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Synthesis of 3-(arylmethylene)isoindolin-1-ones from ynamides by Heck–Suzuki–Miyaura domino reactions. Application to the synthesis of lennoxamine

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Abstract—Substituted 3-(arylmethylene)isoindolin-1-ones can be efficiently synthesized from various ynamides and boronic acids by palladium-catalyzed Heck–Suzuki–Miyaura domino reactions. This methodology has been applied to the total synthesis of lennoxamine and a concise route to this isoindolobenzazepine alkaloid was achieved in eight steps from 2,3-dimethoxybenzoic acid via a key intermediate ynamide.

1. Introduction

Substituted 3-methyleneisoindolin-1-ones of type **A**, and in particular those in which R^3 is an aromatic substituent (R^3 = Ar), are encountered in a number of naturally occurring products such as enterocarpam II, a member of the aristolactam alkaloids family[1] or the secophthalide–isoquinoline ene-lactam fumaridine[2] (Fig. 1).

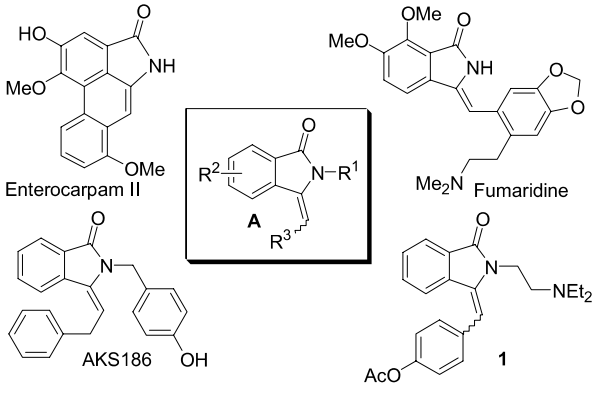

Figure 1. Naturally occurring and/or biologically active substituted 3-methyleneisoindolin-1-ones.

Isoindolin-1-ones of type **A** are also found as the structural feature of biologically active compounds such as AKS186 that displays vasorelaxant properties[3] or compound **1** whose hydrochloride was claimed to exhibit local anesthetic activity superior to that of procaine[4] (Fig. 1).

The synthesis of isoindolin-1-ones of type **A** has elicited considerable synthetic interest as several representative general strategies have been developed (Scheme 1). In the earliest routes [routes (a), Scheme 1], phthalimides of type **B** were often considered as starting materials and were converted to isoindolin-1-ones of type **A** by Wittig reaction with stabilized phosphoranes[5] or addition of organometallic reagents followed by dehydration of the resulting 3-hydroxyphthalimidines.[3,6] However, this approach can lead to a mixture of regioisomers in the case of an unsymmetrical substrate.[3,6] Furthermore, the synthesis of 3-(arylmethylene)-isoindolin-1-ones of type **A** where R^3 = Ar by the latter route requires the use of benzylic Grignard reagents as nucleophiles whose preparation is not always trivial. More recently, an interesting alternative benzylation procedure of phthalimides of type **B**, based on the photodecarboxylation of arylacetates, has been developed.[7] Phthalides of type **C** (or the corresponding open-chain keto-benzoic acids) are also useful precursors since they can be readily converted to compounds of type **A** by treatment with primary amines, followed by dehydration [route (b), Scheme 1].[8] Another general route towards substituted 3-methyleneisoindolin-1-ones of type **A** relies on an ortholithiation–anionic cyclization sequence initiated by treatment of *N*-acyl-2-bromobenzamides of type **D** with

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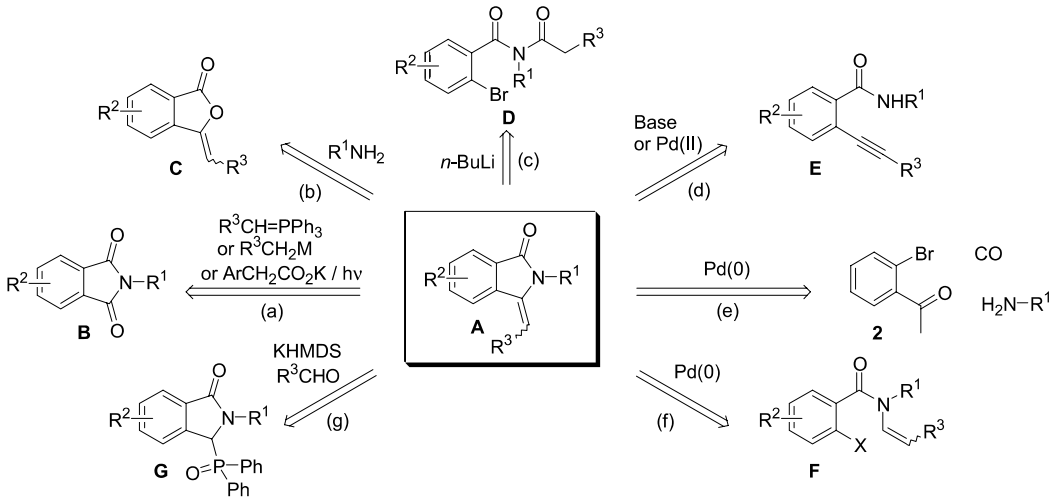
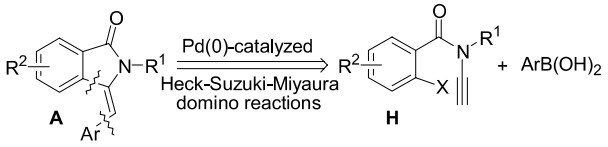


Scheme 1. Representative synthetic strategies towards substituted 3-methyleneisoindolin-1-ones of type **A**.

n-butyllithium, followed by dehydration of the resulting 3-hydroxyphthalimidines [route (c), Scheme 1].[9] Efficient syntheses of isoindolin-1-ones of type **A** have also been achieved by cyclization of 2-alkynylbenzamides of type **E** induced by treatment with a base or a palladium(II) catalyst [route (d), Scheme 1].[10,11] Interestingly, the disubstituted alkynes of type **E** are readily available by Sonogashira cross-coupling reactions involving 2-halobenzamides as substrates and, in some cases, both transformations leading to isoindolin-1-ones of type **A** have been carried out in a one-pot sequence.[10c] A palladium(0)-catalyzed three-component reaction involving 2-bromoacetophenone **2** and a variety of primary amines under carbon monoxide pressure can also be used to synthesize 3-methyleneisoindolin-1-ones of type **A** ($R^3=H$) [route (e), Scheme 1].[12] A related process has been described from 2-bromoaryl ketones wherein a titanium–isocyanate complex was used as the nitrogen donor.[13] Alternative palladium(0)-catalyzed processes towards compounds of type **A** exploit the synthetic potential of intramolecular Heck reactions of enamide derivatives of type **F** [route (f), Scheme 1].[14] Finally, the Horner condensation of 3-(diphenylphosphinoyl)isoindolin-1-ones of type **G** with a variety of aldehydes constitutes a particularly interesting entry to isoindolin-1-ones of type **A** that has culminated with several applications to natural products synthesis [route (g), Scheme 1].[15] Besides these main representative strategies, other reactions leading to isoindolin-1-ones of type **A** have also been reported.[16]

In recent years, the synthetic application of ynamides has expanded enormously.[17] Indeed, these stable electron-deficient variants of ynamines can participate in several transformations usually carried out with alkynes such as thermal, metal- or Lewis acid-catalyzed cycloadditions,[18–21] platinum(II)-catalyzed cycloisomerization,[22] ring-closing metathesis,[23] titanium(II)-mediated coupling reactions,[24] carbocupration,[25] hydroboration[26] and hydrohalogenation[27] followed by cross-coupling reactions, as well as sigmatropic rearrangements.[28] Some radical cyclization cascades involving ynamides as substrates have also been reported as a route to various nitrogen heterocycles, including substituted isoindolin-1-ones of type **A**.[29]

We became interested in the development of an alternative synthetic strategy towards a variety of (*E*)-3-(arylmethylene)isoindolin-1-ones of type **A** that proceeds from ynamides of type **H** and arylboronic acids and relies on Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions (Scheme 2).

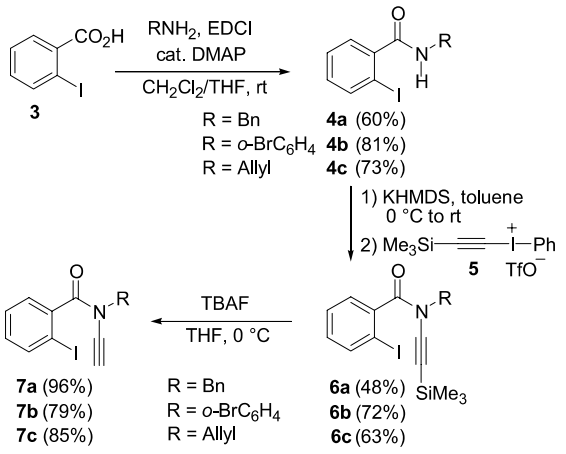


Scheme 2. Synthesis of 3-(arylmethylene)isoindolin-1-ones of type **A** by Heck–Suzuki–Miyaura domino reactions from ynamides of type **H**.

When we began our investigations on this project, hydrostannation[30] and an heteroannulation strategy towards 2-aminoindoles, based on the nucleophilic addition of amines to the triple bond of ynamides activated by an intramolecular arylpalladium(II) complex,[31] were the only reported examples of palladium-catalyzed processes involving ynamides as substrates. Herein, we report a full account of our work on the synthesis of 3-(arylmethylene)-isoindoloin-1-ones by Heck–Suzuki–Miyaura domino reactions involving ynamides,[32] as well as its application to the total synthesis of the natural product lennoxamine.

2. Results and discussion

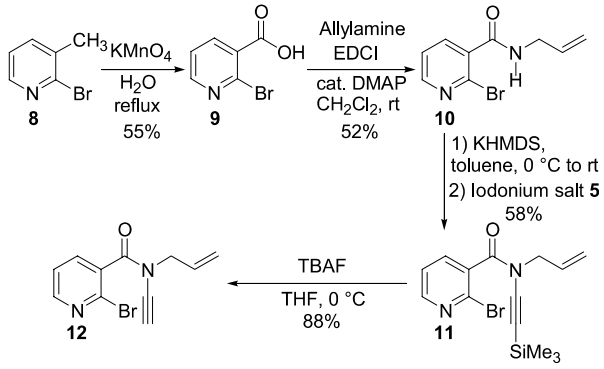
In order to investigate the feasibility of the Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions as a route to isoindolinones of type **A**, several ynamides of type **H** were prepared from 2-iodobenzoic acid **3**. This carboxylic acid was coupled with benzylamine, 2-bromobenzylamine and allylamine *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), cat. DMAP, CH_2Cl_2 or CH_2Cl_2/THF, rt] to afford the corresponding 2-iodobenzamides **4a** (60%), **4b** (81%) and **4c** (73%), respectively. After formation of the potassium amides (KHMDS, toluene, 0 °C to rt) and addition of the alkynyliodonium salt **5**,[33] the trimethylsilyl-substituted ynamides **6a** (48%), **6b** (72%) and **6c** (63%) were obtained in acceptable yields.[18a] Subsequent



Scheme 3. Preparation of ynamides **7a**–**7c**.

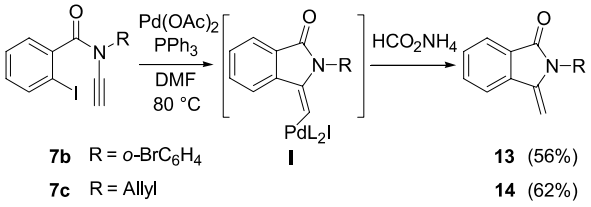
desilylation by using tetra(*n*-butyl)ammonium fluoride (TBAF) in THF finally provided the ynamides **7a** (96%), **7b** (79%) and **7c** (85%), respectively (Scheme 3).

