Cl_2C_6H_3$	OH
18	OH	3,5-$Cl_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
19	OH	$C_{11}H_{23}$	OH
20	OH	$C_{11}H_{23}$	NH-3,5-$(CH_3)_2C_6H_3$
21	OH	O*t*-Bu	NH-3,5-$(CH_3)_2C_6H_3$

	R	R^1	R^2
22	3,5-$(CH_3)_2C_6H_3$	O*t*-Bu	NH-3,5-$(CH_3)_2C_6H_3$
23	3,5-$(CH_3)_2C_6H_3$	3,5-$(CH_3)_2C_6H_3$	NHC_4H_9
24	3,5-$(CH_3)_2C_6H_3$	3,5-$(CH_3)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
25	3,5-$(NO_2)_2C_6H_3$	3,5-$(CH_3)_2C_6H_3$	NHC_4H_9
26	NH-3,5-$(CH_3)_2C_6H_3$	O*t*-Bu	OH
27	NH-3,5-$(CH_3)_2C_6H_3$	O*t*-Bu	NH-3,5-$(CH_3)_2C_6H_3$
28	NH-3,5-$(CH_3)_2C_6H_3$	3,5-$(NO_2)_2C_6H_3$	OH
29	NH-3,5-$(CH_3)_2C_6H_3$	3,5-$(NO_2)_2C_6H_3$	NHC_4H_9
30	NH-3,5-$(CH_3)_2C_6H_3$	3,5-$(CH_3)_2C_6H_3$	OH
31	NH-3,5-$(CH_3)_2C_6H_3$	3,5-$(CH_3)_2C_6H_3$	NHC_4H_9
32	NH-3,5-$(CH_3)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$	OH

	R	R^2
33	3,5-$(CH_3)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
34	NH-3,5-$(CH_3)_2C_6H_3$	NH-3,5-$(CH_3)_2C_6H_3$
35	NH-3,5-$(CH_3)_2C_6H_3$	OH

Figure 1 L-Proline and (4*R*)-hydroxy-L-proline derivatives.

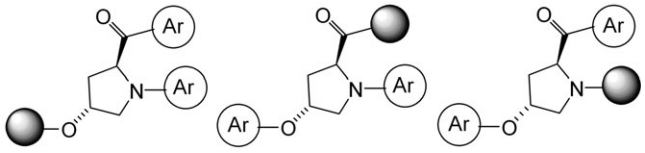
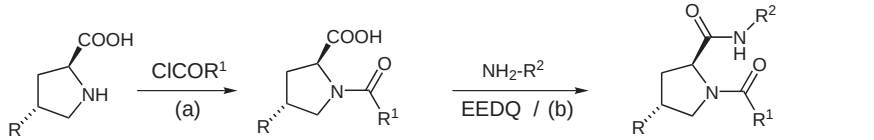


Figure 2 Possibilities to graft chiral selectors derived from (4*R*)-hydroxy-L-proline onto the chromatographic matrix.

compounds led us to modify the reaction conditions. Thus, the lack of reactivity of **11** in dichloromethane was attributed to the low solubility of this compound in the solvent. The use of DMF as a solvent allowed us to obtain the amide **12**. Nevertheless, the yield was low (27%) after 17 hours of reaction and only after 70 hours of reaction was a maximum yield of 72% attained. The preparation of **14** required the addition of methanol as a cosolvent in the reaction. In this case, the lack of solubility of the salt formed between the acid **13** and *n*-butylamine at the beginning of the reaction prevented the formation of the desired amide **14** when methanol was not added.

As usual in *N*-acylproline derivatives,[20] the rotation of the *N*-acyl bond is restricted in all the compounds prepared. This restriction resulted either in the duplicity of peaks both in ^1H and ^{13}C NMR spectra or in the broadening of signals in which coupling constants were hardly measurable for most of these compounds. Two-dimensional ^1H-^1H and ^1H-^{13}C correlation spectra were recorded when necessary to correctly assign signals to the two rotational isomers. The relative population of rotational isomers depends on substitution. Thus, while the rotamer assigned as *s-cis* was hardly detectable for certain *N*-(3,5-dimethylbenzoyl), *N*-(3,5-dichlorobenzoyl) and *N*-docecanoyl derivatives (up to 10–15%, calculated on ^1H NMR spectra using deuterated chloroform as solvent), *N*-(3,5-dinitrobenzoyl) derivatives showed populations up to 30% of this minor rotational isomer either in chloroform or in



R: H Pro
R: OH HPro

N-acyl-L-proline derivatives
(**1**, **5**, **9**, **11**, **13**, **17** and **19**)

N-acyl-L-prolinamide derivatives
(**2**-**4**, **6**-**8**, **10**, **12**, **14**, **15**, **18** and **20**)

Scheme 1 *Conditions*: (a) 1 N NaOH, 0 °C; (b) CH_2Cl_2 (DMF for **12** and CH_2Cl_2–MeOH for **14**).

methanol. In compounds containing a *N*-boc group, two singlets (relative integration: 1:1.4) were usually observed when spectra were acquired at room temperature. These singlets collapsed into a single signal when the temperature increased to 70 °C.

The lipophilicity of compounds **2**–**4** and **6**–**8** was comparatively estimated on the basis of a TLC essay on silica gel. When eluting with ethyl acetate, the R_f for these compounds were almost homogeneously distributed within the range from 0.60 to 0.40, and provided an interesting series of chiral selectors with the same chiral scaffold and distinct lipophilicity. The *N*′-(3,5-dimethylphenyl)-L-prolinamides **4** and **8** were the most lipophilic and the *N*′-butyl-L-prolinamides **2** and **6** were the most polar compounds in that group. In all cases, the *N*-(3,5-dinitrobenzoyl) derivatives were more lipophilic than their *N*-(3,5-dimethylbenzoyl) counterparts.

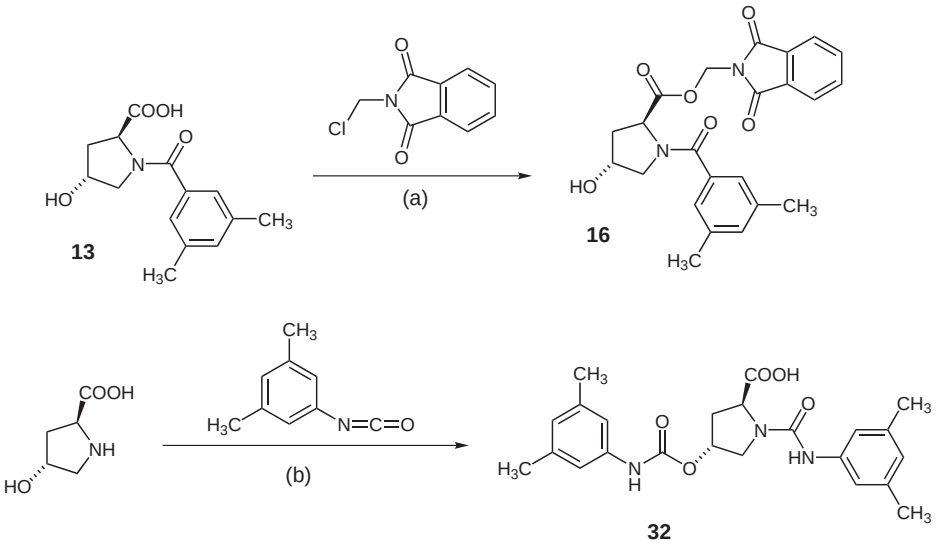
Attempts to Obtain O-Acyl Derivatives of (4R)-Hydroxy-L-proline

The preparation of *N*-acetyl-*O*-benzoyl-L-hydroxyproline and its *O*-debenzoylated analogue has been described.[21] The lability of *O*-acyl derivatives of hydroxyl amino acids, such as hydroxyproline and serine under mild basic conditions, can be deducted from this study. The absence of *O*-acyl derivative in the direct acylation of hydroxyproline with acyl halides can be attributed to this lability, which may be related to the presence of the free carboxylic acid. Thus, to obtain chiral selectors with the carboxyl group free to be grafted onto the chromatographic matrix, the phthalimidomethyl group was chosen as a protecting group removable in mild acidic conditions. Although the protection of carboxylic acids with this group in free amino acids has been reported,[22] the direct protection of (4*R*)-hydroxy-L-proline by the reaction with phthalimidomethyl chloride was not possible. However, a moderate yield of **16** was obtained from the *N*-acyl derivative **13** (Scheme 2). The *O*-acylation of derivative **16** was then attempted in biphasic Schotten–Baumann conditions or in refluxing pyridine, but without success. The starting product was recovered in all assays. At this point, taking into account the chemical stability required for a compound used as a chiral selector, the carbamate function was considered in the derivatization of the hydroxyl group.

O-(3,5-Dimethylphenylaminocarbonyl) Derivatives of (4R)-Hydroxy-L-proline

The direct double derivatization of (4*R*)-hydroxy-L-proline with 3,5-dimethylphenyl isocyanate was carried out in anhydrous pyridine (Scheme 2). Compound **32** was obtained in 78% yield after purification by crystallization. Most of the (4*R*)-hydroxy-L-proline derivatives prepared showed six separate signals for the six protons of the pyrrolidine ring. However, usually it was not possible to measure the complete set of coupling constants. In this context, compound **32** was an exception. The clear coupling pattern for the cycloaliphatic protons of this compound allowed the unequivocal direct assignment of each signal in the monodimensional ^{1}H NMR spectrum (200 MHz) (Figure 3).

Compounds mono-derivatized with 3,5-dimethylphenyl isocyanate were obtained from the N-protected amino acid (Scheme 3). Thus, compound **26** is a key intermediate in the synthesis of chiral selectors that have either the carboxy (**28**, **30**) or the amino groups (**34**) free to be bonded to the chromatographic matrix. Compound **26** was first obtained from commercially available dicyclohexylammonium *N-tert*-butoxycarbonyl-(4*R*)-hydroxy-L-prolinate. Because of the interference of dicyclohexylamine present in the reaction as a counter-ion in the starting product, an excess of 3.5 equivalents of 3,5-dimethylphenyl isocyanate was determined as the optimum ratio of reagents for the reaction. In these conditions, **26** was obtained in 45% yield. The reaction was not improved ei-



Scheme 2 *Conditions*: (a) DMSO, 70 °C; (b) pyridine, 115 °C.

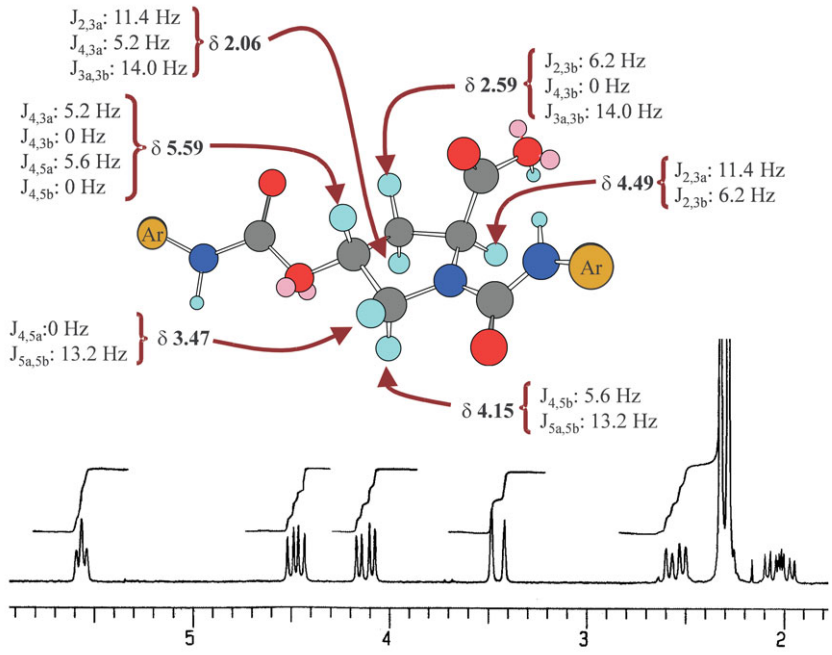
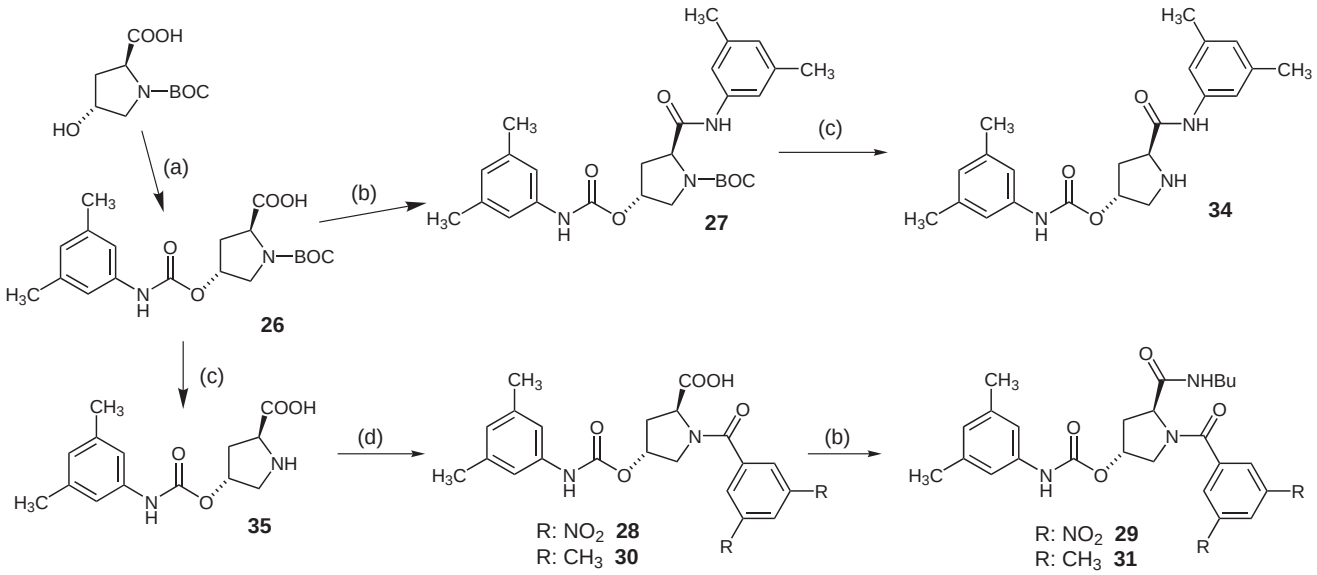


