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A concise Friedländer/Buchwald-Hartwig approach to the total synthesis of quindoline, a bioactive natural indoloquinoline alkaloid, and toward the unnatural 10-methylquindoline

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A new approach toward the synthesis of quindoline, a recognized indoloquinoline alkaloid, is reported. The sequence comprises the synthesis of 2-(2-nitrophenyl)quinoline through an optimized Friedländer condensation of 2-amino benzaldehyde with 2-nitroacetophenone, followed by the selective C-3 bromination of the quinoline moiety to direct the cyclization, reduction of the nitro group and a final Buchwald-Hartwig cyclization. In addtion, quindoline was also converted to the unnatural 10-methylquindoline by reaction with dimethyl carbonate under DBU promotion. It was found that the non-directed reductive cyclization of 2-(2-nitrophenyl)quinoline results in indazolo[2,3-*a*]quinoline, instead of yielding quindoline. DFT calculations were employed to explain this reaction outcome; this finding suggested that the result of a previously reported total synthesis of quindoline should be revised.

Introduction

Cryptolepis sanguinolenta (Lindl.) Schlachter (Periplocaceae), known as nibima, kadze or gangamau, is a thin-stemmed twining and scrambling shrub with an orange-colored sap in the cut stem, which becomes red on ripening. This climbing vine grows in West and Central Africa, where decoctions of its roots have been traditionally used for treating various health conditions, including malaria, bacterial respiratory diseases, hypertension, hepatitis, jaundice, diarrhea and inflammation.[1]

C. sanguinolenta ranks among the most widely explored sources for herbal drugs. The extracts of this plant and some natural products isolated from them proved to be anti-inflammatory, anti-plasmodial, anti-bacterial[2] and anti-cancer[3a] agents. It has been estimated that about 40% of all Ghanaian herbal antimalarials contain *C. sanguinolenta* or its extracts as key components.[3b]

The phytochemical analysis of *C. sanguinolenta* has shown that the plant is a rich source of indoloquinoline alkaloids and that the latter are responsible for the observed biological activities. These heterocycles are a small and unique family of compounds, not exclusive to *C. sanguinolenta*, characterized by displaying differently fused indole and quinoline rings.[4]

The monomeric indoloquinolines (Figure 1) include quindoline (**1**),[5a] cryptolepine (**2**),[5b,c] neocryptolepine (**3**),[5d] quindolinone (**4**),[6a] cryptosanguinolentine (**5**),[6b] 11-isopropyl cryptolepine (**6**),[6c,d] cryptolepinone (**7**)[7a] and quinindoline (**8**).[7b]

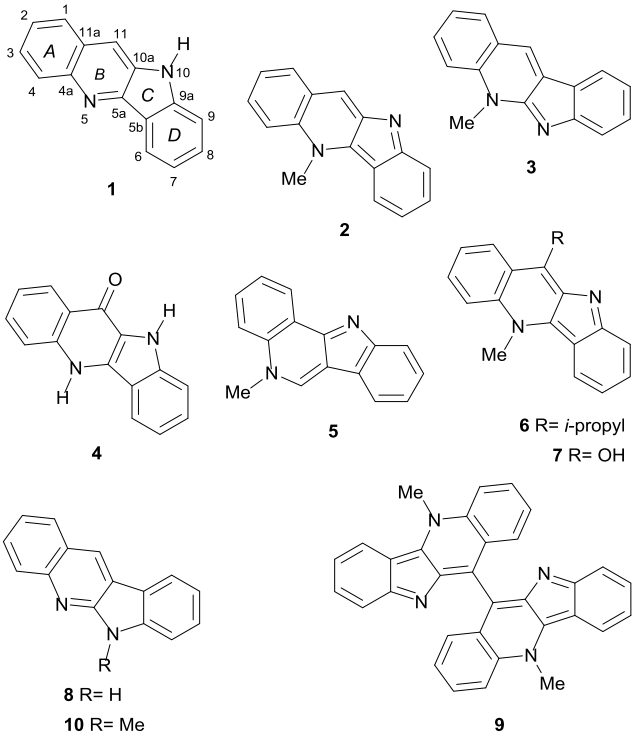

Figure 1. Chemical structures of representative examples of the indoloquinoline alkaloids. Quindoline (**1**), cryprolepine (**2**), neocryptolepine (cryptotackieine (**3**), quindolinone (**4**), cryptosanguinolentine (**5**), 11-isopropyl cryptolepine (**6**), cryptolepinone (**7**), quinindoline (**8**), biscryptolepine (**9**) and the unnatural 6-methylquinindoline (**10**).

