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A Highly Convergent Synthesis of Tricyclic N-Heterocycles Coupling an Ugi Reaction with a Tandem S_N2'-Heck Double Cyclization

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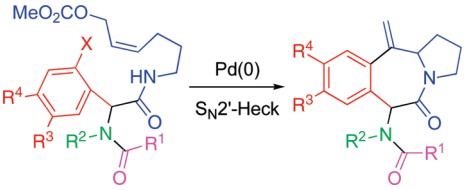

A small library of natural product-like compounds has been assembled by coupling an Ugi multicomponent reaction with two postcondensation transformations, carried out in one-pot fashion: a S_N2' cyclization followed by an intramolecular Heck reaction.

Introduction

The process of drug discovery often requires rapid entry to a broad array of molecular architectures of heterocyclic nature: to achieve this goal, several approaches have been proposed. The diversity-oriented synthesis paradigm[1] and the generation of collections of nature-inspired structures[2] are two particularly useful approaches to produce libraries that effectively cover the chemical space of biologically relevant structures. The latter approach is based on the awareness that natural products are a source of many new drugs and that these have been selected by their evolutionary history for biological activity.[3]

Our group has been involved in several projects aimed at the development of highly convergent syntheses of heterocycles, privileged structures in drug discovery. Our contribution in this field has been attained mainly by coupling multicomponent reactions, as Ugi or Passerini (U- or P-MCR) reactions that typically lead to acyclic peptidic or depsipeptidic skeletons, with a secondary transformation. This methodology enables generation of various heterocyclic systems.[4] The high rate of complexity increase per synthetic step and the introduction of up to four diversity points fits particularly well into the guiding principles of DOS.

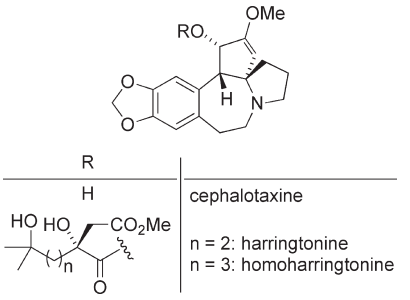

FIGURE 1. Cephalotaxus alkaloids.

An exceptionally relevant group of natural substances is represented by alkaloids. Within this class, a particularly interesting category are the rare Cephalotaxus alkaloids (Figure 1), extracted from the evergreen conifer *Cephalotaxus harringtonia*, well represented by the parent member cephalotaxin bearing a pentacyclic skeleton and featuring a unique benzazepine moiety. Their naturally occurring esters, harringtonine and homoharringtonine, are highly effective for the treatment of acute human leukemia and are currently undergoing advanced clinical trials. Homorarringtonine is also a potent in vitro agent against a strain of chloroquine-resistant *Plasmodium falciparum*, responsible for malaria.[5]

(1) Schreiber, S. L.; Burke, M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.
(2) (a) Shang, S.; Tan, D. S. *Curr. Opin. Chem. Biol.* **2005**, *9*, 248–258. (b) Nandy, J. P.; Prakesch, M.; Khadem, S.; Thirupathi Reddy, P.; Sharma, U.; Arya, P. *Chem. Rev.* **2009**, *109*, 1999–2060.
(3) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829–837.
(4) (a) Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23–41. (b) Basso, A.; Banfi, L.; Riva, R. *Eur. J. Org. Chem.* **2010**, 1831–1841. (c) Banfi, L.; Basso, A.; Riva, R. In *Topics in Heterocyclic Chemistry*; Springer-Verlag: Berlin/Heidelberg, 2010; Vol. 23, pp 1−40.
(5) Kantarjian, H. M.; Talpaz, M.; Santini, V.; Murgo, A.; Cheson, B.; O'Brien, S. M. *Cancer* **2001**, *92*, 1591–1605.

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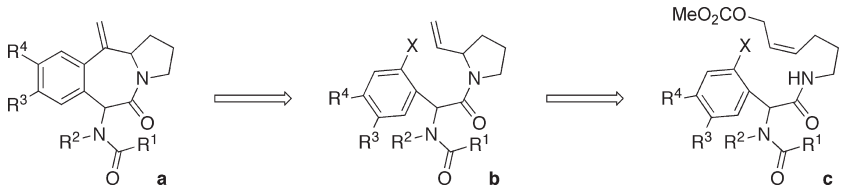

FIGURE 2. Retro-synthetic plan.

We were attracted by the structure of these compounds, since we foresaw the possibility for a quick access to a simplified version of its skeleton. We planned, therefore, to synthesize a library of original, nature-inspired compounds through the strategy described in the retro-synthetic plan reported in Figure 2.

In detail, we planned to couple an U-MCR (to access key intermediate **c**) with a Pd(0)-mediated S_N2' cyclization (yielding to **b**), where the secondary amide acts as the nucleophile,[6,7] and completing the transformation into **a** by means of an intramolecular Heck reaction. Although tandem Ugi/Heck strategies[8] and examples of intramolecular Heck cyclization followed by a second Pd(0)-catalyzed reaction in a tandem mode are known,[9] the novelty of our protocol stems from the combination of two palladium-catalyzed secondary transformations in a one-pot fashion. In the chemistry described herein, the Heck cyclization occurs second, thanks to the formation of the vinylpyrrolidine moiety. To the best of our knowledge, this is unprecedented.

Results and Discussion

The key substrates for this protocol are represented by isocyanide **1**, bearing an allylic alcohol protected as methyl carbonate, that acts as the leaving group in the S_N2' cyclization, and by a series of *o*-halobenzaldehydes containing the aryl halide moiety needed for the Heck step. The synthesis of **1** and the related MCR reactions have been previously optimized, although on other substrates.[6]

Following that protocol, we assembled from the polyfunctionalized isocyanide **1** a series of Ugi products **2** with up to five points of diversity (four of them designed to remain in the final tricyclic derivatives) (Scheme 1) in excellent yields. We then turned our attention to the double post-Ugi cyclization. Initially, we studied the two postcondensation transformation as separate steps. As far as the S_N2' cyclizations were concerned, they could be performed in excellent yields to afford pyrrolidines **3** using the previously optimized Pd(0)-catalyzed conditions (Table 1).[6]

This first cyclization was poorly stereoselective, the diastereomeric ratios being in all cases in the range 51:49/60:40 (HPLC). This disappointing stereoselectivity, however, gives the opportunity to prepare a diverse collection of compounds, as long as the two diastereoisomers can be separated, by a single combination of reagents.

Separation of the two diastereomers by chromatography was not possible at this stage, but it was easily done at the end of the synthetic sequence. Therefore, the purified diastereomeric mixtures of **3** were directly submitted to the following Heck cyclization without accurate spectroscopic characterization. In **3**, the restricted rotation around the two amide bonds gives rise to various rotamers, resulting in very complex ^1H or ^{13}C spectra at room temperature, whereas at 120 °C, broad peaks were always observed.[6,10] The situation was further complicated by the presence of two inseparable diastereomers. HPLC showed in all cases an overall purity ≥95% (sum of diastereoisomers) and allowed the determination of the diastereomeric ratio.

In principle, the intramolecular Heck reaction might afford two different constitutional isomers arising from a 7-exo (**4**) or a 8-endo (**6**) attack, but isomerized derivatives such as **5** also can be reasonably expected (Figure 3). Previous synthetic approaches in the field of alkaloids[11] showed a preference for 7-exo products, but the special substitution pattern of our compounds made the results not fully predictable.

We first optimized the reaction on compound **3a**. At room temperature, the rate of reaction was very slow, and in some cases, the reaction did not even start; heating was therefore required. For our purposes, we found the use of microwave heating at 120 °C to be particularly convenient. We had to carefully select the catalyst, the phosphine ligand, the solvent, and most of all, the base (Table 2). Several Pd catalysts were tested [$Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$]: all of them promoted the cyclization, but the latter proved to be the most effective. In particular, $Pd(OAc)_2$ caused also a partial dehalogenation of starting **3a**, which obviously prevented the Heck cyclization (entry 2, Table 2).

Addition of the phosphine ligand was required; otherwise, the yields were unsatisfactory (entry 5, Table 2). A careful selection of the ligand and of its relative amount (with respect to the catalyst) was also very important: we found an equimolar amount (relative to Pd) of 1,2-diphenylphosphinoethane (DPPE) to be the best. Nevertheless, the most crucial parameter to be optimized turned out to be the base. Heck reactions are usually performed in the presence of triethylamine. Even if the yield was in one case excellent (92%) (entry 8, Table 2), the results were poorly reproducible, both in terms of yield and conversion.

(6) Banfi, L.; Basso, A.; Cerulli, V.; Guanti, G.; Riva, R. *J. Org. Chem.* **2008**, *73*, 1608–1611.

(7) (a) Bulusu, M. A. R. C.; Waldstätten, P.; Tricotet, T.; Rochais, C.; Steck, A.; Bacher, M. *Tetrahedron Lett.* **2004**, *45*, 5833–5836. (b) Berkowitz, D. B.; Gourhari Maiti, G. *Org. Lett.* **2004**, *6*, 2661–2664.

(8) (a) Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 417–420. (b) Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155–3158. (c) Umkehrer, M.; Kalinski, C.; Kolb, J.; Burdack, C. *Tetrahedron Lett.* **2006**, *47*, 2391–2393. (d) Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, *47*, 4683–4686. (e) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119–5122. (f) Dai, W.-M.; Shi, J. Y.; Wu, J. L. *Synlett* **2008**, 2716–2720.

(9) (a) Ruck, R. T.; Huffman, M. A.; Kim, M. K.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711–4714. (b) Zegar, S.; Tokar, C.; Enache, L. A.; Rajagopol, V.; Zeller, W.; O'Connell, M.; Singh, J.; Muellner, F. W.; Zembower, D. E. *Org. Process Res. Dev.* **2007**, *11*, 747–753.

(10) Banfi, L.; Basso, A.; Guanti, G.; Merlo, S.; Repetto, C.; Riva, R. *Tetrahedron* **2008**, *64*, 1114–1134.

(11) (a) Ikeda, M.; Hirose, K.; El Bialy, S. A. A.; Sato, T.; Yakura, T.; Bayomi, S. M. M. *Chem. Pharm. Bull.* **1998**, *46*, 1084–1089. (b) Tietze, L. F.; Burkhardt, O.; Henrich, M. *Liebigs Ann.* **1997**, 1407–1413. (c) Tietze, L. F.; Schirok, H.; Wöhrmann, M.; Schrader, K. *Eur. J. Org. Chem.* **2000**, 2433–2444.

SCHEME 1. Ugi Reaction Followed by a Two-Step S_N2'−Heck Sequence

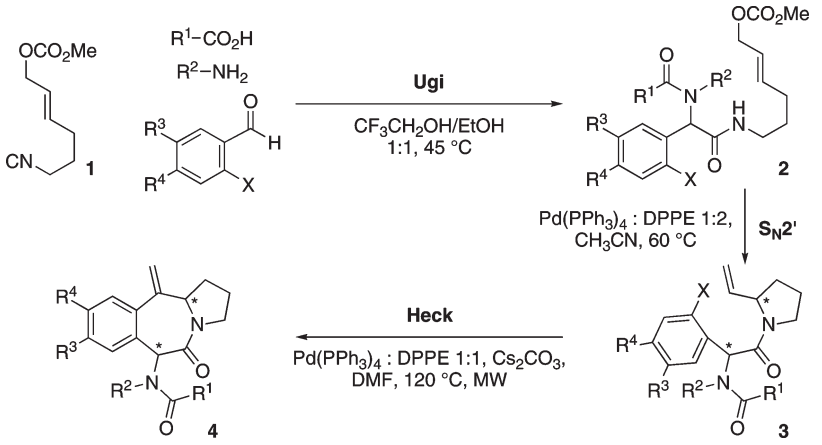

TABLE 1. Ugi Reaction Followed by S_N2' Reaction[a]

						yield[b] (%)	
entry	R^1	R^2	R^3	R^4	X	Ugi[c]	S_N2'
1	Et	Bn	H	H	Br	**2a**: 96	**3a**: 98
2	Et	Bn	H	H	I	**2b**: 94	**3b**: 95
3	Et	*n*Bu	H	H	Br	**2c**: 85	**3c**: 99
4	Ph	*i*Bu	F	H	Br	**2d**: 78[d]	**3d**: 96
5	Ph	*i*Bu	H	H	I	**2e**: 77	**3e**: 90
6	CH_2OMe	Bn	OCH_2O		Br	**2f**: 84	**3f**: 94
7	CH_2OMe	CH_2(2-furyl)	H	H	I	**2g**: 86	**3g**: 100
8	CH_2OMe	CH_2(2-furyl)	F	H	Br	**2h**: 81	**3h**: 95
9	CH_2OMe	Ph	H	H	I	**2i**: 89	**3i**: 95
10	$(CH_2)_2$-NHCbz	CH_2(2-furyl)	F	H	Br	**2j**: 72[d]	**3j**: 95

[a]The experimental conditions depicted in Scheme 1 have been followed. [b]After chromatography. [c]In the U-MCR either all the reagents have been mixed together at the same time (entries 1−3) or the imine has been preformed before addition of **1** and R^1-CO_2H (entries 4−10). [d]In this case, a variable amount of the Passerini product has also been isolated.