Figure 3 Full assignment of pyrrolidine proton signals in the ^{1}H NMR spectra of **32**.

ther by using DMF as a nonbasic polar solvent or by adding dibutyltin dilaurate, a catalyst in the preparation of carbamates.[23,24] Only *N*,*N*′-bis(3,5-dimethylphenyl)urea from the decomposition of the isocyanate during the workup procedure, and *N*-(3,5-dimethylphenyl)-*N*′,*N*′-dicyclohexylurea, from the reaction of the latter with dicyclohexylamine were obtained when DMF was used. No increase in the yield of **26** was detected when using the catalyst. The commercialization of the free *N*-boc-protected amino acid allowed us to use it as starting material. In this case, the amount of 3,5-dimethylphenyl isocyanate used was reduced to 1.5 equivalents with respect to the amino acid and the yield in **26** increased up to 90%.

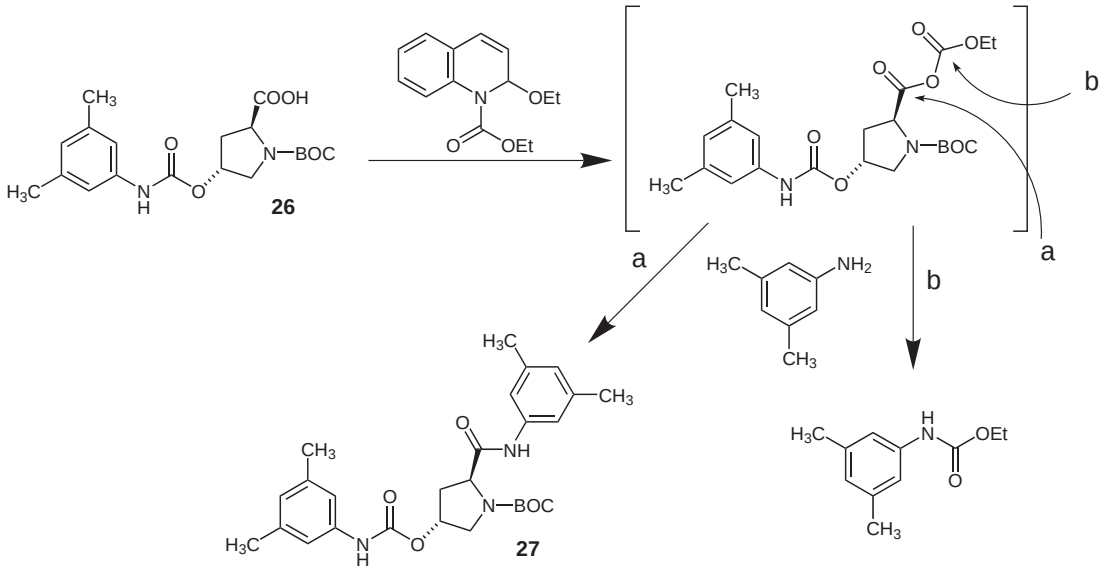
The derivatization of the carboxy group of **26** by reaction with 3,5-dimethylaniline in the presence of EEDQ yielded **27**. In the same reaction, ethyl *N*-(3,5-dimethylphenyl)carbamate was isolated. The detection of ethyl *N*-(2-thiazolyl)carbamate as a by-product in the formation of an amide link has been reported when using EEDQ.[25] However, although these authors propose a direct reaction between the amine and the coupling agent, we suggest that in our case this product results from the reaction of the



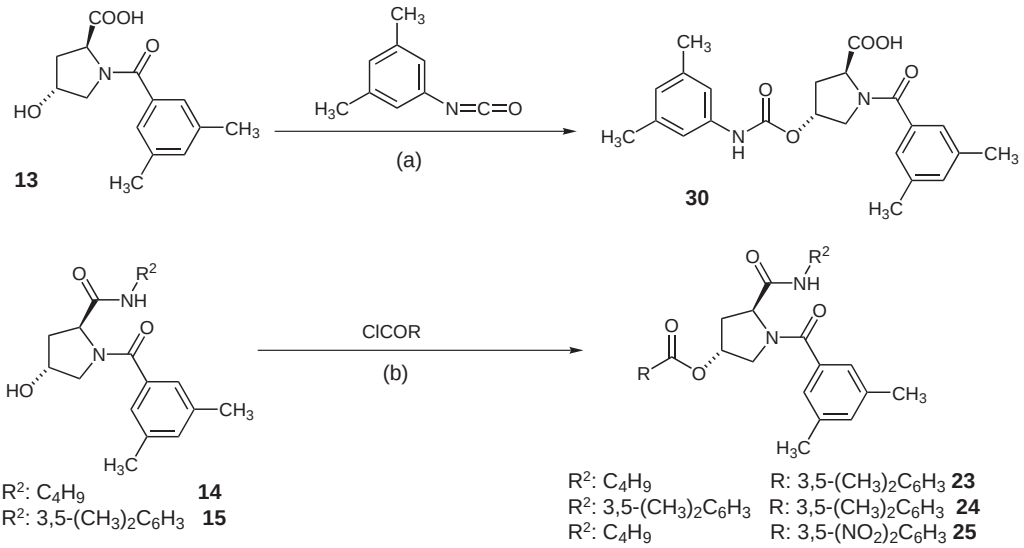
Scheme 3 *Reagents and conditions*: (a) 3,5-$Me_2C_6H_3NCO$, pyridine, 115 °C; (b) RNH_2, EEDQ, CH_2Cl_2, r.t.; (c) TFA/CH_2Cl_2 (30:70), r.t.; (d) 3,5-$R_2C_6H_3COCl$, 1 N NaOH, 0 °C.

aniline on the carbonate intermediate when EEDQ is used as coupling agent (Scheme 4). The steric hindrance caused by the *tert*-butoxycarbonyl group promotes the formation of this by-product. This mechanism explains the absence of the same by-product when using 3,5-dimethylaniline and EEDQ on other substrates. The steric hindrance between the *tert*-butoxycarbonyl group and the dimethylphenyl group in **27** can also be seen in the ^{1}H NMR spectrum, which particularly lacked resolution for this compound in $CDCl_3$ at room temperature. When pyridine-d_5 was used as solvent instead of $CDCl_3$ all signals in the ^{1}H NMR spectrum were duplicated. The same spectrum recorded at 70 °C showed single broad absorptions. The removal of the *N*-*tert*-butoxycarbonyl group with TFA produced **34** in a high yield.

The removal of the protecting group on **26**, followed by the reaction with the appropriate acyl chloride, yielded the acids **28** and **30**, but only in moderate to low yields. Alternatively, **30** was obtained from **13** by reaction with 3,5-dimethylphenyl isocyanate (Scheme 5). This alternative route allowed the preparation of **30** from (4*R*)-hydroxy-L-proline with a higher global yield (39% *versus* 10%). However, it was not possible to obtain **28** from **11** by the analogous reaction. Compound **28** was not detectable in the complex mixture resulting from the treatment of **11** with 3,5-dimethylphenyl isocyanate. Compounds **28** and **30** were further derivatized by the reaction with *n*-butylamine. Amides **29** and **31**, respectively, were obtained in moderate yields.



Scheme 4



Scheme 5 *Conditions*: (a) pyridine, 115 °C; (b) 2 N NaOH/$CHCl_3$ (20:80), r.t.

O-Acyl Derivatives of (4R)-Hydroxy-L-proline

Further derivatization can be introduced on compounds which still have a free hydroxyl group. Thus, the reaction of **14** and **15** with the appropriate acyl chloride under biphasic Schotten–Baumann conditions yielded **23**, **24**, and **25** (Scheme 5). The preparation of **23** or **24** from **14** confirms the involvement of the free acid in the lability of the ester function on position 4, since the reversal order of derivatization does not allow to obtain the doubly acylated compounds. However, in spite of the several reaction conditions tested, it was not possible to obtain the corresponding *O*-acyl derivatives from **20**.

The preparation of *O*-acyl derivatives was also possible from *N*-boc-(4*R*)-hydroxy-L-proline by the reversal of derivatization order relating to the preparation of **34** (Scheme 6). Thus, **21** was successfully obtained in a high yield by coupling of 3,5-dimethylaniline on the amino acid. The formation of ethyl 3,5-dimethylphenylcarbamate as a by-product in this reaction was also detected. The ester **22** was prepared satisfactorily by the *O*-acylation of **21**. However, it was not possible to obtain the 3,5-dinitrobenzoyl derivative of **21** when using 3,5-dinitrobenzoyl chloride, in spite of the diverse reaction conditions tested. As in the case of **27**, the slow molecular mobility in the NMR time scale for **22** resulted in spectra that lacked resolution at room temperature. The removal of the *N*-protecting group of this compound with TFA under the same conditions used for **26** and **27** allowed us to obtain the amine **33** in a high yield.

All organic solutions were dried over Na_2SO_4. ^1H and ^{13}C NMR spectra were recorded either on a Varian Gemini-200 instrument, a Varian Gemini-300, a Varian Mercury 400 or a Varian VXR500. The field of the instrument used is indicated in each case. Chemical shifts are quoted in δ values downfield from TMS, and *J* values are given in Hz. All melting points are uncorrected. Optical rotation values were determined in a Perkin-Elmer 241 polarimeter. Elemental analyses were performed on a CE Instruments apparatus Mod. EA 1108 (Carlo Erba Instruments, Milan, Italy) using standard conditions by the Serveis Científico-Tècnics de la Universitat de Barcelona (Spain).

N-Acyl Derivatives of L-Proline and (4*R*)-Hydroxy-L-proline; General Procedure (Scheme 1)

Following the method described,[16] the corresponding amino acid L-proline or (4*R*)-hydroxy-L-proline (8.7 mmol) was dissolved in aq 1 N NaOH (10 mL) and cooled in an ice-bath. The appropriate acyl chloride (9.6 mmol) and aq 1 N NaOH (15 mL) were added separately and simultaneously over 20 min. The solution was stirred at r.t. for 90 min and acidified with conc. HCl (pH 2–3).

N-(3,5-Dinitrobenzoyl)-L-proline (1)

The precipitate obtained was collected by filtration and crystallized from 96% EtOH; yield: 83%; mp 176–177 °C (Lit.[4] mp 177 °C); $[\alpha]_D^{20}$ –89.4 (*c* = 1, abs EtOH) [Lit.[4] $[\alpha]_D^{25}$ –91.0 (*c* = 1, abs EtOH)].

^1H NMR (500 MHz, $CDCl_3/CD_3OD$): δ = 1.94 (m, 1 H, C^4H_a), 2.03 (m, C^4H_2, *s-cis*), 2.07 (m, 1 H, C^4H_b), 2.12 (m, 1 H, C^3H_a), 2.20 (m, C^3H_a, *s-cis*), 2.25 (m, C^3H_b, *s-cis*), 2.34 (m, 1 H, C^3H_b), 3.47 (m, 1 H, C^5H_a), 3.62 (m, 1 H, C^5H_b), 3.85 (m, C^5H_2, *s-cis*), 4.38 (dd, C^2H, *s-cis*), 4.62 (dd, 1 H, *J* = 5, 8.5 Hz, C^2H), 8.56 (d, $C^{2',6'}H$, *s-cis*), 8.72 (d, 2 H, $C^{2',6'}H$), 8.99 (t, $C^{4'}H$, *s-cis*), 9.05 (t, 1 H, $C^{4'}H$).