A structurally related ynamide possessing a pyridine ring was also prepared from 2-bromo-3-methylpyridine **8**. This latter compound was oxidized with potassium permanganate to generate 2-bromonicotinic acid **9**[34] (55%) which was coupled with allylamine (EDCI, cat. DMAP, CH_2Cl_2, rt) to afford the corresponding amide **10** (52%). After deprotonation with KHMDS and condensation with trimethylsilyliodonium salt **5**,[33] the resulting ynamide **11** (58%) was desilylated (TBAF, THF, 0 °C) to deliver the terminal ynamide **12** (88%) (Scheme 4).



Scheme 4. Synthesis of ynamide **12** containing a pyridine ring.

Since the planned strategy towards 3-(arylmethylene)-isoindolin-1-ones of type **A** from ynamides of type **H** involved two different Pd(0)-catalyzed steps, it was of interest to initially examine the feasibility of the Heck reaction.[35] Thus, ynamides **7b** and **7c** (Scheme 3) were treated with a catalytic amount of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) in DMF at 80 °C and the reaction was carried out in the presence of ammonium formate (1.5 equiv) as the reducing agent, in order to regenerate the Pd(0) catalyst from the intermediate σ-vinylpalladium complexes of type **I**.[35] Under these conditions, the desired 3-methyleneisoindolin-1-ones **13** and **14**[12] were generated and isolated in 56% and 62% yield, respectively. It is noteworthy that the presence of an arylbromide in substrate **7b** did not alter the course of the reaction, and the carbon–bromine bond in the final product **13** was also unaffected (Scheme 5).



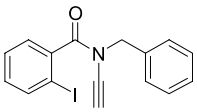
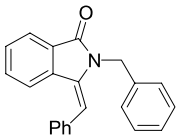
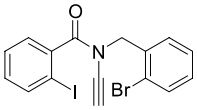
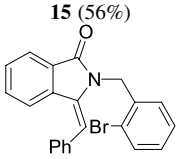
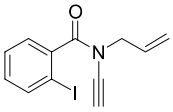
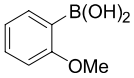
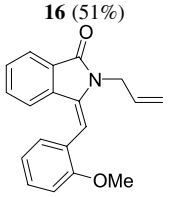
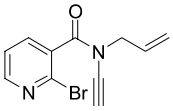
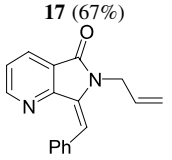
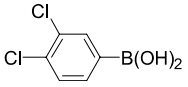
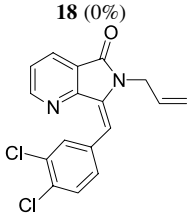
Scheme 5. Reductive Heck reaction applied to ynamides of type **H**.

Having demonstrated that ynamides were viable substrates in carbopalladation processes, the Suzuki–Miyaura coupling reactions[36] of the intermediate σ-vinylpalladium complexes of type **I** could be next examined, with the goal of achieving both processes in a domino fashion from the starting ynamides (Table 1). When ynamide **7a** was treated with benzeneboronic acid in the presence of aqueous sodium hydroxide as the base and a catalytic amount of $Pd(PPh_3)_4$ (5 mol%) in refluxing 1,2-dimethoxyethane (DME), the corresponding 3-benzylideneisoindolin-1-one **15** was obtained in acceptable yield (48%) as a single geometric isomer. Additional experiments revealed that THF was also a suitable solvent for this reaction and other palladium catalysts were then screened. Thus, the use of $Pd(dba)_2$ led to a slightly increased yield of **15** (59%) but the optimal result (70% yield) was obtained when a combination of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) was used to catalyze the reaction. Interestingly, the heterogeneous catalyst Pd/C was also effective and led to the isoindolinone **15** albeit in slightly diminished yield (56%) (Table 1).

The Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions were applied to ynamide **7b** in the presence of benzeneboronic acid and ynamide **7c** in the presence of 2-methoxybenzeneboronic acid, under optimized conditions [$Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), aqueous NaOH, THF, reflux]. The resulting 3-(arylmethylene)-isoindolin-1-ones **16** (51%) and **17** (67%) were obtained in moderate to good yields, as single geometric isomers. Subjecting the ynamide **12**, containing a pyridine ring, to the Heck–Suzuki–Miyaura domino reactions with benzeneboronic acid and 3,4-dichlorobenzeneboronic acid, under the previously optimized conditions, afforded the pyrrolopyridinones **18** (52%) and **19** (68%), respectively. It is worth mentioning that the use of the heterogeneous catalyst Pd/C was unsatisfactory in the case of ynamide **12**, presumably due to poisoning of the catalyst by the nitrogen atom of the pyridine ring (Table 1).

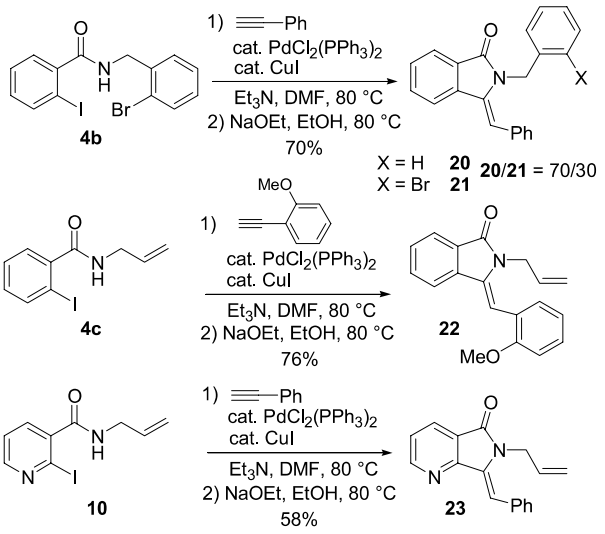
Apparently, in the case of ynamides **7a**–**c** and **12**, the Heck–Suzuki–Miyaura domino reactions afforded the corresponding 3-(arylmethylene)isoindolin-1-ones **15**, **16** and **17** or the pyrrolopyridinones **18** and **19** as single geometric isomers. The (*E*)-configuration of the known isoindolin-1-one **15** was readily assigned by NMR and comparison with the literature data.[8a,10c] In order to unambiguously assign the configuration of the isoindolinones **16** and **17** as well as that of the pyrrolopyridinone **19**, authentic samples of their corresponding geometric isomers

Table 1. Heck–Suzuki–Miyaura domino reactions involving ynamides

Ynamides	Reagents: boronic acid, Pd catalyst (5 mol%), base, solvent	Product (yield)
	$PhB(OH)_2$	
	$Pd(PPh_3)_4$, aqueous NaOH, DME	**15** (48%)
7a	$Pd(dba)_2$, aqueous NaOH, THF	**15** (59%)
	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**15** (70%)
	Pd (10%)/C, aqueous NaOH, THF	**15** (56%)
	$PhB(OH)_2$	
7b	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**16** (51%)
		
7c	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**17** (67%)
	$PhB(OH)_2$	
12	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**18** (52%)
	Pd (10%)/C, aqueous NaOH, THF	**18** (0%)
12		
	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**19** (68%)

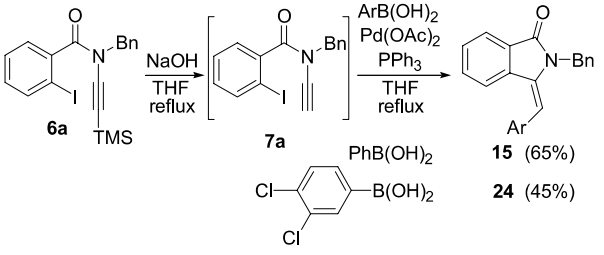
having a trisubstituted double bond of (*Z*) configuration were prepared by a different route.[10c] According to this latter strategy, the *N*-(2-bromobenzyl)-2-iodobenzamide **4b** was subjected to a Sonogashira coupling reaction with phenylacetylene in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (3.5 mol%), CuI (8 mol%) and Et_3N (4 equiv) in DMF at 80 °C. After work-up, the resulting 2-alkynylbenzamide was not purified but directly cyclized under alkaline conditions (NaOEt, EtOH, reflux), the latter reaction having been demonstrated to involve an *anti*-addition across the carbon–carbon triple bond.[10] Under these conditions, the amide **4b** led to a 70/30 mixture of the known (*Z*)-3-benzylideneisoindolin-1-one **20**[8a,10c] and the desired (*Z*)-3-(2-bromobenzylidene)isoindolin-1-one **21**. Substantial reduction of the carbon–bromine bond of the 2-bromobenzyl nitrogen substituent also took place as a side-reaction during the Sonogashira coupling reaction. It is noteworthy that such a side-reaction was not observed when ynamide **7b** was converted to the 3-(arylmethylene)isoindolin-1-one **16** by Heck–Suzuki–Miyaura domino reactions. Similarly, the *N*-allyl-2-iodobenzamide **4c** and the *N*-allyl-2-bromonicotinamide **10** were coupled with (2-methoxyphenyl)acetylene and with phenylacetylene, respectively. The resulting intermediate disubstituted alkynes underwent subsequent ring-closure by treatment with sodium ethoxide in refluxing ethanol, to afford the (2-methoxybenzylidene)isoindolin-1-one **22** (76%) and the pyrrolopyridinone **23** (58%) with high (*Z*) stereoselectivity ((*Z*):(*E*)≥95:5) (Scheme 6). Comparison of the spectral data of compounds **20–23** with those of isoindolin-1-ones **15–17** and the pyrrolopyridinone **18** confirmed that the latter products were obtained as single geometric isomers of (*E*) configuration. The configuration of the other 3-(arylmethylene)isoindolinones described in this study was attributed on the basis of these results. The observed stereochemical outcome was in agreement with the fact that carbopalladation of alkynes involves a *syn*-addition process and cross-coupling reactions of σ-vinylpalladium complexes are known to generally proceed with retention of the olefinic configuration.[35] Some exceptions to both trends have been reported but they appear limited to particular classes of substrates.[37,38]

As the Suzuki–Miyaura cross-coupling reactions require the presence of a base,[36] and because alkynylsilanes are known to be deprotected under these conditions, it was envisaged to carry out a one-pot sequence starting from the



Scheme 6. Preparation of the (*Z*)-3-benzylideneisoindolin-1-ones **20**–**22** and the (*Z*)-pyrrolopyridinone **23**.

trimethylsilylynamide **6a**. Indeed, treatment of **6a** with aqueous NaOH in THF at reflux generated the terminal ynamide **7a** in situ that underwent the subsequent Heck–Suzuki–Miyaura domino reactions by addition of benzeneboronic acid or 3,4-dichlorobenzeneboronic acid and the palladium catalyst. Under these conditions, the 3-(arylmethylene)isoindolinones **15** and **24** were obtained in 65% and 45% overall yield, respectively (Scheme 7).



Scheme 7. One-pot desilylation and Heck–Suzuki–Miyaura reactions from ynamide **6a**.

Having demonstrated that ynamides could efficiently participate in palladium(0)-catalyzed Heck–Suzuki–Miyaura reactions, it was envisaged to highlight the interest of this methodology by an application to the synthesis of the natural product lennoxamine.

