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Diastereoselective Synthesis of High Functionalized 4-Imidazolidinone-Tetrahydro-β-Carboline Hybrids via Divergent Post-Ugi Transformation

Valerio Morlacci,[a] Antonio Arcadi,[a,*] Massimiliano Aschi,[a] Marco Chiarini,[b] Nicola Demitri,[c] Doriano Lamba,[d] Caterina Momoli,[a] Laura Palombi,[a] and Vito Vece[a,*]

[a] Dipartimento di Scienze Fisiche e Chimiche, Università degli studi dell'Aquila. Via Vetoio-67100 Coppito (AQ)- Italy.
Phone: +39 0862 433774
Fax: +39 0862 434203
E-mail: antonio.arcadi@univaq.it; vito.vece@univaq.it
[b] Dipartimento di Bioscienze e Tecnologie Agroalimentari e Ambientali, Università degli Studi di Teramo, Via R. Balzarini, 64100 Teramo – Italy
[c] Elettra Sincrotrone Trieste S.C.p.A, Area Science Park – Basovizza, Strada Statale n° 14 Km. 163.5, I-34149 Trieste – Italy
[d] Istituto di Cristallografia – C.N.R.– Sede Secondaria di Trieste-Area Science Park – Basovizza-Building Q1 – Room 106- Strada Statale 14 – Km. 163.5- I-34149 Trieste – Italy

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This work is dedicated to Prof. Stephen Hanessian for his important contributions in the field of organic chemistry.

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Abstract: An easily scalable and highly diastereoselective synthesis of challenging 1,2,5,6,11,11*b*-hexahydro-*3H*-imidazo[1′,2′:1,2]pyrido[3,4-*b*]indol-3-ones is accomplished through divergent transformation of Ugi 4-CR products. The trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated intramolecular condensation of a series of Ugi 4-CR adducts generates a *N*-acylimidinium intermediate which undergoes ring closure to selectively afford the target title compounds in good to high yields.

Keywords: 4-imidazolidinones; β-carbolines; Post-Ugi cyclization; TMSOTf; N-acylimidinium intermediates

Imidazopyridoindoles (Figure 1) represent highly privileged scaffolds as drug candidates. In particular, a synthetic combinatorial library of imidazopyridoindoles exhibited inhibition of β-amyloid-induced neurotoxicity.[1] Additionally, fused *5H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indoles **A** have shown hypnotic activities and anti-proliferative properties against human breast cancer cells.[2] Much less investigated, nonetheless equally interesting, are the corresponding regioisomeric *5H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indoles **B**.[3] Indeed, related derivatives, such as the natural alkaloid Peganumine A, a dimeric bridged tetrahydro-β-carboline fused

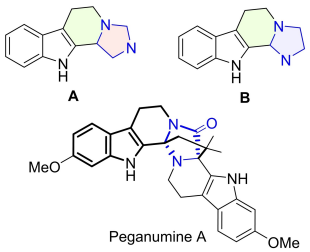


Figure 1. Imidazopyridoindole scaffolds and Peganumine A.

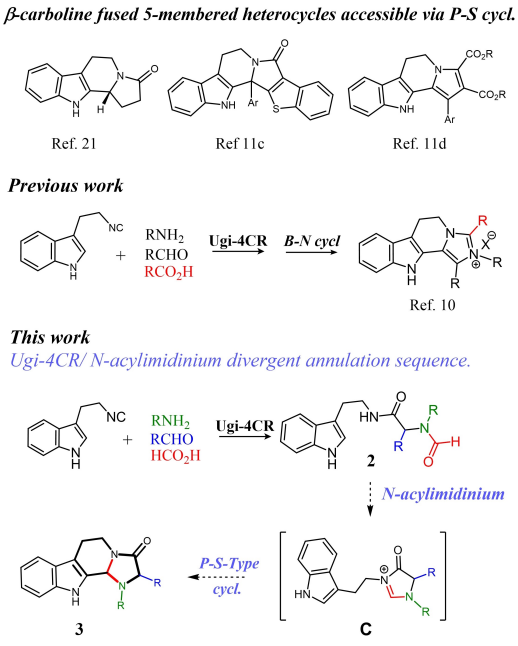
with a 4-imidazolidinone ring, also resulted as anti-cancer lead candidates.[4]

To bridge this gap, we focused on an expansion of post-Ugi chemistry. Effectively, the combining of multicomponent reactions (MCRs),[5] particularly the 4-component Ugi reaction (Ugi-4CR),[6] with the post-transformation of Ugi-adducts, is widely recognized as one of the most powerful tools for accessing complex polyheterocyclic architectures.[7] In fact, these synthetic sequences benefit from convergence, atom economy and versatility of the MCRs as well as the diversity arising from countless post-Ugi transformations, which include functional group interconversions,[8a] rearrangements,[8b] redox,[8c] addition and substitution reactions[8d] etc.

