Efficient Synthesis of Chiral Isoquinoline and Pyrido[1,2-*b*]-isoquinoline Derivatives via Intramolecular Heck Reactions

Francisco Sánchez-Sancho, Enrique Mann, Bernardo Herradón*

Instituto de Química Orgánica General, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain
Fax: (+34) 91–5644–853, e-mail: herradon@iqog.csic.es

Received January 14, 2001; Accepted february 16, 2001

Keywords: biaryls; intramolecular Heck reaction; isoquinolines; pyrido[1,2-*b*]-isoquinolines; palladium.

Abstract: The palladium(0)-catalyzed reaction of derivatives of γ-amino-α,β-unsaturated esters bearing an *N*-(2-iodobenzoyl) substituent results in an intramolecular Heck reaction, the outcome of which depends on the structure of the substrate as well as on the experimental conditions. The methodology developed has been applied to the efficient syntheses of chiral isoquinoline and pyrido[1,2-*b*]isoquinoline derivatives.

Introduction

Partially reduced isoquinoline (e.g., **A**, Figure 1)[1] and pyrido[1,2-*b*]isoquinoline (e.g., **B**)[2,3] derivatives are frequently found in a variety of natural products and biologically active compounds. Although several syntheses of these heterocycles have been reported,[4–6] most of them have yielded racemic materials or have furnished scantily functionalized compounds. In connection with an ongoing project on the synthesis of peptide conjugates bearing peptidic fragments on a heterocyclic scaffold,[7,8] we have required efficient accesses to some chiral functionalized heterocycles with isoquinoline and pyrido[1,2-*b*]isoquinoline backbones (**A** and **B**). The retrosynthetic analysis for these compounds is indicated in Figure 1 and involves intramolecular Heck reactions[9] as the key steps for the formation of the bicyclic and tricyclic systems. The substrates for these cyclizations (compounds **C** and **D**) can be prepared, in enantiomerically pure form, from readily available chiral amino acids (**E**) and amino alcohols (**F**), respectively. In this paper we report straightforward and stereoselective syntheses of some enantiomerically pure isoquinoline (**5**) and pyrido[1,2-*b*]isoquinoline (**10**) derivatives. Furthermore, we describe some interesting observations that show that the outcome of the Heck cyclization of *N*-(2-iodobenzoyl)-γ-amino-α,β-unsaturated esters and related compounds depends on the experimental conditions and the structure of the substrate. During the development of this project,[7,10] the synthesis of isoquinoline derivatives

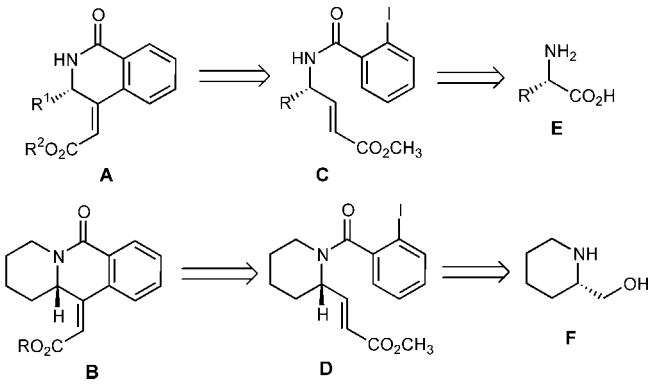


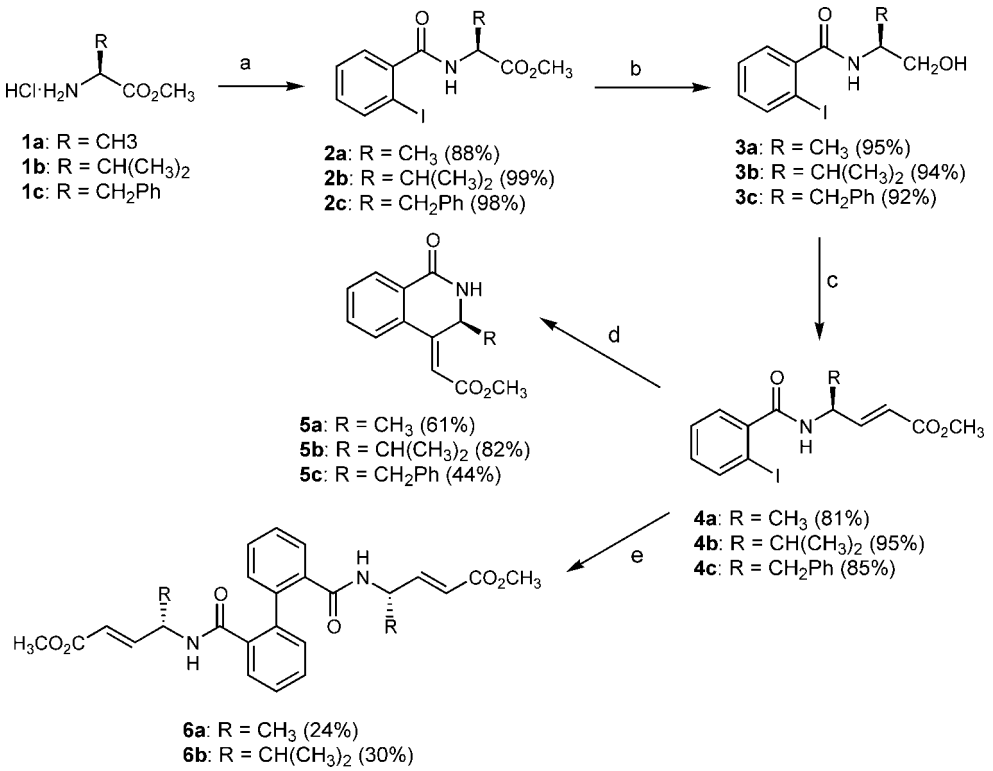
Figure 1. Structure of the target molecules and retrosynthetic analysis of the heterocycles **A** and **B**.

using intramolecular Heck reaction has been reported by the groups of Tietze,[11] Goff,[12] Gibson,[13] and De Mesmaeker.[14]

Results and Discussion

The synthesis of the isoquinolidinone derivatives **5a–c** is indicated in Scheme 1. The hydrochlorides of (*S*)-alanine methyl ester (**1a**), (*S*)-valine methyl ester (**1b**), and (*S*)-phenylalanine methyl ester (**1c**) were converted in nearly quantitative yield to the corresponding *N*-(2-iodobenzoyl) derivatives **2a**, **2b**, and **2c**, respectively, by acylation with 2-iodobenzoyl chloride. Compounds **2a–c** were transformed in high yield to the corresponding *N*-acylated-1,2-amino al-

  1615-4150/01/34301-360–368 $ 17.50-.50/0



Scheme 1. Synthesis of the isoquinolidinones **5a**, **5b**, and **5c**; and the biphenyls **6a** and **6b**.
(a) *o*-I-C_6H_4COCl (1 mol equiv), 1 M aqueous K_2CO_3 (4 mol equiv), THF, 0 °C to r. t., overnight. (b) $LiBH_4$ (3 mol equiv), MeOH (5 mol equiv), THF, –10 °C to r. t., 30 minutes. (c) (i) DMSO (3.2 mol equiv), $(COCl)_2$ (1.6 mol equiv), CH_2Cl_2, –70 °C; Et_3N (5.8 mol equiv), –70 °C to r. t.; (ii) $Ph_3P{=}CHCO_2CH_3$ (1.5 mol equiv), r. t., overnight. (d) $Pd(OAc)_2$ (0.035 mol equiv), Ph_3P (0.11 mol equiv), Et_3N (2 mol equiv), CH_3CN, 70 °C, 48 hours. (e) $Pd(OAc)_2$ (0.06 mol equiv), Ph_3P (0.3 mol equiv), Et_3N (2 mol equiv), $AgNO_3$ (1 mol equiv), CH_3CN, 80 °C, 60 hours.

