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Straightforward Synthesis of Isoellipticine by Palladium-Catalysed Coupling Reactions

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Our novel synthetic route to isoellipticine featured palladium-catalyzed intramolecular reactions for the construction of the B ring of the pyridocarbazole nucleus. The adequate palladium-catalyzed reaction depended upon the oxidation conditions that were applied in order to prepare the immediate synthetic precursor. When CAN was used to make the quinone intermediate, an oxidative cyclization through a double C–H bond activation was applied. Conversely, when the oxidation condition involved TCCA as oxidant, a direct C–H arylation was employed. Both approaches showed similar efficiencies in order to construct the pyridocarbazole nucleus. Isoellipticine was prepared in only 5 steps with a 21%–23% overall yield.

Introduction

Pyridocarbazole nuclei have caught the attention of synthetic organic and medicinal chemists due to their broad variety of biological activities.[1] Isoellipticine (**1**) and ellipticine (**2**) are the most commonly known compounds of this class and they have an excellent anticancer activity that is related to their abilities to strongly intercalate into DNA base pairs (Figure 1).[2] Some important anticancer chemotherapeutic agents exert their action by interfering directly with the DNA. Compounds containing a planar structure based on fused aromatic rings can act as a DNA intercalator, causing enzymatic blockade and reading errors during the replication process. Among the structural requirements for such a behavior of these polyaromatic rings is the existence of a "2-phenylnaphthalene" structural pattern which is present in a significant number of anticancer compounds.[3] The "2-phenylnaphthalene" pattern mimics a purine-pyrimidine base pair and facilitates the intercalation process. The charge separation in the pyridocarbazoles is caused by the simultaneous presence of fused pyridine and pyrrole rings and it is complementary to the charge separation that is brought on by the hydrogen bonding among the pyrimidine and purine base pairs. The combination of this two matched effects strengthens the intercalation process.[3]

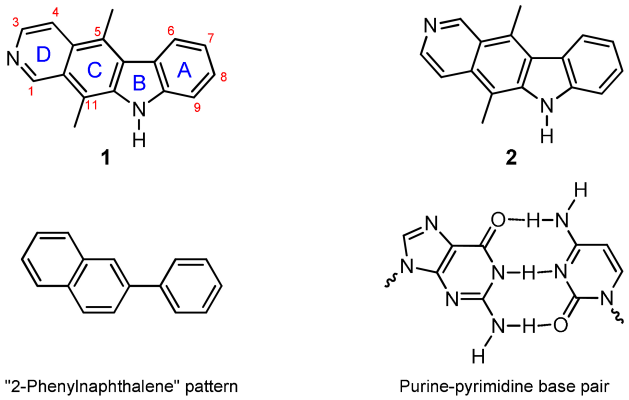

Figure 1. Structures of isoellipticine (**1**) and ellipticine (**2**), the 2-phenylnaphthalene pattern for some anticancer compounds, and its similarity with a purine-pyrimidine base pair.

Palladium-catalyzed oxidative cyclization through double C–H bond activation,[4] as well as direct C–H arylation of arene compounds,[5] has been proven as ingenious strategies to the construction of natural products scaffolds. The original concept was investigated independently by Miller[6] and Shanon[7] and then improved by Knölker and co-workers by the use of 1 atm molecular oxygen as terminal oxidant for the Pd catalyzed cross dehydrogenative-coupling (CDC) reaction of diarylamines and arylaminoquinones.[8] Usually, this reaction works more efficiently for arylaminoquinones than it does for diarylamines, probably due to coordination of the quinone moiety to palladium(II) which assists in the reoxidation of palladium(0).[9,10] The palladium(II)-catalyzed oxidative C–C bond formation of diarylamines was further improved by Knölker and co-workers by the use of concerted metalation-deprotonation (CMD) conditions, copper(II) acetate, and molecular oxygen to synthesize several carbazole alkaloids.[11] Conversely, in the case of intramolecular direct arylation of aryl halides or pseudohalides, although the presence of an oxidant is not required, the use of DMF or DMA as solvents, alkaline metal carbonates, and phosphine ligands is essential.[12] This approach has the advantage of saving unnecessary bifunctionalization in the

