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Efficient access to (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives by orthopalladation and carbonylation of methyl arylglycinate substrates

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ABSTRACT

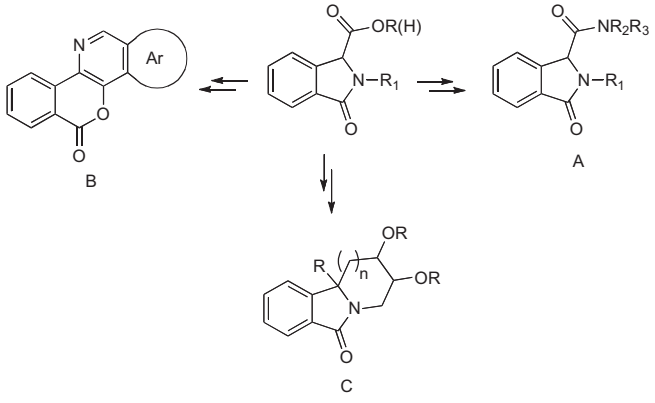
The orthopalladation of methyl arylglycinate derivatives has been studied. The reaction proceeds efficiently for different electron-withdrawing and electron-releasing substituents at the aryl ring. The carbonylation of the orthopalladated complexes affords, in a single step, substituted (1*H*)-isoindolin-1-one-3-carboxylates. These compounds constitute valuable synthetic intermediates and can be transformed diastereoselectively into octahydroisoindole-1-carboxylic acid derivatives, an important scaffold in the synthesis of many biologically active compounds.

1. Introduction

Isoindolinone is the core skeleton present in a great variety of natural compounds with important biological activities.[1,2] In particular, the 3-substituted isoindolinone ring system is an integral part of naturally occurring substances, such as lennoxamine or nuevamine[3] and it is present in the structure of many pharmacophores.[4] In fact, some of its derivatives possess anxiolytic activity and are of interest as sedatives, hypnotics, and muscle relaxants.

Apart from the fact that (1*H*)-isoindolin-1-one-3-carboxylic acid can be considered as a fused proline, many derivatives are particularly relevant because they are valuable synthetic intermediates in the preparation of several compounds that display interesting biological activities (Scheme 1). Thus, this compound is an essential scaffold in the synthesis of potential drugs useful in the treatment of pain disorders[5] or arrhythmias[6] (compounds type A).

In addition, (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives are used as intermediates in the synthesis of polycyclic systems structurally related to biologically active alkaloids. Thus, they have been transformed into polycyclic compounds type B, structurally related to alkaloids possessing a benzopyranisoquinoline skeleton.[7]



Scheme 1. (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives as synthetic intermediates.

This family of substances, in many cases, exhibit a remarkable physiological activity[8] (anti-inflammatory, dopaminergic, and antidepressant). (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives have also been used in the synthesis of novel polycyclic azacompounds structurally related with pyrrolizidine and indolizidine derivatives.[9] Alkaloids characterized by these skeletons often display biological activities as glycosidases inhibitors. Therefore they can be

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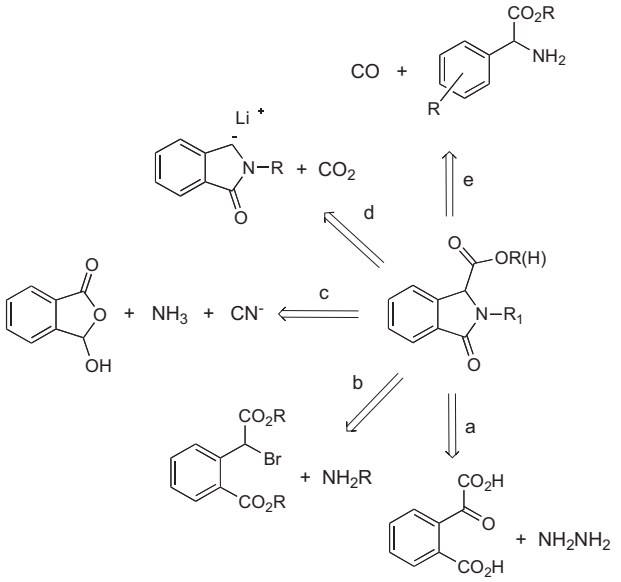
used for the treatment of many diseases, such as diabetes, cancer, and viral infections.[10]

Due to the utility of (1*H*)-isoindolin-1-one-3-carboxylic acid as the starting material in the preparation of such compounds, many synthetic approaches have been described in literature (Scheme 2). Thus, the pattern compound can be obtained from phthalonic acid by treatment with hydrazine and reduction with zinc[11] or by cyclization of alkyl α-bromohomophthalates in the presence of amines[7b] (paths a and b). Other preparative pathways to the synthesis of this compound consist of the addition of ammonia and cyanide to phthalaldehydic acid[12] (path c) and in the nucleophilic attack of 3-metalated isoindolinones to CO_2[13] (path d).



Scheme 2. Retrosynthetic analysis for (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives.

The great interest of (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives makes necessary efforts to find a general procedure to give access to differently substituted derivatives that could be used in the synthesis and exploration of new biologically active compounds and pharmacophores. The synthetic methodologies described above occur with medium to high yields, but they are not easily extended to the synthesis of compounds with different substituents in the aromatic ring and, to the best of our knowledge, a general procedure of general scope has never been reported.

