

HETEROCYCLES, Vol. 60, No. 1, 2003, pp. 57 - 71

Received, 23rd August, 2002, Accepted, 11th November, 2002, Published online, 15th November, 2002

SYNTHESIS OF HETEROCYCLIC γ -AMINO- α,β -UNSATURATED ACID DERIVATIVES AND PEPTIDE-HETEROCYCLE HYBRIDS[†]

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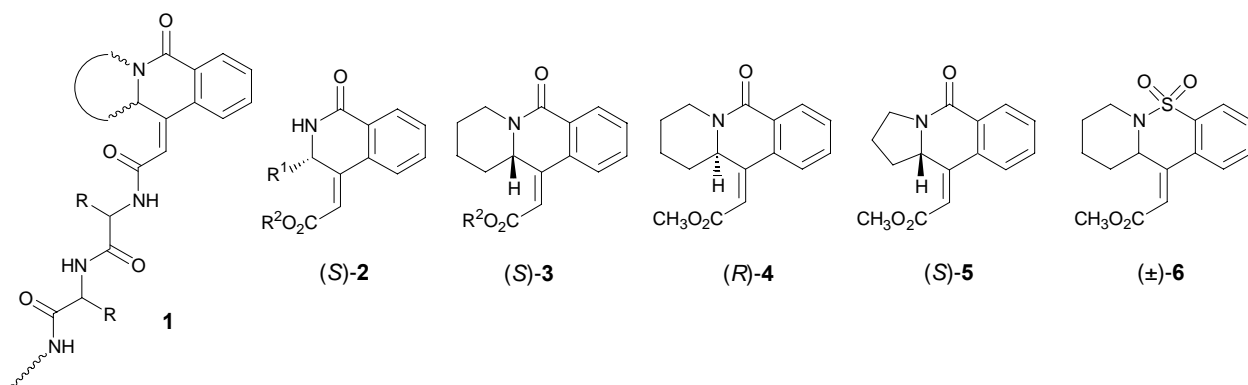
Abstract- The syntheses of the γ -amino- α,β -unsaturated esters [(*R*)-**4**, (*S*)-**5**, and (\pm)-**6**] are reported. The methodology for the preparation of these triannular heterocycles involves two synthetic sequences from *N*-substituted amino alcohols: a ‘one-pot’ sequential Swern oxidation-Wittig reaction and an intramolecular Heck reaction. The γ -amino- α,β -unsaturated ester [(*R*)-**4**] has been used for the synthesis of the peptide-heterocycle hybrids (**19-21**).

INTRODUCTION

Polyannular heterocyclic compounds¹ are frequently found as natural products² and as synthetic biological active compounds.³ In connection with an ongoing project on the synthesis of compounds of type (**1**) (*peptide-heterocycle hybrids*), we have required different functionalized polyannular heterocycles as scaffolds. Structurally, the peptide-heterocycle hybrids (**1**) possess a peptide chain linked to a polyannular heterocycles, and they are prepared by condensation of the corresponding peptide derivative with the heterocyclic carboxylic acid. It is worth to mention that some of the compounds of type (**1**) are inhibitors of the protease calpain.^{4,5}

Recently, we have reported the synthesis of heterocycles with indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (*yohimbane*), isoquinolino[3,2-*a*]isoquinoline (*berberane*), pyrido[1,2-*b*]isoquinoline, and isoquinoline backbones.⁶ As a further extension, we have disclosed efficient synthesis of chiral isoquinoline [(*S*)-**2**] and pyrido[1,2-*b*]isoquinoline [(*S*)-**3**] derivatives in enantiomerically pure forms.⁷ We have found that both the biological activities as well as the conformations of the peptide-heterocycle hybrids (**1**) depend on the structure of the heterocycle.⁸

[†] Dedicated to the memory of Profesor Manuel Lora-Tamayo.



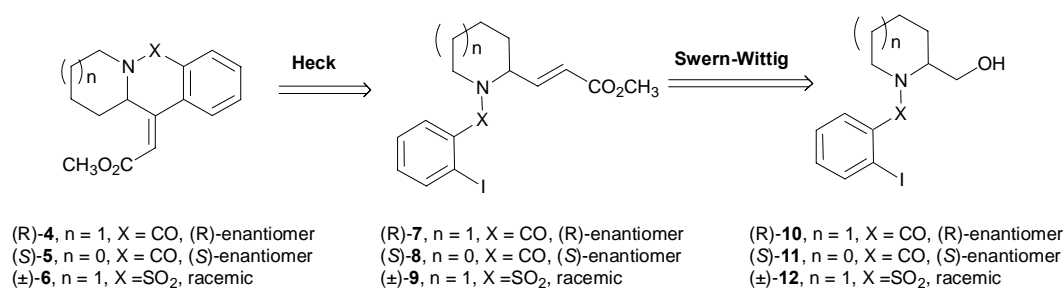
With the objective to study further the influence of the heterocyclic fragment on the properties of the peptide-heterocycle hybrids (**1**), we have required the triannular heterocycles (**4-6**). The compound [(*R*)-**4**] is enantiomer of the heterocycle previously used as scaffold, and it can provide information on the influence of the stereochemistry of the scaffold on the properties (biological activity and conformational preferences) of the hybrids (**1**). The pyrrolo[1,2-*b*]isoquinoline derivative [(*S*)-**5**] would provide data on the effect of the size of the rings in the fused heterocyclic system. Finally, the heterocycle [(±)-**6**] is an analogue with sulfonamide functionality (sultam) instead of the lactam. Since the amide and sulfonamide groups have quite different steric characteristics and hydrogen-acceptor capacities, quite distinct properties are expected for the lactam and the sultam derivatives; moreover, many sulfonamides possess biological activity.⁹ In this paper, we report the synthesis of the above mentioned heterocycles as well as the application of the pyrido[1,2-*b*]isoquinoline [(*R*)-**4**] to the preparation of peptide-heterocycle hybrids.

RESULTS AND DISCUSSION

Our previous works^{6,7} have shown that the intramolecular Heck reaction¹⁰ is a convenient method for the synthesis of polyanular heterocycles. Consequently, we have also planned the synthesis of the target molecules (**4-6**) employing the same methodology. The retrosynthetic analysis is indicated in Scheme 1. The target molecules would be prepared by the Heck reaction of the corresponding *o*-iodobenzamide (**7**, **8**) or *o*-iodobenzenesulfonamide (**9**), which in turn would be obtained from readily available *N*-substituted amino alcohols (**10-12**) by a sequential Swern-Wittig reaction.¹¹

The synthesis of the pyrido[1,2-*b*]isoquinoline [(*R*)-**4**] is indicated in Scheme 2. The chiral, enantiomerically pure, starting material [(*R*)-**13**] was obtained using enzymatic reactions catalyzed by the enzyme acylase I (AA-I) from *Aspergillus* species. Although the natural activity of AA-I is the hydrolysis of the amide bond of *N*-acyl amino acids,¹² we have previously shown that this enzyme is also able to catalyze the acylation of amines and alcohols in the presence of an acylating agent in an anhydrous organic solvent.¹³ The method has been previously used for the synthesis of chiral secondary alcohols,¹⁴ amino alcohols,¹⁵ and peptides.