^{13}C NMR (75.5 MHz, $CDCl_3/CD_3OD$): δ = 22.3 (C^4H_2, *s-cis*), 25.1 (C^4H_2), 29.1 (C^3H_2), 31.1 (C^3H_2, *s-cis*), 47.0 (C^5H_2, *s-cis*), 49.9 (C^5H_2), 59.5 (C^2H), 61.3 (C^2H, *s-cis*), 119.5 ($C^{4'}H$, *s-cis*), 119.9 ($C^{4'}H$), 127.0 ($C^{2',6'}H$, *s-cis*), 127.4 ($C^{2',6'}H$), 139.0 ($C^{1'}$), 139.9 ($C^{1'}$, *s-cis*), 148.2 ($C^{3',5'}$), 164.9 (CON), 173.1 (CO_2H).

N-(3,5-Dimethylbenzoyl)-L-proline (5)

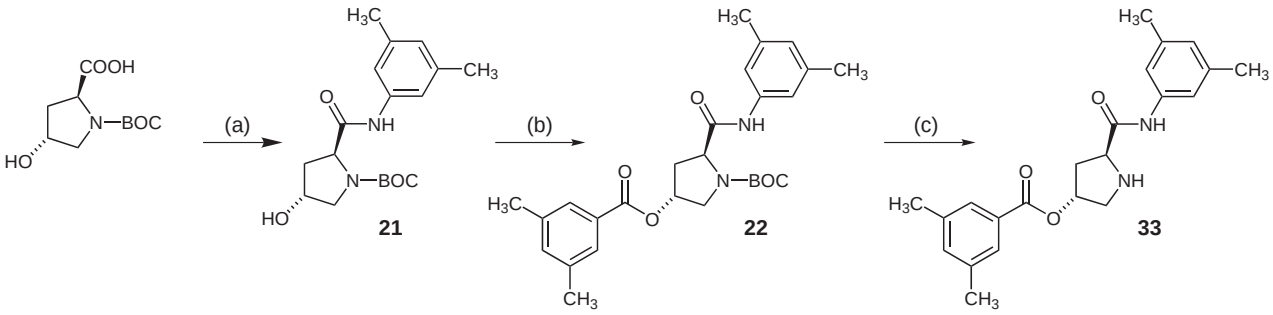
The mixture obtained was extracted with EtOAc. The organic extracts were washed with H_2O, dried, filtered and the solvent was removed under reduced pressure. The resulting solid was crystallized from EtOH–H_2O; yield: 69%; mp 143–144 °C; $[\alpha]_D^{20}$ +74.1 (*c* = 1, 96% EtOH).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.92 (m, 1 H, C^4H_a), 1.99 (m, 1 H, C^4H_b), 2.10–2.50 (m, 2 H, C^3H_2), 2.34 (s, 6 H, 2 ArCH_3), 3.57 (t, 2 H, C^5H_2), 3.75 (t, C^5H_2, *s-cis*), 4.35 (dd, C^2H, *s-cis*), 4.74 (dd, 1 H, *J* = 5, 8 Hz, C^2H), 7.09 (s, 1 H, $C^{4'}H$), 7.15 (s, 2 H, $C^{2',6'}H$), 7.95 (br s, 1 H, CO_2H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.1 (2 CH_3Ar), 22.1 (C^4H_2, *s-cis*), 25.0 (C^4H_2), 28.7 (C^3H_2), 30.8 (C^3H_2, *s-cis*), 46.1 (C^5H_2, *s-cis*), 50.2 (C^5H_2), 59.3 (C^2H), 61.4 (C^2H, *s-cis*), 124.0 ($C^{2',6'}H$, *s-cis*), 124.6 ($C^{2',6'}H$), 131.3 ($C^{4'}H$, *s-cis*), 131.8 ($C^{4'}H$), 135.3 ($C^{1'}$), 137.8 ($C^{3',5'}$), 171.2 (CON), 174.8 (CO_2H), 175,6 (CO_2H, *s-cis*).

N-(3,5-Dichlorobenzoyl)-L-proline (9)

The resulting mixture was extracted with EtOAc. The solid obtained from the organic extracts was crystallized from EtOH–H_2O; yield: 80%; mp 108–111 °C; $[\alpha]_D^{20}$ –75.6 (*c* = 1, abs EtOH).



Scheme 6 *Reagents and Conditions*: (a) 3,5-$Me_2C_6H_3NH_2$, EEDQ, CH_2Cl_2, r.t.; (b) 3,5-$Me_2C_6H_3COCl$, 2 N NaOH/$CHCl_3$ (25:75), r.t.; (c) TFA/CH_2Cl_2 (30:70), r.t.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (m, 1 H, C^4H_a), 2.07 (m, 1 H, C^3H_a), 2.18 (m, 1 H, C^4H_b), 2.33 (m, 1 H, C^3H_b), 3.53 (m, 1 H, C^5H_a), 3.60 (m, 1 H, C^5H_b), 3.76 (m, C^5H_2, *s-cis*), 4.32 (d, C^2H, *s-cis*), 4.69 (dd, 1 H, C^2H), 7.29 (s, $C^{2',6'}H$, *s-cis*), 7.38 (s, $C^{4'}H$, *s-cis*), 7.44 (s, 3 H, $C^{2',6'}H$ and $C^{4'}H$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.2 (C^4H_2, *s-cis*), 25.1 (C^4H_2), 29.3 (C^3H_2), 30.1 (C^3H_2, *s-cis*), 46.6 (C^5H_2, *s-cis*), 50.1 (C^5H_2), 59.4 (C^2H), 61.0 (C^2H, *s-cis*), 125.7 ($C^{2',6'}H$), 128.6 ($C^{2',6'}H$, *s-cis*), 130.4 ($C^{4'}H$), 133.4 ($C^{4'}H$, *s-cis*), 135.2 ($C^{3',5'}$), 138.3 ($C^{1'}$), 167.4 (CONH), 175.6 (CO_2H).

Anal. Calcd for $C_{12}H_{11}Cl_2NO_3$: C, 50.02; H, 3.85; Cl, 24.61; N, 4.86. Found: C, 50.10; H, 4.05; Cl, 24.31; N, 4.65.

N-(3,5-Dinitrobenzoyl)-(4*R*)-hydroxy-L-proline (11)

The solid obtained was collected by filtration and crystallized from Et_2O–hexane; yield: 40%; mp 116–117 °C; (Lit.[4] mp 100 °C); $[\alpha]_D^{20}$ –154.5 (*c* = 1, 96% EtOH) [Lit.[4] $[\alpha]_D^{25}$ –129.5 (*c* = 1, abs EtOH)].

^{1}H NMR (200 MHz, CD_3OD): δ = 2.27 (m, 1 H, C^3H_a), 2.39 (m, 1 H, C^3H_a, *s-cis*), 2.54 (m, 1 H, $J_{3a,3b}$ = 12 Hz, C^3H_b), 2.73 (m, C^3H_b, *s-cis*), 3.52 (dd, 1 H, C^5H_a), 3.83 (dd, C^5H_a, *s-cis*), 3.93 (m, C^5H_b, *s-cis*), 3.99 (dd, 1 H, $J_{5a,5b}$ = 12 Hz, $J_{4,5b}$ = 3.6 Hz, C^5H_b), 4.55 (m, 1 H, C^4H), 4.62 (m, C^4H, *s-cis*), 4.72 (dd, C^2H, *s-cis*), 4.86 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 8 Hz, C^2H), 8.84 (d, $C^{2',6'}H$, *s-cis*), 8.92 (d, 2 H, $C^{2',6'}H$), 9.16 (t, $C^{4'}H$, *s-cis*), 9.19 (t, 1 H, $C^{4'}H$).

^{13}C NMR (50.3 MHz, CD_3OD): δ = 38.8 (C^3H_2), 40.7 (C^3H_2, *s-cis*), 56.3 (C^5H_2, *s-cis*), 58.9 (C^5H_2), 59.6 (C^2H), 61.1 (C^2H, *s-cis*), 69.4 (C^4H, *s-cis*), 71.1 (C^4H), 120.9 ($C^{4'}H$, *s-cis*), 121.3 ($C^{4'}H$), 128.5 ($C^{2',6'}H$, *s-cis*), 128.8 ($C^{2',6'}H$), 140.0 ($C^{3',5'}$), 140.6 ($C^{3',5'}$, *s-cis*), 149.9 ($C^{1'}$), 167.6 (CON), 174.7 (CO_2H, *s-cis*), 175.2 (CO_2H).

N-(3,5-Dimethylbenzoyl)-(4*R*)-hydroxy-L-proline (13)

The resulting mixture was extracted with EtOAc. The solid obtained from the evaporation of the organic extracts was crystallized from EtOH–H_2O; yield: 50%; mp 194–195 °C; $[\alpha]_D^{20}$ –121.0 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3/CD_3OD$): δ = 2.16 (m, 1 H, C^3H_β), 2.33 (s, 6 H, 2 CH_3Ar), 2.41 (m, 1 H, C^3H_α), 3.48 (m, 1 H, C^5H_α), 3.77 (dd, 1 H, $J_{5\alpha,5\beta}$ = 11.5 Hz, $J_{4,5\beta}$ = 4 Hz, C^5H_β), 4.20 (br s, 1 H, OH), 4.42 (m, 1 H, C^4H), 4.52 (m and m, C^2H and C^4H, *s-cis*), 4.75 (dd, 1 H, $J_{2,3\alpha} = J_{2,3\beta}$ = 8.8 Hz, C^2H), 7.04 (s, ArH, *s-cis*), 7.09 (s, 1 H, $C^{4'}H$), 7.15 (s, 2 H, $C^{2',6'}H$).

^{13}C NMR (75.5 MHz, $CDCl_3/CD_3OD$): δ = 21.0 (CH_3Ar), 37.4 (C^3H_2), 39.4 (C^3H_2, *s-cis*), 54.8 (C^5H_2, *s-cis*), 57.8 (C^5H_2 and C^2H), 60.6 (C^2H, *s-cis*), 68.1 (C^4H, *s-cis*), 69.6 (C^4H), 124.2 ($C^{2',6'}H$, *s-cis*), 124.8 ($C^{2',6'}H$), 131.0 ($C^{4'}H$, *s-cis*), 132.0 ($C^{4'}H$), 135.2 ($C^{1'}$), 137.9 ($C^{3',5'}$), 171.5 (CON), 174.0 (CO_2H).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.51; H, 6.20; N, 5.38.

N-(3,5-Dichlorobenzoyl)-(4*R*)-hydroxy-L-proline (17)

The solid obtained was crystallized from EtOH–H_2O; yield: 70%; mp 223–225 °C; $[\alpha]_D^{20}$ –116.4 (*c* = 1, abs EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (m, 1 H, C^3H_a), 2.20 (m, C^3H_a, *s-cis*), 2.40 (m, 1 H, C^3H_b), 3.44 (d, 1 H, C^5H_a), 3.69 (m, C^5H_a, *s-cis*), 3.75 (dd, 1 H, C^5H_b), 3.85 (m, C^5H_b, *s-cis*), 4.33 (m and br s, 2 H, C^4H and OH), 4.44 (m, C^4H, *s-cis*), 4.54 (dd, C^2H, *s-cis*), 4.75 (dd, 1 H, C^2H), 7.37 (s, $C^{2',6'}H$, *s-cis*), 7.41 (s, $C^{4'}H$, *s-cis*), 7.45 (s, 3 H, $C^{2',6'}H$ and $C^{4'}H$).

^{13}C NMR (100.6 MHz, $CDCl_3/CD_3OD$): δ = 37.4 (C^3H_2), 39.0 (C^3H_2, *s-cis*), 55.0 (C^5H_2, *s-cis*), 57.6 (C^5H_2), 57.9 (C^2H), 59.8 (C^2H, *s-cis*), 67.8 (C^4H, *s-cis*), 69.5 (C^4H), 125.4 ($C^{2',6'}H$, *s-cis*), 125.6 ($C^{2',6'}H$), 128.2 ($C^{4'}H$, *s-cis*), 130.2 ($C^{4'}H$), 135.0 ($C^{3',5'}$), 138.2 ($C^{1'}$), 167.7 (CON), 173.8 (CO_2H).

Anal. Calcd for $C_{12}H_{11}Cl_2NO_4$: C, 47.39; H, 3.65; Cl, 23.31; N, 4.61. Found: C, 47.50; H, 3.75; Cl, 23.10; N, 4.45.