The use of organometallic complexes as intermediates in organic syntheses provides preparative pathways complementary, even sometimes alternative, to the classical organic procedures previously detailed. Orthopalladated complexes of a wide prospect of ligands react smoothly with carbon monoxide, incorporating this molecule to the organic skeleton of the ligand.[14] Usually, this well known reaction occurs in three steps, namely the bonding of the CO, its subsequent migratory insertion and the final reductive elimination with concomitant C–C and/or C–X coupling. The synthesis of many carbo- and heterocycles has been achieved in this way, and the (1*H*)-isoindolin-1-ones are not an exception (path e). In fact, several reports have appeared during the last years showing a renewed interest on this subject.[15]

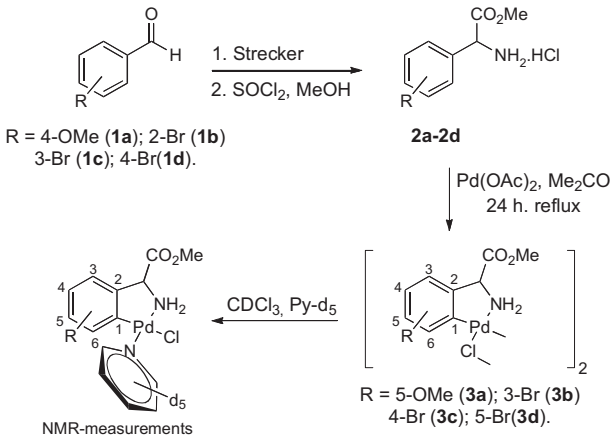
However, the synthesis of (1*H*)-isoindolin-1-ones containing a strong electron-attracting group at the benzylic Cα atom has not been reported until recently. A report by our group described the stoichiometric carbonylation of methyl (*R*)-phenylglycinate,[16] while García et al. have reported a catalytic version of the process using quaternary derivatives of phenylglycine and phenylalanine as starting compounds.[15h]

Here we report the Pd-mediated carbonylation of a series of arylglycine derivatives, containing both electro-withdrawing and electron-releasing groups in different positions of the aryl ring. The reaction affords the corresponding substituted (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives, expanding the scope of previous procedures and providing a general access to this class of compounds. In addition, this method starts from arylglycines, which are easily available in a few steps via a Strecker synthesis from commercial aromatic aldehydes, uses mild reaction conditions and allows isolation of pure compounds without need of further chromatographic purifications.

2. Results and discussion

2.1. Synthesis of the orthopalladated complexes

According to that exposed above, the first stage in this strategy involved the synthesis of the methyl arylglycinate derivatives **2a**–**d**, which were easily prepared starting from commercially available aldehydes **1a**–**d** via conventional Strecker reaction[17] and later esterification with methanol and thionyl chloride. The reaction of these species with $Pd(OAc)_2$, in order to obtain the corresponding orthopalladated complexes, has been carried out under the same experimental conditions as those reported previously by Fuchita et al.[18] (Scheme 3).



Scheme 3. Synthesis and characterization of the orthopalladated complexes.

Complexes **3a**–**d** were obtained as yellowish-orange solids in moderate yields. The chromatographic purification of the crude mixtures was necessary in all cases, due to the presence of variable amounts of the coordinated complexes $[PdCl_2L_2]$ (L=amino ester). In spite of this, we have found that the reaction works with similar yields in the presence of electron-releasing (**3a**) or electron-withdrawing (**3b**–**d**) substituents at the aryl group, and regardless these substituents are in *ortho*- (**3b**), *meta*- (**3c**) or *para*- (**3d**) positions with respect to the amino ester fragment. These facts confer a wide scope of applicability to this method.

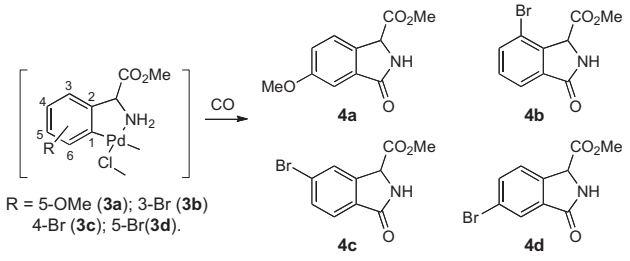
The characterization of organometallic derivatives **3a**–**d** has been performed through the usual methods. All complexes show correct elemental analyses and mass spectra for the proposed dinuclear stoichiometries. The IR spectra show strong absorptions due to the carbonyl stretch (around 1730–1740 cm^{-1}) and the N–H stretch (3200–3300 cm^{-1} region). In order to simplify the NMR spectra of **3a**–**d**, and to achieve a rigourous assignation of signals, the spectra have been measured in presence of a small amount of pyridine-d_5. This is a very common feature when complicated spectra are expected due to the simultaneous presence of stereoisomers and geometric isomers. The pyridine cleaves the halide

bridge and affords a mononuclear complex with the pyridine bonded *trans* to the N atom of the orthopalladated ligand (see Scheme 3).[19] In this way, only a set of signals is expected, and all signals can be clearly identified and assigned.

The comparison of the ^{1}H NMR spectra of complexes **3a**–**d** with those of the precursors **2a**–**d** show clearly the disappearance of one signal due to an aromatic proton, with concomitant change of the corresponding spins systems. The ^{13}C NMR spectra of **3a**–**d** show peaks assigned to six chemically unequivalent aromatic C nuclei. Both facts suggest that the C–H bond activation process and the Pd incorporation have taken place at the aryl ring. Moreover, the *N*-bonding to the Pd metal center of the NH_2 moiety is clearly inferred from the deshielding of the aminic H protons, which appear as unequivalent due to the presence of the stereogenic Cα atom. Therefore, the C,*N*-chelating mode of the orthopalladated amino ester ligand is evident from the NMR data. In addition, one of the signals of the cyclopalladated ring (H_6) in the aromatic region appears strongly shielded, due to the anisotropic shielding promoted by the pyridine ring.[19] All these data are in good agreement with the proposed structure in Scheme 3 for complexes **3**.