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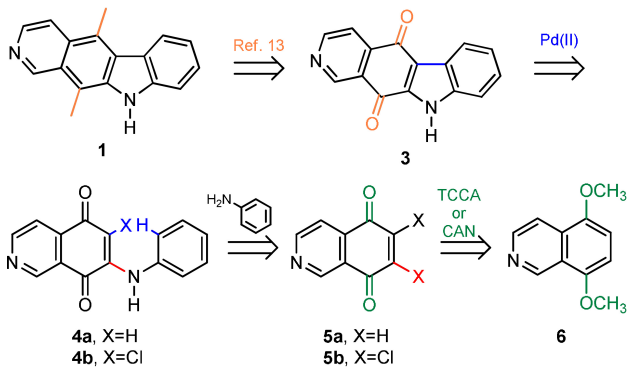
substrate, which brings to it superior atom economy. Moreover, an intramolecular direct arylation of aryl halides or pseudohalides does not require the presence of a proximal directing group, since C–X bond already drives the regiochemistry of the process. Nevertheless, it is less used in total synthesis than oxidative cyclization through double C–H bond activation, as it requires an extra step to pre-functionalize the substrate with a halogen or a pseudohalogen.

In this work, we present a full account of two different strategies by using palladium-catalyzed reactions to construct B ring of isoellipticine (**1**): an oxidative cyclization through double C–H bond activation, and a direct C–H arylation. Both of these procedures could be identified as a Type I approach as defined by Gribble and Saulnier for pyridocarbazole nuclei syntheses.[13] By using a divergent strategy for the oxidation of a 1,4-dimethoxyarene, C–H or C–Cl bonds were efficiently introduced in the synthetic intermediates. Both of the intermediates were able to furnish the cyclization product, isoellipticinequinone (**3**), in good yields and high regioselectivity. Since the carbon-halogen bond was introduced during the oxidative-demethylation of a common intermediate in only one step, there was no drawback to the synthetic approach.

Results and Discussion

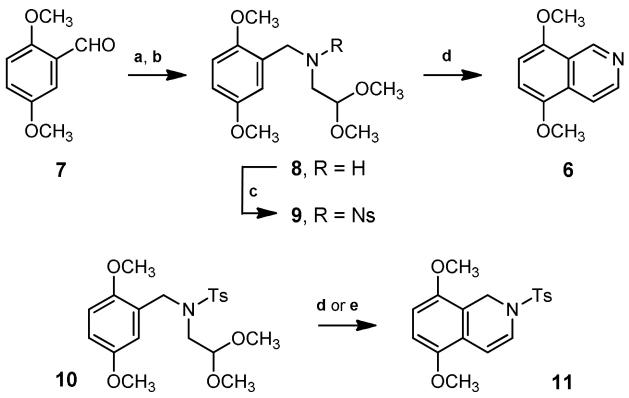
Our approach to isoellipticine (**1**) was based on the introduction of the a phenylamino moiety at position 7 of an isoquinoline-5,8-dione (Scheme 1). Depending upon the oxidation



Scheme 1. Retrosynthetic approach to isoellipticine (**1**).

conditions needed to prepare the isoquinoline-5,8-diones (**5a** or **5b**), they might bear two hydrogen atoms or two halogen atoms at positions 6 and 7 as we demonstrated previously.[14] In both of the cases, the nucleophilic addition was expected to occur preferentially at position 7. In the case of 7-(phenylamino)isoquinoline-5,8-dione (**4a**), a subsequent palladium-catalyzed oxidative cyclization through double C–H bond activation furnished isoellipticinequinone (**3**). Compound **3** was also prepared by direct C–H arylation from 6-chloro-7-(phenylamino)isoquinoline-5,8-dione (**4b**). Isoellipticinequinone (**3**) promptly furnished isoellipticine (**1**) as published elsewhere (Scheme 1).[13]

