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A Diastereocontrolled Route to 10-Arylpyrrolo[1,2-*b*]isoquinolines

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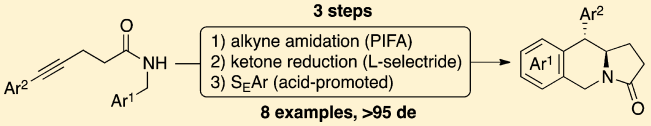
Supporting Information

ABSTRACT: The diastereocontrolled preparation of a series of 10-aryl-substituted pyrroloisoquinolines is achieved through a synthetic design that involves two key cyclization steps. First, the iodine(III)-mediated reaction of a series of *N*-benzylpentynamides leads to the generation of the 5-aroylpyrrolidinone skeletons. Finally, after reduction of the generated ketone group into the corresponding carbinol, the effect of a number of different acidic conditions was studied to assist the second cyclization step that occurs through an aromatic electrophilic substitution process. The study of the stereochemical course of this step led us to conclude that it takes place through a S_N1 mechanism with very high (>95% anti) diastereocontrol.



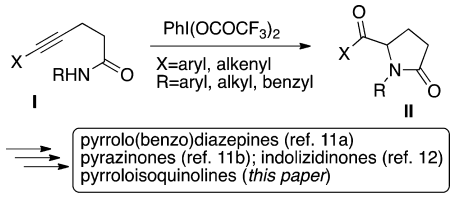
1. INTRODUCTION

The preparation of isoquinoline-based heterocycles has been a recurrent theme for synthetic organic chemists. The reason for such attraction can probably be found in the opportunities that this platform offers to assess novel and efficient synthetic designs, and also in the fact that such a nitrogenated heterocyclic framework is a fundamental core of numerous drugs and biologically active natural products. In particular, the pyrrolo[1,2-*b*]isoquinoline nucleus is present in some natural products such as lycorine[1] and the phenanthroindolizidine alkaloids.[2]

Besides the selection of the Friedel−Crafts reaction applied to *N*-arylmethylpyroglutamic acids and related substrates as one of the most recurrent approaches to the construction of this kind of heterocycle,[3] a number of more elaborated procedures for this task can be found in the literature. These include (a) the lithium−iodine exchange reaction on *N*-(*o*-iodobenzyl)-pyrrole-2-carboxamides under Parham cyclization conditions,[4] (b) the intramolecular ring closure of 2-substituted isoquinoline *N*-oxides,[5] (c) the Cu(II) carboxylate-promoted intramolecular carboamination reactions of variously substituted *γ*-alkenyl amides,[6] (d) the proper manipulation of 2-(2′-methoxycarbonylbenzyl)pyrrolidines or 2-acetyl-3-carboxy-1,2,3,4-tetrahydroisoquinolines,[7] (e) the electroreductive intramolecular coupling of phthalimides with aromatic aldehydes,[8] and (f) the application of the Pummerer reaction conditions to 2-substituted-*N*-benzylpyrrolidinones.[9]

Interestingly, although it can be considered a main entrance to the construction of N-containing heterocycles, the list shown above does not include the amination of alkynes as the source for the synthesis of such a biologically important structural motif. In this context, our group has demonstrated that the intramolecular amidation of properly substituted alkynes **I** can be performed in the presence of the hypervalent iodine reagent PIFA [bis(trifluoroacetoxy)phenyliodane] to yield a series of 5-aroyl- and 5-alkenoyl-2-pyrrolidinones of type **II** (see Scheme 1).[10] The subtle selection of different groups (X and R in **I**) and the manipulation of the resulting pyrrolidinone derivative have been of great value for the preparation of a number of different heterocycles. For instance, different pyrrolodiazepinone and pyrrolobenzodiazepinone derivatives have been obtained from *N*-(3-aminopropyl)-, *N*-(2-aminomethylphenyl)-, and *N*-(2′-nitrobenzyl)-substituted pyrrolidinones. Similarly, a series of pyrrolopyrazinones has been prepared from *N*-(2′-aminoethyl)-pyrrolidinones by the insertion, in both cases, of an additional reductive amination step.[11] More recently this strategy has been applied to the construction of polyhydroxylated indolizidines.[12] In this paper, therefore, our efforts to introduce this intramolecular metal-free alkyne amidation procedure in a synthetic design directed to the diastereocontrolled construction of 10-aryl-substituted pyrrolo[1,2-*b*]isoquinolines will be disclosed.

Scheme 1. PIFA-Mediated Construction of Substituted Pyrrolidinones



2. RESULTS AND DISCUSSION

Our retrosynthetic proposal (see Scheme 2) was conceived as the combination of two key cyclization steps. We considered that the target skeleton **III** should be obtained from **IV** through an intramolecular acid-promoted Friedel−Crafts alkylation reaction. It was also envisaged that the required hydroxy group could be generated by reduction of the keto-carbonyl

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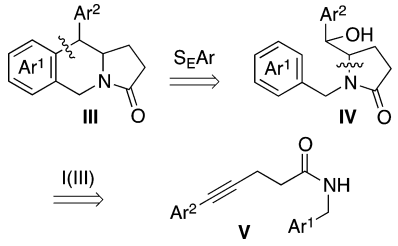
Scheme 2. Key Retrosynthetic Disconnections for the Pyrroloisoquinoline Skeleton



group that is developed (see **II**) after the I(III)-mediated cyclization of **V**.

With this plan in mind, pentynoic acid (**1**) was selected as the backbone to insert on it all the elements required for the generation of intermediate **V**. Thus, its transformation into amides **3a–e** (see Scheme 3) was accomplished in almost quantitative yields, for most cases, by employing a number of different benzylamines **2**. Then, a Sonogashira coupling reaction was selected to include activated and nonactivated aryl groups at the terminal position of the triple bond.[13] This step required the use of a series of aryl halides **4** in combination with Pd(0) and Cu(I) catalysts in the presence of diethylamine to achieve pentynamides **5a–h** (51–99%). When all parts of substrates **5** were assembled, they were subjected to the PIFA-mediated cyclization conditions. Hence, treatment with a slight excess of PIFA in trifluoroethanol (TFEA) as solvent, followed by aqueous basic workup, afforded a series of *N*-benzylpyrrolidinones **6a–h** in moderate to good yields (32–79%).

Because the stereochemical relationships between substrates and products can be employed as a clue to understand the mechanistic insights of a given reaction, we were interested in preparing pyrrolidinols **7** both in diastereochemically pure forms and as mixtures of syn/anti isomers. Previous reports from our group[14] on the stereocontrolled reduction of related 5-alkenoylpyrrolidinones led us to anticipate that variable mixtures of stereoisomers will be obtained, depending on the reduction agent to be employed. In fact, under the action of $NaBH_4$, 5-aroylpyrrolidinones **6** gave rise to mixtures of (*syn*/*anti*)-**7** with de values ranging from 0% to 74% (see Table 1), and contrarily the use of a sterically demanding reducing agent such as L-selectride in THF at −78 °C yielded a series of 5-(1′-hydroxybenzyl)pyrrolidinones **7** with an almost complete diastereoselection.[15] As the only exception, the sterically crowded ketone group in **6a** happened to be inert in the presence of the latter reagent.

Before subjecting the required substrates **7a–h** to the acid-catalyzed S_EAr cyclization step, we considered the preparation

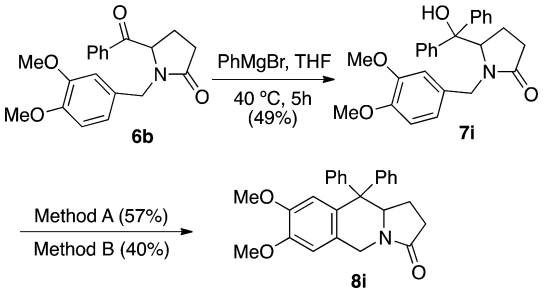
Table 1. Synthetic Details for Intermediates 5–7

				% yield		
entry	Ar^1	Ar^2	series	**5**	**6**	**7**[a]
1	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	**a**	81	58	85 (68)/–[b]
2	3,4-$(MeO)_2C_6H_3$	Ph	**b**	95	41	60 (0)/90 (>95)
3	Ph	Ph	**c**	99	32	71 (32)/72 (>95)
4	Ph	3,4-$(MeO)_2C_6H_3$	**d**	81	57	70 (74)/51 (>95)
5	4-$(MeO)C_6H_4$	Ph	**e**	51	65	73 (23)/88 (>95)
6	3-$(MeO)C_6H_4$	Ph	**f**	60	79	63 (10)/74 (>95)
7	2-naphthyl	Ph	**g**	84	67	64 (48)/84 (>95)
8	Ph	2-thienyl	**h**	81	77	75 (40)/87 (>95)