2.2. Synthesis of (1*H*)-isoindolinones by carbonylation

The complexes **3a**–**d** react smoothly with CO in $CHCl_3$ at room temperature giving the corresponding methyl (1*H*)-isoindolin-1-one-3-carboxylates **4a**–**d** with excellent yields (Scheme 4). The carbonylation process takes place under mild reaction conditions (CO 1 atm; 25 °C, 12 h). During reaction the formation of black Pd is evident. However, the isolation of **4a**–**d** as analytically pure solids is achieved after a very simple workup, namely the filtration to eliminate the metallic Pd^0, evaporation of the solvent and precipitation with Et_2O. The yields of isolated product are in all studied cases around or higher than 90%, in spite of the presence of substituents of different electronic nature (Br vs OMe) located at different positions (*ortho*-, *meta*- ,and *para*). Particularly interesting are the bromo-substituted derivatives **4b**–**d**, since they could be used as starting compounds in further Pd-catalyzed C–C and/or C-heteroatom couplings (Suzuki, Stille, Sonogashira, or others). Therefore, both the C–H activation and the carbonylation are produced in a wide array of substrates. The general method here presented provides access to a wide range of starting materials, avoids extreme reaction conditions and/or unstable reagents and uses cheap precursors like arylic aldehydes.



Scheme 4. Synthesis of the (1*H*)-isoindolin-1-one derivatives **4a**–**d** by carbonylation of the orthopalladated complexes **3a**–**d**.

The characterization of the methyl (1*H*)-isoindolin-1-one-3-carboxylates has been carried out on the basis of their spectroscopic and analytic data. The NMR spectra of **4a**–**d** show the same pattern of resonances as that observed for their precursors **3a**–**d**, and a new signal in the ^{13}C NMR spectra due to the carbonylic amide. The IR spectra of **4a**–**d** also show a new strong absorption around 1690 cm^{-1}, due to the new carbonyl moiety. Moreover, the X-ray crystal structure of compound **4c** has been determined by X-ray diffraction methods. A molecular drawing of this compound is shown in Fig. 1. The comparison of the structural parameters of **4c** with analogous isoindolinones shows an identical pattern of bond distances and angles, within experimental error, and does not merit further discussion.[16]

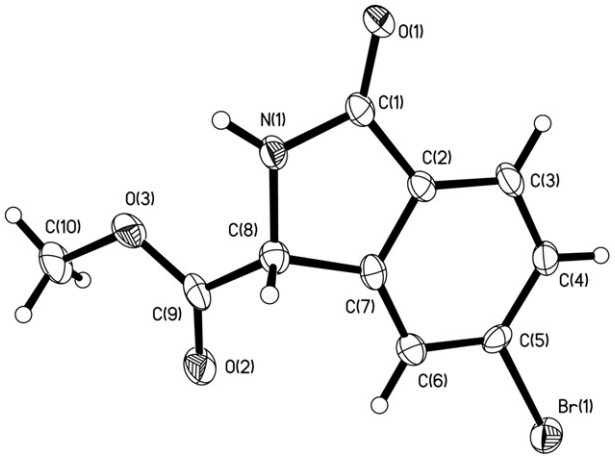
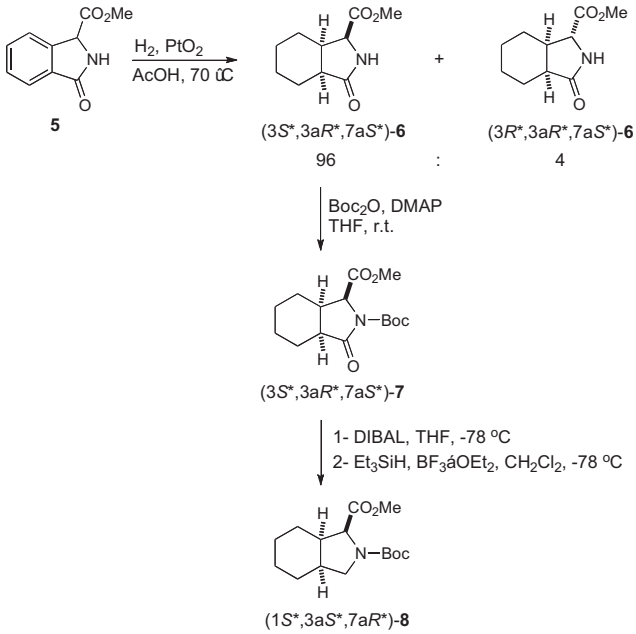


Fig. 1. Molecular drawing of compound **4c**. Ellipsoids of non-hydrogen atoms have been drawn at 50% probability.

2.3. Synthesis of octahydroisoindole derivatives by hydrogenation of (1*H*)-isoindolinones

As exposed in the Introduction, isoindolin-1-one-3-carboxylic acid derivatives are valuable synthetic intermediates in the preparation of several compounds. Herein we report a synthetic route that allows their transformation into octahydroisoindole-1-carboxylic acid derivatives (Scheme 5).



Scheme 5. Synthesis of protected (1*S**,3a*S**,7a*R**) octahidroisoindole-1-carboxylic acid starting from methyl (1*H*)-isoindolin-1-one-3-carboxylate.