3. Synthesis of lennoxamine

Polycyclic nitrogen containing heterocycles are encountered in naturally occurring alkaloids and numerous physiologically active drugs.[39] Lennoxamine, an isoindolobenzazepine alkaloid belonging to the *aporhoedane* series, was extracted from the Chilean plant *Berberis darwinii*. This natural product exists as a racemate (Fig. 2).[40]

Although this compound has no important biological activity, its unique structural feature, five- and seven-membered rings fused with an aromatic moiety, has elicited considerable synthetic interest and several total syntheses of

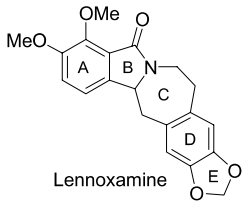
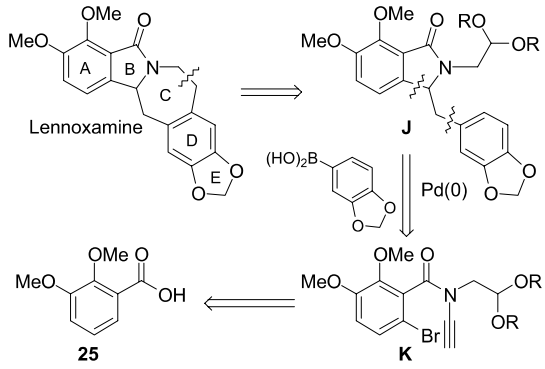


Figure 2. Structure of lennoxamine.

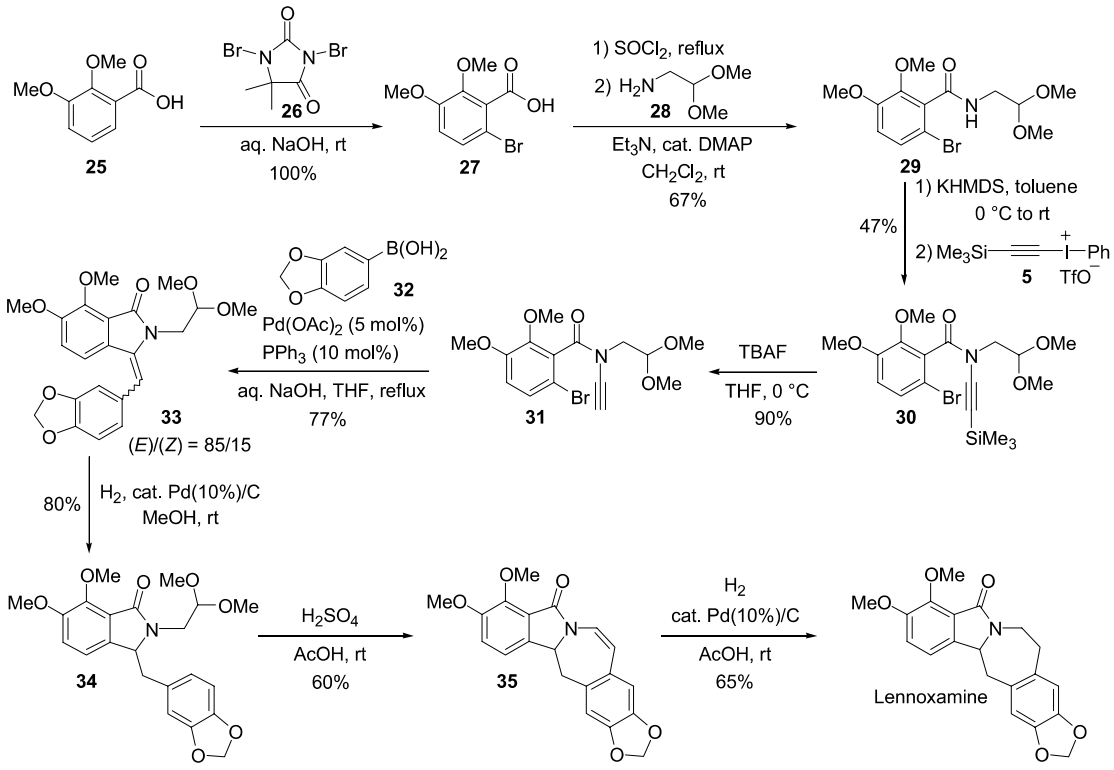
this natural product have been reported relying on the construction of ring B or/and ring C as the key steps.[15b,41] As previous syntheses of lennoxamine indicate that the seven-membered ring can arise from the cyclization of an isoindolinone of type **J** under acidic conditions followed by catalytic hydrogenation,[15b,41o] it was envisaged to apply the Heck–Suzuki–Miyaura reactions to an ynamide of type **K**. The latter compound should be prepared from 2,3-dimethoxybenzoic acid **25** (Scheme 8).



Scheme 8. Retrosynthetic analysis of lennoxamine.

The synthesis of lennoxamine (Scheme 9) started with the bromination of 2,3-dimethoxybenzoic acid **25** with 1,3-dibromo-5,5-dimethylhydantoin **26** (aqueous NaOH, rt) which led to 2,3-dimethoxy-6-bromobenzoic acid **27** in quantitative yield.[42] Initial attempts to couple the carboxylic acid **27** with aminoacetaldehyde dimethyl acetal **28** (EDCI, cat. DMAP, CH_2Cl_2, rt) provided the corresponding secondary amide **29** in low yield (35%). Therefore, the carboxylic acid **27** was converted to the corresponding acyl chloride ($SOCl_2$, reflux) and the latter was coupled with aminoacetaldehyde dimethyl acetal **28** (Et_3N, cat. DMAP, CH_2Cl_2, rt) to afford the secondary amide **29** (67% overall yield, one-pot process). After formation of the potassium amide (KHMDS, toluene, 0 °C to rt) and condensation with the alkynyliodonium salt **5**, the ynamide **30** was obtained in relatively modest yield (47%).[43] The trimethylsilyl group was then removed by treatment of **30** with TBAF in THF to afford the terminal ynamide **31** (90%). The next key stage of our synthetic strategy was to construct ring B and hence elaborate the isoindolinone core of lennoxamine by the palladium-catalyzed Heck–Suzuki–Miyaura domino reactions.

The terminal ynamide **31** was treated with a catalytic amount of $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and a base (aqueous NaOH) in the presence of the commercially available boronic acid **32** that incorporates both the D and E rings of the natural product (THF, reflux). Under these



Scheme 9. Synthesis of lennoxamine.

conditions, the Heck–Suzuki–Miyaura domino reactions proceeded smoothly and the resulting 3-(arylmethylene)-isoindolin-1-one **33** was isolated in 77% yield but as a mixture of two geometric isomers [(*E*):(*Z*)=85:15] (Scheme 9). The (*E*) configuration of the major isomer was readily assigned by comparison with the spectroscopic data reported for this compound.[15b]

This latter result was in sharp contrast with our initial observation that 3-(arylmethylene)isoindolin-1-ones of type **A** were obtained with high (*E*) stereoselectivity by Heck–Suzuki–Miyaura domino reactions from ynamides of type **H**. Although we cannot rule out that an isomerization may have occurred during the palladium-catalyzed domino reactions,[37] the particular structure of the 3-(arylmethylene) isoindolin-1-one **33**, which bears a rather electron-rich enamide moiety, may explain a possible isomerization subsequent to its formation. The latter could take place through a reversible protonation of the double bond or a hydration–dehydration pathway.[6–8,15e] A photochemical process could also not be excluded due to the light sensitivity of compound **33**.

However, this lack of stereoselectivity in the synthesis of compound **33** had no consequence for the total synthesis of lennoxamine since the mixture of geometric isomers was subsequently hydrogenated (cat. Pd (10%)/C, 1 atm H_2, MeOH, rt) to afford the 3-(arylmethyl)isoindolin-1-one **34** in 60% yield. Completion of the total synthesis was achieved from compound **34**, as previously reported,[15b] by treatment under acidic conditions (H_2SO_4 in AcOH, rt) that served to elaborate the seven-membered ring (ring C) and generate dehydrolennoxamine **35** (60%). This latter compound was finally hydrogenated (cat. Pd (10%)/C, 1 atm H_2, AcOH, rt) to afford lennoxamine in 65% yield (Scheme 9). The spectroscopic and analytical data of this compound were in perfect agreement with those reported in the literature.[41]

4. Conclusion

We have reported an efficient and stereoselective access to (*E*)-3-(arylmethylene)isoindolin-1-ones by using Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions involving ynamides and arylboronic acids. The interest of this methodology, which further expands the synthetic utility of ynamides, has been highlighted by its application to the preparation of the natural product lennoxamine. A concise route to this isoindolobenzazepine alkaloid was achieved from 2,3-dimethoxybenzoic acid (eight steps, 7% overall yield) via an intermediate ynamide from which the isoindolone core of the natural product was elaborated by Heck–Suzuki–Miyaura domino reactions.

5. Experimental

5.1. General procedures

Infrared (IR) spectra were recorded on a Perkin-Elmer 298 or a Bruker Tensor 27 (IR-FT), wavenumbers are indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC 300 at 300 MHz in $CDCl_3$ (unless otherwise specified) and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet or overlap of non-equivalent resonances),

integration. ^{13}C NMR spectra were recorded on a Bruker AC 300 at 75 MHz in $CDCl_3$ and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s, quaternary C; d, CH; t, CH_2; q, CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column)—5971 MS (70 eV). Mass spectra with chemical ionization (CI^+) and high-resolution mass spectra (HRMS) were performed by the Centre de Spectrochimie Organique de l'Ecole Normale Supérieure Ulm (Paris). Elemental analyses were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI). THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, CH_3CN, toluene, Et_3N, DMF were distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on Merck $60F_{254}$ silica gel plates visualized either with a UV lamp (254 nm), or by using solutions of *p*-anisaldehyde/H_2SO_4/AcOH in EtOH or $KMnO_4/K_2CO_3$ in water followed by heating. Flash chromatography was performed with SDS 60 silica gel (230–400 mesh).

5.2. Preparation of ynamides of type H

5.2.1. *N*-Benzyl-2-iodobenzamide (4a). To a solution of 2-iodobenzoic acid **3** (5.00 g, 20.2 mmol) in a mixture of CH_2Cl_2 (200 mL) and THF (50 mL) at 0 °C were successively added DMAP (493 mg, 4.03 mmol, 0.2 equiv), benzylamine (2.4 mL, 22 mmol, 1.1 equiv) and EDCI (5.40 g, 28.2 mmol, 1.4 equiv) portionwise. After 12 h, the reaction mixture was hydrolyzed with water and extracted with CH_2Cl_2. The combined organic extracts were successively washed with a 1 M aqueous solution of hydrochloric acid, a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from absolute EtOH to afford 4.08 g (60%) of **4a** as a white powder; mp 126 °C; IR 3420, 1660, 1585, 1510, 1300, 1015, 750 cm^{-1}; ^1H NMR δ 7.78 (d, J=7.7 Hz, 1H), 7.35–7.25 (m, 7H), 7.04 (m, 1H), 6.43 (br s, 1H, NH), 4.53 (d, J=5.5 Hz, 2H); ^{13}C NMR δ 169.1 (s), 141.9 (s), 139.7 (d), 137.5 (s), 131.0 (d), 128.6 (d, 2C), 128.1 (d), 128.0 (d, 3C), 127.5 (d), 92.4 (s), 44.0 (t); MS-EI *m/z* (relative intensity) 337 (M^+, 92), 336 (19), 231 (100), 210 (45), 203 (32), 192 (13), 132 (15), 105 (22), 104 (16), 91 (31), 77 (19), 76 (25).