[a]Isolated yields for the reduction of **6a–h** with $NaBH_4$ and with L-selectride. %de shown in parentheses for each case. [b]Unaltered starting material was completely recovered.

of **7i** to establish a preliminary optimization process. With such a model, no stereochemical concerns had to be contemplated and, more importantly, the success of the reaction would be expedited by, presumably, the generation of a highly stable bis-benzylic carbocation. Therefore, the desired pyrrolidinol **7i** was easily prepared by addition of a slight excess of PhMgBr solution to 5-benzoylpyrrolidinone **6b** at 40 °C (see Scheme 4). With carbinol **7i** in hand, and with the aim to generate the

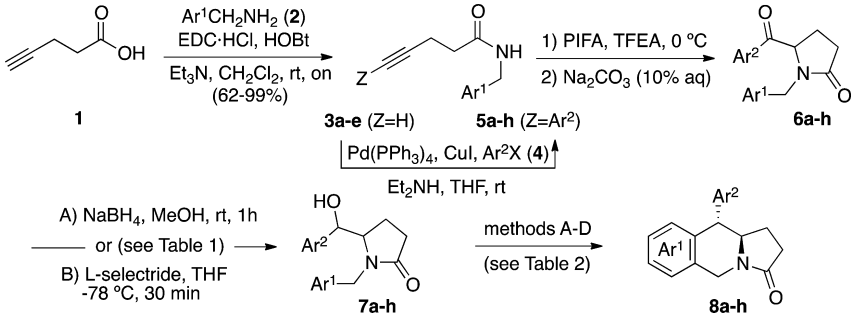
Scheme 4. Synthesis of Pyrroloisoquinoline 8i



pyrroloisoquinoline skeleton **8i**, two different acidic conditions (H_2SO_4/TFA in CH_2Cl_2, and $AlCl_3$ in CH_2Cl_2) were evaluated and also confirmed in both cases (methods A and B).

Encouraged by these results, the series of diastereomerically pure carbinols **7a–h**[16] was subjected to the same reaction

Scheme 3. Synthesis of Pyrroloisoquinolines 8



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conditions to produce heterocycles **8a–g** with variable yields (see Table 2) and, with the only exception of **8g**, almost

Table 2. Preparation of Pyrroloisoquinolines 8a–i from 7a–i[a]

entry	7	8	method A, % yield	method B, % yield	method C, % yield	method D, % yield
1	**i**	**i**	57	40		
2	**a**	**a**	84	41	29	85
3	**b**	**b**	25	46	46	29
4	**c**	**c**	–[b]	93	64	61
5	**d**	**d**	48	64	53	76
6	**e**	**e**	–[b]	–[c]	–[b]	35
7	**f**	**f**/**f′**	–[d]	30[e]	–[f]	–[b]
8	**g**	**g**	–[b]	–[b]	–[g]	51 (10)[h]
9	**h**	**h**	–[i]	–[i]	–[i]	–[i]

[a]Method A: H_2SO_4 (30 equiv), TFA (3 equiv), CH_2Cl_2, reflux, 2 h; method B: $AlCl_3$ (2 equiv), CH_2Cl_2, reflux, 1 d; method C: H_2SO_4 (30 equiv), HOAc, rt, overnight; method D: $FeCl_3{\cdot}6H_2O$ (2 equiv), CH_2Cl_2, reflux, 1 d. [b]Unaltered starting material was completely recovered. [c]Ester **10e** was isolated in 57% yield (80% de). [d]Trifluoroester **9f** was isolated in 11% yield (34% de). [e]As a mixture of regioisomers (87/13). [f]Ester **10f** was isolated in 83% yield (54% de). [g]Ester **10g** was isolated in 52% yield (82% de). [h]Diastereomeric excess shown in parentheses. [i]A complex mixture of compounds was obtained. Trifluoro ester **9h** was isolated in 7% yield (50% de) with method A.

complete diastereocontrol (>95% de, determined by ^{1}H NMR) in all cases and under all reaction conditions. To face the inertness of carbinol **7e** (entry 6), which can be easily explained by the lack of proper activation at both aromatic rings, the original list of reaction conditions A and B was extended to conditions C (H_2SO_4, HOAc) and conditions D ($FeCl_3{\cdot}6H_2O$, CH_2Cl_2) and, in fact, the use of iron trichloride resulted in the sole option. On the other hand (entry 7), the transformation of pyrrolidinol **7f** took place with a perceptible lack of regioselectivity, leading to the formation of a nonseparable mixture of **8f** and **8f′** in a diminished yield. Once again (entry 8), application of conditions D was the only option to prepare benzopyrroloisoquinoline **8g**.[17] Finally, it should be mentioned that in those cases (substrates **7e–g**) where the cyclization step was a difficult task, the corresponding trifluoro esters **9** and esters **10** were also obtained in variable yields (see Figure 1).

The discussion on the actual mechanism (S_N2 vs S_N1) for the ring closure step leading to the isoquinoline skeleton was easily clarified by inspection of the stereochemical composition of the corresponding product when starting from either diastereomeric mixtures and diastereomerically pure samples of **7a,b**, obtained, respectively, in the reduction step with both reducing agents (see entries 1 and 2, Table 1). The formation, in both cases, of the same and unique stereoisomer (>95% de) led us to consider a stepwise mechanism through the formation of a benzylic carbocation rather than a concerted process from a protonated alcohol (see Figure 2).

In addition, the determination of the relationships between protons located at positions 5, 10, and 10a through the performance of a number of NOE experiments led us to assign an anti stereochemistry for heterocycles **8a–f**.[18] Figure 3 shows a possible explanation for this tendency that results from a steric hindrance generated between the pyrrolidine nucleus and the aryl ring (Ar^2) in conformer **VII**. This model also explains the absence of diastereocontrol in the formation in **8g** because

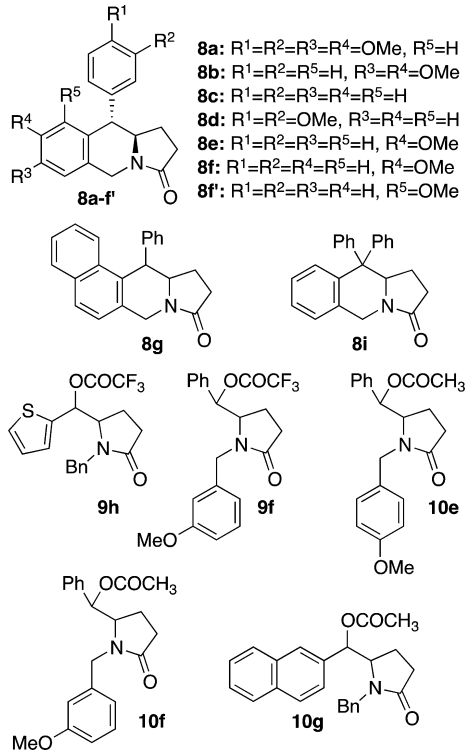

Figure 1. Series of pyrroloisoquinolines **8**, trifluoro esters **9**, and esters **10** synthesized.

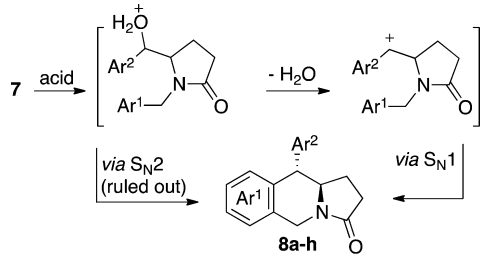

Figure 2. Alternative concerted and stepwise mechanisms for the formation of pyrroloisoquinolines **8**.

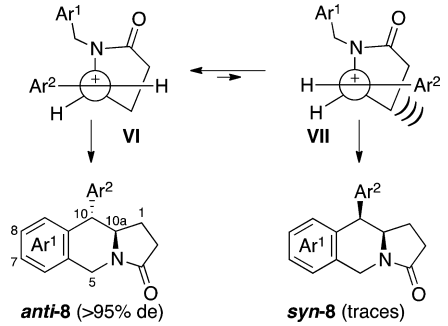

Figure 3. Suggested explanation for the stereochemical outcome in the formation of *anti*-pyrroloisoquinolines **8**.

of an additional interaction between the sterically demanding naphthyl group (Ar^2) and the *N*-benzyl group that leaves conformer **VI** and **VII** equally disfavored.