The *N*-protected amino alcohol [(±)-**13**] was submitted to a transesterification catalyzed by AA-I using

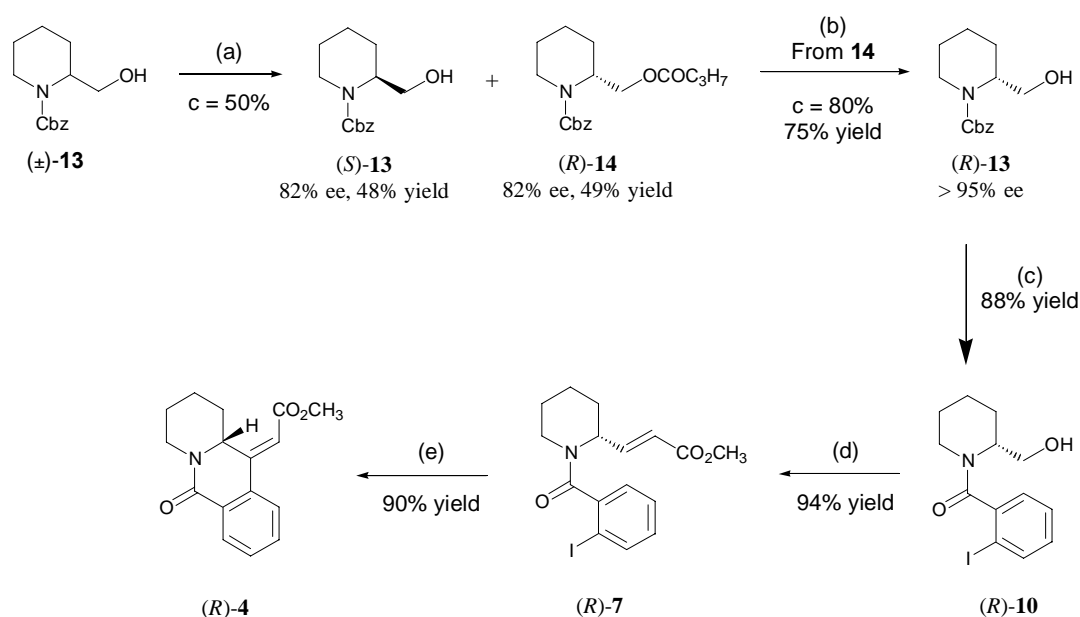


Scheme 1

vinyl butyrate as acylating agent.¹⁶ The kinetic resolution was carried out up to a *ca.* 50% conversion to give, after chromatographic separation, the alcohol [(*S*)-**13**] (82% ee) and the butyrate [(*R*)-**14**] (82% ee). The enantiomerically enriched (*R*)-**14** (82% ee) was submitted to a second enzymatic reaction: a hydrolysis catalyzed by AA-I. The advantages of the enzymatic hydrolysis *versus* the chemical hydrolysis are twofold. First, the enzymatic procedure is carried out under very mild experimental conditions, avoiding the facile N- to O-acyl migration found with similar compounds.¹⁷ On the other hand, the enzymatic hydrolysis allows increasing the enantiomeric purity of the target molecule. Since the starting butyrate [(*R*)-**14**] was 82% ee, we carried out this second enzymatic reaction up to a *ca.* 80% conversion, giving the alcohol [(*R*)-**13**] in enantiomerically pure form in 75% yield (37% overall yield for the two steps). The benzyloxycarbonyl group of the *N*-protected amino alcohol [(*R*)-**13**] was removed by hydrogenation to give (*R*)-2-hydroxymethylpiperidine, which without purification, was acylated with *o*-iodobenzoyl chloride to provide (*R*)-**10**; that, in turn, was submitted to a two-step ‘one-pot’ sequential Swern oxidation-Wittig olefination with methyl triphenylphosphoranylideneacetate in dichloromethane. We have found that this is a practical procedure that avoids the manipulation of sensitive *N*-acylated α -amino aldehydes (prone to hydration and racemization).⁷ The reaction was totally stereoselective giving the γ -amino- α,β -unsaturated ester [(*R*)-**7**] with *E*-configuration ($J = 15.9$ Hz between the olefinic protons).¹⁸ Finally, the Heck reaction of (*R*)-**7** was carried out at room temperature under Overman’s conditions¹⁹ to give the tricyclic compound [(*R*)-**4**] as a single diastereoisomer and regioisomer (Scheme 2). The structure of (*R*)-**4** was ascertained by comparison with the enantiomer,⁷ and its enantiomeric purity was over 95%, as assessed by comparison with the data of (*S*)-**4** and by transformation to peptide-heterocyclic hybrids (see below).

A similar methodology was also suitable for the synthesis of the chiral pyrrolo[1,2-*b*]isoquinoline [(*S*)-**5**] (Scheme 3). The known²⁰ *N*-protected amino alcohol [(*S*)-**11**] was submitted to the ‘one-pot’ sequential Swern oxidation-Wittig reaction to give the (*E*)- α,β -unsaturated ester (**8**) as a single stereoisomer ($J = 15.6$ Hz between the two olefinic protons). The key intramolecular Heck reaction was first attempted as described for compound (**7**) (Overman’s conditions at room temperature, see Scheme 2); but the desired pyrrolo[1,2-*b*]isoquinoline derivative [(*S*)-**5**] was obtained in low yield (37 %) after a prolonged reaction

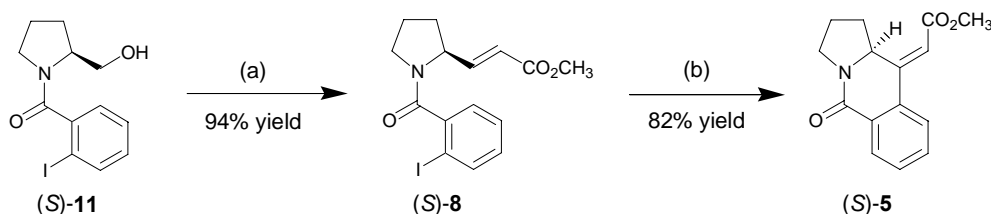
time. The different reactivity between **7** and **8** might be attributed to the conformational preferences (including rotamers around the amide bond) of *N*-acylated piperidines and *N*-acylated pyrrolidines, that can be translated to a higher steric hindrance in the cyclization leading to the pyrrolo[1,2-*b*]isoquinoline ring system. After extensive experimentation, we achieved satisfactory results on performing the Heck cyclization under similar condition, but in the absence of Ag(I) and in refluxing acetonitrile.²¹ This procedure afforded the target pyrrolo[1,2-*b*]isoquinoline [(*S*)-**5**] in 82% yield, as a single regioisomer (exocyclic olefin) and stereoisomer (*Z*-olefin). The structure of **5** was confirmed by a NOESY experiment that showed the proximity between H-9 (the *peri*-aromatic proton) and the olefinic proton.



Scheme 2. (Cbz = Benzyloxycarbonyl). (a) AA-I (300 U/mmol), vinyl butyrate (1.5 mol equiv.), toluene, rt, 6 h. (b) AA-I (300 U/mmol), phosphate buffer (pH 7.0), H₂O, rt, 7 h. (c) (i) H₂ (45 psi), Pd/C, MeOH, rt, 8 h; (ii) *o*-IC₆H₄COCl, 13N NaOH, H₂O, THF, overnight. (d) (i) DMSO (2.8 mol equiv.), (COCl)₂ (1.4 mol equiv.), CH₂Cl₂, -70°C, 1.5 h; Et₃N (5 mol equiv.), -70°C to rt, 1 h; (ii) Ph₃P=CHCO₂CH₃ (1.3 mol equiv.), rt, overnight. (e) Pd(OAc)₂ (0.03 mol equiv.), Ph₃P (0.1 mol equiv.), Et₃N (2 mol equiv.), AgNO₃ (1 mol equiv.), CH₃CN, rt, overnight.