N-Dodecanoyl-(4*R*)-hydroxy-L-proline (19)

The solid obtained was collected by filtration and crystallized from Et_2O–hexane; yield: 74%; mp 86–87 °C; $[\alpha]_D^{20}$ –39.3 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, $C^{12'}H_3$), 1.24 (m, 16 H, $C^{4'-11'}H_2$), 1.62 (m, 2 H, $C^{3'}H_2$), 2.20 (m, 1 H, $J_{3a,3b}$ = 13.2 Hz, $J_{2,3a}$ = 8 Hz, $J_{4,3a}$ = 4.4 Hz, C^3H_a), 2.34 (t, 2 H, CH_2CO), 2.43 (m, 1 H, $J_{2,3b}$ = 8 Hz, $J_{4,3b}$ = 4.4 Hz, C^3H_b), 3.52 (dd, 1 H, $J_{5a,5b}$ = 11 Hz, $J_{4,5a}$ = 2.6 Hz, C^5H_a), 3.65 (dd, 1 H, $J_{4,5b}$ = 4.4 Hz, C^5H_b), 4.57 (m, 1 H, C^4H), 4.65 (dd, 1 H, C^2H), 5.45 (br s, 2 H, OH and CO_2H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 ($C^{12'}H_3$), 22.6 ($C^{11'}H_2$), 24.6 ($C^{3'}H_2$), 29.5 ($C^{4'-9'}H_2$), 31.9 ($C^{10'}H_2$), 34.5 ($C^{2'}H_2$), 37.0 (C^3H_2), 55.1 (C^5H_2), 58.0 (C^4H), 69.7 (C^2H), 174.3 and 174.4 (CO_2H and CON).

N-Acyl-L-prolinamide Derivatives; General Procedure

Method A, *Scheme 1*: The appropriate amine (1.1 mmol) was added to a solution of the corresponding *N*-acyl derivative (**1**, **5**, **9**, **17** or **19**) and EEDQ (1.1 equiv) in CH_2Cl_2 (20 mL). The mixture was stirred at r.t. for 24 h. The resulting solution was washed with 2 N HCl, 5% $NaHCO_3$ and H_2O. The solid obtained from the organic extracts was crystallized from the appropriate solvent.

N-(3,5-Dinitrobenzoyl)-*N*′-(butyl)-L-prolinamide (2)

Yield: 68%; mp 139–140 °C (EtOH–H_2O); $[\alpha]_D^{20}$ –87.0 (*c* = 1, 96% EtOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, $C^{4''}H_3$), 1.36 (m, 2 H, $C^{3''}H_2$), 1.52 (m, 2 H, $C^{2''}H_2$), 1.92 (m, 1 H, C^4H_a), 2.05 (m, C^4H_2, *s-cis*), 2.15 (m, 1 H, C^3H_a), 2.21 (m, 1 H, C^4H_b), 2.40 (m, 1 H, C^3H_b), 3.13 (m, $C^{1''}H_2$, *s-cis*), 3.29 (m, 2 H, $C^{1''}H_2$), 3.48 (m, 1 H, C^5H_a), 3.69 (m, 1 H, C^5H_b), 3.85 (m, C^5H_2, *s-cis*), 4.16 (m, C^2H, *s-cis*), 4.64 (dd, 1 H, C^2H), 5.72 (br s, NH, *s-cis*), 6.48 (br s, 1 H, NH), 8.60 (d, $C^{2',6'}H$, *s-cis*), 8.72 (m, 2 H, $C^{2',6'}H$), 9.04 (d, $C^{4'}H$, *s-cis*), 9.10 (m, 1 H, $C^{4'}H$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.6 ($C^{4''}H_3$), 19.9 ($C^{3''}H_2$), 22.3 (C^4H_2, *s-cis*), 25.5 (C^4H_2), 28.3 ($C^{2''}H_2$), 31.4 (C^3H_2), 32.1 (C^3H_2, *s-cis*), 39.4 ($C^{1''}H_2$), 48.0 (C^5H_2, *s-cis*), 50.4 (C^5H_2), 60.7 (C^2H), 63.3 (C^2H, *s-cis*), 119.5 ($C^{4'}H$, *s-cis*), 120.0 ($C^{4'}H$), 127.2 ($C^{2',6'}H$, *s-cis*), 127.6 ($C^{2',6'}H$), 139.3 ($C^{1'}$), 148.3 ($C^{3',5'}$), 165.3 (CON), 170.2 (CONH).

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.61; H, 5.52; N, 15.08.

N-(3,5-Dinitrobenzoyl)-*N*′-(octadecyl)-L-prolinamide (3)

Yield: 62%; mp 132–133 °C (96% EtOH); $[\alpha]_D^{20}$ –32.8 (*c* = 1, pyridine).

^{1}H NMR (200 MHz, $CDCl_3/CD_3OD$): δ = 0.88 (t, 3 H, CH_3), 1.25 (m, 30 H, $C^{3''-17''}H_2$), 1.54 (m, 1 H, $C^{2''}H_2$), 1.95 (m, 1 H, C^4H_a), 2.21 (m, 3 H, C^4H_b and C^3H_2), 3.06 (t, $C^{1''}H_2$, *s-cis*), 3.27 (t, 2 H, $C^{1''}H_2$), 3.47 (m, 1 H, C^5H_a), 3.76 (m, 1 H, C^5H_b), 4.18 (m, C^2H, *s-cis*), 4.57 (dd, 1 H, C^2H), 8.63 (m, $C^{2',6'}H$, *s-cis*), 8.83 (m, 2 H, $C^{2',6'}H$), 9.06 (m, $C^{4'}H$, *s-cis*), 9.12 (m, 1 H, $C^{4'}H$).

^{13}C NMR (50.3 MHz, $CDCl_3/CD_3OD$): δ = 14.1 ($C^{18''}H_3$), 22.7 ($C^{17''}H_2$), 25.6 (C^4H_2), 26.9 and 28.0 (C^3H_2 and $C^{3''}H_2$), 29.2–30.8 ($C^{4''-16''}H_2$), 31.9 ($C^{2''}H_2$), 39.9 ($C^{1''}H_2$), 50.3 (C^5H_2), 60.7 (C^2H), 120.1 ($C^{4'}H$), 127.6 ($C^{2',6'}H$), 139.4 ($C^{1'}$), 148.5 ($C^{3',5'}$), 165.2 (CON), 169.7 (CONH).

Anal. Calcd for $C_{30}H_{48}N_4O_6$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.29; H, 8.63; N, 9.94.

***N*-(3,5-Dinitrobenzoyl)-*N′*-(3,5-dimethylphenyl)-L-prolinamide (4)**
Yield: 41%; mp 230–231 °C (acetone–hexane); $[\alpha]_D^{20}$ –49.4 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3/CD_3OD$): δ = 2.00 (m, 1 H, C^4H_a), 2.28 (m, 3 H, C^4H_b and C^3H_2), 2.30 (s, 6 H, 2 CH_3Ar), 3.57 (m, 1 H, C^5H_a), 3.80 (m, 1 H, C^5H_b), 4.35 (dd, C^2H, *s-cis*), 4.76 (dd, 1 H, C^2H), 6.70 (s, $C^{4''}$H, *s-cis*), 6.77 (s, 1 H, $C^{4''}$H), 6.86 (s, $C^{2'',6''}$H, *s-cis*), 7.22 (s, 2 H, $C^{2'',6''}$H), 8.64 (d, $C^{2',6'}$H, *s-cis*), 8.87 (d, 2 H, $C^{2',6'}$H), 8.91 (m, $C^{4'}$H, *s-cis*), 9.13 (m, 1 H, $C^{4'}$H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 21.0 (2 CH_3Ar), 22.7 (C^4H_2, *s-cis*), 24.8 (C^4H_2), 29.8 (C^3H_2), 31.6 (C^3H_2, *s-cis*), 47.2 (C^5H_2, *s-cis*), 49.9 (C^5H_2), 61.1 (C^2H), 62.0 (C^2H, *s-cis*), 117.3 ($C^{2'',6''}$H), 118.8 ($C^{4'}$H, *s-cis*), 119.6 ($C^{4'}$H), 124.9 ($C^{4''}$H), 125.2 ($C^{4''}$H, *s-cis*), 127.0 ($C^{2',6'}$H, *s-cis*), 127.4 ($C^{2',6'}$H), 137.6 ($C^{3'',5''}$), 138.6, 139.1 and 140.0 ($C^{1''}$, $C^{1'}$ and $C^{1'}$, *s-cis*), 147.8 ($C^{3',5'}$, *s-cis*) , 148.0 ($C^{3',5'}$), 164.4 (CON), 164.9 (CON, *s-cis*), 169.6 (CONH), 170.0 (CONH, *s-cis*).

Anal. Calcd for $C_{20}H_{20}N_4O_6$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.26; H, 4.95; N, 13.43.

***N*-(3,5-Dimethylbenzoyl)-*N′*-(butyl)-L-prolinamide (6)**
Yield: 40%; mp 82–83 °C (Et_2O–hexane); $[\alpha]_D^{20}$ –76.2 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, $C^{4''}H_3$), 1.34 (m, 2 H, $C^{3''}H_2$), 1.48 (m, 2 H, $C^{2''}H_2$), 1.78 (m, 1 H, C^4H_a), 2.01 (m, 2 H, C^3H_a and C^4H_b), 2.33 (s, 6 H, 2 CH_3Ar), 2.47 (m, 1 H, C^3H_b), 3.26 (m, 2 H, $C^{1''}H_2$), 3.50 (m, 2 H, C^5H_2), 4.75 (dd, 1 H, C^2H), 7.09 (m, 3 H, ArH), 7.12 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.6 ($C^{4''}H_3$), 19.9 ($C^{3''}H_2$), 21.1 (2 CH_3Ar), 22.3 (C^4H_2, *s-cis*), 25.3 (C^4H_2), 26.9 ($C^{2''}H_2$), 28.3 (C^3H_2, *s-cis*), 31.4 (C^3H_2), 39.2 ($C^{1''}H_2$), 46.6 (C^5H_2, *s-cis*), 50.4 (C^5H_2), 59.6 (C^2H), 63.2 (C^2H, *s-cis*), 123.9 ($C^{2',6'}$H, *s-cis*), 124.5 ($C^{2',6'}$H), 131.7 ($C^{4'}$H), 136.1 ($C^{1'}$), 137.9 ($C^{3',5'}$), 170.9 and 171.5 (2 CON).

Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.10; H, 8.96; N, 9.43.

***N*-(3,5-Dimethylbenzoyl)-*N′*-(octadecyl)-L-prolinamide (7)**
Yield: 42%; mp 93–94 °C (96% EtOH); $[\alpha]_D^{20}$ –51.3 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, CH_3), 1.25 (m, 30 H, $C^{3''–17''}H_2$), 1.52 (m, 1 H, $C^{2''}H_a$), 1.80 (m, 1 H, C^4H_a), 2.00 (m, 2 H, C^4H_b and C^3H_a), 2.33 (s, 6 H, 2 CH_3Ar), 2.50 (m, 1 H, C^3H_b), 3.25 (m, 2 H, $C^{1''}H_2$), 3.50 (m, 2 H, C^5H_2), 4.28 (m, C^2H, *s-cis*), 4.75 (m, 1 H, C^2H), 7.09 (m, 3 H, ArH), 7.10 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1 ($C^{18''}H_3$), 21.2 (2 CH_3Ar), 22.6 ($C^{17''}H_2$), 25.3 (C^4H_2), 26.9 (C^3H_2 and $C^{3''}H_2$), 29.2–29.6 ($C^{4''–16''}H_2$), 31.9 ($C^{2''}H_2$), 39.5 ($C^{1''}H_2$), 50.4 (C^5H_2), 59.6 (C^2H), 124.6 ($C^{2',6'}$H), 131.7 ($C^{4'}$H), 136.0 ($C^{1'}$), 138.0 ($C^{3',5'}$), 170.8 and 171.6 (2 CON).

Anal. Calcd for $C_{32}H_{54}N_2O$: C, 77.06; H, 10.91; N, 5.62. Found: C, 77.40; H, 10.91; N, 5.62.