Octahydroisoindole-1-carboxylic acid, a [*c*]-fused bicyclic proline analogue, has proven to be an essential scaffold in the synthesis of biologically active compounds and constitutes the core structure of molecules that can be useful in the treatment of osteoarthritis and rheumatoid arthritis,[20] in the inhibition or prevention of leukocyte adhesion and leukocyte adhesion mediated pathologies[21] or as antihypertensive agents.[22]

As shown in Scheme 5, the first step in this route involved the reduction of the benzene ring in **5**. Compound **5** was obtained as previously described in our research group.[16] The hydrogenation of the aromatic ring was achieved following the procedure previously described by some of us.[23] The process was completed smoothly under atmospheric pressure of hydrogen gas using platinum(IV) oxide as catalyst and provided the stereoisomers (3*S**,3a*R**,7a*S**)-**6** and (3*R**,3a*R**,7a*S**)-**6** in a 96:4 ratio, which was established by analysis of the relative intensities of the appropriate signals in ^{1}H NMR spectra of the crude. This stereoselectivity in the reduction process can be explained considering that benzene ring hydrogenation in **5** takes place from the less hindered face, i.e., that opposite to where carboxylate group lies. The relative configuration in (3*S**,3a*R**,7a*S**)-**6** was confirmed by a 2D NOESY experiment, which showed a NOE interaction between 3-H and 7a-H.

Compound (3*S**,3a*R**,7a*S**)-**6** was separated by column chromatography and transformed into the *N*-Boc derivative (3*S**,3a*R**,7a*S**)-**7** by treatment with di-*tert*-butyl dicarbonate. The introduction of a Boc group in nitrogen improved the lactam carbonyl group electrophilia and allowed its reduction to a methylene group by reaction with DIBAL and triethylsilane to afford the octahydroisoindole-1-carboxylic acid derivative (1*S**,3a*S**,7a*R**)-**8** with a 65% overall yield starting from **5**.

3. Conclusion

The orthopalladation of substituted arylglycine derivatives and subsequent carbonylation of the respective metalated complexes affords the corresponding (1*H*)-isoindolin-1-one-3-carboxylates in good yields. This synthetic route is of general applicability and can be considered as complementary to other preparative methods. The hydrogenation of the methyl (1*H*)-isoindolin-1-one-3-carboxylate takes place under mild reaction conditions and gives the octahydroisoindole-1-carboxylic acid derivative, this step occurring diastereoselectively.

4. Experimental

4.1. General

All reagents were used as received from commercial suppliers without further purification. Thin-layer chromatography (TLC) was performed on Macherey–Nagel Polygram® SIL G/UV$_{254}$ precoated silica gel polyester plates. The products were visualized by exposure to UV light (254 nm), iodine vapors or charring with cerium molybdate stain [aqueous solution of phosphomolybdic acid (2%), $CeSO_4\cdot 4H_2O$ (1%) and H_2SO_4 (6%)]. Column chromatography was performed using 60 Å (0.04–0.063 mm) silica gel from Macherey–Nagel. Melting points were determined on a Gallenkamp apparatus. IR spectra were registered on a Nicolet Avatar 360 FTIR or a Perkin–Elmer Spectrum One IR spectrophotometer; ν_{max} is given for the main absorption bands. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer at 25 °C using the residual solvent signal as the internal standard; chemical shifts (δ) are expressed in parts per million and coupling constants (J) in hertz. Electrospray Ionization (ESI)/Atmospheric Pressure Chemical Ionization (APCI) mass spectra were recorded using an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonic GmbH, Bremen, Germany) equipped with a standard ESI/APCI source. Samples were introduced by direct infusion with a syringe pump. Nitrogen served both as the nebulizer gas and the dry gas. Helium served as a cooling gas for the ion trap and collision gas for MS_n experiments. Other mass spectra (2-DIT) were recorded from CH_2Cl_2 solutions on a Bruker MicroFlex spectrometer. Elemental analyses were carried out on a Perkin–Elmer 2400-B microanalyzer. High-resolution mass spectra were obtained on a Bruker Microtof-Q spectrometer.

4.2. X-ray diffraction

Crystals of adequate quality for X-ray measurements were grown by diffusion of Et_2O into a CH_2Cl_2 solution of the crude **4c** at 25 °C. A single crystal was mounted at the end of a quartz fiber in a random orientation, covered with magic oil and placed under the cold stream of nitrogen. Data collection was performed at low temperature (150 K) on an Oxford Diffraction Xcalibur2 diffractometer using graphite-monochromated Mo-Kα radiation (λ=0.71073 Å). A hemisphere of data was collected based on three ω-scan or φ-scan runs. The diffraction frames were integrated using the program CrysAlis RED[24] and the integrated intensities were corrected for absorption with SADABS.[25] The structures were solved and developed by Patterson and Fourier methods.[26] The structures were refined to F_0^2, and all reflections were used in the least-squares calculations.[27] Crystallographic data (excluding structure factors) for the structure of **4c** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 815111. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.3. General procedure for the synthesis of methyl arylglycinate derivatives

A mixture of NaCN (343 mg, 7.0 mmol) and NH_4Cl (375 mg, 7.0 mmol) in H_2O (3 mL) was stirred at room temperature for 10 min. Then, aldehyde **1** (7.0 mmol) in MeOH (3 mL) was added. The reaction mixture was stirred at room temperature for 24 h. Then, water (8 mL) was added and the organic solvent was evaporated. The remaining aqueous phase was extracted with dichloromethane and the organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was dissolved in aqueous HCl 6 N (9 mL) and stirred under reflux for 3 days. Then, the reaction mixture was evaporated under vacuum and the white solid obtained treated with a mixture of isopropanol/water. The precipitated solid (NH_4Cl) was filtered off and the remaining solution evaporated.