Given the above, advancements in post-Ugi transformations still represent a highly active research field aimed at overcoming bottlenecks in the synthesis of target bioactive heterocycles, natural products, and macrocycles.[9]

As part of ongoing interest in this field,[10a] a two-step strategy involving Ugi isocyanide based multicomponent reactions (IMCRs) followed by a Bischler-Napieralski (B–N) heterocyclization directly enabled the synthesis of trisubstituted 5,6-dihydroimidazo[1,2-a]pyrimidines [1′,5′:1,2]-pyrido[3,4-*b*]indol-2-ium salts (Scheme 1, previous work).[10b]

Currently, one of the most popular reactions usually associated with MCRs is the Pictet-Spengler (*P–S*) ring closure.[11] For more than a century, this reaction has found myriad of applications especially towards the synthesis of isoquinoline and indole alkaloid frameworks, also performed in asymmetric fashion.[12]



Scheme 1. Previous works and current strategy.

Standard substrates for this venerable reaction are electron-rich β-arylethylamine or tryptamine derivatives, along with aldehydes or ketones. The amine and the carbonyl derivative react to produce an aminal, which is subsequently dehydrated under acidic conditions to afford the corresponding iminium ion. The iminium ion then undergoes a typical *6-endo-trig* cyclization, yielding a six-membered azaheterocycle.[13]

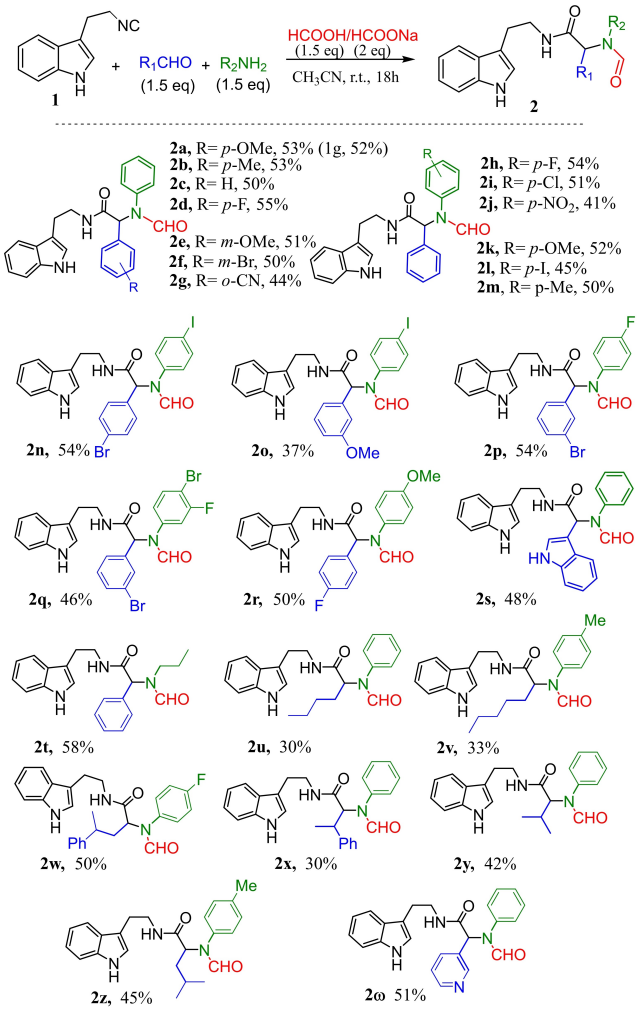
While significant attention has been given to *P-S*-type cyclization involving iminium or *N*-acyliminium intermediates,[14] so far, the annulation reactions of *N*-acylimidinium intermediates have remained unexplored.