Changing the base to cesium carbonate led to a reproducible enough reaction, and moreover, it was always possible to drive the reactions to completion (entry 1, Table 3). Initially, we performed the reaction in acetonitrile, one of the most widely used solvents for the Heck reactions, but after several experiments, we found that DMF was better suited.

The two diastereomers of **4a** could be easily separated at this stage by chromatography and were fully characterized (see below). Although the diastereomeric ratio was similar to the one determined on **3a** (55:45 vs 60:40), we wanted to verify the correspondence of the major diastereomers. Separation at the level of **3a** was definitely difficult, but we succeeded in obtaining small amounts (∼10 mg) of the separated diastereomers and to submit them independently to the Heck reaction. Surprisingly, the major isomer afforded *cis*-**4a** in only 48% yield, whereas the minor isomer gave *trans*-**4a** in 93% yield (*cis* and *trans* are referred to the relative position of the hydrogens bonded to the two stereogenic carbons). Therefore, the Heck cyclization is highly dependent on the relative configuration of the starting haloarene, and the moderate overall yield (69%) is due only to the poorer contribution of the *cis* adduct **4a**. As can be seen from Table 3, this behavior was found to be pretty general, and *trans*-**4** was in most cases isolated as the major diastereomer.

The scope of the methodology was also transferred to the other pyrrolidines. With the exception of compounds **3g** and **3j**, which underwent extensive decomposition under the reaction conditions, all of other derivatives were smoothly converted into the tricyclic derivatives.

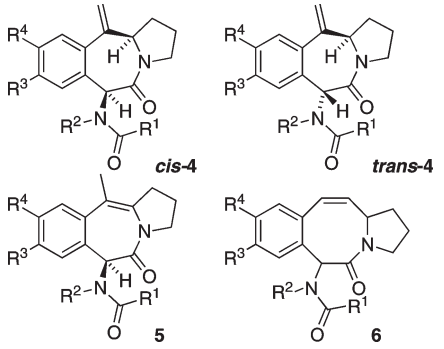

FIGURE 3. Possible intramolecular Heck products (racemic form).

In all cases, the major products were the diastereomeric *cis* and *trans* 7-exo derivatives **4**. In addition to them, we were, however, able to detect and isolate (sometimes as inseparable mixtures) small amounts of other Heck products, including derivatives arising from intermolecular reactions (see Table 3). In some cases, we identified, among them, 8-endo derivatives **6**. For example, starting from the diastereomeric mixture of **3d** (entry 4, Table 3), *cis*-**4d** was obtained only in traces, and a single diastereomer of **6d** (presumably the *cis* one) was isolated instead. On the contrary, the reaction of the other diastereomer, leading to *trans*-**4d** proceeded efficiently as usual. In addition, in the reaction mixture derived from compound **3h** (entry 8, Table 3), we were also able to isolate the isomerized adduct **5h** as an inseparable mixture with *cis*-**4h**.

The nature of the halogen atom influences the reaction outcome, with the cyclization running faster and cleaner when iodo derivatives were employed (compare entries 1 and 2 of Table 3, leading to the same tricyclic derivative).

The relative configuration of *cis*- and *trans*-**4a** was unambiguously established as follows. First, a series of NOE experiments displayed the interactions between the protons shown in Figure 4. The most diagnostic result is the very strong NOE effect between the H bonded to the two stereogenic centers observed in *cis*-**4a** (higher R_f in TLC), while this NOE was completely absent in *trans*-**4a** (lower R_f in TLC). *trans*-**4a** displayed, on the other side, a strong NOE between the benzylic H and the aromatic H in the *peri* position.

TABLE 2. Optimization of the Heck Cyclization Conditions for Preparation of 4a

entry[a]	catalyst (%)	phosphine	phosphine/catalyst[b]	base (equiv)[c]	solvent	temp, microwave heating[d]	comments, yield[e,f]
1	$Pd(OAc)_2$ (20%)	PPh_3	3:1	Et_3N (10)	MeCN	60 °C, no MW	sluggish
2	$Pd(OAc)_2$ (20%)	PPh_3	3:1	Et_3N (10)	MeCN	150 °C, MW	not complete and partial dehalogenation, up to 50%
3	$Pd(PPh_3)_2Cl_2$ (10%)	PPh_3	1:1	Et_3N (2)	MeCN	120 °C, MW	not complete, 35%
4	$Pd(PPh_3)_2Cl_2$ (10%)	PPh_3	1:1	Et_3N (2)	DMF	120 °C, MW	up to 70%
5	$Pd(PPh_3)_4$ (10%)	no phosphine		Et_3N (2)	DMF	120 °C, MW	up to 30%
6	$Pd(PPh_3)_4$ (10%)	DPPE	2:1	Et_3N (2)	DMF	120 °C, MW	traces of cyclization products
7	$Pd(PPh_3)_4$ (10%)	DPPE	1:1	Et_3N (2)	DMF	100 °C, no MW	no reaction
8	$Pd(PPh_3)_4$ (7−10%)	DPPE	1:1	Et_3N (2−3)	DMF	120 °C, MW	up to 92%, not reproducible

[a]Cyclization attempts have been performed on substrate **3a** (X = Br). [b]Molar ratio. [c]Equivalents with respect to the substrate. [d]All reactions performed under microwave heating have been done in a closed vessel. [e]In most cases, the reaction was performed more than once, and for this reason, an average yield is reported. [f]Yield includs all Heck products.

TABLE 3. Heck Cyclization under Optimized Conditions[a]

entry	substrate	X	yield (%)[b] [**4** (*cis*/*trans* ratio)]	yield (%)[c] (side products)
1	**3a**	Br	**4a**: 69 (45:55)	15
2	**3b**	I	**4a**: 81 (54:46)	13
3	**3c**	Br	**4c**: 68 (37:63)	14
4	**3d**	Br	**4d**: 26 (trace:∼100)	20 (**6d**)
5	**3e**	I	**4e**: 61 (30:70)	35
6	**3f**	Br	**4f**: 63 (48:52)	15
7	**3g**	I	**4g**: −	
8	**3h**	Br	**4h**: 41 (39[d]:61)	26
9	**3i**	I	**4i**: 65 (37:63)	20
10	**3j**	Br	**4j**: −	

[a]The experimental conditions depicted in Scheme 1 have been followed. [b]Sum of the isolated yields of separated *cis* and *trans* diastereomers; the *cis*/*trans* ratio was determined by weight. [c]See text. [d]This is actually an unseparable 61:39 mixture of *cis*-**4h** and **5h**.

This result is in agreement with the proposed relative configuration because, according to the rigid conformation of these compounds, this benzylic hydrogen occupies an equatorial position in *trans*-**4a**, whereas it is axial in *cis*-**4a**. Finally, a strong effect, although not diagnostic for the attribution of relative configuration, was found between the exo methylene H directed toward the aromatic ring and the aromatic H in the homoallylic position.

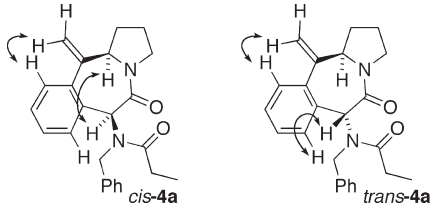

FIGURE 4. Significant NOE effects in *cis*- and *trans*-**4a**.

These results, obtained in solution, are also in perfect agreement with the solid-state structure, determined through single-crystal X-ray analysis on *trans*-**4a**. As can be seen in Figure 5,[12] the benzylic H occupies an equatorial position, with the C−H bond being nearly coplanar with the aromatic ring, whereas the bulky tertiary amide is nearly orthogonal to the same plane. Accordingly, in *cis*-**4a**, the tertiary amide is expected to be equatorial and the hydrogen axial (as demonstrated by the absence of a NOE with the *peri* hydrogen). The nearly coplanar position of the bulky tertiary amide is expected to determine an unfavorable steric interaction with

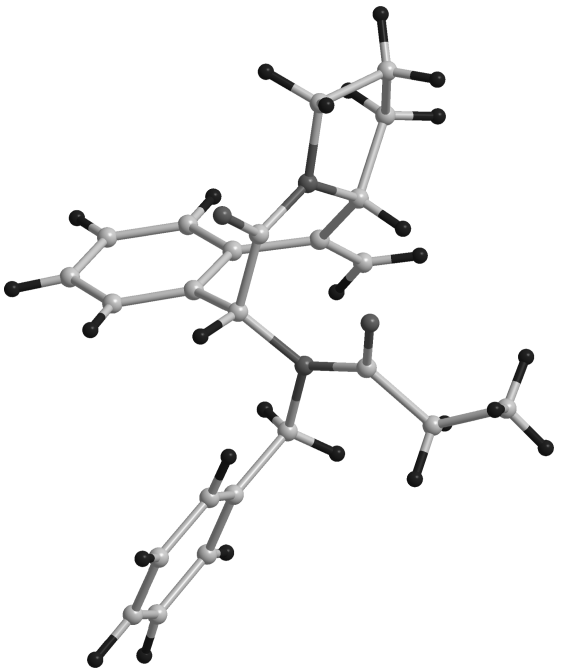

FIGURE 5. X-ray structure of *trans*-**4a**.

the *peri* hydrogen, and this may explain the more difficult formation of this stereoisomer.

Another important feature shown by crystallography is the position of the exo methylene: in the crystal structure of *trans*-**4a** it is not coplanar with the aromatic ring, thus preventing an extended conjugation.

The relative configuration of the other compounds **4** was assigned thanks to strong spectroscopic and chromatographic analogies.

The two stereoisomers of **4** were always well separated in TLC, and the *cis* diastereomer was always the one with higher R_f. Proton spectra showed interesting analogies: the benzylic proton alway resonates downfield in the *cis* stereoisomer (δ 5.74−6.47) with respect to the *trans* one (δ 4.75−5.50) with a difference in chemical shift up to 1.69 ppm (average $\Delta\delta$ 1.23). An opposite trend is displayed in the ^{13}C NMR spectra, where the corresponding carbon of the *cis* stereoisomer is always upfield (δ 57.8−65.3) with respect to the *trans* (δ 65.9−69.1) with a difference in chemical shift up to 10.3 ppm (average $\Delta\delta$ 6.6).[13] A less remarkable but recurrent difference is shown by

(12) Figure 5 shows a ball and stick model of *trans*-**4a** obtained from the ORTEP included in the Supporting Information.

(13) Additional details are reported in the Supporting Information.