Thionyl chloride (1.1 mL, 14.51 mmol) was added dropwise to an ice-cooled solution of the residue obtained above in dry methanol (18 mL). The resulting solution was stirred at room temperature for 24 h. The solvent was concentrated under vacuum and the resulting residue was liophilized and washed with small portions of ethyl acetate to afford the corresponding methyl arylglycinate derivative.

*4.3.1. Methyl (4-methoxyphenyl)glycinate hydrochloride (**2a**).* White solid (941 mg, 4.06 mmol, 58%). Mp 186–188 °C, (lit.[28] 187–189 °C). IR (KBr): ν=3448, 3018, 1741, 1616 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.03 (br s, 3H, NH_3), 7.42 (d, J=8.8 Hz, 2H, Ar), 7.00 (d, J=8.8 Hz, 2H, Ar), 5.19 (s, 1H, α-H), 3.77 (s, 3H, OMe), 3.70 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=169.12 (CO), 160.05 (Ar), 129.72 (Ar), 124.46 (Ar), 114.37 (Ar), 55.32 (OMe), 54.75 (α-C), 53.08 (OMe) ppm. HRMS (ESI): calcd for $C_{10}H_{14}NO_3$ $[M-Cl]^+$ 196.0968; found 196.0960.

*4.3.2. Methyl (2-bromophenyl)glycinate hydrochloride (**2b**).* White solid (884 mg, 3.15 mmol, 45%). Mp 166–168 °C. IR (KBr): ν=3450, 3019, 1749, 1598 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.36 (br s, 3H, NH_3), 7.75 (dd, J=7.9, 1.0 Hz, 1H, Ar), 7.65 (dd, J=7.9, 1.5 Hz, 1H, Ar), 7.50 (td, J=7.9, 1.0 Hz, 1H, Ar), 7.39 (td, J=7.9, 1.5 Hz, 1H, Ar), 5.42 (s, 1H, α-H), 3.70 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=168.01 (CO), 133.43 (Ar), 132.15 (Ar), 131.68 (Ar), 129.51 (Ar), 128.62 (Ar), 124.13 (Ar), 54.82 (α-C), 53.48 (OMe) ppm. HRMS (ESI): calcd for $C_9H_{11}BrNO_2$ $[M-Cl]^+$ 243.9968; found 243.9960.

*4.3.3. Methyl (3-bromophenyl)glycinate hydrochloride (**2c**).* White solid (982 mg, 3.50 mmol, 50%). Mp 198–200 °C. IR (KBr): ν=3434,

3020, 1753, 1602 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=9.19 (br s, 3H, NH_3), 7.80 (t, J=1.8 Hz, 1H, Ar), 7.66 (ddd, J=7.9, 1.8, 1.0 Hz, 1H, Ar), 7.56–7.52 (m, 1H, Ar), 7.43 (t, J=7.9 Hz, 1H, Ar), 5.35 (s, 1H, α-H), 3.72 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=168.40 (CO), 135.01 (Ar), 132.44 (Ar), 131.19 (Ar), 131.13 (Ar), 127.45 (Ar), 121.96 (Ar), 54.56 (α-C), 53.37 (OMe) ppm. HRMS (ESI): calcd for $C_9H_{11}BrNO_2$ $[M-Cl]^+$ 243.9968; found 243.9964.

*4.3.4. Methyl (4-bromophenyl)glycinate hydrochloride (**2d**).* White solid (1.080 g, 3.85 mmol, 55%). Mp 184–186 °C. IR (KBr): ν=3430, 3018, 1750, 1601 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=9.23 (br s, 3H, NH_3), 7.67 (d, J=8.5 Hz, 2H, Ar), 7.49 (d, J=8.5 Hz, 2H, Ar), 5.31 (s, 1H, α-H), 3.70 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=168.50 (CO), 131.99 (Ar), 131.95 (Ar), 130.61 (Ar), 123.03 (Ar), 54.66 (α-C), 53.30 (OMe) ppm. HRMS (ESI): calcd for $C_9H_{11}BrNO_2$ $[M-Cl]^+$ 243.9968; found 243.9962.

4.4. General orthopalladation procedure

A mixture of the corresponding α-amino ester hydrochlorides **2a**–**d** (1 equiv) and $Pd(OAc)_2$ (1 equiv) in acetone were refluxed for 24 h. The resulting solution was filtered through a plug of Celite, and purified by silica gel chromatography using ethyl acetate as eluent. The evaporation of solvent allowed the isolation of the respective orthopalladated complexes **3a**–**d**.

In the case of the synthesis of complex [Pd(μ-Cl){C_6H_3-(CH(CO_2Me)NH_2)-2-Br-3}]$_2$ (**3b**) a mixture of several species was obtained. The main component of this mixture (around 90%), was complex **3b**. This mixture could not be purified by column chromatography, therefore it was employed as starting material for the synthesis of the corresponding isoindolinone **4b**.