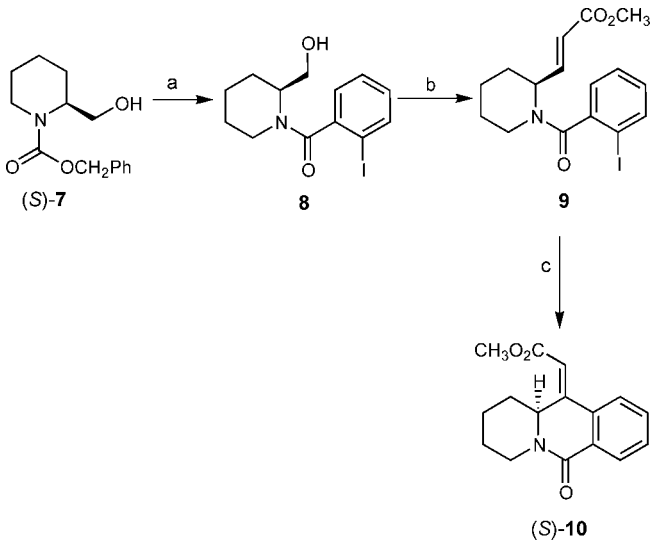
cohols **3a**, **3b**, and **3c** by reduction of the methoxycarbonyl group with lithium borohydride/methanol.[15] The preparation of the *N*-acylated-γ-amino-α,β-unsaturated esters **4a–c** was achieved by two-step, one-pot sequential Swern–Wittig reactions[16,17,18] from alcohol **3a–c**, that we have previously shown to be an efficient method for this kind of transformation.[19,20] This reaction is totally stereoselective, giving the *E*-olefin as the single product. The overall conversions of **1a–c** to **4a–c** proceeded in four steps and high yield (68% for **4a**, 89% for **4b**, and 77% for **4c**).[21]

With a ready access to compounds **4a-c**, we set out to perform the key cyclization. The Heck reaction has been carried out under a diversity of variants,[22] which include modifications in the source of palladium(0), ligand, solvent, additives, as well as some other experimental parameters. In our previous work,[7] we found that both Jeffery's conditions[23,24] [$Pd(OAc)_2$, Ph_3P, KOAc, Bu_4NI] and Overman's conditions[25,26] [$Pd(OAc)_2$, Ph_3P, $AgNO_3$, Et_3N] worked efficiently. We have found that the outcome of the palladium(0) catalyzed reaction of **4a–c** depends on the experimental conditions. Thus, when compounds **4a** and **4b** were submitted to the Heck–Overman procedure, we did not obtain the expected isoquinolidinones **5a** and **5b**, but the biaryls **6a** and **6b** (Scheme 1).[27] A plausible explanation for the formation of the biphenyls **6** is through an oxidative dimerization of an arylpalladium intermediate promoted by silver(I), which is consistent with the finding that compounds **6** are not formed in the absence of silver nitrate. Recently, Lemaire[28] and Rawal,[29] independently, have reported Ullmann-type reactions catalyzed by palladium complexes, but in some cases the 2,2'-disubstituted biaryl could not be obtained[29] or have been prepared in low yield.[28] We have not optimized the experimental procedure for the synthesis of **6a** and **6b**, and although these compounds were actually obtained in low yields of isolated products, it is worthy of mention that the biphenyls **6a** and **6b** were the single reaction products, the starting materials **4a** and **4b** accounting for the rest of the material.[30,31]

On the other hand, when the (*S*)-valine derivative **4b** was reacted under the Heck–Jeffery conditions,[23] the isoquinolidinone **5b** was obtained as the single product, albeit in low yield.[32] More satisfactory re-

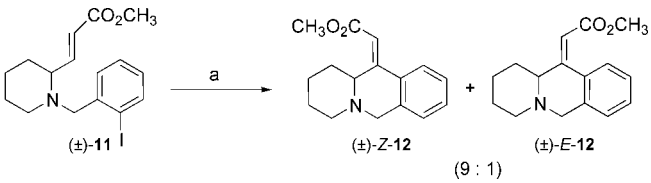
sults were achieved using Heck–Overman conditions[25] in the absence of a silver(I) salt, thus the *N*-(2-iodobenzoyl)-γ-amino-α,β-unsaturated esters **4a** and **4b** were transformed to the heterocycles **5a** and **5b** in good yields as single stereoisomers and regioisomers (Scheme 1).[33,34] On the other hand, we have found that **4c** reacted more slowly, and, although **5c** was obtained as a single olefinic regioisomer and stereoisomer, it was racemic.[35]

The synthesis of the chiral pyrido[1,2-*b*]isoquinoline derivative (*S*)-**10** is depicted in Scheme 2. (*S*)-*N*-Benzyloxycarbonyl-2-(hydroxymethyl)piperidine (**7**), that is available through a chemo-enzymatic approach,[19,36] was *N*-deprotected and acylated with 2-iodobenzoyl chloride to give the amide **8**, that, in turn, was submitted to a one-pot sequential Swern oxidation–Wittig olefination[16] to give the *E*-olefin **9** as a single diastereoisomer. The Heck cyclization was done under both Jeffery's and Overman's conditions, observing that meanwhile the Heck–Overman conditions afforded enantiomerically pure (*S*)-**10** in quantitative yield as a single stereoisomer at the exocyclic double bond,[37] and that the Heck–Jeffery conditions did not give any of **10**, and only starting material (**9**) was recovered.



Scheme 2. Synthesis of the pyrido[1,2-*b*]isoquinolone **10**.
(a) (i) H_2 (45 p.s.i.), Pd–C, MeOH, r.t., 8 hours; (ii) *o*-I-C_6H_4COCl (1 mol equiv), 13 M aqueous NaOH (4 mol equiv), THF, 0 °C to r.t., overnight (86%, 2 steps). (b) (i) DMSO (2.8 mol equiv), $(COCl)_2$ (1.4 mol equiv), CH_2Cl_2, –70 °C; Et_3N (5 mol equiv), –70 °C to r.t.; (ii) $Ph_3P{=}CHCO_2CH_3$ (1.3 mol equiv), r.t., overnight (98%, 2 steps). (c) $Pd(OAc)_2$ (0.03 mol equiv), Ph_3P (0.1 mol equiv), Et_3N (2 mol equiv), $AgNO_3$ (1 mol equiv), CH_3CN, r.t., overnight (98%).

For the sake of comparison, the deoxo analogue of **10** (compound **11**)[38] furnished the expected tricyclic compound (**12**) as a 9:1 mixture of the *Z* and *E*-isomers under Jeffery's conditions (Scheme 3), and did not react under Overman's conditions.[39]



Scheme 3. Result of the Heck reaction of the 2-(iodo)benzylamine **11**.
(a) $Pd(OAc)_2$ (0.05 mol equiv), Ph_3P (0.15 mol equiv), KOAc (4 mol equiv), $(nBu)_4N^+I^-$ (1.1 mol equiv), DMF, 80 °C, 6 hours, (75%).

Conclusion

We have reported efficient (short, high yielding, and totally selective) syntheses of the functionalized chiral heterocycles **5a**, **5b**, and **10** using intramolecular Heck reaction as the key step. It is worthy of mention that regio- and stereo-defined trisubstituted olefins are generated in the Heck reaction, a goal that has been reported to be difficult.[12,14b,40] The presence of two kinds of carbonyl compounds and an electrophilic double bond makes compounds **5** and **10** interesting chiral building blocks for further selective transformations. The first application of these chiral heterocycles to the synthesis of novel peptide-heterocycle hybrids has been realized, and will be reported in a forthcoming paper.[8]

Experimental Section

General Methods

All the reactions with sensitive materials were carried out using dry solvents under an argon atmosphere. All the solvents and reagents were commercially available and, unless otherwise indicated, were used as received. Anhydrous solvents were purchased from ALDRICH® kept over molecular sieves under argon atmosphere. ^1H NMR and ^{13}C NMR spectra were measured in Varian UNITY 500, Varian INOVA 300, Varian Gemini 200, or Bruker AM 200 spectrometers; 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). ^1H NMR spectra were referenced to the chemical shit of either TMS (δ = 0.00 ppm) or the residual proton in the deuterated solvent. ^{13}C NMR spectra were referenced to the chemical shift of the deuterated solvent. The multiplicity of the signals in the ^{13}C NMR spectra was determined by APT, DEPT, or HMQC experiments. The IR spectra were measured in a Perkin-Elmer 657 spectrometer; the frequencies in the IR spectra are indicated in cm^{-1}. All the mass spectra were low-resolution using electron-impact ionization and were recorded in either RMU-GMG spectrometer (Hitachi-Perkin-Elmer). 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.[41]

General Procedure for the *N*-Acylation of 1a–c; Synthesis of the Amides 2a–c

K_2CO_3 (4.0 mol equiv) was added to a solution of **1** in H_2O–THF (1:1, ca. 8 mL per mmol). The mixture was cooled at 0 °C and portionwise treated with 2-iodobenzoyl chloride (1.0 molar equivalent). The reaction mixture was allowed to warm up to room temperature overnight. THF was removed by evaporation in vacuum, and the aqueous phase was extracted with AcOEt. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated to give the amides **2a–c**, whose analytical and spectroscopic data are indicated below.