5.2.2. *N*-(2-Bromobenzyl)-2-iodobenzamide (4b). This compound was synthesized from 2-bromobenzylamine (2.1 g, 11 mmol), 2-iodobenzoic acid (2.5 g, 10 mmol) in the presence of EDCI (2.3 g, 12 mmol) and DMAP (244 mg, 2 mmol) in CH_2Cl_2 (100 mL), as described for the preparation of **4a** from benzylamine. After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 3.36 g (81%) of **4b** were obtained as white solid; mp 154 °C; IR 3277, 1644, 1585, 1540, 1305, 1242, 1027, 1013, 986, 743, 719, 684, 666 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.98 (t, J=5.9 Hz, 1H, NH), 7.91 (d, J=7.7 Hz, 1H), 7.64 (dd, J=7.7, 1.1 Hz, 1H), 7.56–7.38 (m, 4H), 7.27–7.16 (m, 2H), 4.47 (d, J=5.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 169.1 (s), 142.7 (s), 139.2 (d), 137.4 (s), 132.4 (d), 130.9 (d), 129.0 (d), 128.9 (d), 128.2 (d), 128.0 (d), 127.7 (d), 122.3 (s), 93.5 (s), 43.0 (t); MS-EI *m/z* (relative intensity) 337 ($M+H-Br^+$, 15), 336 ($M-Br^+$, 100), 231 (27), 203 (13), 107 (14), 76 (12). Anal. Calcd for $C_{14}H_{11}BrINO$: C, 40.42; H, 2.66; N, 3.37. Found: C, 40.12; H, 2.66; N, 2.90.

5.2.3. *N*-Allyl-2-iodobenzamide (4c). This compound was synthesized from allylamine (1.7 mL, 22 mmol), 2-iodobenzoic acid (5.00 g, 20.2 mmol) in the presence of EDCI (4.90 g, 25.4 mmol) and DMAP (493 mg, 4.03 mmol) in CH_2Cl_2/THF (80 mL/110 mL), as described for the preparation of **4a** from benzylamine. After purification by flash chromatography (petroleum ether/EtOAc: 60:40), 4.22 g (73%) of **4c** were obtained as a white powder; mp 106 °C; IR 3410, 3350, 1645, 1580, 1510, 1300, 1260, 1010, 990, 730 cm^{-1}; ^1H NMR δ 7.83 (d, J=7.7 Hz, 1H), 7.36–7.32 (m, 2H), 7.07 (m, 1H), 6.16 (br s, 1H, NH), 5.93 (ddt, J=17.3, 10.3, 5.9 Hz, 1H), 5.29 (dq, J=17.3, 1.5 Hz, 1H), 5.17 (dq, J=10.3, 1.5 Hz, 1H), 4.02 (dt, J=5.9, 1.5 Hz, 2H); ^{13}C NMR δ 169.0 (s), 142.0 (s), 139.7 (d), 133.5 (d), 131.0 (d), 128.1 (d), 128.0 (d), 116.8 (t), 92.3 (s), 42.3 (t); MS-EI *m/z* (relative intensity) 287 (M^+, 10), 272 (3), 232 (8), 231 (100), 203 (21), 160 (11), 105 (4), 77 (6), 76 (17).

5.2.4. *N*-Benzyl-2-iodo-*N*-trimethylsilylethynyl-benzamide (6a). To a solution of **4a** (2.84 g, 8.43 mmol) in toluene (100 mL) at 0 °C was added KHMDS (15.3 mL, 15% in toluene, 10.1 mmol, 1.2 equiv). After 2 h at 0 °C, the iodonium salt **5** (4.55 g, 10.1 mmol, 1.2 equiv) was added. After 24 h at rt, the reaction mixture was filtered through Celite (toluene/ether: 80:20). The filtrate was evaporated under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc gradient: 90:10–60:40) to afford 1.75 g (48%) of **6a** as a white powder; mp 57 °C; IR 2180, 1680, 1580, 1430, 1370, 1290, 1250, 820, 760, 745 cm^{-1}; ^1H NMR δ 7.79 (dd, J=7.7, 0.7 Hz, 1H), 7.50–7.45 (m, 2H), 7.40–7.31 (m, 4H), 7.28 (dd, J=7.7, 1.8 Hz, 1H), 7.08 (apparent td, J=7.7, 1.8 Hz, 1H), 4.82 (s, 2H), −0.11 (s, 9H); ^{13}C NMR δ 171.1 (s), 141.3 (s), 138.7 (d), 135.2 (s), 130.6 (d), 129.2 (d, 2C), 128.4 (d, 2C), 128.1 (d), 127.8 (d), 127.6 (d), 96.3 (s), 92.1 (s), 76.1 (s), 51.6 (t), −0.43 (q, 3C); MS-EI *m/z* (relative intensity) 433 (M^+, 8), 418 ($M-Me^+$, 5), 306 (4), 232 (7), 231 (55), 203 (15), 92 (8), 91 (100), 76 (7).

5.2.5. *N*-(2-Bromobenzyl)-2-iodo-*N*-trimethylsilylethynylbenzamide (6b). This compound was prepared from **4b** (1.50 g, 3.60 mmol), KHMDS (14.4 mL, 0.5 M in toluene, 7.20 mmol, 2 equiv) and iodonium salt **5** (3.25 g, 7.20 mmol, 2 equiv) in toluene (85 mL), as described for the preparation of **6a** from **4a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 95:5) to afford 1.32 g (72%) of **6b** as a yellow solid; mp 140 °C; IR 2180, 1685, 1585, 1570, 1370, 1295, 1250, 1025, 985, 850, 750, 700 cm^{-1}; ^1H NMR δ 7.83 (d, J=8.1 Hz, 1H), 7.60 (dd, J=7.7, 1.1 Hz, 1H), 7.55 (dd, J=7.7, 1.5 Hz, 1H), 7.40–7.32 (m, 3H), 7.20 (apparent td, J=7.7, 1.5 Hz, 1H), 7.12 (m, 1H), 5.00 (s, 2H), 0.13 (s, 9H); ^{13}C NMR δ 171.1 (s), 141.1 (s), 138.8 (d), 134.3 (s), 132.8 (d), 130.8 (d), 130.5 (d), 129.5 (d), 127.9 (d), 127.6 (d), 127.4 (d), 124.1 (s), 95.6 (s), 92.2 (s), 76.5 (s), 51.2 (t), −0.44 (q, 3C); MS-EI *m/z* (relative intensity) 513 ($M[^{81}Br]^+$, 4), 511 ($M[^{79}Br]^+$, 4),

498 (6), 496 (6), 432 (7), 232 (10), 231 (100), 203 (30), 172 (7), 171 (88), 170 (8), 169 (91), 90 (13), 89 (9), 76 (15).

5.2.6. *N*-Allyl-2-iodo-*N*-trimethylsilylethynyl-benzamide (6c). This compound was prepared from **4c** (2.50 g, 8.71 mmol), KHMDS (30.7 mL, 0.5 M in toluene, 15.3 mmol, 1.8 equiv) and iodonium salt **5** (7.53 g, 16.7 mmol, 1.9 equiv) in toluene (200 mL), as described for the preparation of **6a** from **4a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 95:5–90:10) to afford 2.10 g (63%) of **6c** as a white waxy solid; mp <45 °C; IR 2180, 1665, 1585, 1360, 1290, 1250, 840, 760, 740 cm^{-1}; ^1H NMR δ 7.81 (dd, J=8.1, 0.9 Hz, 1H), 7.41–7.27 (m, 2H), 7.10 (ddd, J=8.1, 7.4, 0.9 Hz, 1H), 5.98 (ddt, J=16.5, 10.3, 6.2 Hz, 1H), 5.41 (dq, J=16.5, 1.5 Hz, 1H), 5.32 (dq, J=10.3, 1.5 Hz, 1H), 4.27 (dt, J=6.2, 1.5 Hz, 2H), −0.07 (s, 9H); ^{13}C NMR δ 171.1 (s), 141.4 (s), 138.7 (d), 130.8 (d), 130.6 (d), 127.6 (d, 2C), 119.3 (t), 96.0 (s), 92.1 (s), 75.6 (s), 50.1 (t), −0.29 (q, 3C); MS-EI m/z (relative intensity) 383 (M^+, 9), 368 ($M-Me^+$, 17), 294 (6), 256 (13), 231 (100), 203 (28), 180 (6), 76 (17). Anal. Calcd for $C_{15}H_{18}INOSi$: C, 47.00; H, 4.73; N, 3.65. Found: C, 47.11; H, 4.74; N, 3.63.

5.2.7. *N*-Benzyl-*N*-ethynyl-2-iodobenzamide (7a). To a solution of **6a** (70 mg, 0.16 mmol) in THF (5 mL) at 0 °C was added tetra(*n*-butyl)ammonium fluoride (TBAF) (0.21 mL, 1 M in THF, 0.21 mmol, 1.3 equiv). After 10 min at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 90:10) to afford 56 mg (96%) of **7a** as a pale yellow solid; mp 100–102 °C; IR 3290, 2140, 1680, 1580, 1355, 1320, 1285, 1250, 1140, 760, 730, 710, 695 cm^{-1}; ^1H NMR δ 7.81 (dd, J=8.1, 0.7 Hz, 1H), 7.52–7.46 (m, 2H), 7.42–7.28 (m, 5H), 7.10 (ddd, J=8.1, 7.4, 1.8 Hz, 1H), 4.87 (s, 2H), 2.60 (s, 1H); ^{13}C NMR δ 170.9 (s), 138.9 (s), 135.0 (s), 130.8 (d), 128.9 (d, 2C), 128.4 (d, 2C), 128.4 (s), 128.1 (d), 127.8 (d, 2C), 91.9 (s), 76.6 (s), 61.7 (d), 51.7 (t); MS-EI m/z (relative intensity) 361 (M^+, 2), 232 (7), 231 (43), 203 (16), 91 (100), 76 (12).

5.2.8. *N*-(2-Bromobenzyl)-*N*-ethynyl-2-iodobenzamide (7b). This compound was synthesized from ynamide **6b** (600 mg, 1.17 mmol) by treatment with TBAF (1.53 mL, 1 M in THF, 1.53 mmol, 1.3 equiv) in THF (15 mL), as described for the preparation of **7a** from **6a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 90:10) to afford 408 mg (79%) of **7b** as an orange solid; mp 105–106 °C; IR 3300, 2150, 1690, 1585, 1350, 1295, 1030, 980, 770, 750 cm^{-1}; ^1H NMR δ 7.86 (br d, J=8.1 Hz, 1H), 7.62 (br d, J=8.1 Hz, 1H), 7.56 (dd, J=7.7, 1.5 Hz, 1H), 7.43–7.35 (m, 3H), 7.23 (dd, J=7.7, 1.5 Hz, 1H), 7.15 (m, 1H), 5.04 (s, 2H), 2.55 (s, 1H); ^{13}C NMR δ 171.0 (s), 140.8 (s), 139.2 (d), 134.2 (s), 133.0 (d), 131.2 (d), 130.3 (d), 129.6 (d), 127.9 (d), 127.8 (d), 127.5 (d), 124.0 (s), 92.2 (s), 76.5 (s), 62.2 (d), 51.4 (t); MS-EI m/z (relative intensity) 271 ($M+H-CH_2(C_6H_4Br)^+$, 100), 243 (5), 242 (5), 215 (3), 116 (32), 89 (36), 88 (13), 63 (7), 62 (8). Anal. Calcd for $C_{16}H_{11}BrINO$: C, 43.67; H, 2.52; N, 3.18. Found: C, 43.89; H, 2.65; N, 3.06.