In addition, several dimeric alkaloids have also been reported; among them biscryptolepine (**9**),[7c] cryptoquindoline,[7a] cryptolepicarboline,[8a] cryptospirolepine,[8b] cryptomisrine[8c] and quindolinocryptotackieine.[8d]

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[b]This article is dedicated to the memories of BSc. María V. Méndez (1987-2019†) and Dr. Edmundo A. Rúveda (1934-2018†), founder and first Director of IQUIR.

Electronic Supplementary Information (ESI) available: NMR spectra of the compounds and details of DFT calculations. See DOI: 10.1039/x0xx00000x

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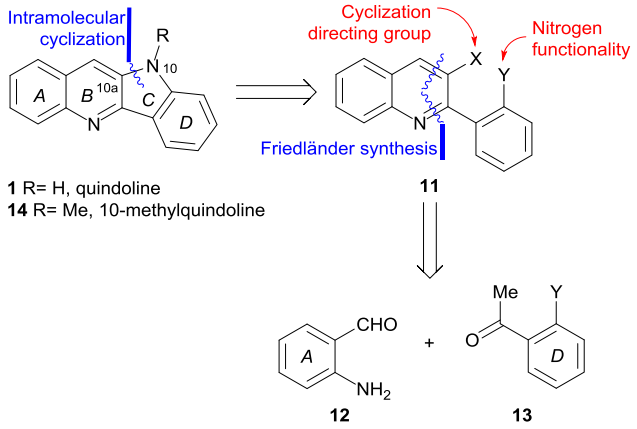
In pursuit of our continued efforts toward the synthesis of structurally unique oxygen-[9] and nitrogen-containing[10] heterocyclic natural products and their analogs, we have recently become interested in the pharmacologically promising indoloquinolines.[11a,b] In this area, we have carried out the total synthesis of neocryptolepine (**3**) as well as the synthesis of the unnatural 6-methylquinindoline (**10**) from a common precursor.[11c]

Quindoline (**1**) is one of the structurally simplest naturally occurring monomeric indoloquinolines. The heterocycle is bioactive and was employed as a synthetic precursor of the more widely known alkaloid cryptolepine (**2**).[12] Quindoline was repeatedly isolated from *C. sanguinolenta*[2d,5a,8c,13] and, lately, from the invasive weed *Justicia betonica* L. (Acanthaceae) in India,[7b] as well as from American sources such as the evergreen climbing shrub *J. secunda* Vahl and the small shrub *Sida rhombifolia* L. (Malvaceae).[14]

We have recently reviewed the synthetic approaches toward quindoline,[15a] finding out that the heterocycle was obtained in the laboratory in connection with the chemistry of indigo, long before it was isolated from a natural source.[16] We have also classified the reported synthetic strategies toward compound **1** in three main groups, according to the chemical structures of the starting materials involved, including a) benzenoids, b) indoles and c) quinolines, noticing that the first group is the oldest and, paradoxically, the least explored one. More recently, another synthesis of quindoline was also reported from benzenoid starting materials.[15b]

To date, the interest in natural products with promising biological activities from the synthetic and medicinal chemistry perspectives remains high. Therefore, herein we wish to report a new approach toward the total synthesis of quindoline, according to a "benzenoid" type strategy (*A* + *D* → *ABD* → *ABCD*), as outlined in the retrosynthetic analysis of Scheme 1. The selective *N*-methylation of **1** toward the unnatural 10-methylquindoline (**14**) is also disclosed.



Scheme 1. Retrosynthetic analysis of quindoline (**1**).