(*S*)-Methyl 2-[(2-Iodobenzoyl)amino]propionate (2a): Starting from **1a** (10 g, 72 mmol), **2a** was obtained as a white solid, which was purified by crystallization from AcOEt/hexane; yield: 21.0 g (88%); mp 126–127 °C. $[\alpha]_D$: +3.8 ($CHCl_3$, c = 1.0); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, J = 8.1 Hz, 1 H), 7.40 (m, 2 H), 7.10 (m, 1 H), 6.40 (broad d, J = 6.2 Hz, 1 H), 4.80 (quintuplet, J = 7.1, 1 H), 3.78 (s, 3 H), 1.55 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0 (s), 169.5 (s), 142.3 (s), 140.8 (d), 132.2 (d), 129.2 (d), 129.1 (d), 93.3 (s), 53.5 (q), 49.5 (d), 19.3 (q); IR (KBr): ν = 3400, 3250, 1730, 1640, 1525, 1320, 1210, 1000 cm^{-1}; MS (EI): *m/z* = 333 (M^+, 15), 274 (53), 231 (100), 203 (22), 132 (6), 105 (9), 76 (37); anal.: calcd. for $C_{11}H_{12}INO_3$: C, 39.66; H, 3.63; N, 4.20; found: C, 39.85; H, 3.91; N, 4.34.

(*S*)-Methyl 2-[(2-Iodobenzoyl)amino]-3-methylbutanonate (2b): Starting from **1b** (10 g, 60 mmol), **2a** was obtained as a white solid, that was purified by crystallization from AcOEt/hexane; yield: 21.5 g (99%); mp 108–109 °C. $[\alpha]_D$: +2.6 ($CHCl_3$, c = 0.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.9 Hz, 1 H), 7.40 (m, 2H), 7.10 (m, 1 H), 6.29 (broad d, J = 8.6 Hz, 1H), 4.77 (dd, J = 8.6 Hz, J = 4.6 Hz, 1 H), 3.77 (s, 3 H), 2.32 (m, 1 H), 1.07 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0 (s), 168.9 (s), 141.7 (s), 149.9 (d), 131.2 (d), 128.3 (d), 128.1 (d), 92.2 (s), 57.4 (d), 52.2 (q), 31.4 (d), 19.0 (q), 17.9 (q); IR (KBr): ν = 3400, 3250, 1720, 1625, 1565, 1525, 1315, 1195 cm^{-1}, 1000; MS (EI): *m/z* = 361 (M^+, 4), 302 (23), 247 (36), 231 (100), 203 (25), 132 (12), 105 (11), 76 (37); anal.: calcd. for $C_{13}H_{16}INO_3$: C, 43.23; H, 4.47; N, 3.88; found: C, 43.08; H, 4.71; N, 3.92.

(*S*)-Methyl 2-[(2-Iodobenzoyl)amino]-3-phenylpropionate (2c): Starting from **1c** (10 g, 46.5 mmol), **2c** was obtained as a white solid, that was purified by crystallization from AcOEt/hexane; yield: 18.6 g (98%); mp 96–97 °C; $[\alpha]_D$: +63.8 ($CHCl_3$, c = 1.2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, J = 7.9 Hz, J = 1.1 Hz, 1 H), 7.38–7.14 (m, 7 H), 7.08 (m, 1 H), 6.27 (broad d, J = 7.8 Hz, 1 H), 5.08 (X of ABX, 1H), 3.76 (s, 3 H), 3.28 (A of ABX, $J_{A,B}$ = 13.9 Hz, 1 H), 3.26 (B of ABX, $J_{A,B}$ = 13.9 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.7 (s), 168.7 (s), 141.3 (s), 140.2 (d), 135.8 (s), 131.4 (d), 129.5 (d, 2 C), 128.7 (d, 2 C), 128.3 (d), 128.2 (d), 127.3 (d), 92.5 (s), 53.7 (d), 52.6 (q), 37.9 (t); IR (KBr): ν = 3380, 3220, 1715, 1620 1500, 1185, 985 cm^{-1}; MS (EI): *m/z* = 409 (M^+, 4), 350 (9), 247 (85), 231 (100), 203 (23), 162 (29), 131 (15), 104 (9), 91 (25), 76 (22); anal.: calcd. for $C_{17}H_{16}INO_3$: C, 49.90; H, 3.94; N, 3.42; found: C, 50.11; H, 4.25; N, 3.51.

General Procedure for the Reduction of the Esters 2a–c; Synthesis of the Alcohols 3a–c

$LiBH_4$ (3 mol equiv) was added to a stirred solution of the ester **2** in THF (ca. 2 mL per mmol) at –10 °C. Then, MeOH (ca. 5.5 mol equiv) was slowly added. The reaction mixture was allowed to warm up to room temperature for 30 minutes and quenched by the addition of H_2O. THF was removed under reduced pressure and the residue was thoroughly extracted with AcOEt. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give the *N*-protected amino alcohols **3a–c**, whose analytical and spectroscopic data are indicated below.

(*S*)-2-[(2-Iodobenzoyl)amino]-1-propanol (3a): Starting from **2a** (7.5 g, 22.5 mmol), the alcohol **3a** (white solid) was obtained, that was purified by crystallization from AcOEt/hexane; yield: 6.5 g (95%); mp 98–100 °C; $[\alpha]_D$: +1.0 ($CHCl_3$, c = 1.0); ^{1}H NMR (200 MHz, $CDCl_3$, mixture of conformers, **M** and **m**): δ = 7.83 (d, J = 7.6 Hz, 1 H, **M**), 7.74 (dd, J = 8.0 Hz, J = 1.6 Hz, 1 H, **m**), 7.50–7.30 (m, 4 H, **M** + **m**), 7.08 (m, 2 H, **M** + **m**), 6.39 (very broad s, 1 H, **m**), 6.02 (broad d, J = 5.1 Hz, 1 H, **M**), 4.25 (m, 2 H, **M** + **m**), 3.83–3.57 (m, 2 H, **M** + **m**), 2.65 (broad s, 1 H, **M**), 1.70 (very broad s, 1 H, **m**), 1.28 (d, J = 6.8 Hz, 3 H, **M**), 1.27 (d, J = 6.8 Hz, 3 H, **m**); ^{13}C NMR (50 MHz, $CDCl_3$, major diastereoisomer): δ = 170.1 (s), 142.9 (s), 140.5 (d), 131.9 (d), 129.0 (d, 2C), 93.4 (s), 66.8 (t), 49.0 (d), 17.6 (q). IR (KBr) ν 3280, 3220, 1615, 1505 1010; MS (EI): *m/z* = 305 (M^+, 2), 274 (59), 248 (39), 231 (100), 203 (31), 148 (11), 105 (29), 76 (22); anal.: calcd. for $C_{10}H_{12}INO_2$: C, 39.37; H, 3.96; N, 4.59; found: C, 39.53; H, 4.04; N, 4.80.