3. CONCLUSION

In conclusion, an efficient and diastereoselective construction of a series of 10-arylpyrroloisoquinolines has been performed in

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only four steps. The synthetic design features an I(III)-mediated alkyne amidation reaction leading to conveniently substituted aroylpyrrolidine derivatives that, upon reduction of the ketone group, are transformed into the corresponding carbinols. It has been demonstrated that these substrates can be converted into the final derivatives under a variety of acidic conditions through a stepwise aromatic alkylation process. This work opens an attractive alternative to the construction of unprecedented C-10 arylated pyrroloisoquinolines.

4. EXPERIMENTAL SECTION

Typical Procedure for the Amidation Reaction. Synthesis of *N*-(3,4-Dimethoxybenzyl)pent-4-ynamide (3a). A solution of 4-pentynoic acid (**1**) (1 g, 8.9 mmol) in 5 mL of CH_2Cl_2 was added to a magnetically stirred solution of EDC·HCl (2.6 g, 13.6 mmol) and HOBt (1.8 g, 13.6 mmol) in 20 mL of the same solvent followed by the addition of a solution of 3,4-dimethoxybenzylamine **2a** (2.0 mL, 13.6 mmol) in 9 mL of CH_2Cl_2. The mixture was cooled to 0 °C, and Et_3N (1.9 mL, 13.6 mmol) was added dropwise and left to react at rt overnight. Then, the reaction was diluted with CH_2Cl_2, water (25 mL) was added, the mixture was decanted, and the organic layer was consecutively washed with 20 mL of HCl (aq, 5%), 20 mL of a saturated solution of aqueous $NaHCO_3$, and 20 mL of a saturated solution of NaCl. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum. The resultant oil was crystallized from Et_2O to afford amide **3a** as a white solid (98%): mp 112−114 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 3H), 6.00 (s, 1H), 4.37 (d, J = 5.6, 2H), 3.85 (s, 6H), 2.53 (t, J = 6.7, 2H), 2.41 (t, J = 6.7, 2H), 1.96 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.7, 149.1, 148.5, 130.7, 120.1, 111.3, 111.2, 83.0, 69.0, 56.0, 55.9, 43.5, 36.4, 15.0; IR (film) ν 3292, 2932, 2210, 1640; MS (M + 1, CI) m/z (%) 248 (30), 247 (34), 151 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{14}H_{17}NO_3{\cdot}H^+$ 248.1287, found 248.1279.

***N*-Benzylpent-4-ynamide (3b).**[19] According to the typical procedure, amide **3b** was obtained from benzylamine (**2b**) and 4-pentynoic acid (**1**) in 98% yield as a white solid after purification by crystallization from Et_2O: mp 56−58 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.23 (m, 5H), 5.91 (s, 1H), 4.47 (d, J = 5.7, 2H), 2.57 (t, J = 6.8, 2H), 2.44 (t, J = 6.8, 2H), 1.99 (t, J = 2.6, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.8, 138.1, 128.7, 127.8, 127.6, 83.0, 69.4, 43.7, 35.4, 14.9; IR (film) ν 3304, 2923, 2246, 1645; MS (M + 1, CI) m/z (%) 188 (100), 91 (26); HRMS (CI, TOF, M + H^+) calculated for $C_{12}H_{13}NO{\cdot}H^+$ 188.1075, found 188.1076.

***N*-(4-Methoxybenzyl)pent-4-ynamide (3c).** According to the typical procedure, amide **3c** was obtained from 4-methoxybenzylamine (**2c**) and 4-pentynoic acid (**1**) in 62% yield as an orange solid after purification by crystallization from Et_2O: mp 87−88 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5, 2H), 6.85 (d, J = 8.5, 2H), 5.98 (s, 1H), 4.37 (d, J = 5.6, 2H), 3.79 (s, 3H), 2.54 (t, J = 6.4, 2H), 2.40 (t, J = 6.4, 2H), 1.96 (t, J = 2.5, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.9, 158.9, 130.3, 129.0, 113.9, 83.0, 69.3, 55.2, 43.0, 35.1, 14.8; IR (film) ν 3296, 2932, 2252, 1642; MS (M + 1, CI) m/z (%) 218 (24), 121 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{13}H_{15}NO_2{\cdot}H^+$ 218.1181, found 218.1191.

***N*-(3-Methoxybenzyl)pent-4-ynamide (3d).**[20] According to the typical procedure, amide **3d** was obtained from 3-methoxybenzylamine (**2d**) and 4-pentynoic acid (**1**) in 99% yield as an orange solid after purification by crystallization from Et_2O: mp 48−50 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.01 (m, 1H), 6.90−6.64 (m, 3H), 4.30 (d, J = 5.7, 2H), 3.71 (s, 3H), 2.56−2.24 (m, 4H), 2.04−1.86 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 159.7, 140.0, 129.5, 119.7, 113.1, 112.5, 83.1, 69.4, 55.1, 43.2, 34.9, 14.8; IR (film) ν 3310, 2915, 2254, 1648; MS (M + 1, CI) m/z (%) 218 (100), 121 (29); HRMS (CI, TOF, M + H^+) calculated for $C_{13}H_{15}NO_2{\cdot}H^+$ 218.1181, found 218.1188.

***N*-(2-Naphthylmethyl)pent-4-ynamide (3e).** According to the typical procedure, amide **3e** was obtained from 2-naphthylamine (**2e**) and 4-pentynoic acid (**1**) in 99% yield as a yellow solid after purification by crystallization from Et_2O: mp 128−129 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−7.99 (m, 1H), 7.89−7.80 (m, 2H), 7.57−7.40 (m, 4H), 5.89 (br s, 1H), 4.90 (d, J = 5.3, 2H), 2.58−2.38 (m, 4H), 1.93−1.92 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.5, 133.9, 133.3, 131.4, 128.8, 128.7, 126.8, 126.6, 126.0, 125.4, 123.6, 82.9, 69.4, 41.9, 35.4, 14.9; IR (film) ν 3305, 2902, 2250, 1634; MS (M + 1, CI) m/z (%) 238 (100), 141 (63), 110 (14); HRMS (CI, TOF, M + H^+) calculated for $C_{16}H_{15}NO{\cdot}H^+$ 238.1232, found 238.1243.

Typical Procedure A for the Sonogashira Coupling Reaction. Synthesis of *N*-(3,4-Dimethoxybenzyl)-5-(3,4-dimethoxyphenyl)pent-4-ynamide (5a). Amide **3a** (2.15 g, 8.7 mmol) was added to a stirred solution of 3,4-dimethoxybromobenzene (**4a**) (1.2 mL, 8.3 mmol), $Pd_3(OAc)_6$ (37 mg, 0.16 mmol), PPh_3 (174 mg, 0.66 mmol), and CuI (31.6 mg, 0.16 mmol) in pyrrolidine (8 mL). Stirring was continued for 2 h at reflux. When cooled, the entire crude reaction mixture was diluted with CH_2Cl_2 and washed with water (30 mL), saturated NH_4Cl (30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography (EtOAc) to afford amide **5a** as a yellow solid that was triturated in hexanes (81%): mp 120−122 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84−6.71 (m, 6H), 5.95 (s, 1H), 4.42 (d, J = 5.6, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 2.78 (t, J = 6.8, 2H), 2.51 (t, J = 6.8, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.0, 149.2, 149.1, 148.5, 130.7, 124.7, 120.0, 114.3, 112.1, 110.9, 86.7, 81.7, 55.9, 43.6, 35.8, 16.0; IR (film) ν 2968, 1738, 1647; MS (M + 1, CI) m/z (%) 384 (100), 383 (37), 218 (18), 151 (74); HRMS (CI, TOF, M + H^+) calculated for $C_{22}H_{25}NO_5{\cdot}H^+$ 384.1811, found 384.1826.