*4.4.1. Synthesis of [Pd(μ-Cl){C_6H_3-(CH(CO_2Me)NH_2)-2-OMe-5}]$_2$ (**3a**).* Compound **2a** (200 mg, 0.86 mmol), $Pd(OAc)_2$ (194 mg, 0.86 mmol) and acetone (200 mL) were reacted as previously described giving [Pd(μ-Cl){C_6H_3-(CH(CO_2Me)NH_2)-2-OMe-5}]$_2$ (**3a**) as a yellow solid.(172 mg, 0.26 mmol, 59%). IR (neat): ν=3367, 3265, 1737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$+py-d_5): δ=6.94 (d, J=8.4 Hz, 1H, Ar), 6.53 (dd, J=8.4, 2.6 Hz, 1H, Ar), 5.57 (d, J=2.6 Hz, 1H, Ar), 4.90 (pseudot, J=8.0 Hz, 1H, CH), 4.66 (br s, 1H, NH), 4.54 (br s, 1H, NH), 3.80 (s, 3H, OMe), 3.51 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+py-d_5): δ=170.87 (CO), 157.27 (Ar), 149.87 (Ar), 123.80 (Ar), 118.55 (Ar), 109.94 (Ar), 105.42 (Ar), 64.70 (CH), 54.97 (OMe), 53.27 (OMe) ppm. Anal. Calcd for $C_{20}H_{24}Cl_2N_2O_6Pd_2$ (672.17): C, 35.74; H, 3.60; N, 4.17. Found: C, 36.29; H, 4.09; N, 4.14. Mass Spect. (MALDI$^+$-DIT) [m/z]: 637.2 $[M-Cl]^+$.

*4.4.2. Synthesis of [Pd(μ-Cl){C_6H_3-(CH(CO_2Me)NH_2)-2-Br-4}]$_2$ (**3c**).* Compound **2c** (242 mg, 0.86 mmol) and $Pd(OAc)_2$ (194 mg, 0.86 mmol) in acetone (200 mL) were reacted as previously described giving [Pd(μ-Cl){C_6H_3-(CH(CO_2Me)NH_2)-2-Br-4}]$_2$ (**3c**) as an orange solid (207 mg, 0.27 mmol, 62%). IR (neat): ν=3312, 3222, 1739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$+py-d_5): δ=7.26 (d, J=2.6 Hz, 1H, Ar), 6.91 (dd, J=8.6, 2.6 Hz, 1H, Ar), 5.89 (d, J=8.6 Hz, 1H, Ar), 5.10 (br s, 1H, NH), 4.92 (m, 1H, CH), 4.57 (br s, 1H, NH), 3.82 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+py-d_5): δ=170.16 (CO), 151.07, (Ar), 134.13(Ar), 129.39 (Ar), 126.15 (Ar), 123.16 (Ar), 118.43 (Ar), 65.02 (s, CH), 52.39 (s, OMe) ppm. Anal. Calcd for $C_{18}H_{18}Br_2Cl_2N_2O_4Pd_2$ (769.91): C, 28.08; H, 2.36; N, 3.64. Found: C, 28.48; H, 2.09; N, 3.23. Mass Spect. (MALDI$^+$-DIT) [m/z]: 385.3 $[M/2]^+$.

*4.4.3. Synthesis of [Pd(μ-Cl){C_6H_3-(CH(CO_2Me)NH_2)-2-Br-5}]$_2$ (**3d**).* Compound **2d** (242 mg, 0.86 mmol) and $Pd(OAc)_2$ (194 mg, 0.86 mmol) in acetone (200 mL) were reacted as previously described giving [Pd(μ-Cl){C_6H_3-(CH(CO_2Me)NH_2)-2-Br-5}]$_2$ (**3d**) as an orange solid (217 mg, 0.28 mmol, 66%). IR (neat): ν=3312, 3222, 1739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$+py-d_5): δ=7.11 (dd, J=8.0, 2.6 Hz, 1H, Ar), 6.98 (d, J=8.0 Hz, 1H, Ar), 6.13 (br s, 1H, Ar), 5.11 (br s, 1H, NH), 4.89 (pseudot, J=8.0 Hz, 1H, CH), 4.56 (br s, 1H, NH), 3.79 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+py-d_5): δ=170.36 (CO), 151.12 (Ar), 135.23 (Ar), 128.15 (Ar), 125.53 (Ar), 122.18 (Ar), 117.66 (Ar), 65.02 (s, CH), 52.39 (s, OMe) ppm. Anal. Calcd for $C_{18}H_{18}Br_2Cl_2N_2O_4Pd_2$ (769.91): C, 28.08; H, 2.36; N, 3.64. Found: C, 28.72; H, 2.09; N, 3.23. Mass Spect. (MALDI$^+$-DIT) [m/z]: 385.7 $[M/2]^+$.

4.5. General carbonylation procedure

A suspension of the corresponding orthopalladated complex **3a**–**d** in chloroform was stirred under CO atmosphere (1 atm) overnight. Then, the dark suspension was filtered through a plug of Celite and the resulting solution was evaporated to dryness. The residue was dissolved in dichloromethane and the addition of *n*-hexane caused the precipitation of the corresponding isoindolones **4a**–**d** as white solids.