We envisaged that the formation of an *N*-acylimidinium intermediate **C** could expand the scope of the post-Ugi transformations of the novel *N*-formyl Ugi adducts **2**, enabling the synthesis of the challenging β-carboline fused imidazolidin-4-ones **3** through a divergent annulation/*N*-acylimidinium-mediated ring closure sequence (Scheme 1, this work).

As a first step, we generated the library of building blocks **2a-ω**, employing aromatic and aliphatic aldehydes, as well as anilines and alkylamines in a Ugi-4CR with 3-(2-isocyanoethyl)-1H-indole **1** and formic acid, under the conditions reported in Scheme 2.

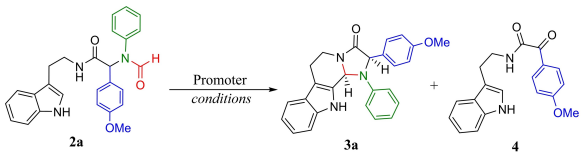
Aromatic aldehydes and anilines having either electron-donating and/or electron-withdrawing groups on the aromatic ring were generally well-tolerated. Thus, the synthesis of valuable Ugi-adducts featuring halogen substituents on the aromatic moieties suitable for further structural elaborations (**2f**, **2l**, **2n** **2p**, **2q**) was smoothly addressed with yields ranging from 45% to 54%. Moreover, despite the acidic reaction conditions, the adduct **2s** containing an additional indole moiety was produced in a surprising 48% yield. Finally, acceptable to good yields were also achieved with aliphatic aldehydes and amines (**2t-ω**).

Having obtained the desired set of *N*-formyl Ugi adducts, we then proceeded by evaluating the feasibility of our working hypothesis using **2a** as a representative model compound. At the outset of the study, we tested a diverse array of metal salts and complexes. As shown in Table 1, upon treatment of **2a** with catalytic amount of JohnPhos Au(MeCN)SbF_6 ($JPAu_{(ACN)}SbF_6$) as well as $Na_2PtCl_6 \cdot 6H_2O$ no reaction took place and the starting material **2a** was recovered after 24 h at 110 °C in 74% and 77% yield, respectively (Table 1, entries 1–2).[15] Disappointing results were obtained with other metal catalysts such as $Cu(OTf)_2$[16] $Zn(OTf)_2$[17] and $Yb(OTf)_3$[18] (Table 1, entries 3–6). In fact, albeit in different extent, these catalysts facilitated the hydrolysis of the *N*-acylimidinium **C** leading to the formation of the α-ketoamide **4** as the prevailing product. Among the metal catalysts examined, AgOTf exhibited superior performance, resulting in a 48% yield of the desired product **3a** when employed in



Scheme 2. Synthesis of Ugi-4CR adducts **2**. Reaction conditions: to a suspension of aldehyde (1.5 equiv.), amine (1.5 equiv.) and sodium formate (2 equiv.) in CH_3CN (3.7 mL), were added in sequence formic acid (1.5 equiv.) and **1** (1.47 mmol). The mixture was stirred at room temperature for 18 h to afford the corresponding adduct **2.**

Table 1. Screening the conditions for the heteroannulation.



Entry	Solvent 0.4 M	Catalyst/ Promoter	°C/h	**3a** (%)[a]	**4** (%)[a]
1	PhMe	$JPAu_{(ACN)}SbF_6$ (5%)	110/24	–(74)	–
2	PhMe	$Na_2PtCl_6 \cdot 6H_2O$ (5%)	110/24	–(77)	–
3	DMF	$Cu(OTf)_2$ (20%)	120/24	–	35
4	Xylene	$Cu(OTf)_2$ (20%)	120/24	–(20)	22
5	DMF	$Zn(OTf)_2$ (20%)	120/24	–	55
6	DMF	$Yb(OTf)_3$ (20%)	120/24	–	74
7	DMF	Ag(OTf) (20%)	120/24	< 10	–
8	DMF	Ag(OTf) (100%)	120/48	48	–
9	DMF	TMSOTf (20%)	120/7	18(61)	< 5[b]
10	DMF	TMSOTf (40%)	120/7	35(52)	< 5[b]
11	DMF	TMSOTf (100%)	120/7	79	< 5[b]
12	DMF	TfOH (100%)	120/7	–(55)	–

[a] Isolated yields. Yields in parentheses refer to recovered starting material **2 a**.
[b] Determined by ^{1}H-NMR on crude mixtures.