Typical Procedure B for the Sonogashira Coupling Reaction. Synthesis of *N*-(3,4-Dimethoxybenzyl)-5-phenylpent-4-ynamide (5b). A solution of $Pd(PPh_3)_4$ (856 mg, 0.74 mmol), CuI (281 mg, 1.48 mmol), and iodobenzene (**4b**) (0.83 mL, 7.4 mmol) in Et_2NH (40 mL) was stirred at rt for 5 min. Then, a solution of the amide **3a** (2.2 g, 8.9 mmol) in THF (5.0 mL) was slowly added, and the mixture was stirred for 4 h. The crude reaction mixture was diluted with EtOAc, filtered, and washed with saturated NH_4Cl. The aqueous phase was extracted with EtOAc (3 × 30 mL), dried over Na_2SO_4, and filtered, and the solvent was eliminated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to afford amide **5b** as a yellow solid that was triturated in hexanes (95%): mp 117−118 °C (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.24 (m, 5H), 6.84−6.70 (m, 3H), 6.00 (s, 1H), 4.42−4.40 (d, J = 5.6, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.78 (t, J = 7.0, 2H), 2.51 (t, J = 7.0, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.9, 149.1, 148.4, 131.5, 130.6, 128.2, 127.9, 123.1, 120.1, 111.2, 88.3, 81.7, 55.9, 55.8, 43.6, 36.7, 16.0; IR (film) ν 2357, 1685, 1275; MS (M + 1, CI) m/z (%) 324 (65), 323 (24), 151 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{20}H_{21}NO_3{\cdot}H^+$ 324.1600, found 324.1609.

***N*-Benzyl-5-phenylpent-4-ynamide (5c).**[21] According to the typical procedure B, amide **5c** was obtained from amide **3b** and iodobenzene (**4b**) in 99% as an orange solid after purification by column chromatography (EtOAc) followed by crystallization from Et_2O: mp 50−53 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.03 (m, 10H), 6.10 (s, 1H), 4.47 (d, J = 5.7, 2H), 2.81−2.76 (m, 2H), 2.53−2.49 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.1, 138.1, 131.6, 128.7, 128.2, 127.9, 127.8, 127.5, 123.3, 88.3, 81.8, 43.7, 35.8, 16.0; IR (film) ν 1645, 2248, 1548; MS (M + 1, CI) m/z (%) 264 (100), 174 (4); HRMS (CI, TOF, M + H^+) calculated for $C_{18}H_{17}NO{\cdot}H^+$ 264.1388, found 264.1382.

***N*-Benzyl-5-(3,4-dimethoxyphenyl)pent-4-ynamide (5d).** According to the typical procedure A, amide **5d** was obtained from amide **3b** and 3,4-dimethoxybromobenzene (**4a**) in 81% as a yellow solid after purification by column chromatography (EtOAc) followed by crystallization from Et_2O: mp 98−101 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.23 (m, 5H), 6.90−6.74 (m, 3H), 6.06 (s, 1H), 4.48 (d, J = 5.7, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.78 (t, J = 7.1, 2H), 2.51 (t, J = 7.1, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.1, 149.2, 148.5, 138.1, 128.7, 127.7, 127.5, 124.7, 115.6, 114.1, 110.9, 86.7, 81.7, 55.9, 55.9, 43.7, 35.8, 16.0; IR (film) ν 1738, 2254, 1512; MS (M + 1,

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CI) *m*/*z* (%) 324 (100), 234 (24), 91 (12); HRMS (CI, TOF, M + H^+) calculated for $C_{20}H_{21}NO_3{\cdot}H^+$ 324.1600, found 324.1614.

***N*-(4-Methoxybenzyl)-5-phenylpent-4-ynamide (5e).** According to the typical procedure B, amide **5e** was obtained from amide **3c** and iodobenzene (**4b**) in 51% as a white solid after purification by column chromatography (EtOAc/hexanes, 1/1) followed by crystallization from Et_2O: mp 90−92 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.28 (m, 5H), 7.20 (d, *J* = 8.6, 2H), 6.77 (d, *J* = 8.6, 2H), 6.08 (s, 1H), 4.40 (d, *J* = 5.5, 2H), 3.75 (s, 3H), 2.57 (t, *J* = 7.0, 2H), 2.49 (t, *J* = 7.0, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.2, 158.9, 131.6, 130.3, 129.1, 128.2, 127.8, 123.4, 114.0, 88.5, 81.7, 55.2, 43.1, 35.6, 16.0; IR (film) ν 1652, 2253, 1535; MS (M + 1, CI) *m*/*z* (%) 294 (38), 121 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{19}H_{19}NO_2{\cdot}H^+$ 294.1494, found 294.1496.

***N*-(3-Methoxybenzyl)-5-phenylpent-4-ynamide (5f).** According to the typical procedure B, amide **5f** was obtained from amide **3d** and iodobenzene (**4b**) in 60% as a yellow solid after purification by column chromatography (EtOAc/hexanes, 1/1) followed by crystallization from Et_2O: mp 68−69 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.05 (m, 5H), 6.94−6.66 (m, 4H), 4.35 (d, *J* = 5.6, 2H), 3.68 (s, 3H), 2.70 (t, *J* = 7.1, 2H), 2.46 (t, *J* = 7.1, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 159.8, 140.1, 123.6, 131.6, 129.5, 128.2, 127.8, 119.8, 113.2, 112.7, 88.8, 81.5, 55.0, 43.4, 35.4, 16.0; IR (film) ν 1642, 2253, 1548; MS (M + 1, CI) *m*/*z* (%) 294 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{19}H_{19}NO_2{\cdot}H^+$ 294.1493, found 294.1499.

***N*-(2-Naphthylmethyl)-5-phenylpent-4-ynamide (5g).** According to the typical procedure B, amide **5g** was obtained from amide **3e** and iodobenzene (**4b**) in 84% as a yellow solid after purification by column chromatography (EtOAc/hexanes, 1/1) followed by crystallization from Et_2O: mp 118−120 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01−7.77 (m, 3H), 7.50−7.24 (m, 9H), 6.27 (br s, 1H), 4.87 (d, *J* = 5.3, 2H), 2.74 (t, *J* = 7.1, 2H), 2.46 (t, *J* = 7.1, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.0, 134.6, 133.8, 133.4, 131.5, 128.8, 128.7, 128.6, 128.2, 127.8, 126.7, 126.0, 125.4, 123.5, 123.3, 88.4, 81.7, 41.8, 35.6, 16.0; IR (film) ν 2250, 1652, 1542; MS (M + 1, CI) *m*/*z* (%) 314 (100), 141 (28); HRMS (CI, TOF, M + H^+) calculated for $C_{22}H_{19}NO{\cdot}H^+$ 314.1545, found 314.1552.

***N*-Benzyl-5-(2-thienyl)pent-4-ynamide (5h).**[21] According to the typical procedure B, amide **5h** was obtained from amide **3b** and 2-iodothiophene (**4c**) in 81% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from Et_2O: mp 70−71 °C (hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.15 (m, 6H), 7.06 (d, *J* = 3.2, 1H), 6.92−6.90 (m, 1H), 6.89 (br s, 1H), 4.38 (d, *J* = 5.9, 2H), 2.74−2.68 (m, 2H), 2.47−2.40 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.0, 137.9, 131.2, 128.4, 127.4, 127.1, 126.6, 126.1, 123.3, 92.4, 74.5, 43.3, 35.0, 16.0; IR (KBr) ν 3292, 1647; MS (EI) *m*/*z* (%) 269 (M^+, 38), 178 (100), 135 (23), 91 (80); HRMS (TOF) calculated for $C_{16}H_{15}NOS$ 269.0874, found 269.0875.

Typical Procedure for the PIFA-Mediated Cyclization Reaction. Synthesis of 5-(3,4-Dimethoxybenzoyl)-1-(3,4-dimethoxybenzyl)pyrrolidin-2-one (6a). A solution of alkynylamide **5a** (2.7 g, 7.0 mmol) in TFEA (112 mL) was stirred and cooled to 0 °C. Then, a solution of PIFA (4.5 g, 10.5 mmol) in 20 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 3 h. For the workup, aqueous Na_2CO_3 (10%) was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was evaporated. Purification of the crude product by flash chromatography (EtOAc) gave pyrrolidinone **6a** as a pure brown oil (58%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 1.7, 1H), 7.27 (d, *J* = 1.7, 1H), 6.77 (d, *J* = 8.4, 1H), 6.67−6.57 (m, 3H), 5.05 (d, *J* = 14.5, 1H), 4.81−4.77 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 3.63−3.65 (m, 4H), 2.42−2.15 (m, 2H), 1.94−1.82 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 195.7, 175.1, 154.0, 149.4, 149.1, 148.5, 128.5, 127.4, 122.7, 121.1, 118.1, 111.1, 110.3, 110.1, 59.8, 56.1, 56.0, 55.8, 55.7, 45.2, 29.8, 23.4; IR (film) ν 1621, 1594; MS (M + 1, CI) *m*/*z* (%) 400 (47), 262 (17), 234 (18), 151 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{22}H_{25}NO_6{\cdot}H^+$ 400.1760, found 400.1747.