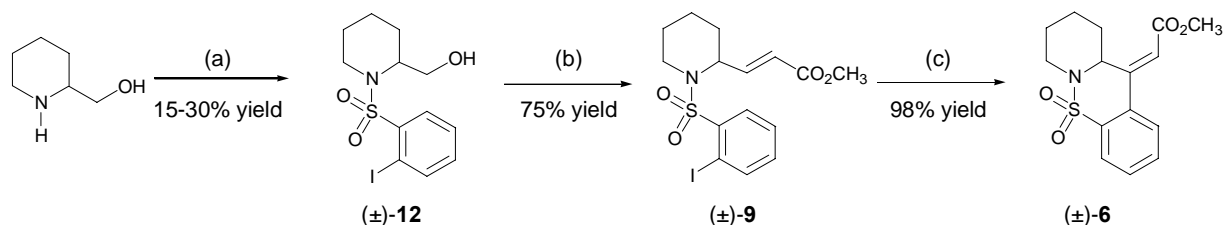
The sulfonamide (**6**) was prepared in racemic form, what is adequate for our comparative study with the lactam (**4**). The synthesis of (±)-**6** started from commercially available 2-hydroxymethylpiperidine, that was sulfonated with *o*-iodobenzenesulfonyl chloride²² under Schotten-Baumann conditions to give the sulfonamide (**12**) (Scheme 4). We found this reaction to be quite capricious, giving variable (and low) yields of **12**. We suspect that the flaws of this reaction arose from some impurities generated during the preparation of *o*-iodobenzenesulfonyl chloride, which we have not been able to eliminate. Since the procedure gave enough quantity of the sulfonamide (**12**), we did not pursue further improvement in the method. The sequential Swern oxidation-Wittig reaction from the alcohol (**12**) went in high yield, giving the *E*-olefin (**9**) as a single stereoisomer (*J* = 16.0 Hz between the two olefinic protons). The Heck cyclization of **9** was done using palladium acetate, triphenylphosphine and triethylamine in refluxing

acetonitrile, producing the target molecule [(±)-**6**] in nearly quantitative yield, with total stereoselectivity and regioselectivity. The stereochemistry at the exocyclic double bond was confirmed by NOE between the olefinic proton and H-1 (the *peri*-aromatic proton).



Scheme 3. (a) (i) DMSO (2.8 mol equiv.), (COCl)₂ (1.4 mol equiv.), CH₂Cl₂, -70°C, 5 h; Et₃N (5 mol equiv.), -70°C to rt, 3 h; (ii) Ph₃P=CHCO₂CH₃ (1.2 mol equiv.), rt, 20 h. (b) Pd(OAc)₂ (0.05 mol equiv.), Ph₃P (0.12 mol equiv.), Et₃N (2 mol equiv.), CH₃CN, reflux, 4.5 h.

As an additional application, the chiral pyrido[1,2-*b*]isoquinoline [(*R*)-**4**] was used for the synthesis of peptide-heterocycle hybrids (Scheme 5). The ester (**4**) was hydrolyzed to the corresponding acid [(*R*)-**15**], that, after activation as mixed anhydride,²³ was separately reacted with the peptide derivatives (**16**, **17**, and **18**), to give the hybrids (**19**, **20**, and **21**), respectively, in unoptimized moderate yields. Both the ¹H- and ¹³C-NMR spectra of each hybrid present single set of signals, what is an indication of their high diastereoisomeric purities and, hence, the enantiomeric purity of the starting heterocycle.



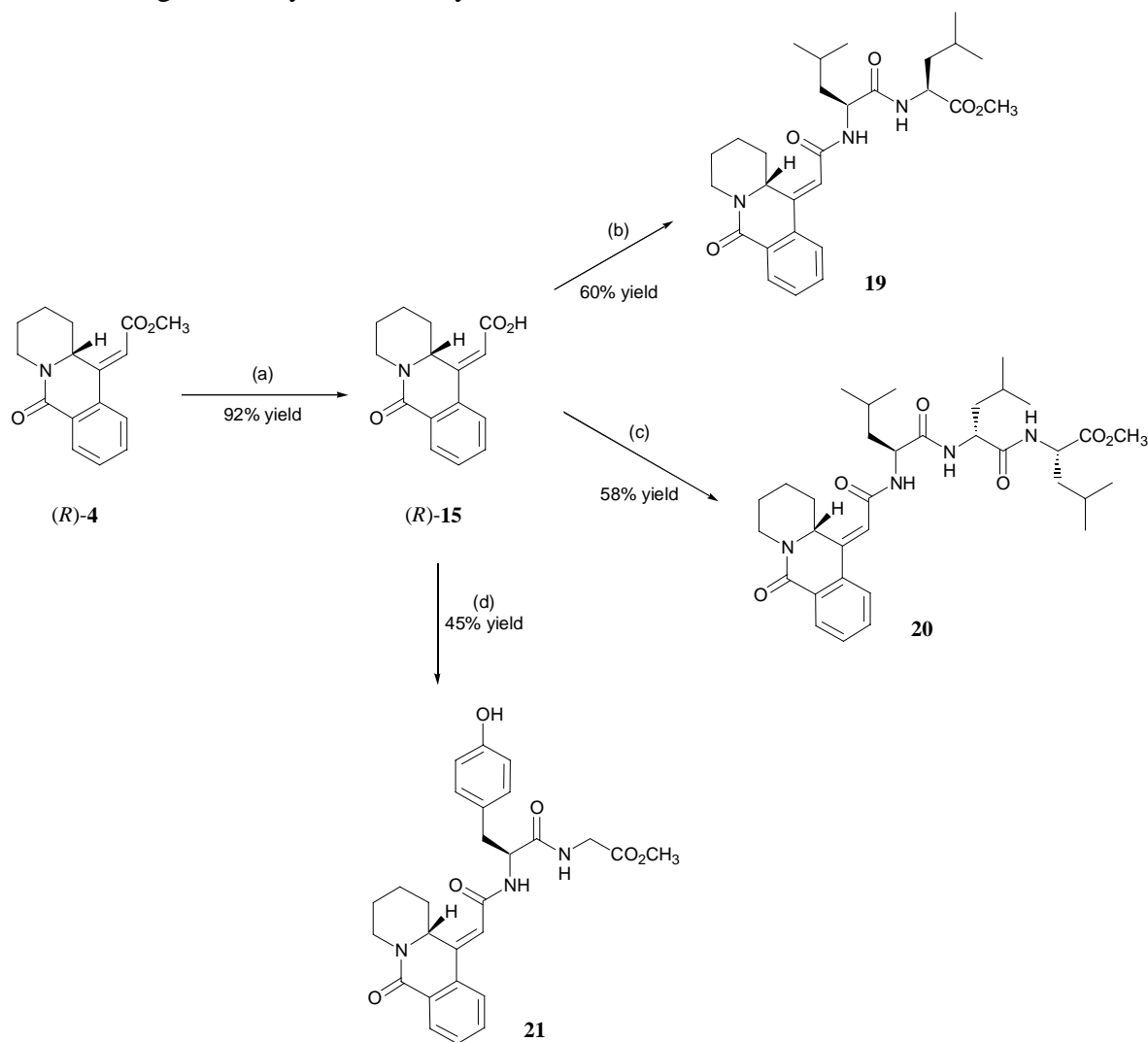
Scheme 4. (a) *o*-IC₆H₄SO₂Cl (1 mol equiv.), 13N NaOH, H₂O, THF, 0°C to rt, 22 h (b) (i) DMSO (2.8 mol equiv.), (COCl)₂ (1.4 mol equiv.), CH₂Cl₂, -70°C, 6 h; Et₃N (5 mol equiv.), -70°C to rt, 4 h; (ii) Ph₃P=CHCO₂CH₃ (1.2 mol equiv.), rt, 16 h. (c) Pd(OAc)₂ (0.05 mol equiv.), Ph₃P (0.12 mol equiv.), Et₃N (2 mol equiv.), CH₃CN, reflux, 5 h.