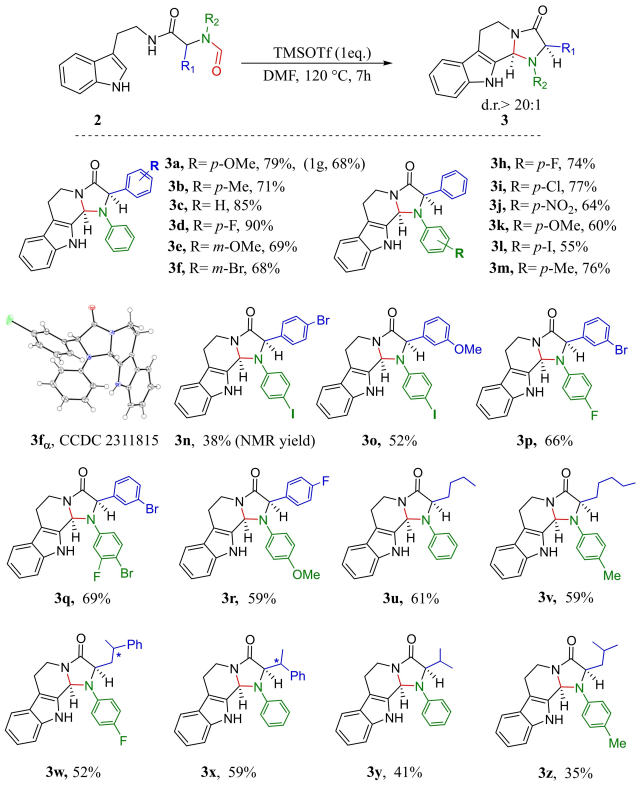
stoichiometric amount (Table 1, entry 8).[19] To our satisfaction, the sequential process occurred with a significantly increased efficiency when stoichiometric amount of the cost-effective TMSOTf was used as Lewis acid promoter (Table 1, entry 11).[20] Conversely, no reaction occurred by replacing TMSOTf with the Brønsted trifluoromethanesulfonic acid (TfOH) (Table 1, entry 12).

Notably, regardless the conditions, the reaction was highly diastereoselective leading almost exclusively to the (R,R)/(S,S)-racemic mixture. The structure and the stereochemistry, tentatively assigned on derivative **3 a** by 2D-NMR experiments (see SI S86 for details), were then definitively ascertained by X-ray of the derivative **3 f** {in scheme 3 is shown the molecular structure of the diastereoisomer (R,R) **3 f$_\alpha$** ; in all the solvatomorphs **3 f$_\alpha$, 3 f$_\beta$** and **3 f$_\gamma$** the R,R and S,S diastereoisomers coexist}. Interestingly, Density Functional Theory (DFT) calculations suggest that the obtained diastereoisomer is 7 kJ/mole more stable than the other in the gas-phase (see SI S99). This difference remains unaltered even in the presence of two solvents with different dielectric constants, i. e. toluene and DMSO. This scarce solvent effect, within the mean field approximation, is essentially due to the same value of the electric dipole moment (i. e. 4.7 Debye) shown by the two diastereoisomers at this level of calculations. DFT calculation was further exploited for an accurate assignment of the chemically non-equivalent geminal hydrogens of the tetrahydropyridine moiety, showing an unequivocal role of carbonyl amide functionality (see SI S98).

With the optimized conditions in hand, we finally investigated the substrate scope of this transformation.

As shown in Scheme 3, the expected domino reaction of the adducts **2**, obtained with *para*- and *meta*-substituted arylaldehydes progressed quite smoothly, yielding the respective derivatives **3** with satisfactory to very good yields (71–90%).

Good to satisfactory yields (60–77%) were also obtained with the adducts **2** showing a similar substitution pattern on the aniline moiety. Likewise,



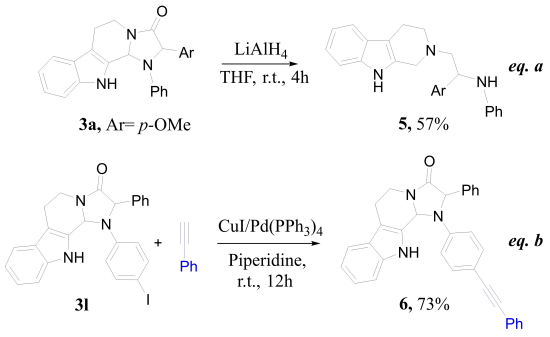
Scheme 3. Substrate scope. Reaction conditions: TMSOTf (1 eq, 0.4 mmol) was added to a solution of **2** (1 eq, 0.4 mmol) in DMF (1 mL). The mixture was stirred at 120 °C for 7 h to afford the corresponding product **3**.

the presence of *para*- and/or *meta*-substituents in both the aromatic rings of the substrates **2n–r** was tolerated, though the iodo-derivative **3n** suffered from separation issues (see SI S17).