TABLE 4. Tandem S_N2'-Heck Sequence Converting 2 into 4

		yield (%)	
entry	substrate[a]	**4** (*cis*/*trans* ratio)[b]	side products
1	**2a**	**4a**: 59 (54:46)	33
2	**2b**	**4a**: 91 (53:47)	8
3	**2c**	**4c**: 58 (43:57)	23

[a]Conditions: (1) $Pd(PPh_3)_4$ (10%), DPPE (10%), DMF, 120 °C, MW, 1 h; (2) Cs_2CO_3 (2 equiv), 120 °C, MW, 1 h. [b]See note b, Table 3.

the allylic α proton to the pyrrolidine nitrogen: it always resonates downfield (δ 4.48−4.79), as a triplet, in the *cis* stereoisomer, whereas in the *trans* one it appears either as a broad triplet, a broad doublet of doublet, or a symmetric multiplet (δ 4.26−4.55), with a difference in chemical shift up to 0.51 ppm (average $\Delta\delta$ 0.24). The differences in chemical shift of the corresponding carbons, on the contrary, are much less pronounced, with the *cis* giving typically higher δ values. On the contrary, no correlation between the chemical shifts and the configuration for the exo methylene hydrogens and carbons was found. Although the methylene carbon usually resonates upfield in the *cis* stereoisomer, the average difference of only 1.25 ppm does not allow a clear correlation.

Having demonstrated the feasibility of the protocol, the following step was to find conditions able to convert the Ugi adducts **2** into **4** in a one-pot manner, without the need of isolating the intermediate pyrrolidines **3**. For this purpose, we had to find conditions consistent with the two palladium(0)-catalyzed processes that have in part different requirements.

Similar conditions were therefore first investigated independently on both reactions. The first cyclization, which, according to the previously reported procedure, can be performed by conventional heating at 60 °C, could also be successfully performed under microwave heating at 120 °C by halving the reaction time. Moreover, acetonitrile, which was previously used for the S_N2' reaction, could be successfully substituted by DMF, the best solvent for the subsequent Heck step. Finally, the same catalyst and ligand were compatible with both reactions. However, it was impossible to perform the whole sequence as a domino process because the presence of a stoichiometric amount of base, necessary for the Heck reaction, turned out to be poorly compatible with the S_N2' step. For these reasons, we preferred a one-pot sequence in which the base was added in the same vessel after consumption of the Ugi product. Then, additional warming under microwave heating allowed the complete conversion into the desired tricyclic derivatives.

The results reported in Table 4 show that the one-pot methodology is indeed comparable or even superior to the two-step sequence. In particular, best results were obtained starting from the iodo derivative **2b** (entry 2, Table 4). Interestingly, this time the *cis*/*trans* ratios were slightly different, compared to the two-step protocol, affording a nearly equimolar mixture of *trans* and *cis* isomers.

Conclusions

In conclusion, we prepared a small library of bifunctionalized Ugi derivatives that have been submitted to a high-yielding two-step secondary transformation mediated by Pd(0). The success in performing the organometallic transformation in a one-pot fashion opens the way to the preparation of highly functionalized polycyclic compounds employing a diversity oriented approach with the generation of high complexity in just two synthetic steps, resulting in a new methodology for building nature-inspired libraries.

Experimental Section

General Experimental Details. Petroleum ether (40−60 °C) is abbreviated as PE. In extractive workup, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were washed with brine, dried over Na_2SO_4, and filtered before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen (Ugi reactions) or ultrapure argon (S_N2' and Heck reactions) atmosphere.

General Procedure for the Ugi Reactions. Without preformation of the imine (entries 1−3, Table 1): A solution of isocyanide **1**, an ∼95:5 mixture of *E* and *Z* diastereomers prepared following our previously reported procedure[6] (0.5−2 mmol), in dry CF_3CH_2OH/EtOH 1:1 (∼0.4 M solution) was treated with activated 4 Å powdered molecular sieves (50 mg/mmol of aldehyde). Aldehyde (1.1 equiv), amine (1.15 equiv), and carboxylic acid (1.2 equiv) were then added. The reaction was stirred at 45 °C until complete (8−16 h).

Preformation of the imine (entries 4−10, Table 1): A solution of aldehyde (1.2 mmol) in dry CF_3CH_2OH/EtOH 1:1 (∼0.4 M solution) was treated with activated 4 Å powdered molecular sieves (50 mg/mmol of aldehyde) and stirred at 45 °C for 6 h. Then isocyanide **1** (1.0 mmol) and acid (1.2 mmol) were added, and the mixture was stirred again at 45 °C until completion of the reaction (4−24 h).

In both procedures, after filtration of the sieves, the mixture was diluted with EtOAc and extracted. Then the organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried, and concentrated in vacuo. The crude was purified by chromatography.

Notice that proton spectra at room temperature are a mixture of two highly prevailing rotamers (with the exception of compound **2i**), and for this reason, they have been recorded at higher temperature (80, 90, or 120 °C). However, in all cases where the ratio of the rotamers at rt is readily accessible by integration of suitable signals, the value is reported in the appropriate section. In the ^{13}C spectra, where the signal of both rotamers can be identified, "M" indicates the major rotamer and "m" the minor one.

2-(*N*-Benzylpropionamido)-2-(2-bromophenyl)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2a). Chromatography with PE/EtOAc 6:4 (+ 1% EtOH) → 1:1 (+ 1% EtOH). Yield: 96%. State: colorless oil. R_f = 0.73 (PE/EtOAc 2:8). IR: ν_{max} 3428, 2985, 1742, 1652, 1440, 1266, 971, 928. HR-MS: calcd for $C_{26}H_{31}BrN_2O_5$ 530.1416, found 530.1412, −0.8 ppm. GC−MS: unsuitable for this analysis. ^1H NMR (DMSO-d_6, temp = 90 °C): δ 1.04 (3H, t, J = 7.2 Hz), 1.48 (2H, quintuplet, J = 7.1 Hz), 2.04 (2H, br q, J = 7.1 Hz), 2.37 (2H, center of m), 3.09 (2H, center of m), 3.72 (3H, s), 4.54 (2H, dd, J = 6.0, 1.2 Hz), 4.49 and 4.77 (2H, AB system, J = 16.5 Hz), 5.52−5.83 (2H, m), 6.10 (1H, br s), 6.90−7.38 (8H, m), 7.43 (1H, d, J = 7.8 Hz), 7.97 [1H, br s; at rt: 2 signals in 61:39 ratio at 8.26 (br t, J = 5.2 Hz) and 8.43 (br t, J = 5.0 Hz), respectively]. ^{13}C NMR (DMSO-d_6): δ 9.2 (m) and 9.3 (M) (CH_3), 25.8 (m) and 26.3 (M) (CH_2), 27.7 (m) and 27.8 (M) (CH_2), 28.9 (CH_2), 38.1 (CH_2), 47.5 (m) and 48.5 (M) (CH_2), 54.5 (CH_3), 61.0 (M) and 63.1 (m) (CH), 67.8 (CH_2), 123.8 (M) and 124.0 (m) (CH), 125.7, 126.3, 126.9, 127.1, 127.5, 127.8, 129.7, 130.0, 130.1, 130.5, 132.6 (9C, CH; 1C, C), 135.3 (m) and 135.9 (M) (C), 135.5 (m) and 135.6 (M) (CH), 138.0 (M) and 138.4 (m), 155.0 (C), 168.3 (m) and 169.0 (M) (C), 173.7 (m) and 174.2 (M) (C).

2-(*N*-Benzylpropionamido)-2-(2-iodophenyl)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2b). Chromatography

with PE/EtOAc 6:4 (+ 1% EtOH). Yield: 94%. State: thick yellow oil. R_f = 0.40 (PE/EtOAc 1:1 + 1% EtOH). IR: ν_{max} 3433, 2993, 1744, 1699, 1441, 1254, 972, 932. HR-MS: calcd for $C_{26}H_{31}IN_2O_5$ 578.1278, found 578.1270, −1.4 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 120 °C): δ 1.06 (3H, t, J = 7.4 Hz), 1.51 (2H, quintuplet, J = 7.2 Hz), 2.02 (2H, br q, J = 6.7 Hz), 2.28−2.47 (2H, m), 2.99−3.18 (2H, m), 3.73 (3H, s), 4.46 and 4.72 (2H, AB system, J = 17.0 Hz), 4.55 (2H, d, J = 6.6 Hz), 5.53−5.84 (2H, m), 5.90 (1H, br s), 6.93−7.20 (6H, m), 7.31−7.37 (2H, m), 7.72 (1H, d, J = 7.8 Hz), 7.71 [1H, br s; at rt: 2 signals in 57:43 ratio at 8.22 (br t, J = 5.4 Hz) and 8.44 (br t, J = 5.2 Hz), respectively]. ^{13}C NMR (DMSO-d_6): δ 9.2 (m) and 9.4 (M) (CH_3), 26.0 (m) and 26.4 (M) (CH_2), 27.8 (m) and 27.9 (M) (CH_2), 28.9 (CH_2), 38.2 (CH_2), 47.6 (m) and 48.5 (M) (CH_2), 54.5 (CH_3), 65.6 (M) and 67.3 (m) (CH), 67.8 (CH_2), 103.5 (m), 103.7 (M) (C), 123.8 (M) and 123.9 (m) (CH), 125.8, 126.0, 126.3, 127.1, 127.3, 127.7, 128.1, 128.3, 129.7, 129.80, 129.83, 130.0 (8C, CH), 135.5 (m) and 135.7 (M) (CH), 138.1 (M) and 138.4 (m) (C), 138.3 (m) and 139.0 (M) (C), 139.4 (CH), 155.0 (C), 168.6 (m) and 169.2 (M) (C), 173.8 (m) and 174.2 (M) (C).

2-(2-Bromophenyl)-2-(*N*-butylpropionamido)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2c). Chromatography with PE/EtOAc 6:4 + 1% EtOH. Yield: 85%. State: thick yellow oil. R_f = 0.41 (PE/EtOAc 1:1 + 1% EtOH). IR: ν_{max} 3433, 3002, 1741, 1668, 1635, 1435, 1265, 971, 933. HR-MS: calcd for $C_{23}H_{33}BrN_2O_5$ 495.1495 ($M^+ - 1$), found 495.1489, −1.1 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 90 °C): δ 0.64 (3H, t, J = 7.2 Hz), 0.74−0.86 (1H, m), 0.97 (2H, hexuplet, J = 7.1 Hz), 1.07 (3H, t, J = 7.4 Hz), 1.27−1.41 (1H, m), 1.54 (2H, quintuplet, J = 7.1 Hz), 2.04 (2H, br q, J = 7.0 Hz), 2.27−2.47 (2H, m), 3.09−3.21 (4H, m), 3.72 (3H, s), 4.54 (2H, dd, J = 6.3, 1.2 Hz), 5.53−5.86 (2H, m), 5.96 (1H, br s), 7.27−7.44 (3H, m), 7.65 (1H, dd, J = 7.8, 0.9 Hz), 7.91 [1H, br s; at rt: 2 signals in 69:31 ratio at 8.18 (br t, J = 5.4 Hz) and 8.43 (br t, J = 5.2 Hz), respectively]. ^{13}C NMR (DMSO-d_6): δ 9.2 (m) and 9.6 (M) (CH_3), 13.3 (m) and 13.4 (M) (CH_3), 19.4 (M) and 19.6 (m) (CH_2), 25.6 (M) and 25.9 (m) (CH_2), 27.9 (m) and 28.0 (M) (CH_2), 28.9 (CH_2), 29.7 (m) and 31.1 (M) (CH_2), 38.1 (CH_2), 44.4 (m) and 45.1 (M) (CH_2), 54.5 (CH_3), 60.9 (M) and 63.0 (m) (CH), 67.76 (m) and 67.80 (M) (CH_2), 123.9 (M) and 124.0 (m) (CH), 125.7 (M) and 126.0 (m) (C), 127.7 (M) and 127.9 (m) (CH), 130.0 (M), 130.27 (m), 130.33 (m), 130.8 (M) (2C, CH), 132.7 (M) and 132.9 (m) (CH), 135.5 (M) and 135.6 (m) (C), 135.7 (M) and 136.2 (m) (CH), 155.0 (C), 168.5 (m) and 169.1 (M) (C), 172.6 (m) and 173.0 (M) (C).