5-Benzoyl-1-(3,4-dimethoxybenzyl)pyrrolidin-2-one (6b). According to the typical procedure, pyrrolidinone **6b** was obtained from amide **5b** in 41% as a brown oil after purification by column chromatography (EtOAc): ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8, 2H), 7.60−7.41 (m, 3H), 6.71−6.64 (m, 3H), 5.12 (d, *J* = 14.5, 1H), 4.88−4.83 (m, 1H), 3.83−3.69 (m, 7H), 2.56−2.32 (m, 3H), 1.96−1.92 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.1, 175.1, 149.2, 148.6, 134.2, 134.0, 128.6, 128.4, 128.1, 121.1, 111.8, 111.1, 60.3, 55.9, 55.8, 45.3, 29.7, 23.1; IR (film) ν 2937, 1690, 1593; MS (M + 1, CI) *m*/*z* (%) 340 (47), 234 (12), 202 (18), 151 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{20}H_{21}NO_4{\cdot}H^+$ 340.1549, found 340.1562.

5-Benzoyl-1-benzylpyrrolidin-2-one (6c).[21] According to the typical procedure, pyrrolidinone **6c** was obtained from amide **5c** in 32% as a brown oil after purification by column chromatography (EtOAc/hexanes, 1/1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5, 2H), 7.63−7.41 (m, 3H), 7.33−6.96 (m, 5H), 5.24 (d, *J* = 15.0, 1H), 4.91−4.84 (m, 1H), 3.80 (d, *J* = 15.0, 1H), 2.56−2.26 (m, 3H), 2.08−1.86 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.0, 175.2, 136.1, 134.2, 134.0, 129.0, 128.7, 128.5, 128.2, 127.7, 60.5, 45.4, 29.5, 23.2; IR (film) ν 3061, 1692, 1595; MS (M + 1, CI) *m*/*z* (%) 280 (100), 174 (10); HRMS (CI, TOF, M + H^+) calculated for $C_{18}H_{17}NO_2{\cdot}H^+$ 280.1338, found 280.1330.

1-Benzyl-5-(3,4-dimethoxybenzoyl)pyrrolidin-2-one (6d). According to the typical procedure, pyrrolidinone **6d** was obtained from amide **5d** in 57% as a yellow oil after purification by column chromatography (EtOAc): ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.07 (m, 7H), 6.78 (d, *J* = 8.4, 1H), 5.16 (d, *J* = 14.8, 1H), 4.92−4.77 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.71 (d, *J* = 14.8, 1H), 2.47−2.23 (m, 3H), 1.95−1.87 (m, 1H): ^{13}C NMR (300 MHz, $CDCl_3$) δ 195.6, 175.3, 154.1, 149.4, 136.2, 128.7, 128.4, 127.7, 127.4, 122.8, 110.4, 110.2, 60.0, 56.1, 56.0, 45.3, 29.6, 23.5; IR (film) ν 3054, 1695, 1594; MS (M + 1, CI) *m*/*z* (%) 340 (100), 174 (7); HRMS (CI, TOF, M + H^+) calculated for $C_{20}H_{21}NO_4{\cdot}H^+$ 340.1549, found 340.1535.

5-Benzoyl-1-(4-methoxybenzyl)pyrrolidin-2-one (6e). According to the typical procedure, pyrrolidinone **6e** was obtained from amide **5e** in 65% as a brown oil after purification by column chromatography (EtOAc): ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4, 2H), 7.56−7.39 (m, 3H), 7.03 (d, *J* = 8.5, 2H), 6.74 (d, *J* = 8.5, 2H), 5.12 (d, *J* = 14.7, 1H), 4.88−4.84 (m, 1H), 3.67−3.70 (m, 4H), 2.55−2.21 (m, 3H), 2.07−1.77 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.0, 175.1, 159.2, 134.2, 134.1, 134.0, 129.9, 128.3, 128.0, 114.1, 60.4, 55.2, 44.8, 29.6, 23.1; IR (film) ν 3029, 1689, 1589; MS (M + 1, CI) *m*/*z* (%) 310 (74), 204 (19), 202 (38), 121 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{19}H_{19}NO_3{\cdot}H^+$ 310.1443, found 310.1447.

5-Benzoyl-1-(3-methoxybenzyl)pyrrolidin-2-one (6f). According to the typical procedure, pyrrolidinone **6f** was obtained from amide **5f** in 79% as a yellow oil after purification by column chromatography (EtOAc/hexanes, 1/1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2, 2H), 7.58−7.48 (m, 4H), 7.38 (t, *J* = 7.7, 1H), 7.10 (t, *J* = 7.7, 1H), 6.73−6.62 (m, 1H), 5.11 (d, *J* = 14.8, 1H), 4.95−4.79 (m, 1H), 3.87−3.61 (m, 4H), 2.47−2.18 (m, 3H), 1.97−1.79 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.9, 175.3, 159.8, 137.5, 134.1, 134.0, 129.8, 128.9, 128.2, 120.5, 113.8, 113.2, 60.6, 55.0, 45.3, 29.4, 23.0; IR (film) ν 2945, 1648, 1596; MS (M + 1, CI) *m*/*z* (%) 310 (100), 204 (11); HRMS (CI, TOF, M + H^+) calculated for $C_{19}H_{19}NO_3{\cdot}H^+$ 310.1443, found 310.1439.

5-Benzoyl-1-(2-naphthylmethyl)pyrrolidin-2-one (6g). According to the typical procedure, pyrrolidinone **6g** was obtained from amide **5g** in 67% as a yellow oil after purification by column chromatography (EtOAc/hexanes, 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.09−7.12 (m, 12H), 5.76 (d, *J* = 14.6, 1H), 4.65−4.60 (m, 1H), 4.24 (d, *J* = 14.6, 1H), 2.59−2.15 (m, 3H), 1.90−1.86 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.2, 174.8, 134.2, 133.9, 133.8, 131.7, 131.6, 129.0, 128.9, 128.7, 128.2, 128.1, 126.9, 126.2, 125.1, 123.9, 60.3, 43.6, 29.7, 23.0; IR (film) ν 3011, 1693, 1598; MS (M + 1, CI)

m/*z* (%) 330 (100), 202 (13); HRMS (CI, TOF, M + H^+) calculated for $C_{22}H_{19}NO_2{\cdot}H^+$ 330.1494, found 330.1492.

1-Benzyl-5-(2-thienylcarbonyl)pyrrolidin-2-one (6h).[21] According to the typical procedure, pyrrolidinone **6h** was obtained from amide **5h** in 77% as a colorless oil after purification by column chromatography (EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 4.7, 1H), 7.54 (d, J = 3.6, 1H), 7.24−7.08 (m, 6H), 5.17 (d, J = 15.0, 1H), 4.72−4.66 (m, 1H), 3.75 (d, J = 15.0, 1H), 2.65−2.12 (m, 3H), 2.07−1.95 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 190.3, 175.1, 140.8, 135.7, 134.9, 132.4, 128.6, 128.4, 128.3, 127.6, 62.2, 45.2, 29.4, 23.4; IR (film) ν 1685; MS (EI) *m*/*z* (%) 285 (M^+, 1), 174 (68), 91 (100); HRMS (TOF) calculated for $C_{16}H_{15}NO_2S$ 285.0824, found 285.0825.

Typical Procedure (Method A) for the Reduction of Pyrrolidinones 6. Synthesis of 1-(3,4-Dimethoxybenzyl)-5-(1′-hydroxy-3,4-dimethoxybenzyl)pyrrolidin-2-one (7a). Solid $NaBH_4$ (86 mg, 2.2 mmol) was added in one portion to a cold (0 °C) solution of pyrrolidinone **6a** (600 mg, 1.5 mmol) in MeOH (15 mL). After 1 h, aq HCl (10%, 10 mL) was added and the temperature was raised to rt. The whole mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. Purification of the crude product by flash chromatography (AcOEt) afforded the diastereomeric mixture of pyrrolidinones (*syn*/*anti*)-**7a** as a chromatographically pure colorless oil in a 84:16 ratio (85% combined yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.26 (m, 2H), 6.76−6.57 (m, 9H), 6.16 (s, 1H), 5.04−4.84 (m, 3H), 4.70 (d, J = 5.3, 1H), 4.25 (d, J = 17.0, 1H), 4.07−3.52 (m, 27H), 2.39−1.72 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.0, 174.2, 149.2, 149.1, 149.0, 148.4, 148.3, 148.1, 145.6, 133.2, 132.5, 132.1, 132.0, 128.5, 128.1, 124.1, 122.0, 120.6, 118.6, 111.7, 111.6, 111.2, 111.0, 109.2, 108.9, 77.2, 75.9, 61.8, 60.1, 56.1, 56.0, 55.9, 55.8, 51.9, 45.6, 30.1, 29.8, 23.7, 21.6; IR (film) 3270,1698; MS (M + 1, CI) *m*/*z* (%) 402 (77), 385 (24), 233 (11), 151 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{22}H_{27}NO_6{\cdot}H^+$ 402.1872, found 402.1871.