5.2.9. *N*-Allyl-*N*-ethynyl-2-iodobenzamide (7c). This compound was synthesized from ynamide **6c** (1.50 g, 3.90 mmol) by treatment with TBAF (5.1 mL, 1 M in THF, 5.1 mmol, 1.3 equiv) in THF (50 mL), as described for the preparation of **7a** from **6a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 70:30) to afford 1.03 g (85%) of **7c** as a white powder; mp 55–57 °C; IR 3300, 2140, 1580, 1360, 1290, 1255, 1015, 935, 770, 740 cm^{-1}; ^1H NMR δ 7.83 (dd, J=8.0, 0.7 Hz, 1H), 7.42–7.30 (m, 2H), 7.11 (apparent td, J=7.7, 1.8 Hz, 1H), 5.99 (ddt, J=16.6, 10.3, 6.3 Hz, 1H), 5.43 (dq, J=16.6, 1.5 Hz, 1H), 5.34 (dq, J=10.3, 1.5 Hz, 1H), 4.31 (dt, apparent br d, J=6.3, 1.5 Hz, 2H), 2.64 (s, 1H); ^{13}C NMR δ 170.8 (s), 140.9 (s), 138.9 (d), 130.9 (d), 130.6 (d), 127.7 (d), 127.5 (d), 119.4 (t), 92.0 (s), 76.6 (s), 61.3 (d), 50.4 (t); MS-EI m/z (relative intensity) 311 (M^+, 4), 271 (15), 232 (8), 231 (100), 203 (33), 182 (5), 76 (24). Anal. Calcd for $C_{12}H_{10}INO$: C, 46.33; H, 3.24; N, 4.50. Found: C, 46.68; H, 3.47; N, 4.29.

5.2.10. *N*-Allyl-2-bromonicotinamide (10). This compound was synthesized from 2-bromonicotinic acid **9**[34] (2.0 g, 9.9 mmol) and allylamine (0.93 mL, 12.4 mmol, 1.25 equiv) in the presence of EDCI (2.3 g, 12 mmol, 1.2 equiv) and DMAP (0.12 g, 0.99 mmol, 0.1 equiv) in CH_2Cl_2 (200 mL) as described for the preparation of **4a** from benzylamine and 2-iodobenzoic acid. After purification by flash chromatography (diethyl ether), 1.25 g (52%) of **10** were obtained as a white solid; mp 97–98 °C; IR 1660, 1580, 1395, 1300, 1055, 990, 930, 820 m^{-1}; ^1H NMR δ 8.31 (dd, J=4.8, 1.8 Hz, 1H), 7.75 (dd, J=7.7, 1.8 Hz, 1H), 7.27 (dd, J=7.7, 4.8 Hz, 1H), 6.79 (br s, 1H, NH), 5.86 (ddt, J=17.3, 10.3, 5.9 Hz, 1H), 5.25 (dq, J=17.3, 1.5 Hz, 1H), 5.14 (dq, J=10.3, 1.5 Hz, 1H), 3.99 (ddt, apparent tt, J=5.9, 1.5 Hz, 2H); ^{13}C NMR δ 165.6 (s), 150.7 (d), 138.3 (s), 138.0 (d), 134.7 (s), 133.0 (d), 122.6 (d), 116.9 (t), 42.4 (t); MS-EI m/z (relative intensity) 242 ($M[^{81}Br]^+$, 5), 240 ($M[^{79}Br]^+$, 5), 227 (20), 225 (20), 186 (97), 184 (100), 161 (23), 158 (30), 156 (31), 76 (17), 56 (6), 51 (7).

5.2.11. *N*-Allyl-2-bromo-*N*-trimethylsilylethynyl-nicotinamide (11). This compound was synthesized from **10** (800 mg, 3.32 mmol), KHMDS (10.6 mL, 0.5 M in toluene, 5.3 mmol, 1.6 equiv) and iodonium salt **5** (2.39 g, 5.30 mmol, 1.6 equiv) in toluene (50 mL), as described for the preparation of **6a** from **4a**. After purification by flash chromatography (petroleum ether/EtOAc: 90:10), 643 mg (58%) of **11** were obtained as a yellow oil; IR 2180, 1685, 1645, 1575, 1555, 1390, 1365, 1295, 1250, 1205, 1165, 1120, 1055, 990, 920, 840, 760, 705, 640 cm^{-1}; ^1H NMR δ 8.42 (dd, J=4.8, 1.9 Hz, 1H), 7.64 (dd, J=7.7, 1.9 Hz, 1H), 7.32 (dd, J=7.7, 4.8 Hz, 1H), 5.93 (ddt, J=17.2, 10.3, 6.2 Hz, 1H), 5.40 (dq, J=17.2, 1.1 Hz, 1H), 5.32 (dq, J=10.3, 1.1 Hz, 1H), 4.27 (dt, J=6.2, 1.1 Hz, 2H), −0.06 (s, 9H); ^{13}C NMR δ 168.0 (s), 150.5 (d), 138.5 (s), 136.5 (d), 134.5 (s), 130.3 (d), 122.1 (d), 119.6 (t), 95.4 (s), 76.3 (s), 50.2 (t), −0.35 (q, 3C); MS-EI m/z (relative intensity) 338 ($M[^{81}Br]^+$, 15), 336 ($M[^{79}Br]^+$, 15), 323 (58), 321 (57), 257 (56), 249 (14), 247 (14), 186 (97), 185 (14), 184 (100), 180 (14), 158 (48), 156 (49), 139 (20), 137 (20), 84 (14), 76 (19), 73 (18). Anal. Calcd for $C_{14}H_{17}BrN_2OSi$: C, 49.85; H, 5.08; N, 8.31. Found: C, 49.89; H, 5.27; N, 8.27.

5.2.12. *N*-Allyl-2-bromo-*N*-ethynylnicotinamide (12). This compound was synthesized from **11** (500 mg, 1.48 mmol) by treatment with TBAF (1.4 mL, 1 M in THF, 1.4 mmol, 1.25 equiv) in THF (18 mL). After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 345 mg (88%) of **12** were obtained as a yellow oil; IR 3305, 2150, 1685, 1580, 1560, 1395, 1365, 1290, 1055, 810, 760, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (dd, J=4.8, 2.0 Hz, 1H), 7.67 (dd, J=7.7, 2.0 Hz, 1H), 7.34 (dd, J=7.7, 4.8 Hz, 1H), 5.95 (ddt, J=17.3, 10.3, 5.9 Hz, 1H), 5.42 (dq, J=17.3, 1.5 Hz, 1H), 5.35 (dq, J=10.3, 1.5 Hz, 1H), 4.31 (dt, J=5.9, 1.5 Hz, 2H), 2.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 167.7 (s), 150.8 (d), 138.3 (s), 136.5 (d), 134.0 (s), 130.1 (d), 122.2 (d), 119.8 (t), 76.1 (s), 61.7 (d), 50.4 (t); MS-EI *m/z* (relative intensity) 266 ($M[^{81}Br]^+$, 29), 264 ($M[^{79}Br]^+$, 29), 199 (33), 197 (34), 186 (96), 184 (100), 158 (62), 156 (65), 77 (20), 76 (49), 50 (20). HRMS (CI^+, CH_4) calcd for $C_{11}H_{10}ON_2^{79}Br$ ($M+H^+$): 264.9976. Found: 264.9974.

5.3. Reductive Heck reaction of ynamides

5.3.1. 2-(2-Bromobenzyl)-3-methylene-2,3-dihydro-1*H*-isoindol-1-one (13) (representative procedure). To a solution of ynamide **7b** (80 mg, 0.18 mmol) in DMF (8 mL) were successively added ammonium formate (17 mg, 0.27 mmol, 1.5 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv) and PPh_3 (4.8 mg, 0.018 mmol, 0.1 equiv). After 1 h at 80 °C, the reaction mixture was cooled to rt, diluted with water and extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 95:5) to afford 34 mg (56%) of **13** as a pale yellow solid; mp 110 °C; IR 1705, 1640, 1395, 1025, 980, 845, 770, 755 cm^{-1}; ^1H NMR δ 7.92 (apparent br d, J=7.5 Hz, 1H), 7.72 (apparent dt, J=7.5, 1.1 Hz, 1H), 7.63 (apparent td, J=7.5, 1.1 Hz, 1H), 7.61–7.53 (m, 2H), 7.24–7.09 (m, 2H), 6.98 (apparent br d, J=7.5 Hz, 1H), 5.18 (d, J=2.6 Hz, 1H), 5.18 (br s, 2H), 4.74 (d, J=2.6 Hz, 1H); ^{13}C NMR δ 167.2 (s), 141.3 (s), 136.4 (s), 135.4 (s), 132.8 (d), 132.3 (d), 129.6 (d), 129.1 (s), 128.8 (d), 127.7 (d, 2C), 123.5 (d), 122.4 (s), 120.0 (d), 90.2 (t), 43.2 (t); MS (CI^+, CH_4) *m/z* (relative intensity) 316 ($M[^{81}Br]+H^+$, 100), 314 ($M[^{79}Br]+H^+$, 100), 234 (17). HRMS (CI^+, CH_4) calcd for $C_{16}H_{13}ON^{79}Br$ ($M+H^+$): 314.0181. Found: 314.0178.

5.3.2. 2-Allyl-3-methylene-2,3-dihydro-1*H*-isoindol-1-one (14).[12] This compound was synthesized from ynamide **7c** (70 mg, 0.22 mmol) in the presence of ammonium formate (21 mg, 0.34 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol, 0.05 equiv) and PPh_3 (5.9 mg, 0.022 mmol, 0.10 equiv) in DMF (9 mL), according to the representative procedure (2 h at 80 °C). After purification by flash chromatography (petroleum ether/EtOAc: 90:10), 21 mg (62%) of **14** were obtained as an orange oil; IR 1710, 1640, 1390, 1340, 1095, 925, 840, 770, 730, 715, 700 cm^{-1}; ^1H NMR δ 7.85 (ddd, apparent dt, J=7.7, 1.1 Hz, 1H), 7.69 (ddd, apparent dt, J=7.7, 1.1 Hz, 1H), 7.59 (ddd, apparent td, J=7.7, 1.1 Hz, 1H), 7.50 (ddd, apparent td, J=7.7, 1.1 Hz, 1H), 5.87 (ddt, J=16.9, 10.3, 5.1 Hz, 1H), 5.22–5.13 (m, 2H), 5.20 (d, J=2.2 Hz, 1H), 4.87 (d, J=2.2 Hz, 1H), 4.43 (dt, J=5.1, 1.6 Hz, 2H); ^{13}C NMR δ 166.7 (s), 141.5 (s), 136.2 (s), 132.2 (d), 131.8 (d), 129.3 (d), 129.1 (s), 123.1 (d), 119.7 (d), 116.6 (t), 89.3 (t), 41.6 (t); MS-EI *m/z* (relative intensity) 186 ($M+H^+$, 13), 185 (M^+, 100), 184 (67), 170 (35), 156 (33), 130 (13), 129 (16), 115 (14), 103 (14), 102 (14), 77 (13), 76 (13).

5.4. Palladium-catalyzed Heck–Suzuki–Miyaura domino reactions involving ynamides

5.4.1. 2-Benzyl-3-(*E*)-benzylidene-2,3-dihydro-1*H*-isoindol-1-one (15) (representative procedure). To a solution of ynamide **7a** (40 mg, 0.11 mmol) in THF (5 mL) were added a 1 M aqueous solution of NaOH (0.17 mL, 0.17 mmol, 1.5 equiv) and benzeneboronic acid (16 mg, 0.14 mmol, 1.2 equiv). To the resulting degassed mixture [argon bubbling, 10 min] were added PPh_3 (3.0 mg, 0.011 mmol, 0.1 equiv) and $Pd(OAc)_2$ (1.3 mg, 0.0055 mmol, 0.05 equiv). After 1.5 h at reflux, the reaction mixture was cooled to rt, hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 75:25) to afford 25 mg (70%) of **15** as a yellow oil; IR 3020, 1695, 1635, 1405, 1335, 1175, 1150, 1115, 970, 820, 765, 735, 695 cm^{-1}; ^1H NMR δ 7.91–7.21 (m, 14H), 6.46 (s, 1H), 5.13 (s, 2H); ^{13}C NMR δ 166.7 (s), 136.7 (s), 135.9 (s), 135.0 (s), 134.9 (s), 131.6 (d), 130.1 (s), 129.4 (d, 2C), 129.2 (d), 128.7 (d, 2C), 128.5 (d, 2C), 127.7 (d), 127.3 (d), 126.9 (d, 2C), 123.4 (d), 123.1 (d), 111.5 (d), 43.1 (t); MS-EI *m/z* (relative intensity) 312 ($M+H^+$, 23), 311 (M^+, 100), 310 ($M-H^+$, 31), 282 (10), 234 (15), 232 (27), 220 (22), 167 (17), 165 (16), 91 (72), 65 (9).