CONCLUSIONS

Summarizing, we have reported the preparation of several functionalized triannular heterocycles that can be used as scaffolds for the synthesis of peptide-heterocycle hybrids. These examples show that the strategy based on sequential Swern oxidation/Wittig olefination/Heck cyclization is an efficient method to obtain this kind of molecules (high overall yield and selectivity). It is worth to mention that the intramolecular Heck reaction provides trisubstituted olefins with total regioselectivity and stereoselectivity, a goal difficult to achieve.²⁴

We have also disclosed the hydrolysis of esters catalyzed by the enzyme acylase I from *Aspergillus* species (AA-I), what is a non-natural activity of this enzyme. This reaction goes with good

enantioselectivity under mild experimental conditions, avoiding side reactions. These results complement our previous findings on the synthetic utility of AA-I.



Scheme 5. (a) 1 M aqueous LiOH (2.0 mol equiv.), THF-H₂O, rt, 4 h (94%). (b) (i) NMM (1.0 mol equiv.), *i*-C₄H₉OCOCl (1.0 mol equiv.), CHCl₃, 0°C, 4 h; (ii) CF₃CO₂H.H-L-Leu-L-Leu-OCH₃ (**16**, 1.2 mol equiv.), NMM (3 mol equiv.), CHCl₃, 0°C to rt, 17 h (c) (i) NMM (1.0 mol equiv.), *i*-C₄H₉OCOCl (1.0 mol equiv.), CHCl₃, 0°C, 4 h; (ii) CF₃CO₂H.H-L-Leu-D-Leu-L-Leu-OCH₃ (**17**, 1.2 mol equiv.), NMM (3 mol equiv.), CHCl₃, 0°C to rt, 17 h. (d) (i) NMM (1.0 mol equiv.), *i*-C₄H₉OCOCl (1.0 mol equiv.), CHCl₃, 0°C, 4 h; (ii) CF₃CO₂H.H-L-Tyr-Gly-OCH₃ (**18**, 1.2 mol equiv.), NMM (3 mol equiv.), CHCl₃, 0°C to rt, 20 h.

We also describe the application of the pyrido[1,2-*b*]isoquinoline derivative [(*R*)-**4**] to the synthesis of peptide-heterocycle hybrids. Our preliminary results indicate that the stereochemistry of the heterocyclic fragment in the peptide-heterocycle hybrids is important for their biological activity: thus, we have found that while the hybrid (**20**) is a poor calpain inhibitor, its epimer having the (*S*)-configuration at the heterocycle is a potent calpain inhibitor.

EXPERIMENTAL

All the reactions with sensitive materials were carried out using dry solvents under argon atmosphere. All the solvents and reagents were commercially available and, unless otherwise indicated, were used as

received. Anhydrous solvents were purchased from Aldrich and kept over molecular sieves under argon atmosphere. The enzyme acylase I from *Aspergillus* species (AA-I) was purchased from Aldrich or Sigma, having a specific activity of *ca.* 0.5 U/mg. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were measured in Varian-UNITY-500, Varian-INOVA-400, Varian-INOVA-300, Varian-GEMINI-200, or Bruker-AM-200; chemical shifts (δ) are reported in parts per million, and the coupling constants are indicated in Hz. Unless otherwise indicated, all the NMR spectra were taken at room temperature (*ca.* 295 K). $^1\text{H-NMR}$ spectra were referenced to the chemical shift of either TMS ($\delta = 0.00$ ppm) or the residual proton in the deuterated solvent. $^{13}\text{C-NMR}$ spectra were referenced to the chemical shift of the deuterated solvent. The multiplicity of the signals in the $^{13}\text{C-NMR}$ spectra was determined by APT, DEPT, or HMQC experiments. All the electron-impact ionization MS were recorded in a RMU-GMG spectrometer (Hitachi-Perkin-Elmer). Electrospray and chemical ionization MS were taken in a Hewlett-Packard MDS-Series 1100 equipment. Combustion analyses were realized in a Carlo Erba EA 1180-Elemental Analyzer. The optical rotations were determined in a Perkin-Elmer 241 MC polarimeter at room temperature (*ca.* 295 K). The melting points were measured on a Kofler hot-stage apparatus and are uncorrected. All the preparative chromatographies were done with silica gel (40-63 nm) using the technique of flash-chromatography.²⁵ The acronym Piq is used for the acyl radicals from **15**. The rest of the amino acids are denoted by the standard three-letters code.

Sequential enzymatic esterification/hydrolysis of 1-benzyloxycarbonyl-2-hydroxymethyl-piperidine [(±)-13]. Synthesis of [(R)-13].

a) AA-I (24 g, 300 U/mmol) was added to a solution of (±)-**13** (10 g, 40.2 mmol) in toluene (250 mL). The mixture was stirred at rt for 5 min, and then was treated with vinyl butyrate (5.2 mL, 40.2 mmol). The mixture was stirred at rt for 6 h, and diluted with CH_2Cl_2 (*ca.* 150 mL). The enzyme was removed by filtration and washed with CH_2Cl_2 . After evaporation of the solvent, the crude product was chromatographed (hexane/EtOAc, gradient from 80:20 to 0:100) to give (R)-**14** (*ca.* 82% ee, 6.3 g, 49% yield) and [(S)-**13**] (4.8 g, 48% yield). The enantiomerically enriched ester [(R)-**14**] was used for the sequential enzymatic hydrolysis.

b) The butyrate [(R)-**14**] (*ca.* 82% ee, 6.3 g, 19.7 mmol) was suspended in a phosphate buffer (pH = 7.0, 200 mL) and treated with AA-I (12 g, 300 U/mmol). The mixture was stirred at rt for 7 h, and treated with EtOAc (400 mL). The phases were separated, and the aqueous one was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine and dried (MgSO_4). Evaporation of the solvent gave a crude product that was chromatographed (hexane/EtOAc, gradient from 80:20 to 0:100) to give the ester (**14**) (1.26 g, 20% yield) and the alcohol [(R)-**13**] (> 95% ee as determined by GLC, 4.6 g, 75%), that was identical to the enantiomer,⁷ except for the sign of the optical rotation. $[\alpha]_{\text{D}} = +28.5^\circ$ (CHCl_3 , $c = 0.9$) ($[\alpha]_{\text{D}} = -30.2^\circ$ for the enantiomer).

Synthesis of (*R*)-2-hydroxymethyl-1-(2-iodobenzoyl)piperidine [(*R*)-10]. A mixture of (*R*)-1-benzyloxycarbonyl-2-hydroxymethylpiperidine (**13**) (2.9 g, 11.6 mmol) and 10% Pd/C (580 mg) in MeOH (50 mL) was hydrogenated at rt under a hydrogen pressure of *ca.* 45 psi in a Parr shaker for 8 h. The solid was filtered off through a short path of celite and washed with MeOH. The solvent was removed at vacuum to give (*S*)-2-hydroxymethylpiperidine (1.3 g, 11.3 mmol, 97%), that without purification was dissolved in THF (10 mL), cooled at 0 °C, and sequentially treated with 13 M aqueous NaOH (3.4 mL, 44.2 mmol) and a solution of *o*-iodobenzoyl chloride (3.0 g, 11.3 mmol) in THF (4 mL). The mixture was allowed to slowly warm up to rt and stirred overnight. Then, saturated aqueous NaHCO₃ solution was added, the aqueous phase was saturated with NaCl, and thoroughly extracted with Et₂O. The organic phase was washed with brine and dried (MgSO₄). Removal of the solvent gave chromatographically homogeneous 2-iodobenzamide (**10**) (3.4 g, 88%). An analytical pure sample was obtained by chromatography (25:75 hexane-EtOAc). White solid, mp 127–130 °C. [α]_D = +27.1° (CHCl₃, *c* = 1.0). ¹H-NMR (300 MHz, CDCl₃, as a mixture of conformers) δ = 7.80 (m, 1H), 7.42–7.17 (m, 2H), 7.10 (m, 1H), 5.00–4.60 (m, 1H), 4.10–3.70 (m, 2H), 3.70–3.20 (m, 1H), 3.20–2.60 (m, 2H), 2.05–1.20 (m, 6H). ¹³C-NMR (50 MHz, CDCl₃, mixture of conformers) δ = 171.1, 170.7, 142.8, 142.4, 140.0, 138.8, 129.90, 129.86, 129.6, 128.3, 128.0, 127.1, 126.5, 92.4, 91.9, 61.2, 60.9, 60.0, 55.8, 50.8, 43.9, 43.2, 37.3, 25.8, 25.6, 25.3, 24.8, 19.7, 19.5, 19.3. MS (EI) *m/z* = 345 (M⁺, < 1), 314 (32), 231 (100), 203 (23), 105 (34), 76 (50), 55 (19), 50 (18), 41 (13). Anal. Calcd for C₁₃H₁₆NO₂I: C, 45.21; H, 4.63; N, 4.05. Found: C, 45.43; H, 4.71; N, 4.03.