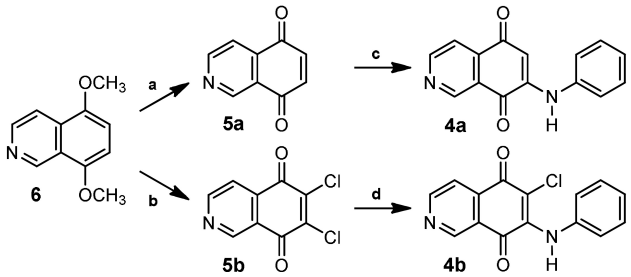
Our synthesis commenced with the preparation of 5,8-dimethoxyisoquinoline (**6**), an adequate substrate capable of generating isoquinoline-5,8-dione (**5a**) or 6,7-dichloroisoquinoline-5,8-dione (**5a**) in one step (Scheme 2). Compound **6** was



Scheme 2. Synthesis of 5,8-dimethoxyisoquinoline **6**. Reagents and conditions: (a) 2,2-dimethoxyethanamine (1 equiv.), $MgSO_4$ (1 equiv.), CH_2Cl_2, 4 h; (b) $NaBH_4$ (5 equiv.), MeOH, 2 h; (c) NsCl (1.1 equiv.), Na_2CO_3 (10% w/w), H_2O/CH_2Cl_2 (1:1), room temp., 6 h; (d) TFA, reflux, 2 h (90% global yield); e) HCl 6 M, reflux, 7 h.

prepared by reductive amination of 2,5-dimethoxybenzaldehyde (**7**) with 2,2-dimethoxy-ethanamine in the presence of $NaBH_4$, followed by derivatization of the intermediate benzylamine (**8**) with *o*-nosyl chloride, succeeded by the afterward Pomeranz-Fritsch reaction to generate the isoquinoline nucleus. The presence of nosyl group was essential for the transformation, since it acted as a protecting group at the first step (Pomeranz-Fritsch cyclization) and as an activating group at the last (dehydrodesulfination/aromatization). Although other sulfonamides can undergo similar reactions, 2-nitrobenzenesulfonyl amide was able to perform dehydrodesulfination/aromatization of **9** in smoother conditions, since the cyclized nosylamide could not be isolated during Pomeranz-Fritsch reaction in HCl/dioxane. Conversely, when *N*-tosyl derivatives (**10**) were used, isoquinoline **6** was obtained only after posterior treatment of the cyclized intermediated **11** with *t*-BuOK/*t*-BuOH at 80 °C for 30 min. 5,8-Dimethoxyisoquinoline (**6**) was obtained in 90% yield from 2,5-dimethoxybenzaldehyde (4 steps in a *one-pot* procedure) by using the *N*-nosylamide route.

Heading towards our aim, compound **6** was subjected to oxidation by CAN/dioxane/HNO_3 at room temperature for 4 h to furnish isoquinoline-5,8-dione (**5a**) (Scheme 3). Alternatively, 6,7-dichloroisoquinoline-5,8-dione (**5b**) was prepared when trichloroisocyanuric acid (TCCA) in H_2O/HCl was used at room temperature for 3 h. Therefore, in both of the cases, the resulting isoquinoline-5,8-dione reaction media was directly treated with aniline to furnish the 7-phenylaminoisoquinoline-5,8-diones (**4a** or **4b**). In the case of the 6-chloro derivative (**4b**), due to the lower reactivity of the dichloroquinone toward a nucleophilic addition, it was necessary to keep the reaction media at 80 °C over a period of 40 h to promote the reaction. In contrast, 7-phenylaminoisoquinoline-5,8-dione (**4a**) needed