Adducts generated with aliphatic aldehydes also demonstrated a good reactivity, leading to the diverse 5-alkyl-imidazolidin-4-ones **3u–z** in acceptable to sufficient yields. Conversely, no reactivity was observed with the substrate **2t** incorporating the alkyl group on the amine moiety, while no productive reactions occurred with substrates **2g** and **2s** and **2ω**. Actually, the ^{1}H NMR analyses on the crude revealed the complete degradation of the starting materials, with *N*-phenylformamide as the most abundant side-product. Indeed, *N*-phenylformamide was isolated in 30% yield from the reaction of **2s.**

Having confirmed the practicability of the current approach through the gram-scale synthesis of **2a** (Scheme 2) and **3a** (Scheme 3), we explored possible elaborations of the products as outlined in Scheme 4.

Based on the relevance of the *N*-substituted tetrahydro-β-carbolines as targeting mu-opioid receptors,[21] we firstly attempted the reduction of the model compound **3a**. Notably, using traditional $LiAlH_4$ as reducing agent, along with the reduction, the opening



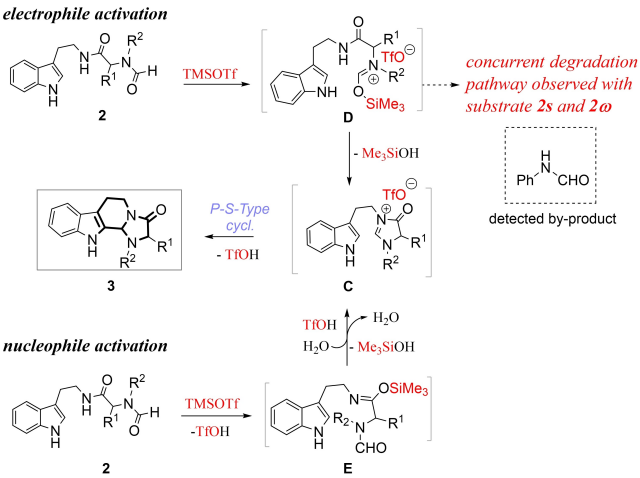
Scheme 4. Further elaborations.

of the imidazolidinone ring occurred, giving the corresponding *N*-substituted tetrahydro-*β*-carboline **5** in 57% yield (*eq. a*).[22]

Moreover, Pd-catalyzed functionalization could become a feasible and concise route to the diversity-oriented synthesis of a variety β-carboline fused imidazolidin-4-ones. Indeed, as illustrated in *eq. b*, the application of the Sonogashira reaction on **3l** demonstrates that halogen-substituted derivatives **3** can serve as molecular platforms for enhancing their molecular diversity.[23]

The proposed reaction pathway can be outlined as depicted in Scheme 5. Very likely, the formation of the target product should proceed via the activation of the formamide unit of the Ugi-4CR adduct **2** by the TMSOTf promoter leading to the intermediate **D**.[24] Accordingly, the ^{13}C NMR spectra of the reaction mixture of the substrate **2o** analyzed at 303 and 333 K showed the prevalent interaction of the promoter with the carbonyl of its formamide moiety (see SI S97).

Notably, the coordination mentioned above could also account for the degradation pathway occasionally observed with specific substrates (**2s** and **2ω**). How-



Scheme 5. Plausible reaction pathway.

ever, the involvement of the intermediate E in the reaction pathway cannot be ruled out.[25]

In conclusion, we have developed a synthetic approach to *5H*-imidazo [1',2':1,2]pyrido[3,4-*b*]indole derivatives through a divergent sequential TMSOTf promoted intramolecular condensation reaction of novel *N*-formyl Ugi-4CR adducts followed by *N*-acylimidinium mediated ring closure. The presented method addresses the synthesis of challenging 4-imidazolidinone-tetrahydro-β-carboline hybrids, in good yields and high diastereoselectivity. The reaction exhibits a broad scope, and large-scale synthesis can be easily achieved.