***N*-(3,5-Dimethylbenzoyl)-*N′*-(3,5-dimethylphenyl)-L-prolinamide (8)**
Yield: 66%; mp 204–205 °C (96% EtOH); $[\alpha]_D^{20}$ –129.0 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.86 (m, 1 H, C^4H_a), 2.05 (m, 2 H, C^4H_b and C^3H_a), 2.27 (s, 6 H, 2 CH_3Ar″), 2.33 (s, 6 H, 2 CH_3Ar′), 2.66 (m, 1 H, C^3H_b), 3.51 (m, 2 H, C^5H_2), 4.99 (dd, 1 H, C^2H), 6.72 (s, 1 H, $C^{4''}$H), 7.08 (s, 1 H, $C^{4'}$H), 7.10 (s, 2 H, $C^{2'',6''}$H), 7.22 (s, 2 H, $C^{2',6'}$H), 9.53 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.1 and 21.2 (2 CH_3Ar′ and 2 CH_3Ar″), 25.2 (C^4H_2), 26.7 (C^3H_2), 50.5 (C^5H_2), 60.5 (C^2H), 117.3 ($C^{2'',6''}$H), 124.6 ($C^{2',6'}$H), 125.4 ($C^{4''}$H), 131.8 ($C^{4'}$H), 135.8 ($C^{1'}$), 138.0 and 138.3 ($C^{3',5'}$ and $C^{3'',5''}$) 138.1 ($C^{1''}$), 168.9 (CON), 172.0 (CONH).

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.20; H, 7.37; N, 7.97.

***N*-(3,5-Dichlorobenzoyl)-*N′*-(3,5-dimethylphenyl)-L-prolinamide (10)**
Yield: 50%; mp 249–250 °C (96% EtOH); $[\alpha]_D^{20}$ +178.7 (*c* = 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (m, 1 H, C^4H_a), 2.09 (m, 1 H, C^3H_a), 2.14 (m, 1 H, C^4H_b), 2.24 (s, 6 H, 2 CH_3Ar), 2.53 (m, 1 H, C^3H_b), 3.48 (m, 1 H, C^5H_a), 3.59 (m, 1 H, C^5H_b), 4.89 (dd, 1 H, C^2H), 6.69 (s, 1 H, $C^{4''}$H), 7.14 (s, 2 H, $C^{2',6'}$H), 7.41 (d, 2 H, $C^{2'',6''}$H), 7.44 (d, 1 H, $C^{4''}$H); 9.14 (br s, 1 H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.2 (2 CH_3Ar), 25.3 (C^4H_2), 27.2 (C^3H_2), 50.5 (C^5H_2), 61.0 (C^2H), 117.4 ($C^{2'',6''}$H), 125.6 ($C^{2',6'}$H), 125.8 ($C^{4''}$H), 130.3 ($C^{4'}$H), 135.3 ($C^{3',5'}$), 137.8 ($C^{1''}$), 138.4 ($C^{3'',5''}$), 138.6 ($C^{1'}$), 168.4 (2 CON).

Anal. Calcd for $C_{20}H_{20}Cl_2N_2O_2$: C, 61.39; H, 5.15; Cl, 18.12; N, 7.16. Found: C, 61.60; H, 5.45; Cl, 17.80; N, 7.05.

***N*-(3,5-Dichlorobenzoyl)-*N′*-(3,5-dimethylphenyl)-(4*R*)-hydroxy-L-prolinamide (18)**
Yield: 55%; mp 273–274 °C ($EtOH–H_2O$); $[\alpha]_D^{20}$ –100.0 (*c* = 1, abs EtOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 2.10 (m, 1 H, C^3H_a), 2.15 (s, 6 H, 2 CH_3Ar), 2.38 (m, 1 H, C^3H_b), 3.42 (d, 1 H, C^5H_a), 3.79 (m, C^5H_2, *s-cis*), 3.86 (m, 1 H, C^5H_b), 4.46 (dd, 1 H, C^4H), 4.54 (m, C^4H, *s-cis*), 4.60 (dd, C^2H, *s-cis*), 4.70 (br s, 1 H, OH), 4.80 (dd, 1 H, C^2H), 6.74 (s, $C^{4''}$H, *s-cis*), 6.78 (s, 1 H, $C^{4''}$H), 6.85 (s, $C^{2'',6''}$H, *s-cis*), 7.24 (s, 2 H, $C^{2'',6''}$H), 7.42 (s, $C^{2',6'}$H and $C^{4'}$H, *s-cis*), 7.62 (s, 3 H, $C^{2',6'}$H and $C^{4'}$H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4 (2 CH_3Ar), 38.2 (C^3H_2), 40.3 (C^3H_2, *s-cis*), 56.0 (C^5H_2, *s-cis*), 58.7 (C^5H_2), 60.5 (C^2H), 62.2 (C^2H, *s-cis*), 68.1 (C^4H, *s-cis*), 69.9 (C^4H), 118.0 ($C^{2'',6''}$H), 118.3 ($C^{2'',6''}$H, *s-cis*), 125.7 ($C^{2',6'}$H, *s-cis*), 125.9 ($C^{4''}H_2$), 126.1 ($C^{2',6'}$H), 126.3 ($C^{4''}$H, *s-cis*), 129.6 ($C^{4'}$H, *s-cis*), 130.2 ($C^{4'}$H), 135.2 ($C^{3',5'}$), 138.4 ($C^{1'}$), 138.5 ($C^{3'',5''}$), 139.4 ($C^{1''}$), 167.5 (CON), 171.1 (CONH).

Anal. Calcd for $C_{20}H_{20}Cl_2N_2O_3$: C, 58.98; H, 4.95; Cl, 17.41; N, 6.88. Found: C, 59.30; H, 5.05; Cl, 17.15; N, 6.63.

***N′*-(3,5-Dimethylphenyl)-*N*-dodecanoyl-(4*R*)-hydroxy-L-prolinamide (20)**
Yield: 45%; mp 132–133 °C ($EtOH–H_2O$); $[\alpha]_D^{20}$ –49.2 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, $C^{12'}H_3$), 1.25 (m, 16 H, $C^{4'–11'}H_2$), 1.68 (m, 3 H, $C^{3'}H_2$ and OH), 1.98 (m, 1 H, $J_{3a,3b}$ = 13 Hz, $J_{2,3a}$ = 8 Hz, C^3H_a), 2.26 (s, 6 H, 2 CH_3Ar), 2.28–2.45 (m, 2 H, $C^{2'}H_2$), 2.77 (dt, 1 H, $J_{2,3b}$ = 4.8 Hz, C^3H_b), 3.45 (dd, 1 H, $J_{5a,5b}$ = 10.6 Hz, $J_{4,5a}$ = 4.4 Hz, C^5H_a), 3.68 (dd, 1 H, $J_{4,5b}$ = 5.4 Hz, C^5H_b), 4.70 (m, 1 H, C^4H), 4.88 (dd, 1 H, C^2H), 6.71 (s, 1 H, $C^{4''}$H), 7.15 (s, 2 H, $C^{2'',6''}$H), 9.46 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.0 ($C^{12'}H_3$), 21.2 (2 CH_3Ar), 22.6 ($C^{11'}H_2$), 24.7 ($C^{3'}H_2$), 29.2–29.5 ($C^{4'–9'}H_2$), 31.8 ($C^{10'}H_2$), 34.7 ($C^{2'}H_2$), 35.9 (C^3H_2), 54.9 (C^5H_2), 59.3 (C^4H), 70.0 (C^2H), 117.4 ($C^{2'',6''}$H), 125.8 ($C^{4''}$H), 137.8 ($C^{1''}$), 138.4 ($C^{3'',5''}$), 169.3 (CONH), 174.2 (CON).

Anal. Calcd for $C_{25}H_{40}N_2O_3$: C, 72.08; H, 9.68; N, 6.72. Found: C, 71.88; H, 9.25; N, 6.72.

_N_-Acyl-(4*R*)-hydroxy-L-prolinamide Derivatives; General Procedure

Method B, *Scheme 1*: Analogous to Method A, the appropriate amine (2.5 equiv) was added to a solution of the *N*-acyl derivative **11** or **13** and EEDQ (2.5 equiv) in DMF (15 mL) for **11** and CH_2Cl_2 (15 mL) for **13**. The mixture was stirred at r.t. and the course of the reaction was controlled by TLC. The workup procedure was the same as in Method A.

_N_-(3,5-Dinitrobenzoyl)-_N′_-(3,5-dimethylphenyl)-(4*R*)-hydroxy-L-prolinamide (12)

After a reaction time of 60 h, CH_2Cl_2 was added and the workup procedure was followed in the usual way. Compound **12** was crystallized from abs EtOH; yield: 72%; mp 215–216 °C; $[\alpha]_D^{20}$ –155.9 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 2.16 (m, 1 H, C^3H_a), 2.20 (s, 6 H, 2 C*H*$_3$Ar), 2.36 (m, 1 H, C^3H_b), 3.38 (dd, 1 H, C^5H_a), 3.76 (m, C^5H_2, *s-cis*), 3.87 (dd, 1 H, $J_{5a,5b}$ = 12 Hz, $J_{4,5b}$ = 4 Hz, C^5H_b), 4.45 (m, 1 H, C^4H), 4.53 (m, C^4H, *s-cis*), 4.84 (dd and br s, 2 H, $J_{2,3a} = J_{2,3b}$ = 8 Hz, C^2H and OH), 6.60 (s, $C^{4''}$H, *s-cis*), 6.64 (s, $C^{2'',6''}$H, *s-cis*), 6.70 (s, 1 H, $C^{4''}$H); 7.15 (s, 2 H, $C^{2'',6''}$H), 8.60 (m, $C^{2',6'}$H, *s-cis*), 8.72 (m, $C^{4'}$H, *s-cis*), 8.82 (m, 2 H, $C^{2',6'}$H), 9.01 (m, 2 H, $C^{4'}$H).

^{13}C NMR (50.3 MHz, CD_3OD): δ = 21.3 (2 *C*H$_3$Ar, *s-cis*), 21.5 (2 *C*H$_3$Ar), 39.5 (C^3H_2), 41.3 (C^3H_2, *s-cis*), 57.6 (C^5H_2, *s-cis*), 59.4 (C^5H_2), 61.7 (C^2H), 62.8 (C^2H, *s-cis*), 69.6 (C^4H, *s-cis*), 71.2 (C^4H), 118.4 ($C^{2'',6''}$H, *s-cis*), 119.2 ($C^{2'',6''}$H), 120.4 ($C^{4'}$H, *s-cis*), 121.2 ($C^{4'}$H), 127.1 ($C^{2',6'}$H), 127.4 ($C^{2',6'}$H, *s-cis*), 128.4 ($C^{4''}$H, *s-cis*), 128.9 ($C^{4''}$H), 139.2, 139.7 and 140.1 ($C^{3'',5''}$, $C^{1'}$ and $C^{1''}$), 150.0 ($C^{3',5'}$), 167.7 (CON), 172.2 (CONH).

Anal. Calcd for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 55.92; H, 4.52; N, 13.19.

_N′_-(Butyl)-_N_-(3,5-dimethylbenzoyl)-(4*R*)-hydroxy-L-prolinamide (14)

MeOH was added to the reaction mixture until the complete dissolution of the precipitate formed on the addition of the amine. After 4 days of reaction, the solid obtained was purified by crystallization from acetone–hexane; yield: 57%; mp 152–153 °C; $[\alpha]_D^{20}$ –90.3 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, $C^{4''}H_3$), 1.34 (m, 2 H, $C^{3''}H_2$), 1.49 (m, 2 H, $C^{2''}H_2$), 1.68 (br s, 1 H, OH), 2.07 (m, 1 H, C^3H_a), 2.32 (s, 6 H, 2 C*H*$_3$Ar), 2.74 (m, 1 H, C^3H_b), 3.25 (q, 2 H, $C^{1''}H_2$), 3.53 (dd, 1 H, C^5H_a), 3.67 (dd, 1 H, $J_{5a,5b}$ = 10 Hz, $J_{4,5b}$ = 3.6 Hz, C^5H_b), 4.48 (m, 1 H, C^4H), 4.92 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 8.6 Hz, C^2H), 7.07 (s, 1 H, $C^{4'}$H), 7.10 (s, 2 H, $C^{2',6'}$H), 7.21 (br s, 1 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.7 ($C^{4''}H_3$), 20.0 ($C^{3''}H_2$), 21.1 (*C*H$_3$Ar), 31.4 ($C^{2''}H_2$), 36.4 (C^3H_2), 39.3 ($C^{1''}H_2$), 58.5 (C^5H_2 and C^2H), 70.1 (C^4H), 125.0 ($C^{2',6'}$H), 132.0 ($C^{4'}$H), 135.6 ($C^{1'}$), 137.9 ($C^{3',5'}$), 171.0 (CON), 172.1 (CONH).

Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.53; H, 8.13; N, 8.99.