*4.5.1. Methyl 6-methoxy-(1H)-isoindolin-1-one-3-carboxylate (**4a**).* Complex **3a** (200 mg, 0.30 mmol) and chloroform (20 mL) under CO atmosphere were employed for the synthesis of the isoindolinone **4a** (118 mg, 0.53 mmol, 90%). Crystals of **4a** $0.25CH_2Cl_2$ were obtained by diffusion of *n*-hexane (10 mL) into a saturated solution of this compound in CH_2Cl_2 (5 mL). IR (neat): ν=3195, 1747, 1695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.58 (d, J=8.4 Hz, 1H, Ar), 7.33 (d, J=2.5 Hz, 1H, Ar), 7.15 (dd, J=8.4, 2.5 Hz, 1H, Ar), 6.51 (br s, 1H, NH), 5.20 (s, 1H, 3-H), 3.86 (s, 3H, OMe), 3.81 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.07 (CO), 169.19 (CO), 160.95 (Ar), 132.89 (Ar), 132.66 (Ar), 124.61 (Ar), 120.76 (Ar), 106.72 (Ar), 58.10 (3-C), 55.79 (OMe), 53.10 (OMe) ppm. Anal. Calcd for $[C_{11}H_{11}NO_4]$ $0.25CH_2Cl_2$ (242.21): C, 55.73; H, 4.78; N, 5.77. Found: C, 55.72; H, 5.09; N, 5.23. Mass Spect. (ESI$^+$) [m/z]: 221.9 $[M]^+$.

*4.5.2. Methyl 4-bromo-(1H)-isoindolin-1-one-3-carboxylate (**4b**).* Compound **4b** was prepared by carbonylation of the crude of the reaction between **2b** and $Pd(OAc)_2$. This mixture of species (112 mg), containing mainly **3b** (90%), was dissolved in chloroform (10 mL) and allowed to stir under CO atmosphere. Obtained: 61.0 mg, 0.226 mmol (86.4% yield). IR (neat): ν=3162, 1742, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.77 (d, J=7.6 Hz, 1H, Ar), 7.66 (d, J=7.6 Hz, 1H, Ar), 7.37 (t, J=7.6 Hz, 1H, Ar), 7.23 (br s, 1H, NH), 5.12 (s, 1H, 3-H), 3.71 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.96 (CO), 166.90 (CO), 140.50 (Ar), 134.87 (Ar), 132.97 (Ar), 130.08 (Ar), 122.17 (Ar), 117.35 (Ar), 58.61 (3-C), 52.15 (OMe) ppm. Anal. Calcd for $[C_{10}H_8BrNO_3]CHCl_3$ (389.46): C, 33.92; H, 2.33; N, 3.59. Found: C, 34.02; H, 2.21; N, 3.70. Mass Spect. (ESI$^+$) [m/z]: 269.9 $[M]^+$.

*4.5.3. Methyl 5-bromo-(1H)-isoindolin-1-one-3-carboxylate (**4c**).* Complex **3c** (150 mg, 0.20 mmol) and chloroform (15 mL) under CO atmosphere were employed for the synthesis of **4c**. (97 mg, 0.36 mmol, 92%). IR (neat): ν=3172, 1744, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.88 (s, 1H, Ar), 7.87 (br s, 1H, NH), 7.69–7.71 (m, 2H, Ar), 5.28 (s, 1H, 3-H), 3.85 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, acetone-d_6): δ=168.87 (CO), 168.40 (CO), 143.61 (Ar), 132.42 (Ar), 131.18 (Ar), 126.91 (Ar), 125.83 (Ar), 125.03 (Ar), 57.95 (3-C), 52.44 (OMe) ppm. Anal. Calcd for $[C_{10}H_8BrNO_3]0.35H_2O$ (276.38): C, 43.47; H, 3.17; N, 5.07. Found: C, 43.47; H, 3.78; N, 4.43. Mass Spect. (ESI$^+$) [m/z]: 269.9 $[M]^+$.

*4.5.4. Methyl 6-bromo-(1H)-isoindolin-1-one-3-carboxylate (**4d**).* In a similar way the synthesis of **4d** was carried out starting from complex **3d** (150 mg, 0.20 mmol) in chloroform (15 mL) under CO atmosphere (98 mg, 0.36 mmol, 93%). IR (neat): ν=3181, 1745, 1706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.00 (s, 1H, Ar), 7.75 (d,

J=7.8 Hz, 1H, Ar), 7.61 (d, J=7.8 Hz, 1H, Ar), 7.25 (br s, 1H, NH), 5.25 (s, 1H, 3-H), 3.84 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.24 (CO), 168.39 (CO), 139.35 (Ar), 135.46 (Ar), 133.14 (Ar), 127.24 (Ar), 125.40 (Ar), 123.64 (Ar), 58.26 (3-C), 53.31 (OMe) ppm. Anal. Calcd for $C_{10}H_8BrNO_3$ (270.08): C, 44.61; H, 3.00; N, 5.21. Found: C, 45.12; H, 2.61; N, 5.53. Mass Spect. (ESI$^+$) [m/z]: 269.9 [M]$^+$.

4.6. Methyl (3*S**,3a*R**,7a*S**)-octahydroisoindol-1-one-3-carboxylate (6)

A solution of methyl isoindolin-1-one-3-carboxylate (400 mg, 2.09 mmol) in acetic acid (8 mL) was hydrogenated at 70 °C and atmospheric pressure using PtO_2 (40 mg) as catalyst. After 48 h the catalyst was filtered off and washed with acetic acid and the solvent evaporated. The resulting residue was purified by flash chromatography (eluent: CH_2Cl_2/^{i}PrOH 95:5) to obtain **6** as a white solid (389 mg, 1.92 mmol, 92%). Mp 146–148 °C. IR (KBr): ν=3226, 1741, 1712 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.36 (br s, 1H, NH), 4.26 (d, J=5.5 Hz, 1H, 3-H), 3.75 (s, 3H, OMe), 2.72–2.63 (m, 1H, 3a-H), 2.60–2.54 (m, 1H, 7a-H), 2.20–2.13 (m, 1H, cyclohexane–CH_2), 1.68–1.36 (m, 4H, cyclohexane–CH_2), 1.20–1.05 (m, 3H, cyclohexane–CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.39 (CO), 170.58 (CO), 58.35 (3-C), 52.28 (OMe), 42.09 (7a-C), 38.52 (3a-C), 23.65 (cyclohexane–CH_2), 23.47 (cyclohexane–CH_2), 22.65 (cyclohexane–CH_2), 22.57 (cyclohexane–CH_2) ppm. HRMS (ESI): calcd for $C_{10}H_{15}NNaO_3$ [M+Na]$^+$ 220.0944; found 220.0946.