Experimental Section

X-ray Crystallography

Pale-yellow single crystals of the compound **3 f**$_{\alpha}$ suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of **3 f** in DMF dissolving 40 mg of the compound in 2 ml of DMF. Colourless rod-like single crystals of the compound **3 f**$_{\beta}$, suitable for X-ray diffraction analysis, were obtained by slow evaporation of a mixture of ethanol and acetone dissolving 2 mg of the compound in 1.9 mL of ethanol and 0.1 mL of acetone.

CCDC 2311815, **2311816** and **2311817** contains the supplementary crystallographic data for compound **3 f** dimethyl formamide (**3 f**$_{\alpha}$), ethanol (**3 f**$_{\beta}$) and solvent-less (**3 f**$_{\gamma}$) solvatomorphs respectively. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.

Typical Procedure for the Synthesis of the Ugi Adducts 2

To a suspension of aldehyde (1.5 equiv.), amine (1.5 equiv.) and sodium formate (2 equiv.) in CH_3CN (3.7 mL), were added, in sequence, formic acid (1.5 equiv.) and 3-(2-isocyanoethyl)-1H-indole **1** (1.47 mmol). The mixture was stirred at room temperature for 18 h, then extracted with DCM (3 times). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate, 8:2 to 6:4) affording the corresponding adducts **2.**

Gram-scale synthesis of **2 a** was performed under the same conditions, using **1** (1 g, 5.87 mmol), benzaldehyde (1,07 mL, 8.81 mmol), aniline (0.80 mL, 8.81 mmol), formic acid (0.33 mL, 8.81 mmol) and sodium formate (0.8 g, 11.75 mmol) in AcN (14.7 mL) and obtaining 1.3 g of **2 a** (52% isolated yield).

Typical Procedure for the for the Synthesis of Imidazolidin-4-one Derivatives 3

TMSOTf (1 eq, 0.4 mmol) was added to a solution of **2** (1 eq, 0.4 mmol) in DMF (1 mL). The solution was stirred at 120 °C for 7 h. Then, the mixture was extracted with AcOEt (3 times). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate, 85:15) affording the corresponding derivative **3** as a solid.

Gram-scale synthesis of **3 a** was performed under the same conditions, using **2 a** (1.28 g, 3 mmol) and TMSOTf (0.55 mL, 3 mmol) in DMF (7.5 mL), and obtaining 0.83 g of **3 a** (68% isolated yield).

Experimental Procedure for the Synthesis Reported in Scheme 4

Synthesis of N-(1-(4-methoxyphenyl)-2-(1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethyl)aniline (5)

A flame-dried 10 mL round-bottom flask equipped with a stirred bar was charged with **3 a** (150 mg, 0.366 mmol), in anhydrous THF (2 mL). Under a stream of N_2, $LiAlH_4$ in THF 1 M (28 mg, 0.733 mmol) was added in portion to control any exotherm. The solution was stirred at room temperature for 4 h. The reaction was cooled to 0 °C, and then slowly quenched by dropwise addition of 2 M NaOH, and H_2O. The crude was extracted with DCM and the organic layer were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash-chromatography (eluent: hexane/EtOAc, 95:5), affording **5** as a white solid (83 mg, 57% yield).

Synthesis of 2-Phenyl-1-(4-(phenylethynyl)phenyl)-1,2,5,6,11,11 b-hexahydro-3H-imidazo[1′,2′:1,2]pyrido[3,4-b]indol-3-one (6)

A mixture of **3 l** (150 mg, 0.297 mmol), Phenylacetilene (65 µL, 0.594 mmol), $Pd(PPh_3)_4$ (34 mg, 0.029 mmol), CuI (6 mg, 0.029 mmol), in Piperidine (2 mL) was stirred at room temperature under nitrogen overnight. Then the solution was concentrated under reduce pressure and the mixture was extracted with AcOEt. The organic layer was washed with water, dried with sodium sulfate, filtered, and concentrated. The purification of the residue by flash chromatography (eluent: hexane/EtOAc, 95:5) afforded **6** as a brown solid (104 mg, 73% yield).

Acknowledgements

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