2-(2-Bromo-4-fluorophenyl)-2-(*N*-isobutylbenzamido)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2d). Chromatography with PE/EtOAc 6:4 + 1% EtOH. Yield: 78%. State: thick pale yellow oil. R_f = 0.57 (PE/EtOAc 1:1). For the preparation of compound **2d**, it was very important to preform the imine before addition of **1** and the acid. Otherwise, a considerable amount (up to 20%) of Passerini adduct (the benzoate with O instead of N-*i*-Bu) was obtained. IR: ν_{max} 3003, 1743, 1669, 1622, 1442, 1193, 971, 928. HR-MS: calcd for $C_{27}H_{32}BrFN_2O_5$ 563.1540 ($M^+ + 1$), found 563.1557, −3.0 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 90 °C): δ 0.56 (3H, t, J = 6.6 Hz), 0.63 (3H, t, J = 6.6 Hz), 1.40 (1H, center of m), 1.54 (2H, quintuplet, J = 7.2 Hz), 2.03 (2H, br q, J = 7.0 Hz), 3.11−3.18 (4H, m), 3.72 (3H, s), 4.55 (2H, dd, J = 6.0, 0.9 Hz), 5.53−5.86 (2H, m), 5.68 (1H, br s; at rt: 2 singlets in 55:45 ratio at 5.26 and 5.92, respectively), 7.16−7.24 (2H, m), 7.36−7.45 (5H, m), 7.71 (1H, dd, J_{H-H} = 8.7 Hz, J_{H-F} = 5.4 Hz), 7.89 (1H, br s). ^{13}C NMR (DMSO-d_6, temp = 90 °C): δ 19.4 (CH_3), 19.6 (CH_3), 27.0 (CH), 27.5 (CH_2), 28.4 (CH_2), 38.0 (CH_2), 53.1 (CH_2), 53.9 (CH_3), 64.1 (CH), 67.2 (CH_2), 116.7 (d, CH, J_{C-F} = 22.4 Hz), 117.3 (d, CH, J_{C-F} = 24.1 Hz), 119.7 (d, C, J_{C-F} = 3.2 Hz), 123.6 (CH), 125.9 (2C, CH), 127.6 (2C, CH), 128.5 (CH), 134.0 (d, CH, J_{C-F} = 8.1 Hz), 134.9 (CH), 136.7 (C), 137.7 (d, C, J_{C-F} = 7.4 Hz), 154.4 (C), 160.7 (d, C, J_{C-F} = 244.1 Hz), 167.7 (C), 171.5 (C).

2-(2-Iodophenyl)-2-(*N*-isobutylbenzamido)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2e). Chromatography with PE/EtOAc 65:35 → 6:4. Yield: 77%. State: thick pale yellow oil. R_f = 0.55 (PE/EtOAc 1:1). IR: ν_{max} 2999, 1738, 1699, 1428, 1247, 1191, 971, 925. HR-MS: calcd for $C_{27}H_{33}IN_2O_5$ 592.1434, found 592.1422, −2.1 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 120 °C): δ 0.54 (3H, t, J = 6.6 Hz), 0.59 (3H, t, J = 6.9 Hz), 1.39 (1H, center of m), 1.54 (2H, quintuplet, J = 7.2 Hz), 2.03 (2H, br q, J = 7.2 Hz), 3.04 and 3.15 (2H, AB part of an ABX system, J_{AB} = 14.4 Hz, J_{AX} = 6.6 Hz, J_{BX} = 7.2 Hz), 3.10−3.17 (2H, m), 3.73 (3H, s), 4.55 (2H, dd, J = 6.3, 1.2 Hz), 5.54−5.86 (2H, m), 5.62 (1H, br s) 7.10 (1H, ddd, J = 8.1, 5.7, 3.6 Hz), 7.39−7.46 (7H, m), 7.55 (1H, br s), 7.94 (1H, d, J = 7.8 Hz). ^{13}C NMR (DMSO-d_6, temp = 80 °C): δ 19.6 (CH_3), 19.8 (CH_3), 27.1 (CH), 27.6 (CH_2), 28.5 (CH_2), 38.0 (CH_2), 52.8 (CH_2), 54.0 (CH_3), 67.3 (CH_2), 68.1 (CH), 102.9 (C), 123.5 (CH), 126.1 (2C, CH), 127.5 (2C, CH), 127.7 (CH), 128.3 (CH), 129.6 (CH), 130.2 (CH), 135.0 (CH), 137.0 (C), 138.2 (C), 139.2 (CH), 154.5 (C), 168.8 (C), 171.4 (C).

2-(*N*-Benzylmethoxyacetamido)-2-(5-bromobenzo[*d*][1,3]dioxol-6-yl)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2f). Chromatography with PE/EtOAc 1:1 + 1% EtOH. Yield: 84%. State: thick pale yellow oil. R_f = 0.57 (CH_2Cl_2/EtOAc 2:8). IR: ν_{max} 3008, 2891, 1739, 1663, 1471, 1247, 1121, 1035, 969, 928. HR-MS: calcd for $C_{27}H_{31}BrN_2O_8$ 590.1264, found 590.1251, −2.2 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 120 °C): δ 1.52 (2H, quintuplet, J = 7.1 Hz), 2.03 (2H, br q, J = 7.2 Hz), 3.09 (2H, center of m), 3.32 (3H, s), 3.73 (3H, s), 4.13 (2H, s), 4.45 and 4.77 (2H, AB system, J = 17.0 Hz), 4.55 (2H, d, J = 6.0 Hz), 5.53−5.85 (2H, m), 5.89 (1H, br s), 5.98 (1H, s), 6.01 (1H, s), 6.87 (1H, s), 6.91 (1H, s), 7.04−7.17 (5H, m), 7.72 (1H, br s). ^{13}C NMR (DMSO-d_6, temp = 80 °C): δ 27.6 (CH_2), 28.4 (CH_2), 38.0 (CH_2), 47.5 (CH_2), 54.0 (CH_3), 58.0 (CH_3), 61.5 (CH), 67.3 (CH_2), 70.4 (CH_2), 101.6 (CH_2), 109.5 (CH), 111.9 (CH), 116.4 (C), 123.6 (CH), 125.7, 126.0, 127.0, (5C, CH), 127.6 (CH), 135.0 (C), 137.5 (C), 146.8 (C), 147.6 (C), 154.5 (C), 168.1 (C), 169.4 (C).

2-(*N*-((Furan-2-yl)methyl))methoxyacetamido)-2-(2-iodophenyl)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2g). Chromatography with PE/EtOAc 3:7 → 25:75. Yield: 86%. State: yellow gum. R_f = 0.39 (PE/EtOAc 2:8). IR: ν_{max} 3425, 2967, 1743, 1664, 1435, 1265, 1196, 1122, 1010, 970, 934. HR-MS: calcd for $C_{24}H_{29}IN_2O_7$ 584.1019, found 584.1010, −1.5 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 1.52 (2H, quintuplet, J = 7.1 Hz), 2.03 (2H, br q, J = 7.4 Hz), 3.12 (2H, center of m), 3.35 (3H, s), 3.72 (3H, s), 4.25 and 4.34 (2H, AB system, J = 14.8 Hz), 4.54 (2H, dd, J = 6.3, 1.2 Hz), 4.35 and 4.60 (2H, AB system, J = 17.1 Hz), 5.53−5.86 (3H, m), 5.70 (1H, br s), 6.14 (1H, dd, J = 3.0, 1.8 Hz), 7.04 (1H, dt, J = 7.5, 1.8 Hz), 7.30−7.33 (2H, m), 7.41 (1H, dt, J = 7.5, 1.2 Hz), 7.72 (1H, dd, J = 8.1, 1.2 Hz), 7.96 [1H, br s; at rt: two signals in 73:27 ratio at 8.24 (br t, J = 5.2 Hz) and 8.35 (br s), respectively]. ^{13}C NMR (DMSO-d_6, temp = 80 °C): δ 27.6 (CH_2), 28.4 (CH_2), 37.9 (CH_2), 40.5 (CH_2), 54.2 (CH_3), 58.0 (CH_3), 65.5 (CH), 67.3 (CH_2), 70.1 (CH_2), 102.6 (C), 106.4 (CH), 109.5 (CH), 123.6 (CH), 127.6 (CH), 129.4 (CH), 129.8 (CH), 135.0 (CH), 137.8 (CH), 139.1 (CH), 141.1 (C), 150.6 (C), 154.5 (C), 168.3 (C), 169.1 (C).

2-(2-Bromo-4-fluorophenyl)-2-(*N*-((furan-2-yl)methyl))methoxyacetamido)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2h). Chromatography with PE/EtOAc 1:1 (+ 1% EtOH) → 3:7 (+ 1% EtOH). Yield: 81%. State: yellow solid. Mp: 59.6−60.2 °C (PE/EtOAc). R_f = 0.26 (PE/EtOAc 1:1 + 1% EtOH). IR: ν_{max} 3430, 2995, 1742, 1667, 1442, 1267, 971, 924. HR-MS: calcd for $C_{24}H_{28}BrFN_2O_7$ 554.1064, found 554.1071, +1.3 ppm.

GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 90 °C): δ 1.52 (2H, quintuplet, J = 7.1 Hz), 2.04 (2H, br q, J = 7.2 Hz), 3.00−3.19 (2H, m), 3.34 (3H, s), 3.72 (3H, s), 4.26 and 4.29 (2H, AB system, J = 14.7 Hz), 4.49 and 4.67 (2H, AB system, J = 17.1 Hz), 4.54 (2H, dd, J = 7.2, 1.2 Hz), 5.53−5.86 (3H, m), 5.93 (1H, br s), 6.18 (1H, dd, J = 3.3, 1.8 Hz), 7.06−7.31 (3H, m), 7.49−7.55 (1H, m), 8.01 (1H, br s). ^{13}C NMR (DMSO-d_6): δ 27.9 (M) and 28.5 (m) (CH_2), 28.9 (M) (CH_2), 38.3 (M) and 38.4 (m) (CH_2), 40.6 (m) and 41.2 (M) (CH_2), 54.6 (M) and 54.9 (m) (CH_3), 58.4 (CH_3), 60.5 (M) and 62.1 (m) (CH), 67.8 (CH_2), 69.8 (M) and 71.3 (m) (CH_2), 106.8 (CH), 110.2 (CH), 117.0 (d, CH, J_{C-F} = 22.6 Hz, only M), 117.4 (d, CH, J_{C-F} = 24.2 Hz, only M), 120.2 (d, C, J_{C-F} = 2.9 Hz), 123.6 (m) and 124.0 (M) (CH), 134.1 (d, CH, J_{C-F} = 8.2 Hz, only M), 135.6 (CH), 137.6 (d, C, J_{C-F} = 7.4 Hz), 141.1 (m) and 142.2 (M) (CH), 150.5 (M) and 151.3 (m) (C), 155.0 (M) and 155.1 (m) (C), 161.2 (d, C, J_{C-F} = 243.2 Hz), 168.1 (M), 169.3 (m), 169.7 (M) and 170.4 (m) (2C).