Typical Procedure (Method B) for the Reduction of Pyrrolidinones 6. Synthesis of 1-(3,4-Dimethoxybenzyl)- 5-(1′-hydroxybenzyl)pyrrolidin-2-one (7b). A solution of L-selectride (0.6 mL, 1.0 M in THF) was added dropwise to a cold (−78 °C) solution of pyrrolidinone **6b** (110 mg, 0.3 mmol) in 3.0 mL of the same solvent, and the stirring was continued at that temperature for 30 min. Then, temperature was raised to rt and 2 mL of an aqueous solution of NaOH (10%) was added. The whole mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. Purification of the crude product by flash chromatography (EtOAc) gave pyrrolidinone **7b** as single diastereoisomer and as a chromatographically pure yellowish oil (90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.15 (m, 5H), 6.70−6.65 (m, 3H), 4.90 (d, J = 14.6, 1H), 4.68 (s, 1H), 4.20−4.18 (m, 1H), 3.96−3.93 (d, J = 14.6, 1H), 3.74 (s, 4H), 3.72 (s, 3H), 1.92−1.70 (m, 3H), 1.18−1.15 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.2, 148.9, 148.3, 141.1, 129.5, 128.3, 127.8, 126.3, 120.6, 111.6, 111.0, 75.0, 61.7, 55.8, 55.7, 45.3, 29.8, 21.4; IR (film) ν 3305, 1692; MS (M + 1, CI) *m*/*z* (%) 342 (67), 204 (46), 174 (77), 151 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{20}H_{23}NO_4{\cdot}H^+$ 342.1705, found 342.1710.

1-Benzyl-5-(1′-hydroxybenzyl)pyrrolidin-2-one (7c). According to the typical procedure A, pyrrolidinone **7c** was obtained from **6c** in a 34:66 ratio (71% combined yield), and as a single diastereoisomer (72%) following procedure B. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the isomer obtained in procedure B is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.15 (m, 10H), 5.06 (d, J = 14.7, 1H), 4.76−4.74 (m, 1H), 4.10 (d, J = 14.7, 1H), 3.75−3.71 (m, 2H), 2.02−1.33 (m, 3H), 0.96−0.85 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.2, 141.0, 137.0, 128.5, 128.4, 128.2, 127.9, 127.4, 126.3, 74.8, 61.8, 45.6, 29.8, 21.3; IR (film) ν 3315, 1690; HRMS (CI, TOF, M + H^+) calculated for $C_{18}H_{19}NO_2{\cdot}H^+$ 282.1416, found 282.1410.

1-Benzyl-5-(1′-hydroxy-3,4-dimethoxybenzyl)pyrrolidin-2-one (7d). According to the typical procedure A, pyrrolidinone **7d** was obtained from **6d** in a 13:87 ratio (70% combined yield), and as a single diastereoisomer (51%) following procedure B. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the isomer obtained in procedure B is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.13 (m, 5H), 6.78−6.74 (m, 3H), 5.01 (d, J = 14.8, 1H), 4.66 (d, J = 5.5, 1H), 4.11 (d, J = 14.8, 1H), 3.82−3.69 (m, 7H, H-5), 3.12 (brs, 1H), 2.10−1.70 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.3, 149.0, 148.7, 137.1, 133.5, 128.5, 128.1, 127.4, 118.6, 110.9, 109.3, 75.1, 61.9, 55.9, 45.7, 29.9, 21.6; IR (film) ν 3280, 1693; MS (M + 1, CI) *m*/*z* (%) 342 (100), 324 (53), 234 (15), 135 (11); HRMS (CI, TOF, M + H^+) calculated for $C_{20}H_{23}NO_4{\cdot}H^+$ 342.1705, found 342.1708.

5-(1′-Hydroxybenzyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (7e). According to the typical procedure A, pyrrolidinone **7e** was obtained from **6e** in a 87:64 ratio (73% combined yield), and as a single diastereoisomer (88%) following procedure B. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the isomer obtained in procedure B is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.21 (m, 5H), 7.07 (d, J = 8.5, 2H), 6.79 (d, J = 8.5, 2H), 4.96 (d, J = 14.6, 1H), 4.73 (s, 1H), 4.14−3.96 (m, 2H), 3.72 (s, 4H), 2.01−1.60 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.2, 158.9, 141.1, 129.6, 129.1, 128.4, 127.9, 126.4, 113.9, 75.0, 61.7, 55.2, 45.0, 29.9, 21.3; IR (film) ν 3284, 1689; MS (M + 1, CI) *m*/*z* (%) 312 (83), 294 (20), 204 (100), 174 (55); HRMS (CI, TOF, M + H^+) calculated for $C_{19}H_{21}NO_3{\cdot}H^+$ 312.1600, found 312.1603.

5-(1′-Hydroxybenzyl)-1-(3-methoxybenzyl)pyrrolidin-2-one (7f). According to the typical procedure A, pyrrolidinone **7f** was obtained from **6f** in a 55:45 ratio (63% combined yield), and as a single diastereoisomer (74%) following procedure B. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the isomer obtained in procedure B is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.18 (m, 6H), 6.80−6.72 (m, 3H), 5.02 (d, J = 14.8, 1H), 4.73 (s, 1H), 4.11 (d, J = 14.8, 1H), 3.78−3.74 (m, 4H), 3.39 (brs, 1H), 2.07−1.75 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.4, 159.7, 141.0, 138.6, 129.6, 128.4, 127.9, 126.4, 120.4, 113.8, 112.7, 74.9, 61.9, 55.2, 45.6, 29.8, 21.4; IR (film) ν 3274, 1694; MS (M + 1, CI) *m*/*z* (%) 312 (100), 294 (58), 204 (37); HRMS (CI, TOF, M + H^+) calculated for $C_{19}H_{21}NO_3{\cdot}H^+$ 312.1600, found 312.1603.

5-(1′-Hydroxybenzyl)-1-(2-naphthylmethyl)pyrrolidin-2-one (7g). According to the typical procedure A, pyrrolidinone **7g** was obtained from **6g** in a 74:26 ratio (64% combined yield), and as a single diastereoisomer (84%) following procedure B. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the isomer obtained in procedure B is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−7.55 (m, 3H), 7.48−7.24 (m, 9H), 5.59 (d, J = 14.9, 1H), 4.80−4.79 (m, 1H), 4.55 (d, J = 14.9, 1H), 4.33 (brs, 1H), 3.65−3.56 (m, 1H), 1.97−1.56 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.5, 140.6, 133.9, 132.2, 131.7, 128.8, 128.7, 128.6, 128.5, 128.4, 127.9, 126.6, 126.4, 125.9, 125.2, 123.7, 75.7, 61.4, 44.0, 29.8, 21.2; IR (film) ν 3265, 1694; MS (M + 1, CI) *m*/*z* (%) 332 (100), 314 (25), 224(50), 141(34); HRMS (CI, TOF, M + H^+) calculated for $C_{22}H_{22}NO_2{\cdot}H^+$ 332.1651, found 332.1648.

1-Benzyl-5-(1′-hydroxy-2-thienylmethyl)pyrrolidin-2-one (7h). According to the typical procedure A, pyrrolidinone **7h** was obtained from **6h** in a 70:30 ratio (75% combined yield), and as a single diastereoisomer (87%) following procedure B. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the isomer obtained in procedure B is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.16 (m, 7H), 6.98−6.84 (m, 1H), 5.15−5.05 (m, 2H), 4.21 (d, J = 14.5, 1H), 3.82−3.76 (m, 1H), 3.06 (brs, 1H), 2.22−1.83 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.4, 144.4, 136.8, 128.6, 128.2, 127.5, 126.8, 125.0, 124.3, 70.9, 60.4, 45.5, 29.7, 20.7; IR (film) ν 3274, 1694; MS (M + 1, CI) *m*/*z* (%) 288 (100), 151 (70); HRMS (CI, TOF, M + H^+) calculated for $C_{16}H_{17}NO_2S{\cdot}H^+$ 288.1058, found 288.1054.