Synthesis of (*R,E*)-methyl 3-[1-(2-iodobenzoyl)piperidin-2-yl]acrylate [(*R*)-7]. A solution of dry DMSO (5.7 mL, 81.2 mmol) in CH₂Cl₂ (50 mL) was dropwise added at -78 °C to a solution of oxalyl chloride (20.1 mL of a 2M solution in hexane, 40.1 mmol) in CH₂Cl₂ (75 mL). After stirring for 30 min at this temperature, a solution of the alcohol (**10**) (10 g, 29 mmol) in CH₂Cl₂ (50 mL) was added *via* cannula. The mixture was stirred at -78 °C for 90 min, and, then, dry (CH₃CH₂)₃N (20 mL, 145 mmol) was slowly added. Stirring was maintained at this temperature while the formation of the aldehyde was monitored by TLC. When the reaction was completed (*ca.* 1 h), solid Ph₃P=CHCO₂Me (11.9 g, 37.7 mmol) was added and the reaction mixture was allowed to warm slowly up to rt overnight. The solvent was removed under vacuum and the crude product was purified by column chromatography (80:20 hexane-EtOAc) to give the α,β -unsaturated esters (**7**) as a single stereoisomer (9.2 g, 94%, NMR evidence). White solid, mp 104–106 °C. [α]_D = +98.0° (CHCl₃, *c* = 1.0). ¹H-NMR (500 MHz, CDCl₃, mixture of conformers) δ = 7.81 (m, 1H), 7.38 (m, 0.7H), 7.32 (m, 0.3H), 7.21 (m, 0.3H), 7.16 (m, 0.2H), 7.11–7.02 (m, 1.5H), 7.05 (dd, *J* = 15.9, 3.8, 0.4H), 6.97 (dd, *J* = 15.9, 3.8, 0.3H), 6.77 (dd, *J* = 15.9, 3.8, 0.3H), 6.28 (dd, *J* = 15.9, 2.2, 0.3H), 5.94 (dd, *J* = 15.9, 2.2, 0.3H), 5.69 (m, 0.7H), 4.73 (m, 0.4H), 4.19 (m, 0.3H), 3.77 (s, 0.8H), 3.75 (s, 1H), 3.74 (s, 1.2H), 3.25 (m, 0.8H), 3.19 (m, 0.4H), 3.01 (m, 0.4H),

2.84 (m, 0.4H), 2.20-1.30 (m, 6H). ^{13}C -NMR (75 MHz, CDCl_3 , mixture of conformers) δ = 169.2 (s), 169.13 (s), 169.09 (s), 166.3 (s), 166.1 (s), 165.8 (s), 147.4 (d), 147.0 (d), 146.9 (d), 143.3 (s), 143.2 (s), 143.1 (s), 139.3 (d), 139.2 (d), 130.1 (d), 130.0 (d), 129.9 (d), 128.4 (d), 128.3 (d), 127.3 (d), 127.2 (d), 126.6 (d), 123.3 (d), 122.6 (d), 125.5 (d), 93.0 (s), 92.8 (s), 92.7 (s), 55.6 (d), 51.33 (q), 51.30 (q), 49.4 (d), 49.2 (d), 43.7 (t), 43.0 (t), 37.8 (t), 30.0 (9t), 28.8 (t), 28.4 (t), 26.1 (t), 25.7 (t), 25.1 (t), 20.5 (t), 20.1 (t). MS (EI) m/z = 338 (M^+ , < 1), 231 (50), 212 (3), 203 (20), 184 (4), 136 (22), 105 (17), 76 (25), 41 (8). Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3\text{I}$: C, 48.12; H, 4.55; N, 3.51. Found: C, 48.49; H, 4.21; N, 3.40.

Synthesis of (*R,Z*)-11-methoxycarbonylmethylidene-2,3,4,6,11,11a-hexahydro-1*H*-pyrido[1,2-*b*]isoquinolin-6-one [(*R*)-4]. $\text{Pd}(\text{OAc})_2$ (152 mg, 0.67 mmol), Ph_3P (600 mg, 2.25 mmol), AgNO_3 (3.8 g, 22.6 mmol), and $(\text{CH}_3\text{CH}_2)_3\text{N}$ (7 mL, 45.1 mmol) were sequentially added to a solution of the 2-iodobenzamide (**7**) (9 g, 22.6 mmol) in dry CH_3CN (90 mL) under argon. The mixture was stirred at rt overnight; then, it was cooled at 0 °C, diluted with H_2O (100 mL) and CHCl_3 (100 mL). The phases were separated, the aqueous one was extracted with CHCl_3 (2 x 60 mL). The combined organic extracts were dried (MgSO_4), the solvent was removed, and the residue was purified by chromatography (80:20 to 70:30 hexane–EtOAc) to give **4** (5.5 g, 90%) as a white solid, mp 120–123°C. $[\alpha]_{\text{D}} = +304^\circ$ (CHCl_3 , $c = 1.07$). ^1H -NMR (300 MHz, CDCl_3) δ = 8.28 (m, 1H), 7.67 (m, 1H), 7.54 (m, 2H), 6.37 (d, $J = 1.4$, 1H), 5.53 (m, 1H), 4.88 (m, 1H), 3.79 (s, 3H), 2.79 (dt, $J = 12.6$, $J = 3.1$, 1H), 1.98-1.42 (m, 6H). ^{13}C -NMR (75 MHz, CDCl_3) δ = 165.8 (s), 160.4 (s), 150.7 (s), 132.6 (s), 132.0 (d), 130.9 (d), 128.7 (d), 128.2 (s), 123.5 (d), 113.6 (d), 59.1 (d), 51.5 (q), 44.9 (t), 34.4 (t), 25.5 (t), 25.0 (t). MS (EI) m/z = 271 (M^+ , 22), 256 (9), 238 (17), 213 (15), 212 (100), 210 (27), 184 (17), 156 (13), 129 (25), 128 (19), 127 (12), 115 (30), 101 (29), 77 (13), 75 (14), 55 (17), 41 (10). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$: C, 70.82; H, 6.32; N, 5.16. Found: C, 70.96; H, 6.16; N, 5.21.