2-(2-Iodophenyl)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)-2-(*N*-(phenyl)methoxyacetamido))acetamide (2i). Chromatography with PE/EtOAc 1:1 + 1% EtOH. Yield: 89%. State: thick pale yellow oil. R_f = 0.26 (PE/EtOAc 1:1). IR: ν_{max} 3426, 2976, 1740, 1669, 1492, 1440, 1235, 1188, 1023, 969, 925. HR-MS: calcd for $C_{25}H_{29}IN_2O_6$: 580.1070; found 580.1070, 0 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 1.52 (2H, quintuplet, J = 7.1 Hz), 2.01 (2H, br q, J = 7.2 Hz), 3.15 (2H, center of m), 3.22 (3H, s), 3.63 and 3.75 (2H, AB system, J = 14.9 Hz), 3.71 (3H, s), 4.54 (2H, dd, J = 6.3, 0.6 Hz), 5.52−5.85 (2H, m), 6.18 (1H, s), 6.82−6.89 (2H, m), 7.03 (1H, br t, J = 7.5, 1.2 Hz), 7.15−7.18 (3H, m), 7.34 (2H, apparent br s), 7.80 (1H, dd, J = 7.8, 0.9 Hz), 8.01 (1H, br t, J = 5.2 Hz). ^{13}C NMR (DMSO-d_6, temp = 60 °C): δ 27.8 (CH_2), 28.6 (CH_2), 38.1 (CH_2), 54.2 (CH_3), 58.0 (CH_3), 67.48 (CH_2), 67.53 (CH), 69.8 (CH_2), 103.6 (C), 123.6 (CH), 127.3 (CH), 127.7 (CH), 128.0 (2C, CH), 129.4 (CH), 129.7 (2C, CH), 130.6 (CH), 135.3 (CH), 137.5 (C), 137.6 (C), 138.8 (CH), 154.6 (C), 168.0 (C), 168.8 (C).

2-(3-(Benzyloxycarbonylamino)-2-(2-bromo-4-fluorophenyl)-*N*-((furan-2-yl)methyl))propionamido)-*N*-(*E*)-6-(((methoxycarbonyl)oxy)hex-4-en-1-yl)acetamide (2j). Chromatography with PE/EtOAc 1:1 → 4:6. Yield: 72%. State: thick pale yellow oil. R_f = 0.26 (PE/EtOAc 1:1). IR: ν_{max} 3437, 2996, 1712, 1501, 1441, 1232, 1013, 972, 925. HR-MS: calcd for $C_{32}H_{35}BrFN_3O_8$ 687.1592, found 687.1585, −1.0 ppm. GC−MS: unsuitable for this analysis. ^{1}H NMR (DMSO-d_6, temp = 90 °C): δ 1.52 (2H, quintuplet, J = 7.2 Hz), 2.03 (2H, br q, J = 7.1 Hz), 2.67−2.83 (2H, m), 2.99−3.21 (2H, m), 3.34 (2H, br q, J = 6.6 Hz), 3.71 (3H, s), 4.51 and 4.68 (2H, AB system, J = 17.7 Hz), 4.54 (2H, dd, J = 6.0, 0.9 Hz), 5.04 (2H, s), 5.53−5.85 (3H, m), 6.00 (1H, br s), 6.18 (1H, dd, J = 3.3, 1.8 Hz), 6.80 (1H, br s), 7.05−7.55 (9H, m), 8.02 [1H, br s; at rt: 2 signals in 78:22 ratio at 8.35 (br t, J = 5.4 Hz) and 8.57 (br t, J = 4.8 Hz) respectively]. ^{13}C NMR (DMSO-d_6, temp = 90 °C): δ 27.5 (CH_2), 28.4 (CH_2), 32.8 (CH_2), 36.6 (CH_2), 38.0 (CH_2), 41.8 (CH_2, very br signal; at rt 42.1), 53.9 (CH_3), 61.0 [CH, very br signal; at rt 59.72 (m) and 60.5 (M)], 64.8 (CH_2), 67.2 (CH_2), 106.4 (CH), 109.6 (CH), 116.3 (d, CH, J_{C-F} = 22.1 Hz), 116.9 (d, CH, J_{C-F} = 24.2 Hz), 119.4 (d, C, J_{C-F} = 2.9 Hz), 123.1 (CH), 127.0, 127.1, 127.7 (5C, CH), 133.6 (d, CH, J_{C-F} = 8.1 Hz), 134.8 (CH), 136.7 (C), 137.5 (br s, C), 141.1 (C), 150.5 (CH), 154.4 (C), 155.4 (C), 162.3 (d, C, J_{C-F} = 243.4 Hz), 167.4 (C), 171.0 (C).

General Procedure for the S_N2' Reactions. A solution of carbonate **2** (400−500 μmol) in dry MeCN (9 mL) was carefully degassed and kept under Ar. Then DPPE (20% with respect to **2**) and Pd(PPh_3)$_4$ (10%) were added, and the reaction was stirred at 60 °C until complete (1−2 h). The same reaction can be successfully performed in the presence of 3% catalyst (and 6% DPPE) without affecting the yield, but the reaction speed is considerably slower (2−4 h). For the workup, the crude was filtered over a Celite pad, and the resulting solution was diluted with water and extracted with EtOAc. After drying and solvent removal, the crude was purified by chromatography to give **3** as a diastereomeric mixture. Pyrrolidines **3** were directly submitted to the following Heck cyclization.

***N*-Benzyl-*N*-(1-(2-bromophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)propionamide (3a).** Chromatography with PE/EtOAc 6:4 → 4:6. Yield: 98%. State: yellow gum. R_f of the two diastereomers: 0.48 and 0.39 (PE/EtOAc 3:7). Dr: 60:40. ***N*-Benzyl-*N*-(1-(2-iodophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)propionamide (3b).** Chromatography with PE/EtOAc 4:6 + 1% EtOH. Yield: 95%. State: yellow gum. R_f: 0.30 both diastereomers (PE/EtOAc 1:1). Dr: 60:40. ***N*-(1-(2-Bromophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)-*N*-butylpropionamide (3c).** Chromatography with PE/EtOAc 1:1 → 4:6. Yield: 99%. State: amber gum. R_f of the two diastereomers: 0.45 and 0.35 (PE/EtOAc 1:1). Dr: 54:46. ***N*-(1-(2-Bromo-5-fluorophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)-*N*-isobutylbenzamide (3d).** Chromatography with PE/EtOAc 75:25 → 65:35. Yield: 96%. State: yellow foam. R_f: 0.39 both diastereomers (PE/EtOAc 3:7). Dr: 55:45. ***N*-(2-Iodophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)-*N*-isobutylbenzamide (3e).** Chromatography with PE/EtOAc 1:1. Yield: 90%. State: yellow gum. R_f of the two diastereomers: 0.59 and 0.55 (PE/EtOAc 4:6). Dr: 54:46. ***N*-Benzyl-*N*-(1-(5-bromobenzo[*d*][1,3]dioxol-6-yl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)-2-methoxyacetamide (3f).** Chromatography with CH_2Cl_2/EtOAc 4:6 → 2:8. Yield: 94%. State: very thick pale yellow oil. R_f of the two diastereomers: 0.54 and 0.46 (CH_2Cl_2/EtOAc 2:8). Dr: 59:41. ***N*-((Furan-2-yl)methyl)-*N*-(1-(2-iodophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)-2-methoxyacetamide (3g).** Chromatography with PE/EtOAc 2:8 → 1:9. Yield: 100%. State: yellow gum. R_f of the two diastereomers: 0.51 and 0.46 (EtOAc). Dr: 52:48. ***N*-(1-(2-Bromo-5-fluorophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)-ethyl)-*N*-((furan-2-yl)methyl)-2-methoxyacetamide (3h).** Chromatography with PE/EtOAc 4:6 + 0.5% EtOH. Yield: 95%. State: pale yellow gum. R_f of the two diastereomers: 0.56 and 0.51 (PE/EtOAc 1:9). Dr: 51:49. ***N*-(1-(2-Iodophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)-2-methoxy-*N*-phenylacetamide (3i).** Chromatography with PE/EtOAc 1:1. Yield: 95%. State: very thick yellow oil. R_f of the two diastereomers: 0.33 and 0.25 (PE/EtOAc 1:1). Dr: 58:42. **3-(((Benzyloxy)carbonyl)amino)-*N*-(1-(2-bromo-5-fluorophenyl)-2-oxo-2-(2-vinylpyrrolidin-1-yl)ethyl)-*N*-((furan-2-yl)methyl)propionamide (3j).** Chromatography with PE/EtOAc 4:6 + 0.5% EtOH. Yield: 95%. State: ivory foam. R_f of the two diastereomers: 0.47 and 0.43 (PE/EtOAc 4:6 + 1% EtOH). Dr: 57:43.

General Procedure for the Heck Cyclization. Pyrrolidine **3** (170 μmol) was dissolved in dry DMF (2 mL) in a MW vessel equipped with a rubber septum. The solution was carefully degassed and kept under Ar. Cs_2CO_3 (2 equiv) and DPPE (10% with respect to **3**) were rapidly added, and the system was degassed. Then Pd(PPh_3)$_4$ (10%) was added, and the suspension was degassed again. The septum was rapidly removed, and the vessel was closed and heated at 120 °C for 1 h using 150 W maximum power (see temperature and power profiles in the Supporting Information). The crude was then filtered over a Celite pad, and the resulting solution was diluted with water and extracted with EtOAc. After drying and solvent removal, the crude was purified by chromatography to give compounds **4**.

(6*R,11a*S**)-6-(*N*-Benzylpropionamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-a]azepin-5(6*H*)-one (*cis*-4a).** Chromatography with PE/EtOAc 1:1 → EtOAc + 1% EtOH. Yield: 31% from **2a**, 44% from **2b**. State: yellow foam. Crystallization from *i*-Pr_2O/CH_2Cl_2 afforded pale yellow crystals. Mp: 130.3−131.6 °C dec. R_f = 0.54 (PE/EtOAc 2:8). IR: ν_{max} 2999, 1641, 1413, 1248, 1184, 1026. HR-MS: calcd for

$C_{24}H_{26}N_2O_2$ 374.1994, found 374.1980, −3.7 ppm. GC−MS: t_R 11.94; *m*/*z* 374 (M^+, 4.6), 317 (12), 227 (26), 213 (100), 212 (16), 211 (47), 210 (5.6), 196 (5.5), 184 (25), 183 (37), 182 (15), 156 (5.8), 155 (7.1), 143 (5.2), 142 (7.9), 141 (6.2), 128 (7.9), 115 (12), 106 (7.7), 91 (62), 65 (8.8), 57 (13). Note: Benzylic C*H*N as the *cis* diastereomer is very difficult to identify because it is usually a very broad signal, hardly distinguishable from the baseline. For this reason, it is necessary to perform proton spectra in DMSO-d_6 at 80−90 °C. ^{1}H NMR (DMSO-d_6, temp = 90 °C): δ 0.90 (3H, t, J = 7.4 Hz), 1.78−1.88 (2H, m), 1.94−2.40 (2H, m), 2.14 (2H, center of m), 3.21 (1H, dt, J = 11.4, 7.6 Hz), 3.51 (1H, ddd, J = 12.3, 7.3, 5.2 Hz), 4.79 (1H, t, J = 7.2 Hz), 4.93 and 5.25 (2H, AB system, J = 16.2 Hz), 5.35 (1H, d, J = 0.9 Hz), 5.37 (1H, d, J = 0.9 Hz), 6.47 (1H, br s), 7.24−7.38 (9H, m). ^{13}C NMR (DMSO-d_6, temp = 90 °C): δ 8.6 (CH_3), 21.5 (CH_2), 26.3 (CH_2), 33.2 (CH_2), 45.8 (CH_2), 50.5 (CH_2), 59.6 (very br signal, CH), 60.0 (CH), 113.6 (CH_2), 124.2, 125.6, 126.4, 127.0, 127.3, 127.5, 127.7 (9C, CH), 135.6 (C), 137.1 (C), 139.3 (C), 147.3 (C), 166.9 (C), 174.9 (C).