_N_-(3,5-Dimethylbenzoyl)-_N′_-(3,5-dimethylphenyl)-(4*R*)-hydroxy-L-prolinamide (15)

After a reaction time of 17 h, the solid obtained was purified by crystallization from EtOH–H_2O; yield: 64%; mp 225–226 °C; $[\alpha]_D^{20}$ –153.8 (*c* = 1.5, $CHCl_3$); $[\alpha]_D^{20}$ –8.7 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (m, 1 H, C^3H_a), 2.26 (m, 6 H, 2 C*H*$_3$Ar″), 2.32 (s, 6 H, 2 C*H*$_3$Ar′), 2.86 (m, 1 H, C^3H_b), 3.56 (dd, 1 H, C^5H_a), 3.65 (dd, 1 H, $J_{5a,5b}$ = 10 Hz, $J_{4,5b}$ = 3.4 Hz, C^5H_b), 4.52 (m, 1 H, C^4H), 5.13 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 8 Hz, C^2H), 6.72 (s, 1 H, $C^{4''}$H), 7.08 (s, 1 H, $C^{4'}$H), 7.12 (s, 2 H, $C^{2',6'}$H), 7.21 (s, 2 H, $C^{2'',6''}$H), 9.50 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.0 and 21.1 (4 *C*H$_3$Ar), 36.9 (C^3H_2), 58.6 (C^5H_2), 59.5 (C^2H), 70.0 (C^4H), 117.4 ($C^{2'',6''}$H), 124.9 ($C^{2',6'}$H), 125.7 ($C^{4''}$H), 132.0 ($C^{4'}$H), 135.3 ($C^{1'}$), 137.7 ($C^{1''}$), 137.9 and 138.3 ($C^{3',5'}$ and $C^{3'',5''}$), 169.5 (CON), 172.1 (CONH).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.25; H, 7.44; N, 7.68.

Phthalimidomethyl _N_-(3,5-Dimethylbenzoyl)-(4*R*)-hydroxy-L-prolinate (16) (Scheme 2)

Following the procedure described,[22] the previously prepared[22] *N*-chloromethylphthalimide (3.9 mmol) was added to a solution of **13** (3.8 mmol) and dicyclohexylamine (3.8 mmol), in DMSO (40 mL). The mixture was stirred at 70 °C for 5 h. After extraction with CH_2Cl_2, the solid obtained was crystallized from Et_2O–hexane; yield: 52%; mp 100–101 °C; $[\alpha]_D^{20}$ –64.2 (*c* = 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.11 (m, 1 H, C^3H_a), 2.27 (s, 6 H, 2 C*H*$_3$Ar), 2.35 (m, 1 H, C^3H_b), 2.73 (br s, 1 H, OH), 3.47 (dd, 1 H, $J_{5a,5b}$ = 10 Hz, C^5H_a), 3.74 (dd, 1 H, $J_{4,5b}$ = 4 Hz, C^5H_b), 4.45 (m, 1 H, C^4H), 4.79 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 8 Hz, C^2H), 5.83 (dd, 2 H, CH_2), 7.00 (s, 1 H, $C^{4'}$H), 7.09 (s, 2 H, $C^{2',6'}$H), 7.80 (m, 2 H, $C^{5'',6''}$H), 7.91 (m, 2 H, $C^{4'',7''}$H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.1 (2 *C*H$_3$Ar), 37.5 (C^3H_2), 57.6 (C^5H_2 and C^2H), 61.0 (CH_2), 70.1 (C^4H), 123.8 ($C^{4'',7''}$H), 124.9 ($C^{2',6'}$H), 131.6 and 131.8 ($C^{4'}$H and $C^{4a'',7a''}$), 134.5 ($C^{5'',6''}$H), 135.5 ($C^{1'}$), 137.7 ($C^{3',5'}$), 165.5 (CON), 170.4 (COO), 170.8 (CONCO).

Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.40; H, 5.25; N, 6.63. Found: C, 65.16; H, 5.32; N, 6.58.

_N,O_-Bis(3,5-dimethylphenylaminocarbonyl)-(4*R*)-hydroxy-L-proline (32) (Scheme 32)

The title compound was obtained by the reaction of (4*R*)-hydroxy-L-proline (500 mg, 3.8 mmol) in anhyd pyridine (15 mL) with 3,5-dimethylphenyl isocyanate (1.24 g, 8.4 mmol). After heating at reflux temperature for 5 h, the mixture was poured into ice/water and extracted with EtOAc. The organic extracts were washed with 2 N HCl and H_2O. The resulting solid was crystallized from EtOH–H_2O; yield: 78%; mp 217–218 °C; $[\alpha]_D^{20}$ +10.2 (*c* = 1, MeOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.06 (m, 1 H, $J_{2,3a}$ = 11.4 Hz, $J_{3a,3b}$ = 14.0 Hz, $J_{4,3a}$ = 5.2 Hz, C^3H_a), 2.30 (s, 6 H, 2 C*H*$_3$Ar), 2.34 (s, 6 H, 2 C*H*$_3$Ar), 2.59 (dd, 1 H, $J_{2,3b}$ = 6.2 Hz, C^3H_b), 3.47 (d, 1 H, $J_{5a,5b}$ = 13.2, C^5H_a), 4.15 (dd, 1 H, $J_{4,5b}$ = 5.6 Hz, C^5H_b), 4.49 (dd, 1 H, C^2H), 5.59 (m, 1 H, C^4H), 6.59 (br s, 1 H, NH), 6.76 (s, 1 H, $C^{4'}$H), 6.96 and 7.01 (s and s, 5 H, $C^{4''}$H, $C^{2',6'}$H and $C^{2'',6''}$H).

^{13}C NMR (50.3 MHz, $CDCl_3$/CD_3OD): δ = 20.9 and 21.1 (*C*H$_3$Ar), 34.5 (C^3H_2), 52.1 (C^5H_2), 61.9 (C^2H), 76.0 (C^4H), 116.4 ($C^{2',6'}$H), 123.6 ($C^{2'',6''}$H), 125.2 ($C^{4'}$H), 130.2 ($C^{4''}$H), 131.0 ($C^{1''}$), 137.2 ($C^{1'}$), 138.5 and 138.8 ($C^{3',5'}$ and $C^{3'',5''}$), 152.1 (HNCOO), 159.1 (NCONH), 172.1 (CO_2H).

Anal. Calcd. for $C_{23}H_{27}N_3O_5$: C, 64.92; H, 6.39; N, 9.87. Found: C, 64.96; H, 6.32; N, 9.98.

_O_-(3,5-Dimethylphenylaminocarbonyl)-(4*R*)-hydroxy-L-proline Derivatives; General Procedures

Method A: 3,5-Dimethylphenyl isocyanate (1.25 g, 8.5 mmol) was added to dicyclohexylammonium *N*-(*tert*-butoxycarbonyl)-(4*R*)-hydroxy-L-prolinate (1 g, 2.4 mmol) in anhyd pyridine (30 mL). The solution was refluxed for 22 h. EtOAc and 2 N HCl were added to the cooled mixture. The organic solution was washed with 2 N HCl and extracted with 50% ammonia. The basic extracts were acidified with 2 N HCl and extracted with EtOAc. The solid resulting from the evaporation of the acidic organic extracts was crystallized from EtOH–H_2O to afford 412 mg (45%) of **26**. *N*-(3,5-Dimethylphenyl)-*N′*,*N′*-dicyclohexylurea (570 mg) and *N*,*N′*-bis(3,5-dimethylphenyl)urea (760 mg) were isolated from the neutral organic extracts by chromatography on silica gel.

***N*-(3,5-Dimethylphenyl)-*N*′,*N*′-dicyclohexylurea**
The solid was crystallized from EtOH–H_2O; mp 262–263 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (m, 20 H, CH_2cycl.), 2.27 (s, 6 H, 2 CH_3Ar), 3.49 (m, 2 H, 2 CH), 6.18 (br s, 1 H, NH), 6.63 (s, 1 H, C^4H), 7.01 (s, 2 H, $C^{2,6}H$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.3 (2 *C*H_3Ar), 25.4 (C^4H_2), 26.3 (C^3H_2 and C^5H_2), 31.8 (C^2H_2 and C^6H_2), 55.3 (CHN), 117.1 ($C^{2′,6′}H$), 124.2 ($C^{4′}H$), 138.4 ($C^{3′,5′}$), 139.1 ($C^{1′}$), 154.5 (CO).

***N*,*N*′-Bis(3,5-dimethylphenyl)urea**
The solid was crystallized from 96% EtOH; mp 278–280 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.22 (s, 12 H, 4 CH_3Ar), 6.60 (s, 2 H, 2 C^4H), 7.07 (s, 4 H, 2 $C^{2,6}H$), 8.46 (s, 2 H, 2 NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 21.3 (Ar*C*H_3), 116.0 ($C^{2,6}H$), 123.6 (C^4H), 137.9 ($C^{3,5}$), 139.8 (C^1), 152.6 (CO).

Method B: 3,5-Dimethylphenyl isocyanate (970 mg, 6.5 mmol) was added to *N*-(*tert*-butoxycarbonyl)-(4*R*)-hydroxy-L-proline (1 g, 4.2 mmol) in anhyd pyridine (30 mL). The solution was refluxed during 22 h. The workup procedure was the same described in Method A. Following this procedure 1.44 g of **26** (90% yield) was obtained after crystallization from EtOH–H_2O.

***N*-(*tert*-Butoxycarbonyl)-(4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-proline (26) (Scheme 3)**
Mp 185–186 °C; $[\alpha]_D^{20}$ –40.2 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 and 1.48 (s and s, 9 H, 3 CH_3), 2.29 (s, 6 H, 2 CH_3Ar), 2.47 (m, 2 H, C^3H_2), 3.72 (m, 2 H, C^5H_2), 4.40 (dd, C^2H, *s-cis*), 4.50 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 8 Hz, C^2H), 5.32 (m, 1 H, C^4H), 6.64 (br s, 1 H, NH), 6.74 (s, 1 H, $C^{4′}H$), 6.99 (s, 1 H, $C^{2′,6′}H$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.3 (*C*H_3Ar), 28.2 [C(*C*H_3)$_3$, *s-cis*], 28.3 [C(*C*H_3)$_3$], 35.2 (C^3H_2), 36.7 (C^3H_2, *s-cis*), 52.0 (C^5H_2, *s-cis*), 52.7 (C^5H_2), 57.6 (C^2H), 57.8 (C^2H, *s-cis*), 72.7 (C^4H, *s-cis*), 73.2 (C^4H), 81.0 [*C*(CH$_3$)$_3$, *s-cis*], 81.4 [*C*(CH$_3$)$_3$], 116.4 ($C^{2′,6′}H$), 125.4 ($C^{4′}H$), 137.2 ($C^{1′}$), 138.7 ($C^{3′,5′}$, *s-cis*), 138.8 ($C^{3′,5′}$), 152.6 (N*C*O$_2$*t*-Bu), 153.8 (HNCOO, *s-cis*), 155.3 (HNCOO), 175.2 (CO_2H, *s-cis*), 177.6 (CO_2H).

Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.92; N, 7.40. Found: C, 60.25; H, 6.98; N 7.42.

***N*-(3,5-Dimethylbenzoyl)-(4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-proline (30) (Scheme 5)**
Following Method B, **30** was obtained from **13** and purified by chromatography on silica gel; yield: 95%; mp 128–129 °C; $[\alpha]_D^{20}$ –123.1 (*c* = 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 6 H, 2 CH_3Ar), 2.28 (s, 6 H, 2 CH_3Ar), 2.58 (m, 1 H, C^3H_a), 2.79 (m, 1 H, C^3H_b), 3.79 (d, 1 H, $J_{5a,5b}$ = 11.8 Hz, C^5H_a), 3.89 (dd, 1 H, $J_{4,5b}$ = 4 Hz, C^5H_b), 4.94 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 8 Hz, C^2H), 5.28 (m, 1 H, C^4H), 6.69 (s, 1 H, $C^{4″}H$), 6.93 (s, 2 H, $C^{2″,6″}H$), 7.03 (s, 1 H, $C^{4′}H$), 7.12 (s, 1 H, $C^{2′,6′}H$), 7.40 (br s, 1 H, NH), 9.60 (br s, 1 H, CO_2H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.1 and 21.3 (*C*H_3Ar), 34.5 (C^3H_2), 56.2 (C^5H_2), 58.2 (C^2H), 73.1 (C^4H), 116.4 ($C^{2″,6″}H$), 125.1 ($C^{2′,6′}H$), 125.2 ($C^{4″}H$), 132.6 ($C^{4′}H$), 134.4 ($C^{1′}$), 137.7 ($C^{1″}$), 138.1 and 138.6 ($C^{3′,5′}$ and $C^{3″,5″}$), 152.6 (HNCOO), 172.0 (CON), 174.0 (CO_2H).

Anal. Calcd for $C_{23}N_{26}N_2O_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 66.98; H, 6.22; N, 6.91.

(4*R*)-(3,5-Dimethylphenylaminocarbonyloxy) and (4*R*)-Hydroxy-L-prolinamide Derivatives; General Procedure
To a solution of the appropriate acid *N*-(*tert*-butoxycarbonyl)-(4*R*)-hydroxy-L-proline, **26**, **28** or **30** (1.3 mmol) and EEDQ (1.7 mmol, 3.3 mmol for **26**) in CH_2Cl_2 (20 mL) the appropriate amine (1.7 mmol, 3.3 mmol for **26**) was added. The solution was stirred at r.t. for 24 h (60 h for **26**). The organic solution was washed with 2 N HCl and aq 5% $NaHCO_3$.