(*S*)-2-[(2-Iodobenzoyl)amino]-3-methyl-1-butanol (3b): Starting from **2b** (13.0 g, 36.0 mmol), **3b** (white foamy solid) was obtained. It was purified by crystallization from AcOEt/hexane; yield: 11.2 g (94%); mp 96–98 °C; $[\alpha]_D$: –29.0 ($CHCl_3$, c = 1.0); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers, **M** and **m**): δ = 7.83 (d, J = 8.0 Hz, 1 H, **M**), 7.74 (d, J = 7.1 Hz, 1 H, **m**), 7.48–7.31 (m, 4 H, **M** + **m**), 7.10–7.04 (m, 2 H, **M** + **m**), 6.41 (broad s, 1 H, **m**), 6.04 (broad d, J = 6.1 Hz, 1 H, **M**), 3.95–3.85 (m, 2 H, **M** + **m**), 3.85–3.72 (m, 4 H, **M** + **m**), 2.80 (broad s, 1 H, **m**), 2.55 (broad s, 1 H, **M**), 1.98 (m, 2 H, **M** + **m**), 1.02 (d, J = 6.7 Hz, 6 H, **M**), 0.99 (d, J = 6.2 Hz, 6 H, **m**); ^{13}C NMR (50 MHz, $CDCl_3$, mixture of conformers): δ = 170.8 (s), 169.0 (s), 143.1 (s), 140.4 (d), 135.1 (d), 132.1 (d), 131.7 (d), 129.2 (d), 128.8 (d), 127.7 (d), 93.1 (s), 64.0 (t), 63.7 (t), 58.2 (d), 58.0 (d), 29.8 (d), 29.6 (d), 20.3 (q), 19.9 (q), 19.8 (q); IR (KBr): ν = 3400, 3250, 1630, 1530; MS (EI): *m/z* = 333 (M^+, 1), 302 (40), 290 (5), 248 (13), 231 (100), 203 (23), 176 (10), 105 (48).

(*S*)-2-[(2-Iodobenzoyl)amino]-3-phenyl-1-propanol (3c): Starting from **2c** (10 g, 24.4 mmol), the alcohol **3c** (white solid) was obtained, that was purified by crystallization from AcOEt/hexane; yield: 8.5 g (92%); mp 139–140 °C; $[\alpha]_D$: –20.6 ($CHCl_3$, c = 1.0); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (dd, J = 7.9 Hz, J = 1.1 Hz, 1 H), 7.37–7.19 (m, 7 H), 7.06 (m, 1 H), 6.02 (broad d, J = 7.6 Hz, 1 H), 4.39 (m, 1 H), 3.86–3.67 (m, 2 H), 3.00 (d, J = 7.3 Hz, 2 H); ^{13}C NMR

(50 MHz, $CDCl_3$): δ = 169.8 (s), 142.1 (s), 139.8 (d), 137.6 (s), 131.2 (d), 129.4 (d, 2C), 128.7 (d, 2C), 128.2 (d), 128.1 (d), 126.8 (d), 92.5 (s), 63.5 (t), 53.3 (d), 36.8 (t); IR (KBr): ν = 3400, 3277, 1645, 1538, 698 cm^{-1}; MS (EI): *m/z* = 381 (M^+, 5), 350 (7), 290 (57), 248 (18), 231 (100), 203 (23), 105 (18), 91 (19), 76 (19); anal.: calcd. for $C_{16}H_{16}INO_2$: C, 50.41; H, 4.23; N, 3.67; found: C, 50.50; H, 4.51; N, 3.76.

General Procedure for the Sequential Swern–Wittig Reaction of 3a–c; Synthesis of the α,β-Unsaturated Esters 4a–c

A solution of dry DMSO (3.2 mol equiv) in CH_2Cl_2 (ca. 2.5 mL per mmol) was dropwise added at –78 °C to a 1 M oxalyl chloride solution in CH_2Cl_2 (1.6 mol equiv, generated from commercially available 2 M solution). After stirring for 25 minutes at this temperature, a solution of the alcohol **3** in CH_2Cl_2 (2 mL per mmol) was added via cannula. The mixture was stirred at –78 °C for 1 hour, and then dry Et_3N (5.8 mol equiv) 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 hour), solid $Ph_3P{=}CHCO_2Me$ (1.5 mol equiv) was added and the reaction mixture was allowed to slowly warm up to room temperature overnight. The solvent was removed under vacuum and the crude product was purified by column chromatography (85 : 15 hexane:AcOEt) to give the α,β-unsaturated esters **4a–c**. The analytical and spectroscopic data of these compounds are indicated below.

(*S*,*E*)-Methyl 4-[(2-Iodobenzoyl)amino]-2-pentenoate (4a): Following the general procedure, from the alcohol **3a** (3.9 g, 12.7 mmol), the α,β-unsaturated ester **4a** was obtained; yield: 3.7 g (80%); white solid; mp 74–76 °C. $[\alpha]_D$: –3.0 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 1 H), 7.39 (m, 2 H), 7.10 (m, 1 H), 6.98 (dd, *J* =15.7 Hz, *J* = 5.0 Hz, 1 H), 6.04 (dd, *J* = 15.7 Hz, *J* = 1.8 Hz, 1 H), 5.76 (broad d, *J* = 7.8 Hz, 1 H), 4.94 (m, 1 H), 3.73 (s, 3 H), 1.42 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9 (s), 166.9 (s), 148.6 (d), 142.0 (s), 140.0 (d), 131.4 (d), 128.4 (d), 128.3 (d), 120.7 (d), 92.6 (s), 51.9 (q), 46.4 (d), 20.0 (q); IR (KBr): ν = 3435, 3265, 1720, 1641, 1531, 1430, 1293, 1196, 1015, 979, 723 cm^{-1}; MS (EI): *m/z* = 359 (M^+, 5), 231 (85), 203 (30), 128 (100), 105 (6), 96 (21), 76 (22); anal.: calcd. for $C_{13}H_{14}INO_3$: C, 43.45; H, 3.93; N, 3.90; found: C, 43.56; H, 3.94; N, 3.86.

(*S*,*E*)-Methyl 4-[(2-Iodobenzoyl)amino]-5-methyl-2-hexenoate (4b): Starting from **3b** (8.6 g, 25.8 mmol), the α,β-unsaturated ester **4b** was obtained; yield: 9.4 g (95%); white solid; mp 82–84 °C; $[\alpha]_D$: –4.3 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 4.2 Hz, 2 H), 7.12 (m, 1 H), 6.94 (dd, *J* = 15.7 Hz, *J* = 5.6 Hz, 1 H) 6.07 (dd, *J* = 15.7 Hz, *J* = 1.5 Hz, 1 H), 5.85 (broad d, *J* = 9.2 Hz, 1 H), 4.72 (m, 1 H), 3.73 (s, 3 H), 2.04 (m, 1 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1 (s), 166.8 (s), 146.5 (d), 142.4 (s), 140.1 (d), 131.4 (d), 128.5 (d), 128.4 (d), 122.2 (d), 92.4 (s), 56.0 (d), 51.9 (q), 32.3 (d), 19.2 (q), 18.6 (q); IR (KBr): ν = 3380, 3220, 2900, 1690, 1615, 1500, 1400 cm^{-1}. MS (EI): *m/z* = 387 (M^+, 3), 344 (23), 248 (5), 231 (100), 203 (25), 156 (34), 140 (10), 114 (10), 105 (12), 76 (28); anal.: calcd. for $C_{15}H_{18}INO_3$: C, 46.53; H, 4.69; N, 3.62; found: C, 46.54; H, 4.93; N, 3.58.

(*S*,*E*)-Methyl 4-[(2-Iodobenzoyl)amino]-5-phenyl-2-pentenoate (4c): Following the general procedure, starting from the alcohol **3c** (7.5 g, 19.6 mmol), the ester **4c** was obtained; yield: 7.2 g (85%); white solid; mp 99–101 °C; $[\alpha]_D$: +1.0 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.9 Hz, 1 H), 7.36–7.05 (m, 8H), 6.99 (dd, *J* = 15.7 Hz, *J* = 5.3 Hz, 1 H) 6.03 (dd, *J* = 15.7 Hz, *J* = 1.7 Hz, 1 H), 5.85 (broad d, *J* = 8.2 Hz, 1 H), 5.13 (m, 1 H), 3.72 (s, 3 H), 3.03 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.0 (s), 166.7 (s), 146.9 (d), 142.0 (s), 140.1 (d), 136.3 (s), 131.4 (d), 129.6 (d, 2 C), 129.0 (d, 2 C), 128.3 (d, 2 C), 127.3 (d), 121.7 (d), 92.5 (s), 51.9 (q), 51.6 (d), 40.4 (t); IR (KBr): ν = 3430, 3270, 1725, 1642, 1529, 1433, 1315, 1173, 1016 cm^{-1}; MS (EI): *m/z* = 435 (M^+, 3), 344 (80), 231 (100), 203 (34), 188 (12), 129 (14), 105 (16), 91 (19); anal.: calcd. for $C_{19}H_{18}INO_3$: C, 52.41; H, 4.17; N, 3.22; found: C, 52.70 ; H, 4.42 ; N, 3.46.