Synthesis of (*S,E*)-methyl 3-[1-(2-iodobenzoyl)pyrrolidin-2-yl]acrylate [(*S*)-8]. A solution of dry DMSO (0.32 mL, 4.48 mmol) in CH_2Cl_2 (2 mL) was dropwise added at -78 °C to a solution of oxalyl chloride (1.12 mL of a 2M solution in hexane, 2.24 mmol) in CH_2Cl_2 (2 mL). After stirring for 30 min at this temperature, a solution of the alcohol (**11**) (531 mg, 1.6 mmol) in CH_2Cl_2 (8 mL) was dropwise added *via* cannula. The mixture was stirred at -78 °C for 2 h, and, then, dry $(\text{CH}_3\text{CH}_2)_3\text{N}$ (1.11 mL, 8.02 mmol) was added. The reaction mixture was left stirring to warm up to rt. After stirring for 3 h, solid $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ (695 mg, 2.080 mmol) was added in one portion. The mixture was stirred at rt for 20 h; the solvent was evaporated, and the residue was chromatographed (80:20 to 60:40 hexane-ethyl acetate) to give (*S*)-**8** (580 mg, 94 %) as a colorless thick oil. $[\alpha]_{\text{D}} = -96.5^\circ$ (CHCl_3 , $c = 1.26$). ^1H -NMR (300 MHz, CDCl_3 , 1.2:1 mixture of conformers) δ = 7.76 (dd, $J = 8.0$, 1.0 Hz, 0.55H, aromatic), 7.74 (dd, $J = 8.0$, 1.0 Hz, 0.45H, aromatic), 7.37 (td, $J = 7.6$, 1.0 Hz, 0.55H, aromatic), 7.26 (td, $J = 7.6$, 1.0 Hz, 0.45H, aromatic), 7.21 (dd, $J = 7.6$, 1.0, 0.55H, aromatic), 7.13-7.00 (m, 1.45H, aromatic), 6.95 (dd, $J = 15.6$,

5.6, 0.45H, olefinic), 6.58 (dd, $J = 15.6, 6.3, 0.55\text{H}$, olefinic), 6.08 (br d, $J = 15.6, 0.55\text{H}$, olefinic), 5.44 (br d, $J = 15.6, 0.45\text{H}$, olefinic), 4.92 (m, 0.55H, H-2), 4.16 (dd, $J = 6.3, 6.0, 0.45\text{H}$, H-2), 3.75 (m, 1H, H-5), 3.71 (s, 1.65H, OCH₃), 3.67 (s, 1.45H, OCH₃), 3.20 (m, 1H, H-5), 2.15 (m, 1H, H-3), 2.05-1.88 (m, 3H, H-3, H-4). ¹³C-NMR (50 MHz, CDCl₃, 1.2:1 mixture of conformers) $\delta = 169.5, 169.1, 166.9, 166.2, 147.0, 146.8, 143.4, 142.9, 139.3, 139.0, 130.5, 130.4, 128.6, 128.1, 127.8, 127.1, 121.2, 92.0, 60.1, 57.4, 51.8, 51.7, 48.9, 46.2, 32.1, 30.8, 24.1, 22.4$. MS (ES, positive ionization mode) $m/z = 386$ (M+1, 100). Anal. Calcd for C₁₅H₁₆NO₃I: C, 46.77; H, 4.19; N, 3.64. Found: C, 46.59; H, 3.98; N, 3.47.

Synthesis of (*S,Z*)-10-methoxycarbonylmethylidene-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]-isoquinolin-5-one [(*S*)-5]. Pd(OAc)₂ (4 mg, 0.018 mmol), Ph₃P (10 mg, 0.038 mmol), and (CH₃CH₂)₃N (89 μ L, 0.64 mmol) were sequentially added to a solution of the 2-iodobenzamide (**8**) (123 mg, 0.32 mmol) in dry CH₃CN (4 mL) under argon. The mixture was heated at reflux for 4.5 h, cooled down to rt, and the solvent was evaporated. The residue was chromatographed (60:40 hexane–EtOAc) to give (*S*)-**5** (67 mg, 82%) as a colourless thick oil. $[\alpha]_{\text{D}} = -133.8^{\circ}$ (CHCl₃, $c = 0.3$). ¹H-NMR (400 MHz, CDCl₃) $\delta = 8.23$ (m, 1H, H-6), 7.68 (m, 1H, H-9), 7.48 (m, 2H, H-7, H-8), 6.50 (d, $J = 2.6$, 1H, olefinic H), 5.13 (dt, $J = 11.0, 2.5$, 1H, H-10a), 4.19 (m, 1H, H-3), 3.74 (s, 3H, OCH₃), 3.32 (m, 1H, H-3), 2.62 (m, 1H, H-1), 1.93 (m, 2H, H-2), 1.46 (dt, $J = 11.2, 1.6$, 1H, H-1). ¹³C-NMR (50 MHz, CDCl₃) $\delta = 166.3$ (CO₂CH₃), 161.0 (C-5), 147.3 (C-10), 132.6 (C-9a), 132.3, 131.1 (C-7, C-8), 129.0 (C-5a), 128.7 (C-6), 123.5 (C-9), 114.9 (olefinic C), 59.4 (C-10a), 51.7 (OCH₃), 44.2 (C-3), 31.7 (C-1), 21.9 (C-2). MS (ES, positive ionization mode) $m/z = 258$ (M+1, 100). Anal. Calcd for C₁₅H₁₅NO₃: C, 70.02; H, 5.88; N, 5.44. Found: C, 6.21; H, 3.98; N, 5.58.

Synthesis of 2-hydroxymethyl-1-(2-iodophenylsulfonyl)piperidine [(±)-12]. 13 M aqueous NaOH (1.9 mL, 24.6 mmol) and a solution of 2-(iodo)benzenesulfonyl chloride (2.2 g, 6.15 mmol) in THF (7 mL) were sequentially added to a solution of racemic 2-hydroxymethylpiperidine (707 mg, 6.15 mmol) in THF (5 mL) at 0°C. The mixture was allowed to slowly warm up to rt and stirred for 20 h. The mixture was saturated with NaCl and thoroughly extracted with ethyl acetate (8 x 20 mL). The combined organic phases were dried (MgSO₄) and the solvent was evaporated. The residue was chromatographed (80:20 to 60:40 hexane-ethyl acetate) to give pure (±)-**12** (706 mg, 30%) as a colourless thick oil. ¹H-NMR (300 MHz, CDCl₃) $\delta = 8.21$ (dd, $J = 8.0, 1.7$, 1H, aromatic H-6), 8.09 (dd, $J = 8.0, 1.1$, 1H, aromatic H-3), 7.48 (td, $J = 7.8, 1.1$, 1H, aromatic H-5), 7.18 (td, $J = 7.6, 1.7$, 1H, aromatic H-4), 4.00 (m, 1H, H-2); 3.95 (dd, $J = 10.8, 8.4$, 1H, CH₂OH), 3.71 (dd, $J = 12.5, 1.1$, 1H, H-6), 3.62 (dd, $J = 10.8, 5.4$, 1H, CH₂OH), 3.10 (distorted td, $J = 12.5, 3.0$, 1H, H-6), 1.95-1.45 (m, 6H, H-3, H-4, H-5). ¹³C-NMR (50 MHz, CDCl₃) $\delta = 143.1$ (aromatic C-3), 141.7 (aromatic C-1), 133.4 (aromatic C-4), 132.2 (aromatic C-6), 128.4 (aromatic C-5), 92.5 (aromatic C-2), 60.9 (CH₂OH), 54.9 (C-2), 41.6 (C-6), 25.1 (2C, C-3, C-5), 19.2 (C-4). MS

(ES, positive ionization mode) $m/z = 382$ ($M+1$, 100). Anal. Calcd for $C_{12}H_{16}NO_3IS$: C, 37.81; H, 4.23; N, 3.67; S, 8.41. Found: C, 37.53; H, 4.18; N, 3.62; S, 8.40.