***N*-(*tert*-Butoxycarbonyl)-*N*′-(3,5-dimethylphenyl)-(4*R*)-hydroxy-L-prolinamide (21) (Scheme 6)**
The solid obtained was purified by chromatography on silica gel; yield: 86%; mp 77–79 °C; $[\alpha]_D^{20}$ –66.8 (*c* = 1, $CHCl_3$).

^{1}H NMR (300 MHz, DMSO-d_6, 70 ºC): δ = 1.31 [br s, 9 H, C(CH$_3$)$_3$], 1.95 (m, 2 H, C^3H_a), 2.15 (m, 1 H, C^3H_b), 2.22 (s, 6 H, 2 CH_3Ar), 3.17 (d, 1 H, C^5H_a), 3.45 (dd, 1 H, C^5H_b), 4.30 (m, 2 H, C^2H and OH), 4.85 (m, 1 H, C^4H), 6.63 (s, 1 H, $C^{4′}H$), 7.21 (s, 2 H, $C^{2′,6′}H$), 9.60 (br s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6, 70 °C): δ = 20.9 (2 *C*H_3Ar), 27.9 [C(*C*H$_3$)$_3$], 39.7 (C^3H_2), 54.9 (C^5H_2), 59.4 (C^2H), 68.0 (C^4H), 78.4 [(*C*(CH$_3$)$_3$], 117.0 ($C^{2′,6′}H$), 124.5 ($C^{4′}H$), 137.3 ($C^{3′,5′}$), 138.7 ($C^{1′}$), 153.4 (NCO_2*t*-Bu), 170.9 (CONH).

Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.93; H, 8.30; N, 8.60.

***N*-(*tert*-Butoxycarbonyl)-*N*′-(3,5-dimethylphenyl)-(4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-prolinamide (27) (Scheme 3)**
The solid obtained was crystallized from Et_2O–hexane; yield: 65%; mp 115 °C; $[\alpha]_D^{20}$ –51.1 (*c* = 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, C(CH$_3$)$_3$], 2.29 (s, 12 H, 4 CH_3Ar), 2.80 (m, 2 H, C^3H_2), 3.67 (m, 2 H, C^5H_2), 4.58 (m, 1 H, C^2H), 5.32 (m, 1 H, C^4H), 6.60 (s, 1 H, $C^{4″}H$), 6.73 (s, 2 H, $C^{4′}H$ and NHCOO), 7.00 (s, 2 H, $C^{2″,6″}H$), 7.15 (s, 2 H, $C^{2′,6′}H$), 9.15 (br s, 1 H, CONH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.2 (2 *C*H_3Ar), 21.3 (2 *C*H_3Ar), 28.2 [C(*C*H$_3$)$_3$], 33.6 (C^3H_2), 52.8 (C^5H_2), 59.1 (C^2H), 73.5 (C^4H), 81.3 [*C*(CH$_3$)$_3$], 116.5 and 117.4 ($C^{2′,6′}H$ and $C^{2″,6″}H$), 125.4 and 125.8 ($C^{4′}H$ and $C^{4″}H$), 137.3 and 137.7 ($C^{1′}$ and $C^{1″}$), 138.5 and 138.7 ($C^{3′,5′}$ and $C^{3″,5″}$), 152.7 and 156.1 (HNCOO and NCO_2*t*-Bu), 168.8 (CONH).

Anal. Calcd for $C_{27}H_{35}N_3O_5$: C, 67.34; H, 7.32; N, 8.73. Found: C, 67.60; H, 7.65; N, 8.53.

***N*-(3,5-Dinitrobenzoyl)-*N*′-(butyl)-(4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-prolinamide (29) (Scheme 3)**
The solid obtained was crystallized from 96% EtOH; yield: 60%; mp 108–110 °C; $[\alpha]_D^{20}$ +123.5 (*c* = 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, $C^{4‴}H_3$), 1.35 (m, 2 H, $C^{3″}H_2$), 1.51 (m, 2 H, $C^{2″}H_2$), 2.25 (m, 6 H, 2 CH_3Ar), 2.44 (m, 1 H, C^3H_a), 2.84 (m, 1 H, C^3H_b), 3.32 (m, 2 H, $C^{1″}H_2$), 3.67 (d, 1 H, C^5H_a), 4.03 (dd, 1 H, C^5H_b), 4.84 (dd, 1 H, C^2H), 5.38 (m, 1 H, C^4H), 6.61 (br s, 2 H, 2 NH), 6.71 (s, 1 H, $C^{4′}H$), 6.90 (s, 2 H, $C^{2′,6′}H$), 8.72 (d, 2 H, $C^{2″,6″}H$), 8.96 (d, $C^{2″,6″}H$, *s-cis*), 9.12 (t, 1 H, $C^{4″}H$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7 ($C^{4‴}H_2$), 20.0 ($C^{3‴}H_2$), 21.3 (2 *C*H_3Ar), 31.4 ($C^{2‴}H_2$), 33.7 (C^3H_2), 39.7 ($C^{1‴}H_2$), 56.2 (C^5H_2), 59.3 (C^2H), 73.9 (C^4H), 116.4 ($C^{2″,6″}H_2$), 120.6 ($C^{4′}H$), 125.8 ($C^{4″}H$), 127.8 ($C^{2′,6′}H$), 136.7 ($C^{1″}$), 138.4 ($C^{1′}$), 138.9 ($C^{3″,5″}$), 148.5 ($C^{3′,5′}$), 152.4 (OCONH), 166.0 (CON), 169.2 (CONH).

Anal. Calcd for $C_{25}H_{29}N_5O_8$: C, 56.92; H, 5.54; N, 13.28. Found: C, 57.10; H, 5.60; N, 12.95.

***N*-(3,5-Dimethylbenzoyl)-*N*′-(butyl)-(4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-prolinamide (31) (Scheme 3)**
The product obtained was crystallized from Et_2O–hexane; yield: 53%; mp 90–91 °C; $[\alpha]_D^{20}$ –11.7 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, $C^{4''}H_3$), 1.31 (m, 2 H, $C^{3''}H_2$), 1.45 (m, 2 H, $C^{2''}H_2$), 2.21 (s, 6 H, 2 CH_3Ar), 2.23 (s, 6 H, 2 CH_3Ar), 2.34 (m, 1 H, C^3H_a), 2.79 (m, 1 H, C^3H_b), 3.27 (m, 2 H, $C^{1''}H_2$), 3.80 (m, 2 H, C^5H_2), 4,97 (dd, 1 H, C^2H), 5.31 (s, 1 H, C^4H), 6.67 (s, 1 H, $C^{4'}$H), 6.87 (s, 2 H, $C^{2,6}$H), 7.05 (s, 1 H, $C^{4'}$H), 7.08 (s, 2 H, $C^{2',6'}$H), 7.23 (t, 1 H, NH), 7.31 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.7 ($C^{4'''}H_3$), 20.0 ($C^{3'''}H_2$), 21.1 and 21.2 (2 CH_3Ar and 2 CH_3Ar), 31.4 ($C^{2'''}H_2$), 33.3 (C^3H_2), 39.4 ($C^{1'''}H_2$), 56.5 (C^5H_2), 58.3 (C^2H), 73.6 (C^4H), 116.4 ($C^{2'',6''}$H), 125.0 ($C^{2',6'}$H), 125.1 ($C^{4''}$H), 132.5 ($C^{4'}$H), 135.0 and 137.3 ($C^{1'}$ and $C^{1''}$), 138.2 and 138.6 ($C^{3',5'}$ and $C^{3'',5''}$), 152.6 (OCONH), 170.1 (CON), 172.2 (CONH).

Anal. Calcd for $C_{27}H_{34}N_3O_4$: C, 69.82; H, 7.32; N, 9.05. Found: C, 69.70; H, 7.30; N, 8.99.

Deprotection of *N*-*tert*-Butoxycarbonyl Derivatives; General Procedure

A solution of either **22**, **27** or **26** (0.8 mmol) in trifluoroacetic acid and CH_2Cl_2 (20 mL, 30:70) was stirred at r.t. for 30 min. The mixture was basified with NH_4OH and extracted with CH_2Cl_2. The solvent was evaporated and the residual solid collected.

N′-(3,5-Dimethylphenyl)-(4*R*)-(3,5-dimethylbenzoyloxy)-L-prolinamide (33) (Scheme 6)

From **22** (1.22 mmol), 402 mg of a white oil that crystallized on standing was obtained; yield: 92%; mp 106–109 °C; $[\alpha]_D^{20}$ +1.39 (*c* = 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (m, 1 H, C^3H_a), 2.30 (s, 6 H, 2 CH_3Ar′), 2.36 (s, 6 H, 2 CH_3Ar″), 2.60 (m, 1 H, C^3H_b), 3.00 (br s, 1 H, NH), 3.15 (m, 1 H, C^5H_a), 3.39 (m, 1 H, C^5H_b), 4.19 (dd, 1 H, C^2H), 5.45 (m, 1 H, C^4H), 6.75 (s, 1 H, $C^{4'}$H), 7.20 (s, 1 H, $C^{4''}$H), 7.24 (s, 2 H, $C^{2',6'}$H), 7.62 (s, 2 H, $C^{2'',6''}$H), 9.55 (br s, 1 H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (2 CH_3Ar′ and 2 CH_3Ar″), 37.5 (C^3H_2), 53.9 (C^5H_2), 60.9 (C^2H), 78.2 (C^4H), 118.0 ($C^{2',6'}$H), 127.0 ($C^{4'}$H), 127.5 ($C^{2'',6''}$H), 130.0 ($C^{1''}$), 135.5 ($C^{4''}$H), 137.9 ($C^{1'}$), 138.5 ($C^{3',5'}$ and $C^{3'',5''}$), 166.5 (COO), 172.5 (CONH).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.85; H, 6.93; N, 7.58.

N′-(3,5-Dimethylphenyl)-(4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-prolinamide (34) (Scheme 3)

The solid was chromatographed on silica gel (hexane–EtOAc, 50:50) and crystallized from EtOH–H_2O; yield: 91%; mp 159–160 °C; $[\alpha]_D^{20}$ –0.7 (*c* = 1, $CHCl_3$); $[\alpha]_D^{20}$ +9.1 (*c* = 1, 96% EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (m, 1 H, C^3H_a), 2.29 (s, 12 H, 4 CH_3Ar), 2.56 (dd, 1 H, $J_{3a,3b}$ = 16 Hz, $J_{2,3b}$ = 8 Hz, C^3H_b), 3.02 (dd, 1 H, $J_{5a,5b}$ = 12 Hz, $J_{4,5a}$ = 3.4 Hz, C^5H_a), 3.30 (dd, 1 H, $J_{4,5b}$ = 1.8 Hz, C^5H_b), 4.12 (dd, 1 H, $J_{2,3a}$ = $J_{2,3b}$ = 8 Hz, C^2H), 5.30 (m, 1 H, C^4H), 6.72 and 6.76 (s and s, 1 H and 1 H, $C^{4'}$H and $C^{4''}$H), 6.90 (br s, 1 H, NHCOO), 7.05 and 7.25 (s and s, 2 H and 2 H, $C^{2',6'}$H and $C^{2'',6''}$H), 9.58 (br s, 1 H, NHCO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.3 (4 CH_3Ar), 36.8 (C^3H_2), 53.3 (C^5H_2), 60.6 (C^2H), 76.9 (C^4H), 116.4 and 117.0 ($C^{2',6'}$H and $C^{2'',6''}$H), 125.0 and 125.9 ($C^{4'}$H and $C^{4''}$H), 137.2 and 138.0 ($C^{1'}$ and $C^{1''}$), 138.6 ($C^{3',5'}$ and $C^{3'',5''}$), 153.1 (NHCOO), 172.7 (CONH).

Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13, N, 11.01. Found: C, 68.94; H, 7.13; N, 11.24.

(4*R*)-(3,5-Dimethylphenylaminocarbonyloxy)-L-proline (35) (Scheme 3)

The solid obtained was crystallized from EtOH; yield: 73%; mp 220–221 °C; $[\alpha]_D^{20}$ +14.4 (*c* = 1, DMSO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.11 (m, 1 H, C^3H_a), 2.19 (s, 6 H, 2 CH_3Ar), 2.24 (m, 1 H, C^3H_b), 3.20 (d, 1 H, C^5H_a), 3.40 (br s, 2 H, NH_2^+), 3.52 (dd, 1 H, C^5H_b), 3.93 (dd, 1 H, $J_{2,3a}$ = $J_{2,3b}$ = 8.5 Hz, C^2H), 5.15 (m, 1 H, C^4H), 6.63 (s, 1 H, $C^{4'}$H), 7.07 (s, 2 H, $C^{2',6'}$H), 9.70 (br s, 1 H, HNCOO).