General Procedure for the Heck Cyclization of the 2-Iodobenzamides 4a–4c; Synthesis of the Dihydroisoquinolones 5a–c

A vigorously stirred solution of $Pd(OAc)_2$ (0.035 mol equiv), Ph_3P (0.11 mol equiv), Et_3N (2 mol equiv), and the amide **4** in dry CH_3CN (24 mL per mmol) was heated at 70 °C for 48 hours under an argon atmosphere. After cooling at room temperature, the mixture was diluted with H_2O and thoroughly extracted with $CHCl_3$. The combined organic extracts were washed with brine and dried ($MgSO_4$); the solvent was removed, and the residue was purified by chromatography (9 : 1 hexane–EtOAc) to give the isoquinoline derivatives **5a–c**. The analytical and spectroscopic data of the lactams **5a**, **5b**, and **5c** are indicated below.

(*S*,*Z*)-4-Methoxycarbonylmethylidene-3-methyl-3,4-dihydro-2*H*-isoquinoline-1-one (5a): From **4a** (850 mg, 2.36 mmol), compound **5a** was obtained as a white solid; yield: 330 mg (61%); mp 185–187 °C; $[\alpha]_D$: –344.1 ($CHCl_3$, *c* = 0.53); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (m, 1 H), 7.63–7.52 (m, 3 H), 6.50 (broad s, 1 H), 6.32 (s, 1 H), 5.71 (m, 1 H), 3.77 (s, 3 H), 1.38 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (s), 163.7 (s), 151.6 (s), 133.8 (s), 133.0 (d), 131.1 (d), 128.5 (d), 128.3 (s), 124.8 (d), 114.5 (d), 51.9 (q), 48.2 (d), 23.9 (q). IR (KBr): ν = 3432, 1716, 1693, 1626, 1597, 1432, 1371, 1282, 1169, 767 cm^{-1}. MS (EI): *m/z* = 231 (M^+, 52), 216 (28), 198 (23), 184 (16), 172 (100), 156 (15), 129 (16), 101 (14), 84 (25); anal.: calcd .for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; found: C, 67.22; H, 5.65; N, 6.14.

(*S*,*Z*)-3-Isopropyl-4-methoxycarbonylmethylidene-3,4-dihydro-2*H*-isoquinoline-1-one (5b): Following the general procedure, the heterocycle **5b** was obtained from **4b** (4.0 g, 10.4 mmol) ass an amorphous foam-like white solid; yield: 2.2 g (82%); mp 38–40 °C; $[\alpha]_D$: –349.2 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.13 (m, 1 H), 7.58–7.50 (m, 3 H), 6.85 (broad s, 1 H), 6.34 (s, 1 H), 5.40 (m, 1 H), 3.76 (s, 3 H), 1.86 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.0 (s), 164.3 (s), 150.8 (s), 135.4 (s), 132.8 (d), 130.7 (d), 128.6 (s), 128.1 (d), 123.8 (d), 116.2 (d), 56.8 (d), 51.7 (q), 35.6 (d), 19.4 (q), 17.9 (q); IR (KBr): ν = 3198, 2962, 1715, 1671, 1597, 1367, 1246, 1167, 768 cm^{-1}; MS (EI): *m/z* = 259 (M^+, 32), 216 (100), 200 (18), 184 (30), 156 (20), 129 (18), 102 (11); anal.: calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; found: C, 69.70; H, 6.45; N, 5.23.

(±)-(*Z*)-4-Methoxycarbonylmethylidene-3-phenyl-3,4-dihydro-2*H*-isoquinoline-1-one (5c): The racemic heterocycle (±)-**5c** was obtained from **4c** (3.0 g, 6.9 mmol)[56] as a white solid; yield: 930 mg (44%); mp 145–146 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.22 (m, 1H), 7.72–7.58 (m, 3H), 7.33–7.20 (m, 5H), 6.44 (s, 1H), 5.98 (broad s, 1H), 5.77 (m, 1H), 3.83 (s, 3H), 3.07 (dd, *J* = 13.0 Hz, *J* = 3.6 Hz, 1H), 2.73 (dd, *J* = 13.0 Hz, *J* = 9.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.7 (s), 164.1 (s), 150.8 (s), 137.6 (s), 134.7 (s), 133.6 (d), 131.8 (d), 130.6 (d, 2C), 129.4 (d, 2C), 129.2 (d), 129.1 (s), 127.7 (d), 125.2 (d), 115.7 (d), 54.7 (d), 52.6 (q), 44.7 (t); IR (KBr): ν = 3432, 1713, 1676, 1434, 1366, 1299, 1245, 1175, 731 cm^{-1}. MS (EI): *m/z* = 307 (M$^+$, 12), 216 (100), 188 (14), 184 (25), 156 (19), 129 (16), 102 (12), 91 (28); anal.: calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56; found: C, 74.55; H, 5.70; N, 4.49.

General Procedure for the Homo-Coupling Reaction of the 2-Iodobenzamides 4a and 4b; Synthesis of the Biphenyls 6a and 6b

A vigorously stirred mixture of **4**, $Pd(OAc)_2$ (0.06 mol equiv), Ph_3P (0.2 mol equiv), Et_3N (2.0 mol equiv), and $AgNO_3$ (1.0 mol equiv) in CH_3CN (60 mL per mmol) was heated at 80 °C for 60 hours under argon. Then, the reaction mixture was cooled down to room temperature, diluted with H_2O and thoroughly extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to provide the crude product, that was a mixture of unreacted starting material (**4**) and biphenyl **5**, that were separated by chromatography (85:15 and 60:40 hexane:EtOAc). The analytical and spectroscopic data of the biphenyls **6a** and **6b** are indicated below.

***(E,E)*-*N,N′*-Di-[1-(methoxycarbonyl)but-1-en-3-yl]-2,2′-biphenyldicarboxamide (6a):** Starting from **4a** (800 mg, 2.2 mmol), the biphenyl **6a** along unreacted **4a** (412 mg, 52%) were obtained following the procedure above indicated; yield of **6a**: 123 mg (24%); mp 56–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of two atropoisomers): δ = 7.59–7.50 (m, 2H), 7.47–7.39 (m, 4H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.16–7.10 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.78 (dd, *J* = 15.8 Hz, *J* = 4.6 Hz, 1H), 6.53 (ddd, *J* = 15.7 Hz, *J* = 7.8 Hz, *J* = 5.2 Hz, 1H), 5.81 (dt, *J* = 15.8 Hz, *J* = 1.9 Hz, 1H), 5.60 (ddd, *J* = 15.7 Hz, *J* = 11.2 Hz, *J* = 1.5 Hz, 1H), 4.63 (m, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 1.5H), 0.96 (d, *J* = 7.1 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of atropoisomers): δ = 169.5 (s), 169.4 (s), 166.8 (s, 2C), 148.5 (d, 2C), 139.2 (s), 138.9 (s), 136.1 (s, 2C), 130.1 (d, 2C), 129.6 (d, 2C), 128.4 (d), 128.2 (d), 127.2 (d), 127.1 (d), 120.3 (d), 120.2 (d), 51.8 (q, 2C), 46.1 (d), 46.0 (d), 20.0 (q), 19.5 (q); IR (KBr): ν = 3435, 1725, 1637, 1543, 1437, 1277, 1177 cm^{-1}; MS (EI): *m/z* = 464 (M$^+$, 14), 432 (8), 336 (44), 308 (100), 224 (29), 206 (28), 196 (31), 181 (86), 152 (25), 128 (24), 113 (26).