4.7. Methyl (3*S**,3a*R**,7a*S**)-*N*-(*tert*-butoxycarbonyl) octahydroisoindol-1-one-3-carboxylate (7)

To a solution of **6** (350 mg, 1.77 mmol) in THF (10 mL) was added di-*tert*-butyl dicarbonate (968 mg, 4.44 mmol) and 4-(dimethylamino)pyridine (19 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 12 h and then the solvent was evaporated under vacuum. The residue was purified by column chromatography (eluent: hexanes/ethyl acetate 7:3) to obtain **7** as a white solid (429 mg, 1.44 mmol, 80%). Mp 91–93 °C. IR (KBr): ν=1773, 1742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.50 (d, J=6.3 Hz, 1H, 3-H), 3.74 (s, 3H, OMe), 2.66–2.50 (m, 2H, 3a-H, 7a-H), 2.18–2.08 (m, 1H, cyclohexane–CH_2), 1.59–1.05 (m, 7H, cyclohexane–CH_2), overlapped with 1.47 (s, 9H, ^{t}Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.18 (CO), 169.54 (CO), 149.88 (CO), 83.45 (^{t}Bu-C), 61.66 (3-C), 52.12 (OMe), 43.39 (7a-C), 33.59 (3a-C), 27.96 (^{t}Bu-CH_3), 24.11 (cyclohexane–CH_2), 23.21 (cyclohexane–CH_2), 22.90 (cyclohexane–CH_2), 22.31 (cyclohexane–CH_2) ppm. HRMS (ESI): calcd for $C_{15}H_{23}NNaO_5$ [M+Na]$^+$ 320.1468; found 320.1471.

4.8. Methyl (1*S**,3a*S**,7a*R**)-*N*-(*tert*-butoxycarbonyl) octahydroisoindol-1-carboxylate (8)

To a stirred solution of **7** (380 mg, 1.28 mmol) in dry THF (7 mL) at −78 °C under argon atmosphere was added a 1M solution of di-*iso*-butylaluminum hydride in hexanes (1.92 mL, 1.92 mmol) dropwise. The reaction mixture was stirred at −78 °C for 2 h and then quenched with a saturated potassium acetate aqueous solution (3 mL) and allowed to warm to room temperature. After that, a 3:1 mixture of diethyl ether and saturated aqueous ammonium chloride (23 mL) was added and the resulting mixture was stirred at room temperature until a suspension was formed. The solid was filtered off under reduced pressure and washed with diethyl ether (2×10 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic extracts were washed with brine (10 mL), dried over magnesium sulfate, filtered, and evaporated. The resulting residue was used for the next step without further purification. To a stirred solution of the residue in dry dichloromethane (7 mL) triethylsilane (0.42 mL, 2.63 mmol) and boron trifluoride etherate (0.37 mL, 3.01 mmol) were added at −78 °C. After being stirred for 3 h at −78 °C, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (10 mL) and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The resulting residue was purified by column chromatography (eluent: hexanes/ethyl acetate 4:1) to afford **8** as a colorless oil (319 mg, 1.12 mmol, 88%). IR (neat): ν=1762, 1712 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (duplicated signals are observed for some protons; asterisks indicate those corresponding to the minor rotamer)=4.33* (d, J=7.0 Hz, 1H, 1-H), 4.28 (d, J=6.9 Hz, 1H, 1-H), 3.72* (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.56–3.48* (m, 2H, 3-H), 3.46–3.36 (m, 2H, 3-H), 2.45–2.37 (m, 1H, 7a-H), 2.35–2.25 (m, 1H, 3a-H), 1.75–1.10 (m, 8H, cyclohexane–CH_2), overlapped with 1.46* (s, 9H, ^{t}Bu), 1.40 (s, 9H, ^{t}Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (duplicated signals are observed for most carbons; asterisks indicate those corresponding to the minor rotamer)=171.58 (CO), 170.97* (CO), 154.90* (CO), 154.33* (CO), 79.77 (^{t}Bu-C), 79.66* (^{t}Bu-C), 63.94 (1-C), 63.44* (1-C), 51.56* (OMe), 51.40 (OMe), 48.48* (3-C), 47.89 (3-C), 40.79 (7a-C), 39.82* (7a-C), 37.05* (3a-C), 36.40 (3a-C), 28.31* (^{t}Bu-CH_3), 28.08 (^{t}Bu-CH_3), 24.67* (cyclohexane–CH_2), 24.60 (cyclohexane–CH_2), 24.02 (cyclohexane–CH_2), 23.98* (cyclohexane–CH_2), 23.25 (cyclohexane–CH_2), 23.24* (cyclohexane–CH_2), 21.16* (cyclohexane–CH_2), 21.11 (cyclohexane–CH_2) ppm. HRMS (ESI): calcd for $C_{15}H_{25}NNaO_4$ [M+Na]$^+$ 306.1676; found 306.1678.

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