Scheme 3. Synthesis of 7-phenylaminoisoquinoline-5,8-diones (**4a** and **4b**). Reagents and conditions: (a) CAN, dioxane/HNO_3, r.t., 4 h; (b) TCCA, H_2O/HCl, 3 h, r.t.; (c) Aniline, dioxane, r.t., 12 h; (d) Aniline, dioxane, 80 °C, 2 h.

only 12 h at room temperature to be produced. Both of the isoquinoline-5,8-diones were obtained in reasonable/good yields: 60% yield for 7-phenylaminoisoquinoline-5,8-dione (**4a**) and 79% yield for the chlorinated derivative **4b**. Interestingly, despite mechanism differences, the observed regiochemistry of both reactions was almost the same: a ~10:1 mixture of isomers. In the case of 6,7-dichloroisoquinoline-5,8-dione (**5a**), the nucleophilic addition of aniline followed by chloride elimination was supposed to occur. Conversely, in the case of the isoquinoline-5,8-dione (**5a**), a conjugate addition to the α,β-unsaturated carbonyl moiety succeeded by the tautomerization of the di-keto intermediate to hydroquinone, and an *in situ* oxidation probably took place.

The regiochemistry of **4a** was unequivocally confirmed by HMBC analysis due to ^{1}H-^{13}C coupling between C8 carbonyl and hydrogen at positions 1 and 7 (see Supporting Information for more details). Conversely, C5 carbonyl showed coupling only with hydrogen at position 4. On the other hand, the identity of **4b** could only be unequivocally confirmed by an X-ray crystallographic analysis (Figure 2), since it was unable to

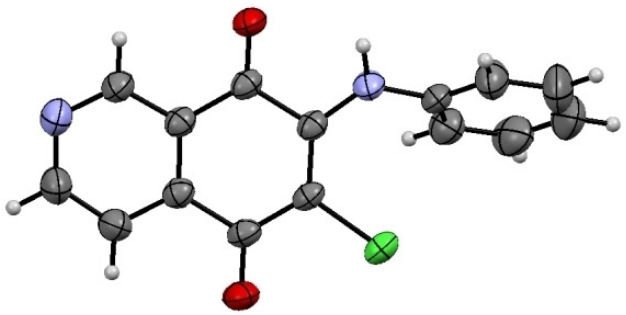
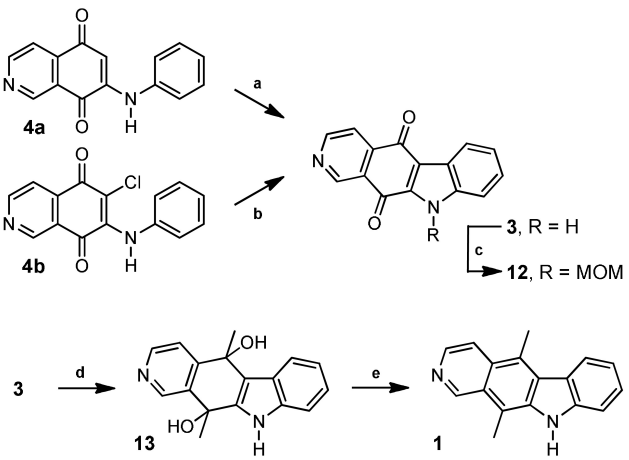


Figure 2. ORTEP representation of 6-chloro-7-phenylaminoisoquinoline-5,8-dione B (**4b**). Ellipsoids displayed at 50% probability.

furnish the same pattern of couplings in NMR experiments as shown by compound **4a**.