***(E,E)*-*N,N′*-Di-[1-(methoxycarbonyl)-3-methylpent-1-en-3-yl]-2,2′-biphenyldicarboxamide (6b):** Starting from **4b** (500 mg, 1.3 mmol), the biphenyl **6b** along unreacted **4b** (325 mg, 65%) were obtained; yield of **6b**: 94 mg (30%), white solid; mp 58–60 °C;^{1}H NMR (300 MHz, $CDCl_3$, mixture of atropoisomers): δ = 52–7.28 (m, 8H), 7.04 (m, 2H), 6.77 (dd, *J* = 15.7 Hz, *J* = 5.5 Hz, 1H), 6.49 (dd, *J* = 15.6 Hz, *J* = 6.3 Hz, 1H), 5.81 (dd, *J* = 15.7 Hz, *J* = 1.3 Hz, 1H), 5.47 (dd, *J* = 15.6 Hz, *J* = 1.2 Hz, 1H), 4.38 (m, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 1.74 (m, 1H), 1.63 (m, 1H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3H); ^{1}H NMR (300 MHz, C_6D_6, 303 K, mixture of atropoisomers): δ = 8.59 (d, *J* = 8.8 Hz, 1H), 8.43 (d, *J* = 8.6 Hz, 1H), 7.44 (m, 2H), 7.12–6.92 (m, 5H), 6.74–6.66 (m, 3H), 6.05 (d, *J* = 15.9 Hz, 1H), 5.71 (d, *J* = 15.6 Hz, 2H), 4.50 (m, 2H), 3.43 (s, 3H), 3.38 (s, 3H), 1.66 (m, 1H), 1.56 (m, 1H), 0.74 (d, *J* = 6.3 Hz, 3H), 0.72 (d, *J* = 6.3 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H), 0.58 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of atropoisomers): δ = 169.6 (s), 169.5 (s), 166.5 (s), 166.4 (s) 146.5 (d), 146.3 (d), 138.8 (s), 138.7 (s), 136.0 (s), 135.9 (s), 129.5 (d), 129.4 (d, 2C), 129.3 (d), 127.9 (d), 127.7 (d), 127.2 (d), 127.0 (d), 121.2 (d), 121.1 (d), 55.7 (d), 55.6 (d), 51.3 (q, 2C), 31.8 (d, 2C), 18.6 (q, 2C), 18.2 (q), 17.7 (q); IR (KBr): ν = 3435, 2962, 1725, 1636, 1543, 1436, 1318, 1175, 1039, 757 cm^{-1}; MS (EI): *m/z* = 520 (M$^+$, 8), 477 (38), 364 (100), 336 (18), 224 (37), 206 (17), 181 (83), 152 (16), 141 (12), 109 (9); anal.: calcd. for $C_{30}H_{36}N_2O_6$: C, 69.21; H, 6.97; N, 5.38; found: C, 69.47; H, 7.05; N, 5.09.

Synthesis of (*S*)-2-Hydroxymethyl-1-(2-iodobenzoyl)piperidine (8)

A mixture of (*S*)-1-benzyloxycarbonyl-2-(hydroxymethyl)piperidine (**7**)[19] (2.9 g, 11.6 mmol) and 10% Pd/C (580 mg) in MeOH (50 mL) was hydrogenated at room temperature under a hydrogen pressure of ca. 45 psi in a Parr shaker for 8 hours. The solid was filtered off through a short bed of Celite and washed with MeOH. The solvent was removed under vacuum to give (*S*)-2-(hydroxymethyl)piperidine (1.3 g, 11.3 mmol, 97% yield), 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 2-iodobenzoyl chloride (3.0 g, 11.3 mmol) in THF (4 mL). The mixture was allowed to slowly warm up to room temperature and stirred overnight. Then, saturated aqueous $NaHCO_3$ solution was added, the aqueous phase was saturated with NaCl, and thoroughly extracted with Et_2O. The organic phase was washed with brine and dried ($MgSO_4$). Removal of the solvent gave chromatographically homogeneous 2-iodobenzamide **8**; yield: 3.4 g (88%). An analytical pure sample was obtained by chromatography (25:75 hexane-AcOEt); white solid; mp 130–132 °C; $[\alpha]_D$: –28.0 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (300 MHz, $CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$, 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; IR (KBr): ν = 3400, 2930, 1600, 1580, 1475, 1440, 1430, 1375, 1285, 1060, 1050, 1015, 1015, 780, 750 cm^{-1}; MS (EI): *m/z* = 345 (M$^+$, < 1), 314 932), 231 (100), 203 (23), 105 (34), 76 (50), 55 (19), 50 (18), 41 (13); anal.: calcd. for $C_{13}H_{16}INO_2$: C, 45.21; H, 4.63; N, 4.05; found: C, 45.43; H, 4.71; N, 4.03.

Synthesis of (*S*,*E*)-Methyl 3-[1-(2-Iodobenzoyl)piperidin-2-y]acrylate (9)

A solution of dry DMSO (11.4 mL, 162.3 mmol) in CH_2Cl_2 (100 mL) was dropwise added at –78 °C to a solution of oxalyl chloride (81.1 mmol) in CH_2Cl_2 (150 mL). After stirring for

30 minutes at this temperature, a solution of the alcohol **8** (20 g, 58 mmol) in CH_2Cl_2 (100 mL) was added via cannula. The mixture was stirred at –78 °C for 90 minutes, and, then, dry Et_3N (40 mL, 290 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 hour), solid $Ph_3P{=}CHCO_2Me$ (23.7 g, 75.3 mmol) was added and the reaction mixture was allowed to warm slowly up to room temperature overnight. The solvent was removed under vacuum and the crude product was purified by column chromatography (80 : 20 hexane : AcOEt) to give the α,β-unsaturated esters **9** as a single stereoisomer; white solid; mp 105–108 °C; $[\alpha]_D$: –99.0 ($CHCl_3$, c = 1.05); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of conformers): δ = 7.81 (m, 1 H), 7.38 (m, 0.7 H), 7.32 (m, 0.3 H), 7.21 (m, 0.3 H), 7.16 (m, 0.2 H), 7.11–7.02 (m, 1.5 H), 7.05 (dd, J = 15.9, 3.8 Hz, 0.4 H), 6.97 (dd, J = 15.9, 3.8 Hz, 0.3 H), 6.77 (dd, J = 15.9, 3.8 Hz, 0.3 H), 6.28 (dd, J = 15.9, 2.2 Hz, 0.3 H), 5.94 (dd, J = 15.9, 2.2 Hz, 0.3 H), 5.69 (m, 0.7 H), 4.73 (m, 0.4 H), 4.19 (m, 0.3 H), 3.77 (s, 0.8 H), 3.75 (s, 1 H), 3.74 (s, 1.2 H), 3.25 (m, 0.8 H), 3.19 (m, 0.4 H), 3.01 (m, 0.4 H), 2.84 (m, 0.4 H), 2.20–1.30 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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); IR (KBr): ν = 2950, 2860, 1725, 1635, 1590, 1425, 1310, 1280, 1200, 1170, 1015, 970, 770, 750, 730; 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 $C_{16}H_{18}INO_3$: C, 48.12; H, 4.55; N, 3.51; found: C, 48.49; H, 4.21; N, 3.40.

Synthesis of (*S*,*Z*)-11-Methoxycarbonylmethylidene-2,3,4,6,11,11a-hexahydro-1*H*-pyrido[1,2-b]isoquinoline-6-one (10)

$Pd(OAc)_2$ (304 mg, 1.35 mmol), Ph_3P (1.2 g, 4.51 mmol), $AgNO_3$ (7.6 g, 45.1 mmol), and Et_3N (14 mL, 90.2 mmol) were sequentially added to a solution of the amide **9** (18 g, 45.1 mmol) in dry CH_3CN (180 mL) under argon. The mixture was stirred at room temperature overnight; then, it was cooled at 0 °C, diluted with H_2O (200 mL) and $CHCl_3$ (200 mL). The phases were separated, the aqueous one was extracted with $CHCl_3$ (2 × 100 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 **10**; yield: 12 g (98%), white solid; mp 124–127 °C; $[\alpha]_D$: –317 ($CHCl_3$, c = 1.07); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (m, 1 H), 7.67 (m, 1 H), 7.54 (m, 2 H), 6.37 (d, J = 1.4 Hz, 1 H), 5.53 (m, 1 H), 4.88 (m, 1 H), 3.79 (s, 3 H), 2.79 (dt, J = 12.6 Hz, J = 3.1 Hz, 1 H), 1.98–1.42 (m, 6 H); ^{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); IR (KBr): ν = 2950, 1715, 1650, 1625, 1595, 1470, 1440, 1430, 1375, 1285, 1195, 1180, 1160, 1100, 1030, 1010, 975, 965, 775, 685 cm^{-1}; 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 $C_{16}H_{17}NO_3$: C, 70.82; H, 6.32; N, 5.16; found: C, 70.96; H, 6.16; N, 5.21.