(6*R,11a*R**)-6-(*N*-Benzylpropionamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*trans*-4a).** Chromatography with PE/EtOAc 1:1 → EtOAc + 1% EtOH. Yield: 38% from **2a**, 37% from **2b**. State: white solid. Crystallization from *i*-Pr_2O/CH_2Cl_2 afforded white crystals. Mp: 160.1−162.9 °C dec. R_f = 0.21 (PE/EtOAc 2:8). IR: ν_{max} 2972, 2881, 1641, 1413, 1189, 1027. HR-MS: calcd for $C_{24}H_{26}N_2O_2$ 374.1994, found 374.1982, −3.3 ppm. GC−MS: t_R 11.85; *m*/*z* 374 (M^+, 2.7), 317 (16), 290 (6.2), 227 (22), 214 (15), 213 (82), 212 (6.2), 211 (20), 184 (15), 183 (5.8), 170 (6.5), 168 (7.6), 156 (6.6), 144 (12), 143 (7.5), 142 (22), 141 (7.4), 130 (12), 129 (11), 128 (9.3), 117 (5.5), 116 (12), 115 (15), 106 (13), 92 (8.8), 91 (100), 70 (27), 65 (14), 57 (24). ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, t, J = 7.5 Hz), 1.71−1.93 (3H, m), 2.28−2.35 (1H, m), 2.45 (2H, center of m), 3.29 (1H, dt, J = 8.6, 7.8 Hz), 3.68 and 4.78 (2H, AB system, J = 17.2 Hz), 3.76 (1H, center of m), 4.40 (1H, br t, J = 8.0 Hz), 4.91 (1H, s), 5.16 (1H, d, J = 1.5 Hz), 5.31 (1H, d, J = 1.2 Hz), 6.83−6.89 (3H, m), 7.11−7.36 (6H, m). ^{13}C NMR ($CDCl_3$): δ 9.6 (CH_3), 22.0 (CH_2), 27.2 (CH_2), 37.4 (CH_2), 47.7 (CH_2), 48.9 (CH_2), 60.2 (CH), 68.1 (CH), 113.5 (CH_2), 126.3, 127.5, 128.4, 128.8, 129.1, 129.5, 130.0 (9C, CH), 132.7 (C), 136.1 (C), 137.2 (C), 149.7 (C), 168.1 (C), 175.3 (C).

(6*R,11a*S**)-6-(*N*-Butylpropionamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*cis*-4c).** Chromatography with PE/EtOAc 4:6 → EtOAc/EtOH 9:1. Yield: 25%. State: yellow gum. R_f = 0.72 (EtOAc + 3% EtOH). IR: ν_{max} 3005, 1724, 1628, 1504, 1419, 1374, 1225, 1039, 923. HR-MS: calcd for $C_{21}H_{28}N_2O_2$: 340.2151, found 340.2146, −1.5 ppm. GC−MS: t_R 10.61; *m*/*z* 340 (M^+, 4.5), 284 (7.9), 283 (36), 227 (11), 214 (17), 213 (100), 212 (24), 211 (76), 210 (11), 200 (5.5), 196 (5.4), 185 (9.2), 184 (59), 183 (88), 182 (31), 170 (8.8), 169 (5.9), 168 (11), 167 (12), 157 (6.1), 156 (13), 155 (21), 154 (9.7), 153 (8.6), 144 (6.7), 143 (12), 142 (19), 141 (16), 130 (13), 129 (13), 128 (19), 127 (6.9), 116 (9.0), 115 (29), 103 (5.2), 77 (5.8), 70 (6.8), 57 (35), 56 (12), 41 (19). ^{1}H NMR (DMSO-d_6, temp = 90 °C): δ 0.89 (3H, t, J = 7.4 Hz), 0.96 (3H, t, J = 7.4 Hz), 1.29 (2H, hexuplet, J = 7.4 Hz), 1.50 (1H, center of m), 1.66−1.79 (1H, m), 1.81−1.93 (2H, m), 1.99−2.39 (2H, m), 2.20 (2H, center of m), 3.30 (1H, dt, J = 11.7, 7.5 Hz), 3.47−3.69 (3H, m), 4.77 (1H, t, J = 7.1 Hz), 5.37 (1H, d, J = 1.5 Hz), 5.39 (1H, d, J = 0.6 Hz), 6.26 (1H, br s), 7.19−7.40 (4H, m). ^{13}C NMR (DMSO-d_6, temp = 90 °C): δ 8.9 (CH_3), 13.0 (CH_3), 19.3 (CH_2), 21.7 (CH_2), 26.0 (CH_2), 31.0 (CH_2), 32.4 (CH_2), 45.9 (CH_2), 47.3 (CH_2), 59.5 (CH), 60.7 (CH), 113.0 (CH_2), 125.0, 126.9, 127.5, 127.6 (4C, CH), 135.4 (C), 137.5 (C), 147.1 (C), 166.8 (C), 173.9 (C).

(6*R,11a*R**)-6-(*N*-Butylpropionamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[d]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*trans*-4c).** Chromatography with PE/EtOAc 4:6 → EtOAc/EtOH 9:1. Yield: 43%. State: yellow gum. R_f = 0.19 (EtOAc + 3% EtOH). IR: ν_{max} 3013, 2890, 1724, 1638, 1509, 1472, 1415, 1374, 1231, 1048, 927. HR-MS: calcd for $C_{21}H_{28}N_2O_2$ 340.2151, found 340.2141, −2.9 ppm. GC−MS: t_R 10.63; *m*/*z* 340 (M^+, 4.5), 284 (8.0), 283 (36), 227 (11), 214 (16), 213 (100), 212 (24), 211 (74), 210 (10), 200 (5.1), 198 (5.0), 196 (5.8), 185 (8.6), 184 (59), 183 (91), 182 (32), 170 (8.8), 169 (6.1), 168 (11), 167 (12), 157 (6.3), 156 (14), 155 (22), 154 (11), 153 (9.3), 144 (7.1), 143 (12), 142 (19), 141 (18), 130 (15), 129 (13), 128 (20), 127 (7.9), 116 (10), 115 (30), 103 (5.7), 77 (6.1), 70 (7.2), 57 (39), 56 (13), 41 (22), 39 (6.3). ^{1}H NMR (DMSO-d_6): δ 0.66 (3H, t, J = 7.4 Hz), 0.86−1.09 (2H, m), 1.02 (3H, t, J = 7.5 Hz), 1.20−1.33 (2H, m), 1.53−1.76 (3H, m), 2.22−2.48 (4H, m), 3.05 (1H, dt, J = 9.9, 7.2 Hz), 3.24 (1H, center of m), 3.35−3.45 (1H, m), 4.26 (1H, br t, J = 7.4 Hz), 4.77 (1H, br s), 5.18 (1H, br s), 5.21 (1H, br s), 7.29−7.44 (4H, m). ^{13}C NMR (DMSO-d_6): δ 9.7 (CH_3), 13.3 (CH_3), 19.2 (CH_2), 21.7 (CH_2), 26.2 (CH_2), 29.3 (CH_2), 36.9 (CH_2), 44.3 (CH_2), 47.3 (CH_2), 59.4 (CH), 66.8 (CH), 114.0 (CH_2), 128.3, 129.1, 129.4, 129.5 (4C, CH), 132.9 (C), 137.3 (C), 149.0 (C), 167.4 (C), 174.1 (C).

(6*R,11a*S**)-8-Fluoro-6-(*N*-isobutylbenzamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*cis*-4d).** Chromatography with PE/EtOAc 6:4 → 1:9 afforded a mixture of *cis*-**4d** and **6d**. These two compounds were nearly completely overlapped in TLC, and therefore, a second chromatography with PE/CH_2Cl_2/Me_2CO 45:45:10 was necessary. Only traces of *cis*-**4d** were isolated, and for this reason, only a partial characterization was performed: anyway, due to very strong spectroscopic analogies with other *cis*-**4** derivatives, the hypothesized structure was reasonably confirmed. State: yellow gum. R_f = 0.37 (PE/CH_2Cl_2/Me_2CO 45:45:10). GC−MS: t_R 11.76; *m*/*z* 406 (M^+, 1.9), 301 (17), 232 (10), 231 (62), 230 (10), 229 (36), 202 (18), 201 (29), 160 (5.1), 133 (8.7), 106 (8.1), 105 (100), 77 (55), 51 (5.5), 41 (9.3). ^{1}H NMR (DMSO-d_6): δ 0.70 (3H, d, J = 6.6 Hz), 0.72 (3H, d, J = 6.6 Hz), 1.70 (1H, center of m), 1.78−1.92 (2H, m), 1.96−2.08 (1H, m), 2.22−2.32 (1H, m), 3.21−3.58 (4H, m), 4.72 (1H, very br s), 5.33 (2H, br s), 5.74 (1H, br s), 7.09−7.54 (8H, m).

(6*R,11a*R**)-8-Fluoro-6-(*N*-isobutylbenzamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*trans*-4d).** Chromatography with PE/Me_2CO 7:3 → 68:32. Yield: 26%. State: yellow gum. R_f = 0.30 (PE/Me_2CO 7:3). IR: ν_{max} 2963, 1636, 1400, 1193, 1026, 701. HR-MS: calcd for $C_{25}H_{27}FN_2O_2$ 406.2057, found 406.2062, +1.3 ppm. GC−MS: t_R 11.79; *m*/*z* 406 (M^+, 0.21), 232 (6.9), 231 (45), 230 (6.9), 229 (25), 202 (14), 201 (23), 200 (9.6), 133 (8.4), 106 (7.7), 105 (100), 77 (48), 41 (6.6). ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 0.46 (3H, d, J = 6.6 Hz), 0.63 (3H, d, J = 6.6 Hz), 1.58−1.92 (4H, m), 2.35−2.43 (1H, m), 2.56 (1H, dd, J = 14.7, 5.1 Hz), 3.13 (1H, dd, J = 14.7, 4.8 Hz), 3.13−3.29 (1H, m), 3.42 (1H, center of m), 4.55 (1H, br dd, J = 8.7, 6.3 Hz), 4.98 (1H, s), 5.36 (1H, d, J = 1.8 Hz), 5.40 (1H, d, J = 1.1 Hz), 7.22 (1H, dt, J = 8.7, 2.7 Hz), 7.37 (1H, dd, J = 8.4, 5.7 Hz), 7.40 (1H, dt, J = 9.3, 2.7 Hz), 7.43−7.50 (5H, m). ^{13}C NMR (DMSO-d_6): δ 19.1 (CH_3), 19.6 (CH_3), 21.3 (CH_2), 25.9 (CH), 37.2 (CH_2), 47.5 (CH_2), 55.0 (br signal, CH_2), 60.0 (CH), 65.9 (CH), 114.4 (CH_2), 116.0 (d, CH, J_{C-F} = 20.9 Hz), 116.3 (d, CH, J_{C-F} = 23.1 Hz), 127.7 (2C, CH), 128.5 (2C, CH), 130.4 (CH), 131.4 (d, CH, J_{C-F} = 8.2 Hz), 133.0 (d, C, J_{C-F} = 3.2 Hz), 135.3 (d, C, J_{C-F} = 8.1 Hz), 135.4 (C), 147.8 (C), 161.6 (d, C, J_{C-F} = 245.6 Hz), 166.1 (C), 172.0 (C).

(6*R,11a*S**)-6-(*N*-Isobutylbenzamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*cis*-4e).** Chromatography with PE/EtOAc 6:4 → EtOAc. Yield: 18%. State: yellow gum. R_f = 0.62 (PE/EtOAc 3:7). IR: ν_{max} 2960, 2868, 1627, 1399, 1261, 1026, 907. HR-MS: calcd for $C_{25}H_{28}N_2O_2$ 388.2151, found 388.2146, +1.3 ppm. GC−MS: t_R 11.79; *m*/*z*: 388 (M^+, 0.36), 283 (12), 281 (6.3), 214 (8.8), 213 (54), 212 (11), 211 (37), 207 (6.9), 184 (26), 183 (33), 182 (15), 155 (6.9), 142 (6.6), 141 (6.5), 128 (7.5), 115 (12), 106 (7.7), 105 (100), 104 (7.8), 77 (64), 57 (5.3), 51 (6.3), 41 (8.8). ^{1}H NMR (DMSO-d_6,

temp = 80 °C): δ 0.70 (3H, d, J = 6.6 Hz), 0.74 (3H, d, J = 6.6 Hz), 1.68−2.05 (4H, m), 3.25 (1H, center of m), 3.30 (1H, dt, J = 15.6, 7.8 Hz), 3.33 (1H, dd, J = 13.8, 8.1 Hz), 3.44−3.56 (1H, m), 3.59 (1H, dd, J = 13.8, 6.6 Hz), 4.54 (1H, br t, J = 7.5 Hz), 5.26 (1H, s), 5.31 (1H, d, J = 1.2 Hz), 5.85 (1H, s), 7.26−7.44 (9H, m). ^{13}C NMR (DMSO-d_6): δ 20.0 (2C, CH_3), 22.1 (CH_2), 27.6 (CH), 33.1 (CH_2), 46.9 (CH_2), 55.3 (very br signal, CH_2), 60.2 (CH), 62.5 (very br signal, CH), 113.9 (CH_2), 125.8, 126.5, 127.5, 127.9, 128.8, 128.3 (9C, CH), 129.2 (C), 135.2 (C), 137.2 (C), 147.4 (C), 165.9 (C), 172.7 (C).