1-(2,3-Dimethoxybenzyl)-5-(hydroxydiphenylmethyl)-pyrrolidin-2-one (7i). A phenylmagnesium bromide solution (0.87 mL, 1.0 M in THF) was added to a solution of pyrrolidinone **6b** (170 mg, 0.5 mmol) in THF (15 mL), and the temperature was raised to 40 °C. After 5 h, 4 mL of a saturated solution of NH_4Cl was added and

the whole mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated. Purification of the crude product by flash chromatography (EtOAc) gave pyrrolidinone **7i** (49%) as an orange chromatographically pure solid that was triturated in hexanes: mp 90−93 °C (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 10H, Harom), 6.77 (d, J = 8.4, 1H), 6.47−6.41 (m, 2H), 4.87 (d, J = 15.0, 1H), 4.60 (s, 1H), 3.88−3.81 (m, 7H), 3.20 (d, J = 15.0, 1H), 2.20−2.15 (m, 1H), 2.04−1.99 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.1, 148.9, 148.3, 145.4, 144.8, 128.5, 127.1, 125.9, 125.8, 119.9, 111.1, 80.1, 63.4, 55.9, 55.9, 45.4, 30.2, 22.9; IR (film) ν 3391, 2938, 1671; MS (M + 1, CI) m/z (%) 418 (100), 400 (27), 280 (15), 250 (43); HRMS (CI, TOF, M + H$^+$) calculated for $C_{26}H_{27}NO_4{\cdot}H^+$ 418.2018, found 418.2034.

Typical Procedures (A−D) for the Synthesis of Pyrroloisoquinolinones 8. *Method A.* H_2SO_4 (aq 2 M, 30 equiv) was added to a solution of pyrrolidinone **7** in CH_2Cl_2. TFA (3 equiv) was then added, and the solution was stirred at reflux for 2 h. For the workup, after cooling, NaOH (aq, 2%) was added and the mixture was extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4 and filtered, and all volatiles were removed. Purification of the crude product by flash chromatography (EtOAc) afforded pyrroloisoquinolines **8a,b,d,i** (see Table 2). All these compounds were obtained as oils.

Method B. Aluminum(III) chloride hexahydrate (2 equiv) was added in one portion to a solution of pyrrolidinone **7** in CH_2Cl_2. After being stirred at reflux for 24 h, the reaction mixture was cooled, quenched with saturated aq K_2CO_3 solution, and then extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4 and filtered, and all volatiles were removed. Purification of the crude product by flash chromatography (EtOAc) afforded the pyrroloisoquinolines **8a−d,f,f′,i** (see Table 2). All these compounds were obtained as oils.

Method C. H_2SO_4 (concd, 30 equiv) was added to a solution of pyrrolidinone **7** in HOAc (10 mL), and the mixture was stirred overnight at room temperature. For the workup, NH_4OH was added at 0 °C and the mixture was extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4 and filtered, and all volatiles were removed. Purification of the crude product by flash chromatography (EtOAc) afforded pyrroloisoquinolines **8a−d** (see Table 2). All these compounds were obtained as oils.

Method D. Iron(III) chloride hexahydrate (2 equiv) was added in one portion to a solution of pyrrolidinone **7** in CH_2Cl_2. After being stirred at reflux for 24 h, the reaction mixture was cooled, quenched with saturated aq K_2CO_3 solution, and then extracted with EtOAc. The organic extracts were dried with Na_2SO_4 and filtered, and all volatiles were removed. Purification of the crude product by flash chromatography (EtOAc) afforded the pyrroloisoquinolines **8a−e,g** (see Table 2). All these compounds were obtained as oils.

(10*R,10a*S**)-10-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (8a).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.50 (m, 2H), 6.64 (m, 2H), 6.22 (s, 1H), 4.97 (d, J = 16.3, 1H), 4.33 (d, J = 16.3, 1H), 3.94−3.46 (m, 14H), 2.49−2.47 (m, 2H), 2.41−2.04 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 149.2, 148.3, 148.1, 147.7, 132.5, 129.5, 124.1, 122.1, 111.9, 111.8, 111.2, 108.6, 60.1, 56.0, 55.9, 55.8, 55.7, 55.6, 42.4, 29.8, 23.7; IR (film) ν 2937, 1739; MS (M + 1, CI) m/z (%) 384 (100), 383 (13); HRMS (CI, TOF, M + H$^+$) calculated for $C_{22}H_{25}NO_5{\cdot}H^+$ 384.1811, found 384.1810

(10*R,10a*S**)-7,8-Dimethoxy-10-phenyl-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (8b).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.04 (m, 5H), 6.63 (s, 1H), 6.14 (s, 1H), 4.98 (d, J = 17.1, 1H), 4.33 (d, J = 17.1, 1H), 4.06−3.44 (m, 8H), 2.50−2.40 (m, 2H), 2.20−1.60 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 148.1, 147.7, 140.2, 129.5, 129.4, 128.8, 127.5, 124.1, 111.9, 108.6, 60.1, 55.9, 55.7, 52.1, 42.4, 29.8, 23.6; IR (film) ν 2937, 1683; MS (M + 1, CI) m/z (%) 324 (100), 323 (13); HRMS (CI, TOF, M + H$^+$) calculated for $C_{20}H_{21}NO_3{\cdot}H^+$ 324.1600, found 324.1609.

(10*R,10a*S**)-10-Phenyl-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (8c).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.06 (m, 8H), 6.71−6.69 (d, J = 7.7, 1H), 5.04 (d, J = 17.7, 1H), 4.43 (d, J = 17.7, 1H), 3.97−3.66 (m, 2H), 2.59−2.34 (m, 2H), 2.16−1.67 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.6, 139.9, 137.5, 131.7, 129.5, 129.0, 128.9, 127.4, 126.8, 126.7, 126.3, 59.9, 52.6, 42.7, 29.8, 23.7; IR (film) ν 2942, 1679; MS (M + 1, CI) m/z (%) 264 (100), 263 (5); HRMS (CI, TOF, M + H$^+$) calculated for $C_{18}H_{17}NO{\cdot}H^+$ 264.1388, found 264.1387.

(10*R,10a*S**)-10-(3,4-Dimethoxyphenyl)-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (8d).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.16 (m, 3H), 7.07−6.62 (m, 4H), 5.03 (d, J = 17.5, 1H), 4.39 (d, J = 17.5, 1H), 3.88−3.67 (m, 8H), 2.47−2.40 (m, 2H), 2.07−1.76 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.0, 149.2, 148.3, 137.6, 132.2, 131.7, 128.9, 126.7 126.6, 126.2, 126.8, 112.0, 111.3, 59.7, 55.9, 55.8, 52.2, 42.6, 29.7, 23.7; IR (film) ν 2944, 1684; MS (M + 1, CI) m/z (%) 324 (100), 323 (8); HRMS (CI, TOF, M + H$^+$) calculated for $C_{20}H_{21}NO_3{\cdot}H^+$ 324.1600, found 324.1607.

(10*R,10a*S**)-8-Methoxy-10-phenyl-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (8e).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.16 (m, 4H), 6.95−6.91 (m, 1H), 6.74−6.57 (m, 3H), 5.02 (d, J = 17.5, 1H), 4.37 (d, J = 17.5, 1H), 3.87−3.69 (m, 5H), 2.53−2.33 (m, 2H), 2.06−1.99 (m, 1H), 1.82−1.72 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 158.3, 140.3, 133.1, 130.2, 129.7, 129.5, 128.8, 127.3, 113.0, 110.7, 60.2, 55.3, 52.0, 42.8, 29.8, 23.6; IR (film) ν 2940, 1686; MS (M + 1, CI) m/z (%) 294 (100), 293 (12); HRMS (CI, TOF, M + H$^+$) calculated for $C_{19}H_{19}NO_2{\cdot}H^+$ 294.1494, found 294.1508.

(10*R,10a*S**)-7-Methoxy-10-phenyl-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (8f) and (10*R**,10a*S**)-9-Methoxy-10-phenyl-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(2*H*)-one (8f′).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−6.75 (m, 14H), 6.57−6.56 (m, 1H), 6.23−6.22 (m, 1H), 5.19−4.96 (m, 2H), 4.39−3.60 (m, 12H), 2.52−1.69 (m, 8H,); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.8, 174.2, 158.3, 158.2, 139.8, 139.7, 138.9, 137.9, 124.0, 123.5, 129.5, 129.3, 128.9, 128.1, 127.5, 127.3, 127.1, 126.4, 114.6, 114.4, 114.0, 112.6, 59.8, 57.1, 55.2, 55.1, 52.8, 49.9, 42.2, 42.1, 29.9, 29.7, 23.8, 21.1; IR (film) ν 2940, 1675; MS (M + 1, CI) m/z (%) 294 (100), 293 (13); HRMS (CI, TOF, M + H$^+$) calculated for $C_{19}H_{19}NO_2{\cdot}H^+$ 294.1494, found 294.1501.