The Heck Reaction of (*S*,*E*)-Methyl 3-[1-(2-Iodobenzyl)piperidin-2-yl]acrylate [(±)-11] under Jeffery Conditions

$Pd(OAc)_2$ (2 mg, 0.01 mmol), Ph_3P (8 mg, 0.03 mmol), KOAc (82 mg, 0.84 mmol), and tetrabutylammonium iodide (85 mg, 0.23 mmol) were sequentially added to a solution of the amine **11** (80 mg, 0.21 mmol) in dry DMF (3 mL) under argon. The mixture was heated at 80 °C for ca. 6 hours (until the all the starting material has reacted, TLC control). The mixture was allowed to cool down to room temperature, the solid was filtered-off, and the solution was diluted with Et_2O (12 mL) and water (3 mL). The phases were separated, the aqueous one was extracted with Et_2O, and the combined ethereal extracts were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (80 : 20 hexane–EtOAc) to give an inseparable 9 : 1 mixture of the olefins (±)-*Z*-**12** and (±)-*E*-**12** as a thick oil. The NMR data for the *Z*-isomer are indicated next; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (m, 1 H), 7.24 (m, 2 H), 7.11 (m, 1 H), 6.14 (d, J = 1.8 Hz, 1 H), 4.35 (m, 1 H), 3.73 (s, 3 H), 3.67 (AB system, $J_{A,B}$ = 14.2 Hz, 1/2ν = 111 Hz, 2 H), 3.05 (m, 1 H), 2.74 (m, 1 H), 1.98–1.42 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 156.4, 138.5, 131.0, 129.3, 127.2, 126.4, 124.5, 112.9, 61.8, 54.6, 52.8, 51.2, 28.6, 25.2, 22.4.

Acknowledgements

Financial support from CICYT (Project AGF98–0805-C02–02) and CAM (Project 08.5/0056/2000–2) is gratefully acknowledged. F. S.-S. thanks the Spanish Ministry of Education for a fellowship.

References and Notes

[1] (a) B. J. Baker, in *Alkaloids: Chemical and Biological Perspectives, Vol. 10* (Ed.: W. S. Pelletier), Pergamon, Oxford, **1996**, pp 357–407; (b) P. Yuen, R. M. Schelkun, B. Szoke, K. Tarczy-Hornoch, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2415–2418; (c) K. W. Bentley, *Nat. Prod. Rep.* **2000**, 247–267.

[2] (a) M Hanaoka, *The Alkaloids*, **1988**, *33*, 141–230; (b) A. Monsees, S. Laschat, M. Hotfilder, J. Wolff, K. Bergander, L Terfloth, R. Fröhlich, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2945–2950; (c) S. Zhao, M. J. Totleben, J. P. Freeman, C. L. Bacon, G. B. Fox, E. O'Driscoll, A. G. Foley, J. Kelly, U. Farrell, C. Regan, S. A. Mizsak, J. Szmuszkovicz, *Bioorg. Med. Chem.* **1999**, *7*, 1637–1646.

[3] Meanwhile the IUPAC nomenclature for the parent ring system of **B** is pyrido[1,2-*b*]isoquinoline (see *Pure Appl.Chem* **1998**, *70*, 143–216), the CAS-nomenclature is benzo[*b*]quinolizidine; which causes some confusion in the literature.

[4] For recent references on the synthesis of chiral partially reduced isoquinolines, see: (a) D. Taniyama, M. Hasegawa, K. Tomioka, *Tetrahedron: Asymmetry* **1999**, *10*, 221–223; (b) B. Wünsch, S. Nerdinger, *Eur. J. Org. Chem.* **1999**, 503–517; (c) R. Yamaguchi, M. Tanaka, T. Matsuda, K. Fujita, *Chem. Commun.* **1999**, 2213–2214; (d) F. A. Davis, Y. W. Andemichael, *J. Org. Chem.* **1999**, *64*, 8627–8634.

[5] For recent references on the synthesis of chiral partially reduced pyrido[1,2-*b*]isoquinolines, see: (a) P. Lienard, J. Royer, J.-C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1991**, *32*, 2489–2492; (b) S. Lebrun, A. Couture, E. Deniau, P. Grandclaudon, *Eur. J. Org. Chem.* **1999**, 2345–2352.

[6] For a comprehensive review on the synthesis of polyannular heterocycles, see: G. P. Ellis, *Synthesis of Fused Heterocycles*, John Wiley and Sons, Chichester, **1992**.

[7] F. Sánchez-Sancho, PhD thesis, Universidad Autónoma de Madrid, Spain, **1999**.

[8] E. Mann, F. Sánchez-Sancho, B. Herradón, to be submitted for publication.

[9] For reviews on some aspects of the Heck reaction, see: (a) R. F. Heck, *Organic Reactions* **1982**, *27*, 345–390; (b) R. F. Heck, in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon Press, Oxford, **1991**, pp 833–863; (c) A. de Meijere, F. E. Meyer, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411; (d) A. Heumann, M. Réglier, *Tetrahedron* **1996**, *52*, 9289–9346; (e) S. E. Gibson, R. J. Middlenton, *Contemp. Org. Synth.* **1996**, *3*, 447–471; (f) M. Shibasaki, C. D. J. Boden, A. Kojima, *Tetrahedron* **1997**, *53*, 7371–7395; (g) G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427–436; (h) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066; (i) A. Yamamoto, Y. Kayaki, K. Nagayama, I. Shimizu, *Synlett* **2000**, 925–937; (j) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321; (k) For a recent review on carbon–carbon bond formation (including Heck reaction) on solid phase, see: B. A. Lorsbach, M. J. Kurth, *Chem. Rev.* **1999**, *99*, 1549–1581.

[10] (a) Chronologically, and based on structural studies, our first synthetic targets were peptidomimetics on the rigid pyrido[1,2-*b*]isoquinoline scaffold (**B**); the synthesis of isoquinoline derivatives (**A**) was done to assess the influence of the rigidity of the template on the structure of the peptidomimetic. (b) It must be remarked that the isoquinoline derivatives described in the present paper are more densely functionalized than the ones reported in refs.[11–14]

[11] (a) L. F. Tietze, R. Schimpf, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1089–1091; (b) L. F. Tietze, R. Schimpf, *Chem. Ber.* **1994**, *127*, 2235–2240; (c) L. F. Tietze, O. Burkhardt, *Liebigs Ann.* **1995**, 1153–1157; (d) L. Tietze, O. Burkhardt, M. Henrich, *Liebigs Ann./Recueil* **1997**, 1407–1413; (e) L. F. Tietze, K. Thede, R. Schimp, F. Sannicolò, *Chem. Commun.* **2000**, 583–584.

[12] D. A. Goff, R. N. Zuckermann, *J. Org. Chem.* **1995**, *60*, 5748–5749.

[13] S. E. Gibson (née Thomas), N. Guillo, M. J. Tozer, *Chem. Commun.* **1997**, 637–638.

[14] (a) S. Berteina, A. De Mesmaeker, *Synlett* **1998**, 1227–1230; (b) S. Berteina, S. Wendeborn, A. De Mesmaeker, *Synlett* **1998**, 1231–1233.

[15] P. Meffre, P. Durand, E. Branquet, F. Le Goffe, *Synth. Commun.* **1994**, *24*, 2147–2152.

[16] R. E. Ireland, D. W. Norbeck, *J. Org. Chem.* **1985**, *50*, 2198–2200.

[17] (a) A. J. Mancuso, S. L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480–2482; (b) For a review on the Swern and related reactions, see: T. V. Lee, in *Comprehensive Organic Synthesis, Vol. 7* (Eds.: B. M. Trost, I. Fleming, S. V. Ley), Pergamon Press, Oxford, **1991**, pp 291–327.

[18] For reviews on the Wittig reaction, see: (a) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927; (b) E. Vedejs, M. J. Peterson, *Topics Stereochemistry* **1993**, *21*, 1–157; (c) K. C. Nicolaou, M. W. Härter, J. L. Gunzner, A. Nadin, *Liebigs Ann./Recueil* **1997**, 1283–1301.