(6*R,11a*R**)-6-(*N*-Isobutylbenzamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*trans*-4e).** Chromatography with PE/EtOAc 6:4 → EtOAc. Yield: 43%. State: yellow gum. R_f = 0.22 (PE/EtOAc 3:7). IR: ν_{max} 3003, 1630, 1405, 1185, 1027, 894. HR-MS: calcd for $C_{25}H_{28}N_2O_2$ 388.2151, found 388.2155, +1.0 ppm. GC−MS: t_R 11.92; *m*/*z* 388 (M^+, 1.2), 283 (17), 281 (5.1), 214 (13), 213 (75), 212 (14), 211 (51), 210 (6.1), 185 (5.1), 184 (33), 183 (41), 182 (16), 167 (5.2), 155 (8.3), 143 (5.0), 142 (7.4), 141 (7.1), 128 (8.1), 115 (12), 106 (7.9), 105 (100), 104 (6.0), 77 (60), 51 (5.6), 41 (8.2). ^{1}H NMR (DMSO-d_6): δ 0.34 (3H, d, J = 6.6 Hz), 0.59 (3H, d, J = 6.3 Hz), 1.51−1.79 (4H, m), 2.38 (1H, dd, J = 16.5, 5.7 Hz), 2.42 (1H, dd, J = 14.7, 3.9 Hz), 3.00−3.16 (2H, m), 3.40 (1H, br t, J = 13.0 Hz), 4.50 (1H, br t, J = 7.6 Hz), 4.89 (1H, s), 5.38 (1H, s), 5.43 (1H, s), 7.34−7.66 (9H, m). ^{13}C NMR (DMSO-d_6): δ 19.0 (CH_3), 19.6 (CH_3), 21.4 (CH_2), 26.0 (CH), 37.3 (CH_2), 47.4 (CH_2), 54.9 (br signal, CH_2), 60.0 (CH), 66.6 (br signal, CH), 114.2 (CH_2), 127.7 (2C, CH), 128.3 (CH), 128.5 (2C, CH), 129.3 (CH), 129.4 (CH), 129.5 (CH), 130.3 (CH), 132.7 (C), 135.6 (C), 136.7 (C), 149.0 (C), 166.6 (C), 172.0 (C).

(6*R,11a*S**)-6-(*N*-Benzylmethoxyacetamido)-11-methylene-8,9-(methylenedioxy)-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo-[1,2-*a*]azepin-5(6*H*)-one (*cis*-4f).** Chromatography with CH_2Cl_2/Me_2CO 9:1 → 7:3 + 0.5% EtOH. Yield: 30%. State: colorless oil. R_f = 0.38 (CH_2Cl_2/Me_2CO 9:1). IR: ν_{max} 2965, 2886, 1648, 1473, 1418, 1251, 1119, 1027, 931. HR-MS: calcd for $C_{25}H_{26}N_2O_5$ 434.1842, found 434.1825, −3.9 ppm. GC−MS: t_R 14.41 (diastereomeric mixture of *cis*- and *trans*-**4f**); *m*/*z* 361 (M^+ − 73, 3.2), 283 (20), 281 (7.6), 257 (21), 256 (8.9), 255 (33), 254 (5.0), 229 (5.1), 228 (28), 227 (26), 226 (16), 214 (5.1), 207 (10), 186 (10), 155 (5.3), 128 (6.6), 115 (9.5), 102 (5.1), 92 (9.3), 91 (100), 89 (7.3), 77 (12), 65 (15), 51 (5.2), 45 (58), 39 (6.0). ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 1.73−2.03 (3H, m), 2.29 (1H, center of m), 3.18−3.30 (1H, m), 3.22 (3H, s), 3.49 (1H, ddd, J = 12.0, 7.8, 4.5 Hz), 3.84 and 4.02 (2H, AB system, J = 14.2 Hz), 4.68 (1H, br t, J = 7.4 Hz), 4.80 and 5.16 (2H, AB system, J = 16.0 Hz), 5.30 (1H, d, J = 1.2 Hz), 5.33 (1H, d, J = 2.0 Hz), 5.97 and 6.00 (2H, AB system, J = 0.9 Hz), 6.22 (1H, br s), 6.76 (1H, s), 6.85 (1H, s), 7.16−7.30 (5H, m). ^{13}C NMR (DMSO-d_6, temp = 60 °C): δ 21.7 (CH_2), 33.6 (CH_2), 46.2 (CH_2), 49.6 (CH_2), 58.1 (CH_3), 59.4 (CH), 60.3 (CH), 70.6 (CH_2), 101.0 (CH_2), 105.2 (CH), 108.2 (CH), 113.8 (CH_2), 126.0 (CH), 126.5 (2C, CH), 127.5 (2C, CH), 129.3 (C), 131.1 (C), 138.8 (C), 146.3 (C), 146.9 (C), 147.1 (C), 166.7 (C), 170.7 (C).

(6*R,11a*R**)-6-(*N*-Benzylmethoxyacetamido)-11-methylene-8,9-(methylenedioxy)-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo-[1,2-*a*]azepin-5(6*H*)-one (*trans*-4f).** Chromatography with CH_2Cl_2/Me_2CO 9:1 → 7:3 + 0.5% EtOH. Yield: 33%. State: colorless oil. R_f = 0.32 (CH_2Cl_2/Me_2CO 8:2). IR: ν_{max} 3013, 2888, 1638, 1473, 1423, 1324, 1197, 1025, 922. HR-MS: calcd for $C_{25}H_{26}N_2O_5$ 434.1842, found 434.1820, −5.0 ppm. GC−MS: see compound *cis*-**4f**. ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 1.55−1.86 (3H, m), 2.27−2.37 (1H, m), 3.19 (1H, ddd, J = 11.7, 9.9, 7.2 Hz), 3.30 (3H, s), 3.42 (1H, ddd, J = 11.7, 8.7, 3.0 Hz), 3.85 and 4.56 (2H, AB system, J = 17.4 Hz), 3.96 and 4.21 (2H, AB system, J = 14.7 Hz), 4.41 (1H, center of m), 4.82 (1H, br s), 5.24 (1H, d, J = 1.2 Hz), 5.31 (1H, d, J = 1.2 Hz), 5.99 and 6.00 (2H, AB system, J = 0.9 Hz), 6.46 (1H, s), 6.88 (1H, s), 6.97−7.00 (2H, m), 7.22−7.34 (3H, m). ^{13}C NMR (DMSO-d_6): δ 21.6 (CH_2), 36.8 (CH_2), 47.1 (CH_2), 47.2 (CH_2), 58.4 (CH_3), 59.2 (CH), 67.2 (CH), 70.2 (CH_2), 101.5 (CH_2), 109.6 (CH), 110.0 (CH), 114.3 (CH_2), 125.3 (C), 126.1 (2C, CH), 127.1 (CH), 128.5 (2C, CH), 131.2 (C), 136.7 (C), 146.8 (C), 147.99 (C), 148.04 (C), 166.5 (C), 170.3 (C).

(6*R,11a*S**)-8-Fluoro-6-(*N*-((furan-2-yl)methyl)methoxyacetamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo-[1,2-*a*]azepin-5(6*H*)-one (*cis*-4h).** Chromatography with PE/Me_2CO 7:3 → 3:7. The isolated product was shown to be a 61:39 (^{1}H NMR) mixture of *cis*-**4h** and **5h** (8-Fluoro-6-(*N*-((furan-2-yl)-methyl)methoxyacetamido)-11-methyl-2,3-dihydro-1*H*-benzo-[d]pyrrolo[1,2-a]azepin-5(6*H*)-one). We were not able to separate them, and therefore, they have been characterized as a mixture. Yield: 10% (*cis*-**4h**); 6% (**5h**). State: yellow gum. R_f = 0.50 (PE/Me_2CO 65:35). IR: ν_{max} 2970, 2881, 1638, 1420, 1260, 1025, 920. HR-MS: calcd for $C_{22}H_{23}FN_2O_4$ 398.1642, found 398.1631, −2.8 ppm. GC−MS: (a) t_R 11.44; *m*/*z* 325 (M^+ − 73, 6.5), 318 (9.8), 232 (14), 231 (88), 230 (13), 229 (14), 214 (9.0), 202 (19), 201 (21), 200 (13), 168 (32), 160 (5.7), 159 (6.7), 146 (7.5), 133 (14), 108 (13), 82 (7.3), 81 (100), 70 (6.5), 53 (25), 45 (72), 41 (5.8); (b) t_R 11.66; *m*/*z* 398 (M^+, 9.7), 317 (30), 289 (5.7), 258 (17), 257 (100), 245 (5.5), 232 (8.5), 231 (50), 230 (7.6), 229 (16), 202 (28), 201 (6.2), 200 (6.8), 188 (5.0), 174 (7.3), 168 (8.1), 146 (5.2), 133 (7.2), 81 (56.4), 53 (12), 45 (38). ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 1.78−1.96 (2H, m, **4h** + **5h**), 2.02−2.14 (1H, m, **4h**), 2.18 (3H, s, **5h**), 2.32 (1H, center of m, **4h**), 2.74 (2H, center of m, **5h**), 3.25 (3H, s, **4h**), 3.29 (3H, s, **5h**), 3.33 (center of m) and 3.49−3.71 (m) (2H, **4h** + **5h**), 4.00 and 4.03 (2H, AB system, J = 14.1 Hz, **4h**), 4.07 (2H, s, **5h**), 4.25 and 4.71 (2H, AB system, J = 16.8 Hz, **5h**), 4.72 (1H, br t, J = 6.6 Hz, **4h**), 4.87 and 4.87 (2H, AB system, J = 16.6 Hz, **4h**), 5.19 (1H, br s, **5h**), 5.37 (1H, d, J = 1.0 Hz, **4h**), 5.40 (1H, br s, **4h**), 6.12 (1H, br dd, J = 3.3, 0.6 Hz, **5h**), 6.15 (1H, br s, **4h**), 6.27 (1H, br dd, J = 3.0, 0.6 Hz, **4h**), 6.35 (1H, dd, J = 3.0, 1.8 Hz, **4h**), 6.36 (1H, dd, J = 3.0, 1.8 Hz, **5h**), 6.89 (1H, dd, J = 10.8, 2.4 Hz, **4h**), 7.02 (1H, dd, J = 10.2, 2.7 Hz, **5h**), 7.07 (1H, dt, J = 9.0, 2.7 Hz, **4h**), 7.20 (1H, dt, J = 8.7, 2.7 Hz, **5h**), 7.41 (1H, dd, J = 8.4, 6.0 Hz, **4h**), 7.51 (1H, dd, J = 1.8, 0.9 Hz, **4h** + **5h**), 7.52 (1H, dd, J = 9.0, 6.0 Hz, **5h**). ^{13}C NMR (DMSO-d_6): δ 19.0 (CH_2), 20.2 (CH_2), 22.4 (CH_3, **5h**), 29.8 (CH_2, **5h**), 32.4 (CH_2, **4h**), 43.6 (CH_2), 46.5 (CH_2), 48.2 (CH_2), 58.30 (CH_3), 58.34 (CH_3), 59.1 (2C, CH), 70.5 (CH_2), 70.6 (CH_2), 107.7 (CH), 108.1 (C, **5h**), 108.2 (CH), 110.44 (CH), 110.47 (CH), 112.1, 112.4, 114.1, 114.4, 114.8, 115.0 (2C, CH; it was not possible to calculate J_{C-F}), 113.7 (CH_2, **4h**), 127.7 (d, CH, J_{C-F} = 8.6 Hz), 130.5 (d, CH, J_{C-F} = 8.2 Hz), 133.7 (d, C, J_{C-F} = 3.0 Hz), 133.8 (C, **5h**), 136.6, 136.7, 137.0, 137.2 (C; it was not possible to calculate J_{C-F}), 142.2 (CH), 142.3 (CH), 145.7 (C), 151.4 (C, **4h**), 161.3 (d, C, J_{C-F} = 243.3 Hz), 161.8 (d, C, J_{C-F} = 242.8 Hz), 165.8 (C), 170.62 (C), 170.64 (C).