Synthesis of (*E*)-methyl 3-[1-(2-iodophenylsulfonyl)piperidin-2-yl]acrylate [(±)-9**].** A solution of dry DMSO (0.10 mL, 1.47 mmol) in CH_2Cl_2 (2 mL) was dropwise added at $-78\text{ }^\circ\text{C}$ to a solution of oxalyl chloride (0.37 mL of a 2M solution in hexane, 0.74 mmol) in CH_2Cl_2 (2 mL). After stirring for 30 min at this temperature, a solution of the alcohol (**12**) (200 mg, 0.525 mmol) in CH_2Cl_2 (3 mL) was dropwise added *via* cannula. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 2 h, and, then, dry $(CH_3CH_2)_3N$ (0.37 mL, 2.63 mmol) was added. The reaction mixture was warmed up to rt. After stirring for 4 h, solid $Ph_3P=CHCO_2Me$ (227 mg, 0.681 mmol) was added in one portion. The mixture was stirred at rt for 16 h; the solvent was evaporated, and the residue was chromatographed (90:10 to 85:15 hexane-ethyl acetate) to give (±)-**9** (171 mg, 75 %) as a colorless thick oil. 1H -NMR (200 MHz, $CDCl_3$) $\delta = 8.19$ (dd, $J = 7.8$, 1.6, 1H, aromatic), 8.10 (dd, $J = 7.8$, 1.2, 1H, aromatic), 7.48 (td, $J = 7.6$, 1.2, 1H, aromatic), 7.19 (td, $J = 7.6$, 1.6, 1H, aromatic), 6.95 (dd, $J = 16.0$, 4.8, 1H, olefinic), 6.06 (dd, $J = 16$, 2.0, 1H, olefinic), 4.82 (m, 1H, H-2), 3.74 (s, 3H, OCH_3), 3.55 (dd, $J = 12.6$, 1.0, 1H, H-6), 3.13 (dt, $J = 12.5$, 3.2, 1H, H-6), 2.20-1.40 (m, 6H, H-3, H-4, H-5). ^{13}C -NMR (50 MHz, $CDCl_3$) $\delta = 166.5$ ($\underline{CO_2CH_3}$), 146.2 (olefinic), 143.1 (aromatic C-3), 141.7 (aromatic C-1), 133.5 (aromatic C-4), 132.1 (aromatic C-6), 128.3 (aromatic C-5), 123.4 (olefinic), 92.6 (aromatic C-2), 54.0 (C-2), 51.8 (OCH_3), 42.3 (C-6), 29.7 (C-5), 25.1 (C-3), 19.4 (C-4). MS (ES, positive ionization mode) $m/z = 453$ ($M+18$, 100), 436 ($M+1$, 82). Anal. Calcd for $C_{15}H_{18}NO_4IS$: C, 41.39; H, 4.17; N, 3.22; S, 7.37. Found: C, 41.65; H, 4.17; N, 3.57; S, 7.09.

Synthesis of [(*RS*),*Z*]-11-methoxycarbonylmethylidene-7,8,9,10,10a,11-hexahydropyrido[1,2-*b*]benzo[*e*][1,2]thiazine-5,5-dioxide [(±)-6**].** $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), Ph_3P (6.6 mg, 0.025 mmol), and $(CH_3CH_2)_3N$ (59 μL , 0.42 mmol) were sequentially added to a solution of the 2-(iodo)phenylsulfonamide (**9**) (92 mg, 0.21 mmol) in dry CH_3CN (3 mL) under argon. The mixture was heated at reflux for 2.5 h. After cooling to rt, the solvent was evaporated. The residue was chromatographed (90:10 hexane-EtOAc) to give (±)-**6** (65 mg, 98%) as a white solid. An analytical pure sample was obtained by crystallization from CH_2Cl_2 /hexane, mp $74\text{--}77^\circ\text{C}$. 1H -NMR (400 MHz, $CDCl_3$, 1.2:1 mixture of conformers) $\delta = 7.82$ (br d, $J = 7.5$, 1H, H-4), 7.62-7.50 (m, 3H, H-1, H-2, H-3), 6.15 (d, $J = 1.7$, 1H, olefinic H), 5.97 (dt, $J = 11.0$, 1.7, 1H, H-10a), 4.07 (m, 1H, H-7), 3.77 (s, 3H, OCH_3), 2.86 (td, $J = 12.0$, 2.5, 1H, H-7), 2.13 (dd, $J = 12.5$, 2.4, 1H, H-10), 1.90-1.25 (m, 5H, H-8, H-9, H-10). ^{13}C -NMR (50 MHz, $CDCl_3$) $\delta = 165.1$ ($\underline{CO_2CH_3}$), 151.8 (C-11), 139.1 (C-4a), 134.3 (C-11a), 132.7, 129.8, 126.8 (C-1, C-2, C-3), 121.4 (C-4), 118.7 (olefinic C), 60.3 (C-10a), 51.8 (OCH_3), 42.2 (C-7), 32.3 (C-10), 24.7 (C-8), 24.2 (C-9). MS (ES, positive ionization mode) $m/z = 308$ ($M+1$, 100). Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.57; N, 4.56; S, 10.43. Found: C, 58.90; H, 5.46; N, 4.42; S, 10.65.

Synthesis of (*R,Z*)-11-carboxymethylidene-2,3,4,6,11,11a-hexahydro-1*H*-pyrido[1,2-*b*]isoquinolin-6-one [(*R*)-15**].** A 1M aqueous solution of LiOH (7.5 mL, 7.5 mmol) was added to a stirred solution of the methyl ester [(*R*)-**4**] (1.0 g, 3.7 mmol) in a 1:1 THF-H₂O mixture (10 mL) at rt. The mixture was stirred for 4 h, and then was treated with 5% aqueous HCl until pH 2. The organic solvent was removed at reduced pressure and the aqueous phase was thoroughly extracted with EtOAc. After drying (MgSO₄) and evaporation of the solvent, the crude acid (**13**) was obtained. It was purified by crystallization from EtOAc to give 939 mg (98% yield) of **13**. White solid, mp 179-182°C. [α]_D = +356.9° (CHCl₃, c = 0.67). ¹H-NMR (300 MHz, CDCl₃) δ = 10.00-9.00 (very br s, 1H, CO₂H), 8.28 (m, 1H, H-7), 7.70 (m, 1H, H-10), 7.55 (m, 2H, H-8, H-9), 6.41 (d, *J* = 1.2, 1H, olefinic H), 5.52 (br d, *J* = 10.6, 1H, H-11a), 4.87 (br d, *J* = 12.7, 1H, H-4), 2.80 (distorted td, 1H, *J* = 12.7, 3.0, 1H, H-4), 2.00-1.42 (m, 6H, H-1, H-2, H-3). ¹³C-NMR (50 MHz, CDCl₃) δ = 168.4 (s), 160.6 (s), 151.0 (s), 132.4 (s), 132.2 (d), 131.0 (d), 128.6 (d), 127.7 (s), 123.6 (d), 114.1 (d), 59.0 (d), 45.1 (t), 34.3 (t), 25.5 (t), 24.7 (t). MS (EI) *m/z* = 257 (M⁺, 45), 212 (100), 198 (20), 184 (28), 155 (22), 129 (26), 115 (34), 101 (38), 77 (25), 75 (24), 63 (12). Anal. Calcd for C₁₅H₁₅NO₃: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.25; H, 6.02; N, 5.67.

General procedure for the synthesis of peptide-heterocycle hybrids (19-21). *N*-Methylmorpholine (NMM, 1.0 mol equiv.) and isobutyl chloroformate (1.0 mol equiv.) were sequentially added to a solution of the acid (**15**) in CHCl₃ (10 mL) at 0°C under argon. Stirring was maintained until no starting material remained (TLC evidence). Then, the mixture was added dropwise to a stirred solution of the corresponding peptide (**16-18**, 1.1 mol equiv., used as trifluoroacetate salts) and NMM (3 mol equiv.) in CHCl₃ (10 mL) at 0°C. The mixture was allowed to warm-up slowly to rt, and stirred until all the starting material has reacted (TLC control). Then, the organic phase was washed with water, 5% aqueous HCl, saturated aqueous NaHCO₃ and water. The organic phase was dried (MgSO₄), and the solvent was removed under vacuum to give a crude product that was purified by flash chromatography (in the solvent indicated for each individual compound). The spectroscopic and analytical data of the peptide-heterocycle hybrids are described below.