With the requisite substrates in hand, we next attempted to construct the pyridocarbazole framework through a palladium (II)-catalyzed oxidative cyclization of **4a** and also by a direct arylation of **4b**. Thus, in order to perform the cyclization through direct C–H arylation compound **4b** was treated with palladium acetate, pivalic acid, potassium carbonate, and copper(II) acetate in dimethylacetamide to provide **3** in 65% yield after 24 h at 130 °C. Other co-oxidants, such as sodium persulfate, silver(I) carbonate, dioxygen, or oxone when used to reoxidize the palladium(0), showed inferior performance. When we were provided with those facts, we also attempted cyclization through double C–H bond activation of compound **4a**. So, 7-(phenylamino)isoquinoline-5,8-dione (**4a**) was treated with palladium acetate, tricyclohexylphosphonium tetrafluoroborate ($PCy_3.HBF_4$) and potassium carbonate in dimethylacetamide at 130 °C to afford **3** in 50% yield. The use of Fagnou's conditions to promote intramolecular direct arylation of **4a** was critical, since it allows a concerted metalation-deprotonation (CMD) to occur at the quinone moiety.[15] Probably, the oxidative addition of palladium(0) at a carbon-chlorine bond was a major drawback of this approach, hence, there was a lowering of the yield for this step. The introduction of a bromine atom at position 6 of isoquinolinedione **5b**, in order to increase the yield of the direct arylation, did not improve the transformation. The use of tribromoisocyanuric acid (TBCA) in H_2O/HBr to oxidize **6** in replacement of TCCA/H_2O/HCl considerably diminished the global yield (< 30%).[14] Oxidations using TBCA were less effective than using TCCA, because of the smaller redox potential of the former reagent and its higher tendency to transfer bromine atoms instead of receiving an electron.[16]

The subsequent reaction of compound **3** with methyllithium afforded the diol **13**. The crude diol mixture was reduced with sodium borohydride in ethanol under reflux to furnish isoellipticine (**1**) in 56% yield (Scheme 4).



Scheme 4. Synthesis of isoellipticine **1**. Reagents and conditions: (a) $Pd(OAc)_2$, PivOH, K_2CO_3, $Cu(OAc)_2$, DMA, 130 °C, 30 h; (b) $Pd(OAc)_2$, K_2CO_3, $PCy_3{\cdot}HBF_4$, DMA, 130 °C, 30 h; (c) NaH, THF, MOMBr; (d) MeLi, TMEDA, THF, 0→100 °C, 48 h (90% global yield); e) $NaBH_4$, EtOH, reflux.

The reduction step involved the successive deoxygenation driven by BH_3 generated in situ and reduction of the

intermediate species. In order to increase the yield of the alkylation-reduction step, we investigated the protection of nitrogen at position 10 of isoquinolinedione to circumvent N–H abstraction due to strong basic conditions. The extra negative charge could reduce the solubility and avoid the required double methylation of quinone at positions 5 and 11. So, compound **3** was treated sodium hydride and methoxymethyl bromide in DMF to furnish the *N*-protected quinone **12** in 85%. Unfortunatelly, we did not observe any considerable improvement of the yield in this step due nitrogen protection. Isoellipticine (**1**) was synthesized in 21–23% in 5 steps from 5,8-dimethoxyisoquinoline (**6**).

Conclusions

In summary, starting with the same known synthetic intermediate, 5,8-dimethoxyisoquinoline (**6**), we have accomplished the synthesis of isoellipticine (**1**) using two complementary intramolecular palladium-catalyzed reactions to construct B ring of the pyridocarbazole compound: an oxidative cyclization through double C–H bond activation or a direct C–H arylation. 5,8-Dimethoxyisoquinoline (**6**) was prepared in a one-pot protocol in an excellent overall yield (90%). On the other hand, isoellipticine was prepared from compound **6** in 5 steps in good overall yields (21–23%). Although oxidative cyclization through double C–H bond activation using $CuSO_4$ as co-oxidant proved to be slightly superior in this substrate, both approaches showed evident applicability to construct the pyridocarbazole nucleus.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cross dehydrogenative-coupling · Direct C–H arylation · Heterocycles · Palladium · Pyridocarbazoles

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