(6*R,11a*R**)-8-Fluoro-6-(*N*-((furan-2-yl)methyl)methoxyacetamido)-11-methylene-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo-[1,2-*a*]azepin-5(6*H*)-one (*trans*-4h).** Chromatography with PE/Me_2CO 7:3 → 3:7. Yield: 25%. State: yellow gum. R_f = 0.29 (PE/Me_2CO 6:4). IR: ν_{max} 3044, 2975, 2878, 1640, 1413, 1242, 1008, 918. HR-MS: calcd for $C_{22}H_{23}FN_2O_4$ 398.1642, found 398.1636, −1.5 ppm. GC−MS: t_R 11.46; *m*/*z* 398 (M^+, 0.23), 317 (5.7), 257 (5.2), 231 (100), 230 (14), 229 (15), 216 (5.0), 214 (9.3), 202 (18), 201 (20), 200 (12), 168 (26), 159 (5.4), 146 (5.8), 133 (10), 108 (9.3), 82 (5.4), 81 (77), 53 (20), 45 (57). ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 1.62−1.86 (3H, m), 2.30−2.38 (1H, m), 3.14−3.25 (1H, m), 3.40−3.49 (1H, m), 3.35 (3H, s), 3.73 and 4.56 (2H, AB system, J = 17.1 Hz), 4.14 and 4.31 (2H, AB system, J = 14.7 Hz), 4.42 (1H, center of m), 4.75 (1H, s), 5.26 (1H, d, J = 1.5 Hz), 5.28 (1H, d, J = 1.5 Hz), 6.09 (1H, dd, J = 3.3, 0.9 Hz), 6.38 (1H, dd, J = 3.3, 1.8 Hz), 6.99 (1H, dd, J = 9.3, 2.7 Hz), 7.22 (1H, dt, J = 8.4, 2.7 Hz), 7.36 (1H, dd, J = 8.4, 6.0 Hz), 7.55 (1H, dd, J = 1.8, 0.6 Hz). ^{13}C NMR (DMSO-d_6): δ 21.5 (CH_2), 36.5 (CH_2), 40.7 (CH_2), 47.3 (CH_2), 58.5 (CH_3),

59.6 (CH), 66.9 (CH), 70.2 (CH_2), 108.1 (CH), 110.4 (CH), 114.6 (CH_2), 116.3 (d, CH, J_{C-F} = 20.7 Hz), 116.6 (d, CH, J_{C-F} = 22.9 Hz), 131.2 (d, CH, J_{C-F} = 8.2 Hz), 133.4 (d, CH, J_{C-F} = 3.2 Hz), 134.3 (d, C, J_{C-F} = 7.9 Hz), 143.0 (CH), 147.3 (C), 149.5 (C), 161.4 (d, C, J_{C-F} = 244.3 Hz), 165.8 (C), 170.6 (C).

(6*R,11a*S**)-11-Methylene-6-(*N*-phenylmethoxyacetamido)-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*cis*-4i).** Chromatography with PE/CH_2Cl_2/Me_2CO/MeOH 15:5:4:1. Yield: 24%. State: colorless oil. R_f = 0.38 (PE/CH_2Cl_2/Me_2CO/MeOH 15:5:4:1). IR: ν_{max} 2992, 2879, 1659, 1413, 1268, 1123, 1024, 916. HR-MS: calcd for $C_{23}H_{24}N_2O_3$ 376.1787, found 376.1773, −3.7 ppm. GC−MS: t_R 11.87; *m*/*z* 376 (M^+, 6.9), 332 (8.1), 331 (33), 303 (14), 219 (5.0), 218 (5.3), 213 (6.2), 212 (23), 211 (100), 210 (7.9), 206 (7.5), 204 (5.3), 185 (7.6), 184 (57), 183 (80), 182 (28), 168 (5.3), 167 (8.1), 156 (5.1), 155 (9.2), 154 (8.7), 153 (5.8), 143 (5.3), 142 (9.7), 141 (16), 135 (14), 129 (8.8), 128 (16), 127 (5.7), 116 (5.8), 115 (24), 106 (6.2), 92 (5.2), 91 (5.5), 77 (22), 51 (8.2), 45 (57), 41 (5.4). ^{1}H NMR (DMSO-d_6, temp = 80 °C) (*cis*-**4i** contains a small amount of **6i** (5−7%), that cannot be separated by chromatography): δ 1.65−2.18 (4H, m), 3.20 (3H, s), 3.41 (1H, dt, *J* = 7.8, 6.0 Hz), 3.54 (1H, ddd, *J* = 12.3, 8.7, 4.5 Hz), 3.73 (2H, s), 4.48 (1H, t, *J* = 7.0 Hz), 5.07 (1H, s), 5.17 (1H, d, *J* = 1.2 Hz), 6.39 (1H, s), 7.10−7.38 (9H, m). ^{13}C NMR (DMSO-d_6): δ 22.1 (CH_2), 31.2 (CH_2), 46.9 (CH_2), 58.1 (CH_3), 59.2 (CH), 65.3 (CH), 70.1 (CH_2), 112.7 (CH_2), 127.3 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.5 (2C, CH), 129.1 (2C, CH), 133.4 (C), 139.1 (C), 140.7 (C), 146.2 (C), 165.6 (C), 168.5 (C).

(6*R,11a*R**)-11-Methylene-6-(*N*-phenylmethoxyacetamido)-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*trans*-4i).** Chromatography with PE/CH_2Cl_2/Me_2CO/MeOH 15:5:4:1. Yield: 41%. State: colorless oil. R_f = 0.30 (PE/CH_2Cl_2/Me_2CO/MeOH 15:5:4:1). IR: ν_{max} 2972, 2876, 1674, 1434, 1188, 1124, 1023, 905. HR-MS: calcd for $C_{23}H_{24}N_2O_3$ 376.1787, found 376.1779, −2.1 ppm. GC−MS: t_R 11.82; *m*/*z* 376 (M^+, 5.4), 332 (6.7), 331 (28), 303 (12), 213 (6.5), 212 (22), 211 (100), 210 (7.7), 206 (6.0), 185 (7.8), 184 (57.7), 183 (84), 182 (29), 168 (5.2), 167 (7.7), 155 (9.3), 154 (8.3), 153 (5.4), 143 (5.4), 142 (9.0), 141 (16), 135 (13), 129 (8.6), 128 (16), 116 (5.6), 115 (24), 106 (6.6), 91 (5.6), 77 (22), 51 (8.4), 45 (57), 41 (5.7). ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 1.61−1.98 (3H, m), 2.35 (1H, center of m), 3.21 (3H, s), 3.24−3.31 (1H, m), 3.52 and 3.86 (2H, AB system, *J* = 15.0 Hz), 3.51−3.57 (1H, m), 4.46 (1H, center of m), 5.29 (1H, d, *J* = 1.8 Hz), 5.37 (1H, d, *J* = 1.5 Hz), 5.50 (1H, s), 7.09−7.26 (9H, m). ^{13}C NMR (DMSO-d_6): δ 22.0 (CH_2), 35.9 (CH_2), 47.4 (CH_2), 58.26 (CH_3), 58.37 (CH), 69.1 (CH), 69.8 (CH_2), 115.5 (CH_2), 127.7 (CH), 128.0 (CH), 128.1 (2C, CH), 128.6 (2C, CH), 128.7 (CH), 128.9 (CH), 130.7 (CH), 132.0 (C), 137.3 (C), 138.4 (C), 148.9 (C), 166.8 (C), 169.8 (C).

(*Z*)-8-Fluoro-6-(*N*-isobutylbenzamido)-1,2,3,12a-tetrahydrobenzo[*e*]pyrrolo[1,2-*a*]azocin-5(6*H*)-one (6d). Chromatography with PE/CH_2Cl_2/Me_2CO 45:45:10. Yield: 20%. State: yellow gum. R_f = 0.37 (PE/CH_2Cl_2/Me_2CO 45:45:10). The relative configuration of the stereogenic centers was not assigned. IR: ν_{max} 3004, 1631, 1254, 1191, 1027. HR-MS: calcd for $C_{25}H_{27}FN_2O_2$ 406.2057, found 406.2050, −1.7 ppm. GC−MS: t_R 11.85; *m*/*z* 406 (M^+, 2.4), 322 (6.5), 301 (7.8), 245 (5.9), 231 (17), 229 (13), 160 (9.6), 134 (6.1), 133 (6.1), 106 (7.9), 105 (100), 77 (40), 70 (6.5), 41 (8.0). ^{1}H NMR (DMSO-d_6, temp = 80 °C): δ 0.60 (3H, d, *J* = 6.9 Hz), 0.68 (3H, d, *J* = 6.6 Hz), 1.48 (1H, center of m), 1.71 (2H, center of m), 1.89 (1H, dt, *J* = 12.6, 6.3 Hz), 2.36 (1H, center of m), 3.01−3.14 (1H, m), 3.38 (1H, dd, *J* = 14.4, 6.9 Hz), 3.48 (1H, dt, *J* = 11.7, 6.8 Hz), 3.74 (1H, dd, *J* = 14.4, 7.5 Hz), 4.98 (1H, center of m), 5.89 (1H, dd, *J* = 15.3, 2.1 Hz), 6.09 (1H, br s), 6.55 (1H, dd, *J* = 13.2, 2.7 Hz), 7.06 (1H, dt, *J* = 8.7, 2.7 Hz), 7.25 (1H, dd, *J* = 9.9, 2.7 Hz), 7.28 (1H, dt, *J* = 8.7, 6.0 Hz), 7.34−7.59 (5H, m). ^{13}C NMR (DMSO-d_6): δ 19.4 (CH_3), 19.6 (CH_3), 22.6 (CH_2), 27.6 (CH), 34.2 (CH_2), 46.6 (CH_2), 54.8 (CH_2), 57.3 (CH), 59.3 (CH), 112.4 (d, CH, J_{C-F} = 23.1 Hz), 114.2 (d, CH, J_{C-F} = 21.4 Hz), 126.7 (CH), 128.4 (4C, CH), 129.5 (d, C, J_{C-F} = 2.8 Hz), 130.6 (CH), 132.7 (d, CH, J_{C-F} = 8.2 Hz), 135.9 (d, C, J_{C-F} = 10.5 Hz), 136.0 (CH), 138.1 (C), 161.3 (d, C, J_{C-F} = 243.6 Hz), 166.9 (C), 174.6 (C).

General Procedure for the One-Pot S_N2'−Heck Cyclization. The same procedure described above for the Heck cyclization was followed, starting this time from Ugi derivative **2**. The same type and amount of solvent, ligand and catalyst were employed, with the exception of Cs_2CO_3. Finally, the closed vessel was heated at 120 °C for 1 h using 150 W maximum power (see temperature and power profiles in the Supporting Information). Then Cs_2CO_3 (2 equiv) was rapidly added, and the vessel was heated again under the same conditions for 1 h (the temperature profile is the same as in the Heck reaction). The final workup was the same as reported for the Heck cyclization.

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Supporting Information Available: General experimental methods, temperature−time profile for the experiments performed in microwave reactor, additional spectroscopic data for compounds **4**, crystallographic data and full-page size ORTEP of *trans*-**4a**, copies of NMR spectra, and X-ray data of *trans*-**4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.