Peptide-heterocycle hybrid (*R*)-Piq-(*S*)-Leu-(*S*)-Leu-OMe (19**).** Starting from 257 mg (1 mmol) of **15**, the reaction was carried out for 17 h to give the hybrid (**19**) (298 mg, 60% yield) as a colorless thick oil after chromatography (80:20 to 50:50 hexane-EtOAc). [α]_D = +119.3° (CHCl₃, c = 1.08). ¹H-NMR (400 MHz, CDCl₃) δ = 8.24 (m, 1H, H-7), 7.58 (m, 1H, H-10), 7.49 (m, 2H, H-8, H-9), 6.54 (d, *J* = 8.3, 1H, NH), 6.38 (d, *J* = 8.2, 1H, NH), 6.23 (d, *J* = 1.1, 1H, olefinic H), 5.68 (d, *J* = 10.5, 1H, H-11a), 4.84 (distorted dd, *J* = 12.9, 2.2, 1H, H-4), 4.59 (m, 2H, H $_{\alpha}$ -Leu), 3.75 (s, 3H, CO₂CH₃), 2.79 (td, *J* = 12.7, 2.9, 1H, H-4), 1.90-1.40 (m, 12H, H-1, H-2, H-3, 2 x [CH₂-CH]-Leu), 0.96 (d, *J* = 6.1, 6H, 2 x CH₃), 0.91 (d, *J* = 6.1, 3H, CH₃), 0.90 (d, *J* = 6.0, 3H, CH₃). ¹³C-NMR (50 MHz, CDCl₃) δ = 173.0 (s), 172.0 (s), 165.1 (s), 160.6 (s), 147.3 (s), 133.2 (s), 132.0 (d), 130.4 (d), 128.7 (d), 128.1 (s), 123.3 (d), 116.2 (d), 58.8 (d),

52.3 (q), 51.7 (d), 50.8 (d), 45.0 (t), 41.2 (t), 41.0 (t), 34.6 (t), 25.6 (t), 25.0 (t), 24.7 (2C, d), 22.8 (2C, q), 22.2 (q), 21.7 (q). MS (ES, positive ionization mode) m/z 520 ($M+Na$, 100). Anal. Calcd for $C_{28}H_{39}N_3O_5$: C, 67.58; H, 7.90; N, 8.44. Found: C, 67.70; H, 8.11; N, 8.69.

Peptide-heterocycle hybrid (R)-Piq-(S)-Leu-(R)-Leu-(S)-Leu-OMe (20). Starting from 257 mg (1 mmol) of **15**, the coupling reaction was carried out for 17 h to give the hybrid (**20**) (354 mg, 58%) as a white solid after chromatography (70:30 to 40:60 hexane-EtOAc), mp 198-201°C. $[\alpha]_D = +172.5^\circ$ ($CHCl_3$, $c = 0.3$). 1H -NMR (303 MHz, $CDCl_3$, 303 K) $\delta = 8.26$ (m, 1H, H-7), 7.58 (m, 1H, H-10), 7.50 (m, 2H, H-8, H-9), 6.76 (d, $J = 8.4$, 1H, NH), 6.55 (d, $J = 8.4$, 1H, NH), 6.38 (d, $J = 7.7$, 1H, NH), 6.27 (s, 1H, olefinic H), 5.59 (br d, $J = 10.2$, 1H, H-11a), 4.85 (distorted dd, $J = 12.7, 2.2$, 1H, H-4), 4.52 (m, 3H, 3 x H_α -Leu), 3.68 (s, 3H, CO_2CH_3), 2.79 (td, $J = 12.7, 3.0$, 1H, H-4_{ax}), 2.00-1.40 (m, 15H, H-1, H-2, H-3, 3 x [CH-CH₂]-Leu), 0.99 (d, $J = 7.1$, 3H, CH_3), 0.970 (d, $J = 6.2$, 3H, CH_3), 0.966 (d, $J = 6.3$, 3H, CH_3), 0.957 (d, $J = 6.0$, 3H, CH_3), 0.94 (d, $J = 5.1$, 3H, CH_3), 0.92 (d, $J = 5.5$, 3H, CH_3). ^{13}C -NMR (75 MHz, $CDCl_3$) $\delta = 173.8$ (s), 172.5 (s), 171.8 (s), 165.4 (s), 161.0 (s), 147.0 (s), 133.7 (s), 132.2 (d), 130.6 (d), 128.9 (d), 128.3 (s), 123.6 (d), 117.1 (d), 59.2 (d), 52.5 (q), 52.3 (d), 51.9 (d), 50.8 (d), 45.4 (t), 41.5 (t), 41.3 (t), 41.1 (t), 34.6 (t), 25.8 (t), 25.13 (t), 25.08 (d, 2C), 25.05 (d), 23.2 (q), 23.1 (q), 23.0 (q), 22.5 (q), 22.3 (q), 22.0 (q). MS (CI, negative ionization mode) m/z 609 (M^- , 1). Anal. Calcd for $C_{34}H_{50}N_4O_6$: C, 66.86; H, 8.25; N, 9.17. Found: C, 67.02; H, 8.47; N, 9.42.

Peptide-heterocycle hybrid (R)-Piq-(S)-Tyr-Gly-OMe (21). Starting from 257 mg (1 mmol) of **15**, the reaction was carried out for 20 h to give the hybrid (**21**) (221 mg, 45% yield) as colorless thick oil after chromatography (25:1 CH_2Cl_2 -MeOH). $[\alpha]_D = +181.7^\circ$ ($CHCl_3$, $c = 0.46$). 1H -NMR (300 MHz, $CDCl_3$, 313 K) $\delta = 8.22$ (m, 1H, H-7), 7.51 (m, 1H, H-10), 7.46 (m, 2H, H-8, H-9), 7.03 (d, $J = 8.4$, 2H, H-3-Tyr, H-5-Tyr), 6.72 (d, $J = 8.4$, 2H, H-2-Tyr, H-6-Tyr), 6.58 (br d, $J = 7.1$, 1H, NH-Tyr), 6.41 (br s, 1H, NH-Gly), 6.21 (s, 1H, olefinic H), 5.50 (d, $J = 11.0$, 1H, H-11a), 4.78 (m, 2H, H-4, H_α -Tyr), 3.98 (m, 2H, H_α -Gly), 3.72 (s, 3H, CO_2CH_3), 3.02 (d, $J = 6.8$, 2H, H_β -Tyr), 2.74 (distorted td, $J = 10.0, 2.4$, 1H, H-4), 1.98-1.37 (m, 16H, H-1, H-2, H-3). ^{13}C -NMR (75 MHz, $CDCl_3$) $\delta = 171.4$ (s), 170.0 (s), 164.8 (s), 160.9 (s), 155.3 (s), 149.4 (s), 147.5 (s), 133.4 (s), 132.1 (d), 130.5 (2C, d), 128.7 (d), 128.2 (s), 127.8 (d), 123.5 (d), 116.4 (d), 115.7 (2C, d), 59.0 (d, C-11a), 54.5 (d, C_α -Tyr), 52.4 (q, OCH_3), 45.2 (t, C-4), 41.3 (t, C_α -Gly), 37.8 (t, C_β -Tyr), 34.4 (t, C-1), 25.6 (t, C-2), 24.9 (t, C-3). MS (ES, positive ionization mode) m/z 492 ($M+1$, 30), 335 (100), 279 (30). Anal. Calcd for $C_{27}H_{29}N_3O_6$: C, 65.97; H, 5.95; N, 8.55. Found: C, 65.87; H, 5.99; N, 8.28.

ACKNOWLEDGEMENTS

Financial support from the Spanish Ministry of Science and Technology (Project BQU2001-2270) and Madrid Autonomous Community (Project 08.5/0056/2000-2) is gratefully acknowledged.

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