5.4.2. 2-(2-Bromobenzyl)-3-(*E*)-benzylidene-2,3-dihydro-1*H*-isoindol-1-one (16). This compound was synthesized from ynamide **7b** (61 mg, 0.14 mmol) and benzeneboronic acid (20 mg, 0.16 mmol, 1.2 equiv) in the presence of $Pd(OAc)_2$ (1.5 mg, 0.007 mmol, 0.05 equiv), PPh_3 (3.6 mg, 0.014 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (0.20 mL, 1 M, 0.20 mmol, 1.5 equiv) in THF (6 mL), according to the representative procedure (2 h at reflux). After purification by flash chromatography (pentane/EtOAc gradient: 95:5–80:20), 27 mg (51%) of **16** were obtained as a yellow solid; mp 178 °C; IR 1700, 1635, 1440, 1410, 1270, 1220, 1175, 1025, 970, 860, 830, 770, 755, 730 cm^{-1}; ^1H NMR δ 7.94 (dt, J=7.3, 1.1 Hz, 1H), 7.61 (dd, J=7.7, 1.1 Hz, 1H), 7.49 (m, 1H), 7.45–7.32 (m, 7H), 7.25 (ddd, apparent td, J=7.3, 1.1 Hz, 1H), 7.15 (ddd, apparent td, J=7.3, 1.8 Hz, 1H), 7.06 (dd, J=7.7, 1.5 Hz, 1H), 6.37 (s, 1H), 5.21 (s, 2H); ^{13}C NMR δ 166.7 (s), 135.6 (s), 135.3 (s), 135.0 (s), 134.8 (s), 132.7 (d), 131.7 (d), 130.0 (s), 129.3 (d, 2C), 129.2 (d), 128.7 (d), 128.5 (d, 2C), 127.7 (d), 127.6 (d), 127.5 (d), 123.4 (d), 123.1 (d), 122.2 (s), 111.7 (d), 43.3 (t).

5.4.3. 2-Allyl-3-(*E*)-(2-methoxybenzylidene)-2,3-dihydro-1*H*-isoindol-1-one (17). This compound was synthesized from ynamide **7c** (116 mg, 0.372 mmol) and 2-methoxybenzeneboronic acid (85 mg, 0.56 mmol, 1.5 equiv) in the presence of $Pd(OAc)_2$ (4.2 mg,

0.018 mmol, 0.05 equiv), PPh_3 (10 mg, 0.037 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (0.56 mL, 0.56 mmol, 1.5 equiv) in THF (10 mL), according to the representative procedure (0.75 h at reflux). After purification by flash chromatography (petroleum ether/EtOAc gradient: 90:10–70:30), 73 mg (67%) of **16** were obtained as a light brown solid; mp 110 °C; IR 1690, 1645, 1600, 1250, 1025, 760, 750 cm^{-1}; ^1H NMR δ 7.85 (br d, $J=7.2$ Hz, 1H), 7.49–7.26 (m, 5H), 7.02–6.95 (m, 2H), 6.49 (s, 1H), 5.94 (ddt, $J=17.0$, 10.2, 5.3 Hz, 1H), 5.25 (dq, $J=17.0$, 1.5 Hz, 1H), 5.23 (dq, $J=10.2$, 1.5 Hz, 1H), 4.57 (dt, $J=5.3$, 1.5 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR δ 166.3 (s), 157.6 (s), 135.5 (s), 135.3 (s), 132.6 (d), 131.4 (d), 131.2 (d), 130.2 (s), 129.6 (d), 129.0 (d), 123.9 (s), 123.1 (d), 123.0 (d), 120.4 (d), 116.9 (t), 110.8 (d), 107.9 (d), 55.6 (q), 41.9 (t); MS-EI *m/z* (relative intensity) 292 ($M+H^+$, 21), 291 (M^+, 100), 290 ($M-H^+$, 23), 276 (13), 262 (17), 260 (18), 232 (18), 219 (32), 206 (14), 190 (14), 185 (31), 184 (43), 182 (18), 170 (39), 165 (19).

5.4.4. 6-Allyl-7-(*E*)-benzylidene-6,7-dihydropyrrolo-[3,4-*b*]pyridin-5-one (18). This compound was synthesized from ynamide **12** (154 mg, 0.58 mmol) and benzeneboronic acid (84.5 mg, 0.68 mmol, 1.2 equiv) in the presence of $Pd(OAc)_2$ (6.4 mg, 0.028 mmol, 0.05 equiv), PPh_3 (15 mg, 0.058 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (0.85 mL, 0.85 mmol, 1.5 equiv) in THF (25 mL), according to the representative procedure (5 h at reflux). After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 78.5 mg (52%) of **18** were obtained as a brown oil; IR 3060, 1695, 1640, 1605, 1575, 1395, 1340, 1280, 1265, 1170, 1100, 920, 795, 770, 735, 695 cm^{-1}; ^1H NMR δ 8.77 (dd, $J=4.8$, 1.8 Hz, 1H), 8.18 (dd, $J=7.7$, 1.8 Hz, 1H), 8.04–7.99 (m, 2H), 7.45–7.32 (m, 4H), 6.57 (s, 1H), 5.95 (ddt, $J=17.2$, 10.3, 5.1 Hz, 1H), 5.30–5.21 (m, 2H), 4.62 (dt, $J=5.1$, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 164.0 (s), 154.8 (s), 152.7 (d), 134.0 (s), 133.8 (s), 132.3 (d), 131.1 (d), 130.9 (d, 2C), 128.3 (d), 127.9 (d, 2C), 124.1 (s), 123.5 (d), 117.2 (t), 115.7 (d), 41.8 (t); MS-EI *m/z* (relative intensity) 262 (M^+, 67), 261 ($M-H^+$, 100), 233 (18), 221 (15), 220 (15), 192 (16), 185 (11), 166 (12), 139 (5), 89 (5), 77 (6). HRMS (CI^+, CH_4) calcd for $C_{17}H_{15}ON_2$ ($M+H^+$): 263.1184. Found: 263.1179.

5.4.5. 6-Allyl-7-(*E*)-(3,4-dichlorobenzylidene)-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-one (19). This compound was synthesized from ynamide **12** (204 mg, 0.754 mmol) and 3,4-dichlorobenzeneboronic acid (173 mg, 0.905 mmol, 1.2 equiv) in the presence of $Pd(OAc)_2$ (8.5 mg, 0.38 mmol, 0.05 equiv), PPh_3 (20 mg, 0.076 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (1.1 mL, 1.1 mmol, 1.5 equiv) in THF (30 mL), according to the representative procedure (1.5 h at reflux). After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 170 mg (68%) of **16** were obtained as a yellow solid; mp 127 °C; IR 1700, 1640, 1610, 1580, 1475, 1400, 1340, 1030, 925, 880, 795, 695, 640 cm^{-1}; ^1H NMR δ 8.78 (dd, $J=4.8$, 1.8 Hz, 1H), 8.21 (br d, $J=2.2$ Hz, 1H), 8.18 (dd, $J=7.7$, 1.8 Hz, 1H), 7.82 (m, 1H), 7.45 (br d, $J=8.1$ Hz, 1H), 7.43 (dd, $J=7.7$, 4.8 Hz, 1H), 6.40 (s, 1H), 5.92 (ddt, $J=17.3$, 10.4, 5.1 Hz, 1H), 5.28 (apparent br d, $J=10.4$ Hz, 1H), 5.24 (apparent br d, $J=17.3$ Hz, 1H), 4.59 (dt, $J=5.1$, 1.8 Hz, 2H); ^{13}C NMR δ 164.0 (s), 154.5 (s), 152.8 (d), 135.4 (s), 133.9 (s), 132.5 (d), 132.0 (d), 131.9 (s), 131.8 (s), 131.3 (d), 130.2 (d), 129.7 (d), 124.1 (s), 124.0 (d), 117.3 (t), 112.6 (d), 41.8 (t); MS-EI *m/z* (relative intensity) 334 ($M[^{37}Cl_2]^+$, 12), 333 ($M[^{37}Cl_2]-H^+$, 20), 332 ($M[^{35}Cl^{37}Cl]^+$, 67), 331 ($M[^{35}Cl^{37}Cl]-H^+$, 67), 330 ($M[^{35}Cl_2]^+$, 100), 329 ($M[^{35}Cl_2]-H^+$, 78), 315 (13), 303 (23), 301 (33), 295 (18), 267 (16), 256 (22), 254 (68), 191 (22), 185 (57), 171 (35). HRMS (CI^+, CH_4) calcd for $C_{17}H_{13}ON_2^{35}Cl_2$ ($M+H^+$): 331.0405. Found: 331.0407.

5.5. Attribution of the configuration of the isoindolin-1-ones 15–17 and the pyrrolopyridinone 18. Synthesis of the geometric isomers of (*Z*) configuration

5.5.1. 2-(2-Bromobenzyl)-3-(*Z*)-benzylidene-2,3-dihydro-1*H*-isoindol-1-one (21). To a solution of **4b** (416 mg, 1.00 mmol) in DMF (5 mL) were successively added $PdCl_2(PPh_3)_2$ (25 mg, 0.035 mmol, 0.035 equiv), CuI (15 mg, 0.080 mmol, 0.08 equiv) and Et_3N (0.56 mL, 4.02 mmol, 4 equiv). After 1 h at rt, phenylacetylene (0.13 mL, 1.2 mmol, 1.2 equiv) was added and the resulting mixture was heated at 80 °C. After 1 h, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was added to a solution of sodium ethoxide in absolute ethanol [prepared by adding Na (70 mg, 3.0 mmol, 3 equiv) in EtOH (20 mL)]. After 2 h at reflux, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and the resulting mixture was evaporated under reduced pressure. The residue was portioned between EtOAc and water and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by flash chromatography (petroleum ether/EtOAc: 90:10) afforded 275 mg (70%) of an inseparable mixture of the known (*Z*)-3-benzylideneisoindolin-1-one **20**[8a,10c] and **21** (70/30 ratio). An analytically pure sample of **21** was obtained after separation by preparative TLC (toluene/ether=96:4) for individual characterization; IR 1705, 1645, 340, 1110, 1025, 980, 955 cm^{-1}; ^1H NMR δ 7.94 (br d, $J=7.0$ Hz, 1H), 7.80 (br d, $J=7.5$ Hz, 1H), 7.67 (td, $J=7.5$, 1.1 Hz, 1H), 7.56 (td, $J=7.5$, 1.1 Hz, 1H), 7.35–6.99 (m, 6H), 6.90 (m, 2H), 6.80 (s, 1H), 6.73 (br d, $J=8.3$ Hz, 1H), 4.81 (s, 2H); ^{13}C NMR δ 168.6 (s), 138.2 (s), 135.7 (s), 134.3 (s), 133.7 (s), 132.35 (d), 132.3 (d), 129.2 (d), 128.7 (d), 128.1 (d, 2C), 128.0 (s), 127.9 (d, 2C), 127.5 (d), 127.1 (d), 126.5 (d), 123.6 (d), 122.2 (s), 119.6 (d), 107.8 (d), 45.8 (t); MS-EI *m/z* (relative intensity) 391 ($M[^{81}Br]^+$, 5), 389 ($M[^{79}Br]^+$, 5), 311 ($M+H-Br^+$, 25), 310 ($M-Br^+$, 100), 232 (11), 170 (8), 168 (8), 165 (11), 90 (7), 89 (6).