^{13}C NMR (50.3 Mz, DMSO-d_6): δ = 21.3 (CH_3), 35.4 (C^3H_2), 50.4 (C^5H_2), 59.9 (C^2H), 73.7 (C^4H), 116.4 ($C^{2',6'}$H), 124.5 ($C^{4'}$H), 138.0 ($C^{3',5'}$), 138.9 ($C^{1'}$), 152.9 (HNCOO), 170.3 (CO_2H).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found : C, 60.15; H, 6.45; N, 9.83.

N-Benzoyl Derivatives of (4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-proline (Scheme 3)

Following the procedure above described for **1** and **5**, compounds **28** and **30** were obtained from **35** and the appropriate acyl chloride.

N-(3,5-Dinitrobenzoyl)-4*(R)*-(3,5-dimethylphenylaminocarbonyloxy)-L-proline (28)

The solid resulting from the workup procedure was chromatographed on silica gel ($CHCl_3$–MeOH, 97:3); yield: 65%; mp 149–150 °C; $[\alpha]_D^{20}$ –99.4 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, acetone-d_6): δ = 2.26 (s, 6 H, 2 CH_3Ar), 2.48 (m, 1 H, C^3H_a), 2.68 (m, 1 H, C^3H_b), 3.85 (d, 1 H, $J_{5a,5b}$ = 12 Hz, C^5H_a), 4.24 (dd, 1 H, $J_{4,5b}$ = 4 Hz, C^5H_b), 4.84 (dd, 1 H, $J_{2,3a}$ = $J_{2,3b}$ = 8 Hz, C^2H), 5.46 (m, 1 H, C^4H), 6.70 (s, 1 H, $C^{4''}$H), 6.73 (s, $C^{4''}$H, *s-cis*), 7.15 (s, 2 H, $C^{2'',6''}$H), 7.25 (s, $C^{2'',6''}$H, *s-cis*), 8.64 (br s, 1 H, NH), 8.79 (d, 2 H, $C^{2',6'}$H), 9.09 (m, 1 H, $C^{4'}$H), 9.14 (d, $C^{2',6'}$H, *s-cis*), 9.22 (m, $C^{4'}$H, *s-cis*).

^{13}C NMR (50.3 MHz, acetone-d_6): δ = 21.8 (CH_3Ar), 36.1 (C^3H_2), 56.8 (C^5H_2), 60.0 (C^2H), 74.4 (C^4H), 117.2 ($C^{2'',6''}$H), 121.2 ($C^{4'}$H), 125.6 ($C^{4''}$H), 128.9 ($C^{2',6'}$H), 139.4 ($C^{3',5'}$), 139.8 and 140.0 ($C^{1''}$ and $C^{3'',5''}$), 149.8 ($C^{1'}$), 153.7 (HNCOO), 166.4 and 166.8 (CON and CO_2H).

Anal. Calcd for $C_{21}H_{20}N_4O_9$: C, 53.40; H, 4.27; N, 11.86. Found: C, 53.56; H, 4.44; N, 11.36.

N-(3,5-Dimethylbenzoyl)-(4*R*)-(3,5-dimethylphenylaminocarbonyloxy)-L-proline (30)

The title compound was obtained in 30% yield after purification by chromatography on silica gel ($CHCl_3$–MeOH, 99:1). Alternatively, compound **30** was obtained from **13** (Scheme 5).

(4*R*)-Acyloxy-L-prolinamide Derivatives; General Procedure

The appropriate acyl chloride (0.8 mmol) and aq 2 N NaOH (1.6 mL) were added separately to a solution of either **14**, **15** or **21** (0.8 mmol) in $CHCl_3$ (8 mL). The mixture was stirred at r.t. and the course of the reaction was controlled by TLC. The mixture was poured into H_2O, and the organic extracts were washed with aq 2 N NaOH. After drying the organic solution (Na_2SO_4), the solvent was removed under reduced pressure.

N-(*tert*-Butoxycarbonyl)-*N*′-(3,5-dimethylphenyl)-(4*R*)-(3,5-dimethylbenzoyloxy)-L-prolinamide (22) (Scheme 6)

After a reaction period of 24 h, the product obtained was chromatographed on silica gel using hexane–EtOAc mixtures as eluent; yield: 60%; yellowish oil; $[\alpha]_D^{20}$ –99.4 (*c* = 1, 96% EtOH).

^{1}H NMR (300 MHz, DMSO-d_6, 60 ºC): δ = 1.19 [s, 9 H, $C(CH_3)_3$], 2.23 (s, 6 H, 2 CH_3Ar), 2.45 (m, 1 H, C^3H_a), 3.45 (m, 1 H, C^3H_b), 3.60 (m, 1 H, C^5H_a), 3.70 (m, 1 H, C^5H_b), 4.45 (m, 1 H, C^2H), 5.43 (m, 1 H, C^4H), 6.70 (s, 1 H, $C^{4'}$H), 7.23 (s, 2 H, $C^{2',6'}$H), 7.33 (s, 1 H, $C^{4''}$H), 7.56 (s, 2 H, $C^{2'',6''}$H), 9.79 (s, 1 H, CONH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (4 CH_3Ar), 29.2 [$C(CH_3)_3$], 33.1 (C^3H_2), 53.6 (C^5H_2), 59.9 (C^2H), 73.9 (C^4H), 81.0 [$C(CH_3)_3$], 118.9 ($C^{2',6'}$H), 126.0 ($C^{4'}$H), 128.5 ($C^{2'',6''}$H), 130.0 ($C^{1''}$), 135.9 ($C^{4''}$H), 136.1 ($C^{1'}$), 138.5 ($C^{3',5'}$), 139.0 ($C^{3'',5''}$), 156.5 (NCOO), 166.5 (COO), 169.5 (CONH).

Anal. Calcd for $C_{27}H_{34}N_2O_5$: C, 69.51; H, 7.34; N, 6.00. Found: C, 69.73; H, 7.77; N, 5.78.

***N′*-(Butyl)-*N*-(3,5-dimethylbenzoyl)-(4*R*)-(3,5-dimethylbenzoyloxy)-L-prolinamide (23) (Scheme 5)**

After a reaction period of 24 h, the solid obtained was crystallized from EtOH–H_2O; yield: 58%; mp 131–132 °C; $[\alpha]_D^{20}$ –104.8 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, $C^{4''}H_3$), 1.36 (m, 2 H, $C^{3''}H_2$), 1.50 (m, 2 H, $C^{2''}H_2$), 2.28 (s, 6 H, 2 C*H*$_3$Ar), 2.35 (s, 6 H, 2 C*H*$_3$Ar), 2.39 (m, 1 H, C^3H_a), 2.99 (m, 1 H, C^3H_b), 3.30 (q, 2 H, $C^{1''}H_2$), 3.80 (m, 2 H, C^5H_2), 5.03 (dd, 1 H, C^2H), 5.49 (m, 1 H, C^4H), 7.06 (s, 3 H, $C^{2',6'}H$ and $C^{4'}H$), 7.20 (s and br s, 2 H, $C^{4'''}H$ and NH), 7.54 (s, 1 H, $C^{2''',6'''}H$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.6 ($C^{4''}H_3$), 20.0 ($C^{3''}H_2$), 21.0 (4 *C*H$_3$Ar), 31.4 ($C^{2''}H_2$), 32.6 (C^3H_2), 39.4 ($C^{1''}H_2$), 56.0 (C^5H_2), 58.0 (C^2H), 73.5 (C^4H), 124.7 ($C^{2',6'}H$), 127.2 ($C^{2''',6'''}H$), 129.3 ($C^{1'''}$), 132.2 ($C^{4'}H$), 135.0 ($C^{4'''}H$), 135.2 ($C^{1'}$), 138.0 ($C^{3',5'}$), 138.2 ($C^{3''',5'''}$), 166.0 (COO), 170.0 (CON), 172.3 (CONH).

Anal. Calcd for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.60; N, 6.22. Found: C, 71.69; H, 7.30; N, 6.29.

***N*-(3,5-Dimethylbenzoyl)-(4*R*)-(3,5-dimethylbenzoyloxy)-*N′*-(3,5-dimethylphenyl)-L-prolinamide (24) (Scheme 5)**

After 68 h, the solid resulting from the workup procedure was crystallized from EtOH–H_2O; yield: 91%; mp 202–203 °C; $[\alpha]_D^{20}$ –211.7 (*c* = 1,5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.27 (s, 6 H, 2 C*H*$_3$Ar), 2.28 (s, 6 H, 2 C*H*$_3$Ar), 2.37 (s, 6 H, 2 C*H*$_3$Ar), 2.46 (m, 1 H, C^3H_a), 3.14 (m, 1 H, C^3H_b), 3.82 (m, 2 H, C^5H_2), 5.24 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 8 Hz, C^2H), 5.54 (m, 1 H, C^4H), 6.75 (s, 1 H, $C^{4''}H$), 7.07 (s, 3 H, $C^{2',6'}H$ and $C^{4'}H$), 7.20 (s, 1 H, $C^{4'''}H$), 7.22 (s, 2 H, $C^{2'',6''}H$), 7.55 (s, 2 H, $C^{2''',6'''}H$), 9.46 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.1 (4 *C*H$_3$Ar), 21.2 (2 *C*H$_3$Ar), 32.0 (C^3H_2), 56.0 (C^5H_2), 59.0 (C^2H), 73.4 (C^4H), 117.4 ($C^{2'',6''}H$), 124.8 ($C^{2',6'}H$), 125.8 ($C^{4''}H$), 127.2 ($C^{2''',6'''}H$), 129.2 ($C^{1'''}$), 132.4 ($C^{4'}H$), 134.9 ($C^{1'}$), 135.0 ($C^{4'''}H$), 137.8 ($C^{1''}$), 138.1, 138.3 and 138.5 ($C^{3',5'}$, $C^{3'',5''}$and $C^{3''',5'''}$), 166.0 (COO), 167.5 (CON), 172.9 (CONH).

Anal. Calcd for $C_{31}H_{34}N_2O_4$: C, 74.67; H, 6.87; N, 5.62. Found: C, 74.30; H, 6.95; N, 5.28.

***N′*-(Butyl)-*N*-(3,5-dimethylbenzoyl)-(4*R*)-(3,5-dinitrobenzoyloxy)-L-prolinamide (25) (Scheme 5)**

After 48 h of reaction, the resulting solid was chromatographed on silica gel (hexane–EtOAc, 60:40); yield: 40%; mp 123–124 °C; $[\alpha]_D^{20}$ –87.5 (*c* = 1, 96% EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, $C^{4''}H_3$), 1.35 (m, 2 H, $C^{3''}H_2$), 1.50 (m, 2 H, $C^{2''}H_2$), 2.34 (s, 6 H, 2 C*H*$_3$Ar), 2.47 (m, 1 H, $J_{3a,3b}$ = 15 Hz, $J_{2,3a}$ = 7.5 Hz, $J_{3a,4}$ = 5 Hz, C^3H_a), 3.12 (m, 1 H, $J_{3b,4}$ = 4 Hz, $J_{2,3b}$ = 7.5 Hz, C^3H_b), 3.28 (q, 2 H, $C^{1''}H_2$), 3.87 (m, 2 H, $J_{5a,5b}$ = 12.5 Hz, C^5H_a), 3.96 (dd, $J_{4,5b}$ = 3.7 Hz, C^5H_b), 5.05 (dd, 1 H, $J_{2,3a} = J_{2,3b}$ = 7.5 Hz, C^2H), 5.61 (m, 1 H, C^4H), 7.11 (s, 1 H, $C^{4'}H$), 7.14 (s, 2 H, $C^{2',6'}H$), 9.03 (dd, 1 H, $C^{2''',6'''}H$), 9.25 (t, 1 H, $C^{4'''}H$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.6 ($C^{4''}H_3$), 19.9 ($C^{3''}H_2$), 21.1 (2 *C*H$_3$Ar), 31.3 ($C^{2'}H_2$), 32.5 (C^3H_2), 39.5 ($C^{1''}H_2$), 55.5 (C^5H_2), 57.6 (C^2H), 76.2 (C^4H), 122.6 ($C^{4'''}H$), 124.8 ($C^{2',6'}H$), 129.2 ($C^{2''',6'''}H$), 132.5 (C^4H), 133.0 ($C^{1''}$), 134.8 ($C^{1'}$), 138.4 ($C^{3',5'}$), 148.5 ($C^{3''',5'''}$), 161.7 (COO), 169.4 (CON), 172.0 (CONH).

Anal. Calcd for $C_{25}H_{28}N_4O_8$: C, 58.59; H, 5.51; N, 10.93. Found: C, 58.51; H, 5.87; N, 10.54.

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