[19] This method avoids the manipulation of sensitive N-protected α-amino aldehydes (chemically unstable and prone to racemization),[20] for a discussion, see: F. Sánchez-Sancho, B. Herradón, *Tetrahedron: Asymmetry* **1998**, *9*, 1951–1965.

[20] For reviews on the synthesis, stability, and applications of *N*-protected amino aldehydes, see: (a) J. Jurczak, A. Golebiowski, *Chem Rev.* **1989**, *89*, 149–164; (b) M. T. Reetz, *Chem. Rev.* **1999**, *99*, 1121–1162.

[21] The reactions can be carried out in multigram scale, and all the intermediates can be purified by crystallization.

[22] For some references, see: (a) R. Grigg, V. Loganathan, V. Santhakumar, V. Sridharan, A. Teasdale, *Tetrahedron Lett.* **1991**, *32*, 687–690; (b) R. Grigg, V. Santhakumar,V. Sridharan, M. Thornton-Pett, A. W. Bridge, *Tetrahedron* **1995**, *49*, 5177–5188; (c) T. Hudlicky, H. F. Olivo, B. McKibben, *J. Am. Chem. Soc.* **1994**, *116*, 5108–5115; (d) S. E. Denmark, M. E. Schnute, *J. Org. Chem.* **1995**, *60*, 1013–1019; (e) D. E. Kaufmann, M. Nouroozian, H. Henze, *Synlett* **1996**, 1091–1092; (f) T. Ohshima, K. Kagechika, M. Adachi, M. Sodeoka, M. Shibasaki, *J. Am. Chem. Soc.* **1996**, *118*, 7108–7116; (g) L. E. Overman, D. J. Poon, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 518–521; (h) L. Ripa, A. Hallberg, *J. Org. Chem.* **1997**, *62*, 595–602; (i) V. B. Birman, V. H. Rawal, *Tetrahedron Lett.* **1998**, *39*, 7219–222; (j) S. E. Gibson (née Thomas), J. O. Jones, R. McCague, M. J. Tozer, N. J. Whitcombe, *Synlett* **1999**, 954–956; (k) J. Priego, J. C. Carretero, *Synlett* **1999**, 1603–1605.

[23] T. Jeffery, *Tetrahedron* **1996**, *52*, 10113–10130, and references cited therein.

[24] For recent reports on the Heck reaction in the presence of tetraalkylammonium salts, see: (a) S. E. Gibson (née Thomas), N. Guillo, R. J. Middleton, A. Thuilliez, M. J. Tozer, *J. Chem. Soc., Perkin Trans 1,* **1997**, 447–455; (b) R. C. Larock, P. Pace, H. Yang, C. E. Russell, S. Cacchi, G. Fabrizi, *Tetrahedron* **1998**, *54*, 9961–9980; (c) R. C. Larock, X. Han, *J. Org. Chem.* **1999**, *64*, 1875–1887.

[25] M. M. Abelman, T. Oh, L. E. Overman, *J. Org. Chem.* **1987**, *52*, 4130–4133.

[26] For recent reports on the Heck reaction in the presence of silver(I) salts, see: (a) L. F. Tietze, R. Hannemann, W. Buhr, M. Lögers, P. Menningen, M. Lieb, D. Starck, T. Grote, A. Döring, I. Schuberth, *Angew.*

Chem. Int. Ed. Engl. **1996**, *35*, 2674–2677; (b) F. Miyazaki, K. Uotsu, M. Shibasaki, *Tetrahedron* **1998**, *54*, 13073–13078; (c) S. Honzawa, T. Mizutani, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 311–314; (d) M. M. Segorbe, J. Adrio, J. C. Carretero, *Tetrahedron Lett.* **2000**, *41*, 1983–1986.

[27] Compounds **6a** and **6b** are obtained as a 1:1 mixture of two atropoisomers (that are diastereoisomers). The optical rotations of both **6a** and **6b** are nearly zero, this can be due to one of the following two possibilities: a) the optical rotation of each atropoisomer is nearly the same, but with opposite sign; b) there has been racemization during the reaction. If this latter circumstance had happened, three atropoisomers would be expected. Work is in progress to investigate this issue as well as to prepare peptidomimetics on biaryl scaffolds. These molecules, that can have interesting properties,[30,31] have been scarcely studied.

[28] J. Hassan, V. Penalva, L. Lavenot, C. Gozzi, M. Lemaire, *Tetrahedron* **1998**, *54*, 13793–13804.

[29] D. D. Hennings, T. Iwama, V. H. Rawal, *Org. Lett.* **1999**, *1*, 1205–1208.

[30] Compounds of type **6** are potential inhibitors of HIV protease, see: M. T. Reetz, C. Merk, G. Mehler, *Chem. Commun.* **1998**, 2075–2076.

[31] Biaryl-substituted peptidomimetics with hydrophobic side–chains can have liquid crystal behavior; for a book treating different aspects of liquid crystals, see: P. J. Collings, *Liquid Crystals. Nature's Delicate Phase of Matter*, Adam Hilger, Bristol, **1990**.

[32] The reaction of **4b** under Jeffery's condition [$Pd(OAc)_2$ (0.08 mol equiv)/Ph_3P (0.3 mol equiv)/KOAc (4 mol equiv)/Bu_4NI (1.1 mol equiv)/DMF/60 °C] is extremely slow, reaching a 10% conversion after 36 hours.

[33] For a recent review on the application of the Heck reaction in the synthesis of polyannular nitrogenated-heterocycles, see: M. Ikeda, S. A. A. El Bialy, T. Yakura, *Heterocycles* **1999**, *51*, 1957–1970.

[34] (a) The *Z*-stereochemistry at the exocyclic double bond was assigned on basis to the existence of NOEs between the olefinic and *H-5* protons in the NOESY spectra of compounds **5**, and latter confirmed by single-crystal X-ray diffraction analysis of a derivative of **5b** (E. Mann, F. Sánchez-Sancho, A. Chana, J. Mahía, M. A. Maestro, B. Herradón, unpublished observations). (b) The stereochemical integrity of the stereogenic centers of all the intermediates was secured by the conversion of **5a** and **5b** to diastereoisomerically pure peptide-heterocycle hybrids.[8] (c) We did not observe the formation of the regioisomers of **5a–c** with the endocyclic double bond, that has been reported in related reactions.[12,14b]

[35] (a) We are currently investigating the cause of this racemization. Interestingly, the lactam proton of **5c** appears 0.6–0.9 ppm more shielded than the corresponding protons in **5a** and **5b** in the ^1H NMR spectra; this shielding seems to indicate an interaction between the amide proton of **5c** and the aromatic ring, that might contribute to an increased acidity of the allylic proton in either **4c** or **5c** (or in both, or in some of the intermediate of the Heck cyclization). For a thorough discussion on the interaction between hydrogen and aromatic compounds, see: G. R. Desiraju, T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford University Press, Oxford, **1999**; (b) An alternative strategy for the synthesis of enantiomerically pure **5c** is through a lipase-catalyzed hydrolysis of racemic **5c** (planned work).

[36] M. Ors, A. Morcuende, M. I Jiménez-Vacas, S. Valverde, B. Herradón, *Synlett* **1996**, 449–451.

[37] (a) The stereochemistry at the double bond was assigned on basis to the existence of a NOE between the olefinic and H-10 protons in the NOESY spectrum of **10**; it was confirmed by a single-crystal X-ray diffraction analysis of racemic **10**. (b) The conversion of (*S*)-**10** into diastereoisomerically pure peptide-heterocycle hybrids[7,8] confirms that the overall transformation of (*S*)-**7** into (*S*)-**10** proceeded without racemization. (c) We did not detect any biaryl compound in these reactions.

[38] F. Sánchez-Sancho, E. Mann, B. Herradón, *Synlett* **2000**, 509–513.

[39] (a) The synthesis of **12** was carried out in the racemic series. (b) Only starting material (> 95% yield) was recovered in the Heck reaction under Overman's conditions.

[40] C. Gürtler, S. L. Buchwald, *Chem. Eur. J.* **1999**, *5*, 3107–3112, and references cited therein.

[41] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.