5.5.2. 2-Allyl-3-(*Z*)-(2-methoxybenzylidene)-2,3-dihydro-1*H*-isoindol-1-one (22). This compound was synthesized from **4c** (287 mg, 1.00 mmol) by a Sonogashira coupling with 2-methoxyphenylacetylene[44] (158 mg, 1.2 mmol, 1.2 equiv) in the presence of $PdCl_2(PPh_3)_2$ (25 mg, 0.035 mmol, 0.035 equiv), CuI (15 mg, 0.080 mmol, 0.08 equiv) and Et_3N (0.56 mL, 4.0 mmol, 4 equiv) in DMF (5 mL) (1.5 h at 80 °C). The resulting crude disubstituted alkyne was cyclized by treatment with a solution of EtONa in EtOH [Na (70 mg) in EtOH (20 mL),

2 h at reflux]. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 90:10) to afford 222 mg (76%) of **22** as a waxy orange solid; IR 1707, 1656, 1595, 1578, 1487, 1460, 1328, 1248, 1216, 1103, 1017, 954, 910, 748, 698 cm^{-1}; ^1H NMR δ 7.85 (d, J=7.5 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H), 7.58 (apparent td, J=7.5, 1.1 Hz, 1H), 7.47 (apparent td, J=7.5, 1.1 Hz, 1H), 7.32 (apparent br td, J=8.1, 1.5 Hz, 1H), 7.25 (br d, J=7.5 Hz, 1H), 6.96 (dd, apparent t, J=7.5 Hz, 1H), 6.89 (br d, J=8.1 Hz, 1H), 6.70 (s, 1H), 5.44 (ddt, J=17.1, 10.3, 5.4 Hz, 1H), 4.85 (dq, J=10.3, 1.5 Hz, 1H), 4.54 (dq, J=17.1, 1.5 Hz, 1H), 4.31 (dt, J=5.4, 1.5 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR δ 168.6 (s), 157.6 (s), 138.5 (s), 134.8 (s), 132.6 (s), 131.9 (d), 131.6 (d), 129.3 (d), 128.8 (d), 128.2 (s), 123.7 (s), 123.2 (d), 119.9 (d), 119.6 (d), 116.1 (t), 110.4 (d), 103.6 (d), 55.4 (q), 43.7 (t); MS-EI *m/z* (relative intensity) 291 (M^+, 100), 290 ($M-H^+$, 24), 276 ($M-Me^+$, 11), 262 (17), 260 ($M-OMe^+$, 18), 232 (18), 219 (21), 206 (15), 185 (30), 184 (42), 182 (15), 185 (30), 184 (42), 182 (15), 170 (37), 165 (21), 152 (10), 102 (9).

5.5.3. 6-Allyl-7-(*Z*)-benzylidene-6,7-dihydropyrrolo-[3,4-*b*]pyridin-5-one (23). This compound was synthesized according to the experimental procedure described for the preparation of **22** from amide **4c**, by a Sonogashira coupling between amide **10** (114 mg, 0.473 mmol) and phenylacetylene (0.063 mL, 0.57 mmol, 1.2 equiv) in the presence of $PdCl_2(PPh_3)_2$ (12 mg, 0.016 mmol, 0.035 equiv), CuI (7.2 mg, 0.038 mmol, 0.08 equiv) and Et_3N (0.26 mL, 1.9 mmol, 4 equiv) in DMF (2.5 mL) (2 h at 80 °C). The resulting crude disubstituted alkyne was cyclized by treatment with a solution of EtONa in EtOH (2 h at reflux) and after purification of the crude material by flash chromatography (petroleum ether/EtOAc gradient: 80:20–70:30), 68 mg (58%) of **23** were obtained as a viscous oil; IR 1700, 1655, 1600, 1585, 1170, 780 cm^{-1}; ^1H NMR δ 8.80 (dd, J=4.9, 1.5 Hz, 1H), 8.15 (dd, J=7.9, 1.5 Hz, 1H), 7.45–7.29 (m, 7H), 5.48 (ddt, J=17.3, 10.5, 5.3 Hz, 1H), 4.93 (dq, J=10.5, 1.5 Hz, 1H), 4.63 (dq, J=17.3, 1.5 Hz, 1H), 4.35 (dt, J=5.3, 1.5 Hz, 2H); ^{13}C NMR δ 166.3 (s), 156.6 (s), 153.3 (d), 134.4 (s), 133.6 (s), 132.2 (d), 131.3 (d), 129.6 (d, 2C), 128.0 (d, 2C), 127.9 (d), 123.7 (d), 121.8 (s), 116.6 (t), 109.4 (d), 43.6 (t); MS-EI *m/z* (relative intensity) 262 (M^+, 67), 261 (100), 233 (17), 221 (17), 220 (13), 192 (15), 185 (10), 166 (10), 139 (5), 89 (5), 77 (6).

5.6. One-pot desilylation–Heck–Suzuki–Miyaura domino reactions from trimethylsilylynamides. 2-Benzyl-3-(*E*)-(3,4-dichlorobenzylidene)-2,3-dihydro-1*H*-isoindol-1-one (24)

To a solution of **7a** (300 mg, 0.692 mmol) in THF (30 mL) was added a 1 M aqueous solution of NaOH (1.7 mL, 1.7 mmol, 2.5 equiv). After 0.5 h at reflux, the resulting mixture was cooled to rt and benzeneboronic acid (158 mg, 0.828 mmol, 1.2 equiv), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol, 0.05 equiv), PPh_3 (18.5 mg, 0.069 mmol, 0.1 equiv) were successively added. After 1.5 h at reflux, the reaction mixture was worked-up as usual. Purification by flash chromatography (petroleum ether/EtOAc: 90:10) gave 119 mg (45%) of **24** as an orange solid; mp 136 °C; IR 1700, 1635, 1470, 1410, 1340, 1315, 770, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (d, J=7.0 Hz, 1H), 7.80–7.05 (m, 11H), 6.27 (s, 1H), 5.10 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 166.7 (s), 137.1 (s), 136.5 (s), 135.2 (s), 134.7 (s), 132.8 (s), 132.0 (d), 131.8 (s), 131.3 (d), 130.6 (d), 130.2 (s), 129.8 (d), 129.0 (d), 128.8 (d), 128.2 (d), 127.5 (d), 126.9 (d, 2C), 123.7 (d), 123.0 (d), 108.4 (d), 43.3 (t); MS-EI *m/z* (relative intensity) 384 ($M[^{37}Cl_2]+H^+$, 1), 383 ($M[^{37}Cl_2]^+$, 6), 382 ($M[^{37}Cl^{35}Cl]+H^+$, 9), 381 ($M[^{37}Cl^{35}Cl]^+$, 32), 380 ($M[^{35}Cl^{35}Cl]+H^+$, 19), 379 ($M[^{35}Cl_2]^+$, 48), 378 (12), 300 (7), 253 (8), 235 (10), 207 (14), 190 (7), 92 (8), 91 (100), 65 (10). HRMS (CI^+, CH_4) calcd for $C_{22}H_{16}ON^{35}Cl_2$ ($M+H^+$): 380.0609. Found: 380.0605.

5.7. Synthesis of lennoxamine

5.7.1. 6-Bromo-2,3-dimethoxybenzoic acid (27).[42] To a solution of 2,3-dimethoxybenzoic acid (2.50 g, 13.7 mmol) in a 0.7 M aqueous solution of NaOH (21 mL) at 0 °C, was added 1,3-dibromo-5,5-dimethylhydantoin (2.16 g, 7.55 mmol, 0.55 equiv). After 6 h at rt, the reaction was quenched by addition of solid sodium sulfite until the yellow color disappeared. The reaction mixture was diluted with ether and acidified to pH=2 by addition of a 1 M aqueous solution of hydrochloric acid. After extraction with ether, the combined extracts were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting viscous oil was dried under reduced pressure to afford 3.58 g (100%) of **27** as a white solid, which was directly engaged in the next step without further purification; mp 110–112 °C; IR 3220 (br), 1734, 1575, 1470, 1416, 1294, 1236, 1177, 1161, 1043, 988, 814, 790, 702, 634 cm^{-1}; ^1H NMR δ 9.53 (br s, 1H), 7.27 (d, J=8.9 Hz, 1H), 6.86 (d, J=8.9 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C NMR δ 170.8 (s), 152.1 (s), 147.0 (s), 130.4 (s), 128.2 (d), 114.9 (d), 108.6 (s), 61.9 (q), 56.1 (q).

5.7.2. 6-Bromo-*N*-(2,2-dimethoxyethyl)-2,3-dimethoxybenzamide (29). To the carboxylic acid **27** (2.86 g, 10.9 mmol) was added thionyl chloride (6 mL) and the resulting mixture was heated at reflux. After 3 h, the reaction mixture was cooled to rt and excess $SOCl_2$ was distilled off under reduced pressure (15 mmHg). The residue was dissolved in CH_2Cl_2 (30 mL) and a solution of aminoacetaldehyde dimethyl acetal **28** (1.80 mL, 16.5 mmol, 1.5 equiv), Et_3N (2.30 mL, 16.5 mmol, 1.5 equiv), and DMAP (67 mg, 0.55 mmol, 0.05 equiv) in CH_2Cl_2 (30 mL) was added at 0 °C. After 5 h at rt, the reaction mixture was hydrolyzed with a 0.5 M aqueous solution of hydrochloric acid and extracted with ether. The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient: 60:40–50:50) to afford 2.57 g (67%) of **29** as a pale yellow solid; mp 90 °C; IR 3420, 3330, 1665, 1570, 1515, 1470, 1410, 1295, 1265, 1080, 1005, 915, 855, 805 cm^{-1}; ^1H NMR δ 7.20 (d, J=8.8 Hz, 1H), 6.77 (d, J=8.8 Hz, 1H), 6.04 (br t, J=5.5 Hz, 1H, NH), 4.50 (t, J=5.5 Hz, 1H), 3.83 (s, 3H) 3.82 (s, 3H) 3.56 (t, J=5.5 Hz, 2H), 3.39 (s, 6H); ^{13}C NMR δ 165.5 (s), 152.0 (s), 146.7 (s), 133.7 (s), 127.9 (d), 114.0 (d), 109.4 (s), 102.4 (d), 61.8 (q), 55.9 (q), 54.2 (q), 54.1 (q), 41.2 (t); MS (CI^+, CH_4) *m/z* (relative intensity) 348 ($M[^{81}Br]+H^+$, 95), 346 ($M[^{79}Br]+H^+$, 95), 319 ($M[^{81}Br]-MeO^+$, 35), 318 ($M[^{81}Br]-MeOH^+$, 100), 317 ($M[^{79}Br]-MeO^+$, 35), 316

($M[^{79}Br]-MeOH^+$, 100). HRMS (CI^+, CH_4) calcd for $C_{13}H_{19}O_5N^{81}Br$ ($M+H^+$): 348.0447. Found: 348.0440.