(10*R,10a*R**) and (10*S**,10a*S**)-12-Phenyl-10,11,11a,12-tetrahydrobenzo[*f*]pyrrolo[1,2-*b*]isoquinolin-9(7*H*)-one (8g).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−6.82 (m, 22H), 5.65 (d, J = 17.7, 1H), 5.53 (d, J = 17.7, 1H), 4.79−4.72 (m, 2H), 4.28−3.93 (m, 4H), 2.57−1.24 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.9, 174.4, 140.6, 139.3, 134.4, 134.1, 132.5, 132.0, 131.8, 130.2, 130.0, 129.8, 129.6, 128.9, 128.7, 128.5, 128.4, 127.7, 127.4, 127.3, 127.1, 126.9, 126.8, 126.6, 126.5, 126.0, 125.9, 125.4, 122.3, 60.0, 57.0, 52.9, 50.0, 41.0, 40.9, 29.9, 29.7, 23.6, 21.0; IR (film) ν 2934, 1681; HRMS (CI, TOF, M + H$^+$) calculated for $C_{22}H_{19}NO{\cdot}H^+$ 314.1544, found 314.1539.

(±)-7,8-Dimethoxy-10,10-diphenyl-1,2,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-3(5*H*)-one (8i). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.19 (m, 9H), 6.78−6.76 (m, 1H), 6.47−6.40 (m, 2H), 4.86 (d, J = 15.0, 1H), 4.62−4.59 (m, 1H), 3.97 (s, 3H), 3.82 (s, 3H), 3.11 (d, J = 15.0, 1H), 2.30−2.19 (m, 3H), 2.02−2.00 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.0, 148.9, 148.2, 145.1, 144.4, 129.3, 128.5, 128.4, 128.3, 127.3, 127.2, 125.9, 119.9, 111.0, 80.1, 63.3, 55.9, 55.8, 45.5, 30.0, 22.8; IR (film) ν 1737 (CO); MS (M + 1, CI) m/z (%) 400 (18), 250 (24), 151 (28); HRMS (CI, TOF, M + H$^+$) calculated for $C_{26}H_{25}NO_3{\cdot}H^+$ 400.1913, found 400.1921.

During the cyclization assays, acetylated (method C) or trifluoroacetylated (method A) byproducts were detected and isolated in variable yields (see Table 2). All these compounds were obtained as oils.

(*R,*R**) and (*R**,*S**)-1-(3-Methoxybenzyl)-5-(1′-trifluoroacetoxybenzyl)pyrrolidin-2-one (9f).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−6.78 (m, 18H), 6.10 (d, J = 2.6, 1H), 5.90 (d, J = 6.3, 1H), 5.17−5.06 (m, 2H), 4.13−3.79 (m, 4H), 3.56 (s, 3H), 2.33−1.84 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.6, 175.4, 157.9 (q, $^2J_{CF}$ = 43.2, $COCF_{3\ maj}$), 160.0, 159.9, 137.8, 137.6, 134.2,

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134.1, 130.0, 129.9, 129.8, 129.7, 129.2, 129.1, 126.6, 125.9, 120.4, 120.3, 113.7, 113.6, 113.5, 113.4, 115.6 (q, ^1J = 293.1, $COCF_{3maj}$), 80.6, 78.2, 60.4, 59.2, 55.2, 55.1, 45.9, 45.0, 29.4, 29.2, 21.3, 19.1; IR (film) ν 1792, 1698; MS (M + 1, CI) m/z (%) 408 (100), 294 (52), 204 (16); HRMS (CI, TOF, M + H^+) calculated for $C_{21}H_{20}F_3NO_4{\cdot}H^+$ 408.1378, found 408.1418.

(*R,*R**) and (*R**,*S**)-1-Benzyl-5-(1′-trifluoroacetoxy-1′-thiophen-2-yl-methyl)pyrrolidin-2-one (9h).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.24 (m, 14H), 7.06−7.01 (m, 2H), 6.30 (d, J = 2.1, 1H), 6.19 (d, J = 6.2, 1H), 5.17−5.09 (m, 2H), 4.20−4.11 (m, 2H), 3.95−3.93 (m, 2H), 2.93−1.91 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.0, 163.9 (q, $^2J_{CF}$ = 43.3, $COCF_{3maj}$), 136.1, 136.0, 135.4, 135.0, 128.9, 128.1, 128.0, 127.9, 127.8, 127.5, 127.2, 127.0, 116 (q, ^1J = 287.1 ($COCF_{3maj}$), 75.6, 75.2, 59.9, 59.2, 45.9, 45.2, 29.3, 29.1, 21.1, 20.0; IR (film) ν 1787, 1695; MS (M + 1, CI) m/z (%) 384 (62), 270 (100), 269 (14), 174 (19), 114 (19); HRMS (CI, TOF, M + H^+) calculated for $C_{18}H_{16}F_3NO_3S{\cdot}H^+$ 384.0881, found 384.0858.

5-(1′-Acetoxybenzyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (10e). Reported data for the major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.14 (m, 6H), 6.75−6.64 (m, 3H), 5.88 (d, J = 5.2, 1H), 5.09 (d, J = 14.6, 1H), 4.13−3.66 (m, 5H), 2.35−2.22 (m, 1H), 2.02 (s, 3H), 1.87−1.70 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.6, 169.6, 159.1, 136.2, 129.5, 128.6, 128.5, 126.5, 114.0, 75.3, 59.4, 55.3, 45.0, 29.5, 21.2, 21.1; IR (film) ν 1743, 1688; MS (M + 1, CI) m/z (%) 354 (95), 294 (100), 204 (23), 174 (34), 121 (51); HRMS (CI, TOF, M + H^+) calculated for $C_{21}H_{23}NO_4{\cdot}H^+$ 354.1705, found 354.1694.

(*R,*R**) and (*R**,*S**)-5-(1′-Acetoxybenzyl)-1-(3-methoxybenzyl)pyrrolidin-2-one (10f).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−6.75 (m, 18H, Harom), 6.11 (d, J = 2.5, 1H), 5.85 (d, J = 2.5, 1H), 5.16−5.06 (m, 2H), 4.05−3.69 (m, 10H), 2.33−2.02 (m, 8H), 1.87−1.80 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.4, 176.3, 175.3, 175.2, 173.4, 169.6, 1, 159.9, 158.5, 137.9, 136.2, 129.8, 129.7, 128.6, 128.5, 128.2, 128.1, 126.5, 125.8, 120.4, 120.2, 113.7, 113.5, 113.2, 113.1, 75.5, 73.1, 60.4, 59.8, 55.2, 55.1, 45.7, 44.6, 30.0, 29.4, 21.2, 18.8, 20.9, 20.7; IR (film) ν 1790, 1684; MS (M + 1, CI) m/z (%) 354 (93), 294 (100), 204 (25), 174 (31), 121 (54); HRMS (CI, TOF, M + H^+) calculated for $C_{21}H_{23}NO_4{\cdot}H^+$ 354.1705, found 354.1696

1-Benzyl-5-[1′-acetoxy-(2-naphthylmethyl)]pyrrolidin-2-one (10g). Reported data for the major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04−7.01 (m, 12H), 5.93 (d, J = 5.6, 1H), 5.69 (d, J = 14.8, 1H), 4.57 (d, J = 14.8, 1H), 3.71−3.67 (m, 1H), 2.18−1.77 (m, 7H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.7, 169.5, 136.3, 133.9, 131.6, 131.4, 129.6, 128.8, 128.7, 128.6, 128.5, 127.3, 126.7, 126.0, 125.3, 123.6, 75.3, 59.6, 44.0, 29.6, 21.1, 21.0 (CH_3); IR (film) ν 1794, 1686; MS (M + 1, CI) m/z (%) 374 (8), 342 (18), 315 (18), 314 (100); HRMS (CI, TOF, M + H^+) calculated for $C_{24}H_{23}NO_3{\cdot}H^+$ 374.1756, found 374.1747.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all new compounds **3**, **5**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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