5.7.3. 6-Bromo-*N*-(2,2-dimethoxyethyl)-2,3-dimethoxy-*N*-trimethylsilylethynylbenzamide (30). To a solution of amide **29** (1.00 g, 2.87 mmol) in toluene (50 mL) at 0 °C, was added KHMDS (11.5 mL, 0.5 M in toluene, 5.74 mmol, 2 equiv). After 2 h at 0 °C, the iodonium salt **5** (2.59 g, 5.74 mmol, 2 equiv) was added to the reaction mixture. After 48 h at rt, the reaction mixture was filtered through Celite (toluene/diethyl ether: 80:20) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient: 90:10–80:20) to afford 596 mg (47%) of **30** as a yellow oil; IR 2180, 1690, 1585, 1575, 1470, 1410, 1355, 1315, 1295, 1250, 1180, 1125, 1090, 1060, 1005, 845, 760, 720, 705, 670, 665, 655, 620 cm^{-1}; ^1H NMR δ 7.21 (d, J=8.8 Hz, 1H), 6.83 (d, J=8.8 Hz, 1H), 4.78 (apparent t, J=5.9 Hz, 1H), 3.89 (s, 3H) 3.85 (s, 3H), 3.84 (dd, ABX syst., J=13.6, 5.9 Hz, 1H), 3.75 (dd, ABX syst., J=13.6, 5.9 Hz, 1H), 3.43 (s, 6H), −0.08 (s, 9H); ^{13}C NMR δ 168.2 (s), 151.9 (s), 146.8 (s), 132.4 (s), 127.4 (d), 114.6 (d), 109.3 (s), 100.8 (d), 96.2 (s), 74.4 (s), 61.4 (q), 56.2 (q), 53.6 (q), 53.5 (q), 48.0 (t), −0.30 (q, 3C); MS (CI^+, CH_4) *m/z* (relative intensity) 446 ($M[^{81}Br]+H^+$, 45), 444 ($M[^{79}Br]+H^+$, 44), 414 (60), 412 (58), 351 (25), 350 (100), 334 (25), 260 (20). HRMS calcd for $C_{18}H_{27}O_5NSi^{81}Br$ ($M+H^+$): 446.0824. Found: 446.0823.

5.7.4. 6-Bromo-*N*-ethynyl-*N*-(2,2-dimethoxyethyl)-2,3-dimethoxybenzamide (31). To a solution of **30** (500 mg, 1.12 mmol) in THF (15 mL) at 0 °C, was added TBAF (1.5 mL, 1 M in THF, 1.5 mmol, 1.3 equiv). After 10 min, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 70:30) to afford 376 mg (90%) of **31** as a pale yellow solid; mp 100–101 °C; IR 3300, 2150, 1690, 1475, 1415, 1355, 1295, 1270, 1090, 1050, 1000, 805, 670, 640 cm^{-1}; ^1H NMR δ 7.23 (d, J=8.5 Hz, 1H), 6.83 (d, J=8.5 Hz, 1H), 4.79 (t, J=5.7 Hz, 1H), 3.89 (s, 3H) 3.85 (s, 3H), 3.85 (dd, ABX syst., J=13.9, 5.7 Hz, 1H), 3.81 (dd, ABX syst., J=13.9, 5.7 Hz, 1H), 3.44 (s, 6H), 2.63 (s, 1H); ^{13}C NMR δ 167.8 (s), 151.7 (s), 146.6 (s), 131.8 (s), 127.4 (d), 114.5 (d), 108.9 (s), 100.7 (d), 77.1 [(NC≡C), the signal corresponding to the other ynamide carbon could not be unambiguously assigned presumably due to overlap], 61.4 (q), 55.9 (q), 53.8 (q), 53.7 (q), 48.5 (t); MS-EI *m/z* (relative intensity) 374 ($M[^{81}Br]+H^+$, 0.4), 373 ($M[^{81}Br]^+$, 3), 372 ($M[^{79}Br]+H^+$, 0.5), 371 ($M[^{79}Br]^+$, 3), 342 (6), 340 (6), 245 (77), 243 (79), 232 (8), 230 (6), 228 (10), 202 (11), 201 (5), 200 (12), 199 (5), 157 (5), 97 (6), 75 (100). HRMS calcd for $C_{15}H_{18}NO_5^{79}Br$ ($M+H^+$): 372.0447. Found: 372.0448.

5.7.5. 3-[(*E*)-(1-Benzo[1,3]dioxol-5-yl)methylidene]-2-(2,2-dimethoxyethyl)-6,7-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one (33). To a solution of ynamide **31** (561 mg, 1.51 mmol) in THF (60 mL) were successively added the arylboronic acid **32** (300 mg, 1.81 mmol, 1.2 equiv), a 1 M aqueous solution of NaOH (2.3 mL, 2.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (17 mg, 0.075 mmol, 0.05 equiv) and PPh_3 (40 mg, 0.15 mmol, 0.1 equiv). After 2 h at reflux, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 60:40) to afford 480 mg (77%) of **33**[15b] as a yellow oil and as a 85/15 mixture of (*E*)/(*Z*) geometric isomers; IR 1690, 1640, 1500, 1430, 1330, 1270, 1235, 1120, 1095, 1035, 935, 825, 740 cm^{-1}; ^1H NMR (only the signals corresponding to the (*E*) major isomer could all be attributed unambiguously) δ 7.09 (d, J=8.5 Hz, 1H), 6.90–6.75 (m, 4H), 6.48 (s, 1H), 6.00 (s, 2H) 4.67 (t, J=5.1 Hz, 1H) 4.06 (s, 3H), 3.94 (d, J=5.1 Hz, 2H), 3.84 (s, 3H), 3.43 (s, 6H); ^{13}C NMR (only the signals corresponding to the major (*E*) isomer could all be attributed unambiguously) δ 164.7 (s), 153.2 (s), 147.7 (s), 146.9 (s), 146.4 (s), 135.5 (s), 129.0 (s), 128.7 (s), 123.0 (d), 122.0 (s), 118.8 (d), 115.8 (d) 109.6 (d), 108.7 (d), 108.4 (d), 102.2 (d), 101.1 (t), 62.2 (q), 56.4 (q), 54.4 (q, 2C), 41.7 (t); MS-EI *m/z* (relative intensity) 414 ($M+H^+$, 3), 413 (M^+, 42), 398 (3), 381 (8), 350 (6), 338 (14), 325 (11), 308 (9), 294 (7), 280 (8), 264 (6), 207 (20), 75 (100).

5.7.6. (1-Benzo[1,3]dioxol-5-yl)methyl-2-(2,2-dimethoxyethyl)-6,7-dimethoxy-2,3-dihydroisoindol-1-one (34). A mixture of **33** (231 mg, 0.559 mmol) and Pd (10%)/C (30 mg, 0.028 mmol, 0.05 equiv) in MeOH (8 mL) was stirred under an atmospheric pressure of hydrogen. After 4 h, the reaction mixture was filtered through Celite (MeOH) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 60:40) to afford 187 mg (80%) of **34**[15b] as a white solid; mp 125–126 °C; IR 1682, 1490, 1440, 1404, 1266, 1245, 1192, 1122, 1094, 1036, 981, 927, 811, 782, 730, 662, 609 cm^{-1}; ^1H NMR δ 6.97 (d, J=8.4 Hz, 1H), 6.65 (d, J=8.4 Hz, 1H), 6.62 (dd, J=8.1, 0.7 Hz, 1H), 6.47–6.41 (m, 2H), 5.90 (d, J=1.4 Hz, 1H), 5.89 (d, J=1.4 Hz, 1H), 4.80 (dd, J=8.1, 3.7 Hz, 1H), 4.54 (dd, J=6.6, 3.6 Hz, 1H), 4.18 (dd, J=14.3, 3.6 Hz, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.31 (dd, J=13.8, 3.8 Hz, 1H), 3.19 (dd, J=14.3, 6.6 Hz, 1H), 2.65 (dd, J=13.8, 8.0 Hz, 1H); ^{13}C NMR δ 166.7 (s), 152.3 (s), 147.5 (s), 147.0 (s), 146.4 (s), 138.9 (s), 129.6 (s), 124.1 (s), 122.7 (d), 118.0 (d), 116.0 (d), 109.7 (d), 108.1 (d), 103.4 (d), 100.9 (t), 62.4 (q), 60.2 (d), 56.7 (q), 55.4 (q), 54.7 (q), 42.2 (t), 37.8 (t); MS-EI *m/z* (relative intensity) 414 ($M-H^+$, 0.1), 384 (5), 281 (16), 280 (100), 249 (12), 248 (79), 206 (6), 205 (4), 190 (5), 176 (4), 162 (4), 135 (9), 77 (6), 75 (12).

5.7.7. Dehydrolennoxamine (35).[15b] To a solution of **34** (115 mg, 0.277 mmol) in AcOH (3 mL) was slowly added H_2SO_4 (0.12 mL, 2.4 mmol, 8.5 equiv). After 3 h at rt, the reaction mixture was neutralized by dropwise addition of 28% aqueous NH_4OH at 0 °C. The resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 60:40) to afford 58 mg (60%) of **35** as a yellow solid; mp 224–225 °C; IR 1689, 1650, 1491, 1450, 1357, 1266, 1237, 1216, 1032, 928, 854, 828, 814, 792, 769 cm^{-1}; ^1H NMR δ 7.18 (s, 2H), 7.10 (d, J=10.5 Hz, 1H), 6.70

(apparent s, 2H), 5.96 (apparent br s, 2H), 5.66 (d, J= 10.5 Hz, 1H), 4.68 (d, J=9.4 Hz, 1H), 4.10 (s, 3H), 3.92 (s, 3H), 3.34 (d, J=15.7 Hz, 1H), 3.00 (dd, J=15.1, 9.4 Hz, 1H); ^{13}C NMR δ 163.6 (s), 152.8 (s), 147.6 (s), 146.7 (s), 146.4 (s), 137.4 (s), 130.0 (s), 129.2 (s), 123.0 (s), 120.0 (d), 117.4 (d), 117.2 (d), 110.5 (d), 110.0 (d), 109.2 (d), 101.2 (t), 62.5 (q), 59.7 (d), 56.8 (q), 42.2 (t); MS-EI *m/z* (relative intensity) 352 ($M+H^+$, 20), 351 (M^+, 100), 350 ($M-H^+$, 9), 336 (8), 322 (8), 207 (11), 160 (48), 130 (18), 102 (14).

5.7.8. Lennoxamine.[15b,41] A mixture of **35** (58 mg, 0.16 mmol) and Pd (10%)/C (17.5 mg, 0.016 mmol, 0.05 equiv) in AcOH (15 mL) was stirred under an atmospheric pressure of hydrogen. After 14 h at rt, the reaction mixture was filtered through Celite (AcOH) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chomatography (petroleum ether/EtOAc: 50:50) to afford 37 mg (65%) of lennoxamine as a white solid; mp 226–228 °C; IR 1679, 1483, 1424, 1263, 1196, 1172, 1035, 934, 834 cm^{-1}; ^{1}H NMR δ 7.16 (d, J=8.3 Hz, 1H), 7.11 (d, J=8.3 Hz, 1H), 6.76 (s, 1H), 6.69 (s, 1H), 5.94 (d, J=1.5 Hz, 1H), 5.93 (d, J=1.5 Hz, 1H), 4.78–4.67 (m, 1H), 4.28 (dd, J= 10.5, 1.5 Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.09 (dd, J=14.7, 1.9 Hz, 1H), 2.93–2.75 (m, 4H); ^{13}C NMR δ 165.2 (s), 152.6 (s), 147.3 (s), 146.4 (s), 146.1 (s), 138.2 (s), 134.8 (s), 131.0 (s), 124.2 (s), 117.0 (d), 116.2 (d), 110.4 (d), 110.3 (d), 101.1 (t), 62.5 (q), 60.2 (d), 56.7 (q), 42.7 (t), 41.1 (t), 35.9 (t); MS (CI^+, CH_4) *m/z* (relative intensity) 354 ($M+H^+$, 100), 353 (8), 318 (10), 316 (10). HRMS calcd for $C_{20}H_{20}NO_5$ ($M+H^+$): 354.1341. Found: 354.1337.

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