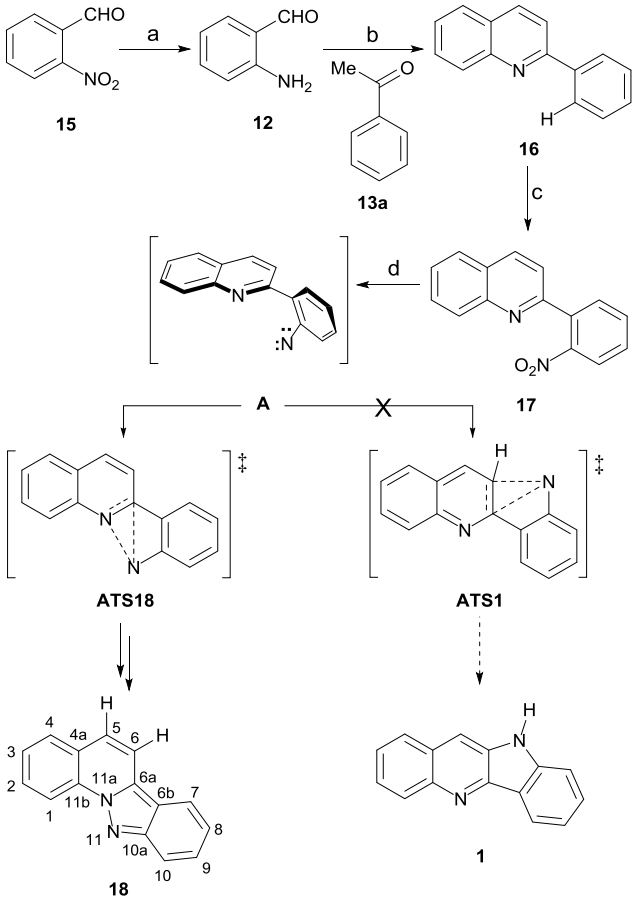
Results and discussion

The initial strategic disconnection at the N-10—C-10a bond level, was made conjecturing that it could be built by means of an intramolecular amination of the quinoline ring with a suitably positioned nitrogen functionality (Scheme 1). However, since C-3 functionalization of 2-substituted quinolines in the absence of an activating/directing group usually requires harsh conditions, the need to install such cyclization facilitating group was also considered. This line of reasoning revealed the 2-arylquinoline **11** as an appropriate precursor of the natural product.

In turn, disconnection of **11** unveiled both, *ortho*-amino benzaldehyde (**12**) and the acetophenone derivative **13** as the ideal starting materials, under the speculation that the heterocycle could be reached by application of the versatile Friedländer quinoline synthesis.[17]

Since the required starting 2-aminobenzaldehyde **12** is costly and highly unstable,[18] to begin the study its accessibility was secured in 96% yield (Scheme 2) from 2-nitrobenzaldehyde (**15**), employing an eco-conscious reduction protocol with iron chips under HCl promotion in a refluxing hydro-alcoholic (1:9 *v/v*) medium.[18b,19]

As planned, the aminoaldehyde **12** was next condensed with acetophenone (**13a**) under Friedländer conditions, employing KOH as base, to afford 97% yield of the 2-phenylquinoline **16**.[18b] Then, the latter was submitted to a copper-mediated chelation-assisted *ortho* C-H nitration with $AgNO_3$ to afford **17**. However, the product yields of this transformation were rather moderate (45% at best), regardless of the solvent employed ($ClCH_2CH_2Cl$, 1,2,3-trichloropropane or $1,2\text{-}Cl_2C_6H_4$).[20a]



Scheme 2. *Reagents and conditions:* a) Fe, 0.1N HCl, EtOH-H_2O (9:1, *v/v*), reflux, 2 h (96%); b) **13a**, KOH, EtOH, reflux, 36 h (97%); c) $Cu(OAc)_2.2H_2O$, $AgNO_3$, $ClCH_2CH_2Cl$, 130°C (closed vessel), 48 h (45%); d) PPh_3, $1,2\text{-}Cl_2C_6H_4$, reflux, 4 days (60%) or PPh_3, $MoO_2Cl_2(DMF)_2$ (0.05 equiv.), PhMe, reflux, 3 days (73%) or $P(OMe)_3$, reflux, 48 h (100%).

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Interestingly, according to the literature, no better results were obtained under assistance of a more expensive rhodium catalyst.[20b] Further, alternative procedures take place affording **17** with inacceptable performances (from traces to less than 25% yield).[21a-d] On the other side, in our hands the Doebner-Miller results reported by the group of Török could not be reproduced,[21e] suggesting that the efficiency of this approach should be improved in order to obtain a suitable synthetic route.

Despite the above difficulties, the so obtained quinoline **17** was forced to react with PPh_3 in refluxing 1,2-$Cl_2C_6H_4$. The expectation was that, by analogy with a previous report of the group of Ray,[22] this would result in a one-pot reductive intramolecular cyclization to afford the final quindoline **1**.

Disappointingly, however, the careful analysis of the ^{1}H NMR spectrum of the resulting heterocyclic compound, obtained in 60% yield, revealed that the actual reaction product was the known indazolo[2,3*a*]quinoline **18**.[21b,23] In addition to the general downfield shift of the signals, as a consequence of the extended resonance system, the pair of doublets assigned to H-5 (δ 7.99, 1H, *J*= 9.1 Hz) and H-6 (δ 7.65, 1H, *J*= 9.1 Hz) confirmed the structure and diagnosed the failure of the originally attempted transformation. Further proof of this outcome was obtained from the analysis of the ^{13}C NMR spectrum of the product (Table 3).

Not unexpectedly, the same outcome was obtained after cyclization of **17** with PPh_3 under $MoO_2Cl_2(DMF)_2$ catalysis (PhMe, reflux, 72 h, 73% yield)[24a,b] and also when $P(OMe)_3$ was employed as the nitro reduction and cyclizing agent (Cadogan-Cameron Wood reaction).

Two possible mechanisms were proposed to account for this observation, based on literature precedents.[24a] In the first one, it was conjectured that **17** may undergo a complete PPh_3-mediated deoxygenation to afford the reactive nitrene **A**.[24c,d] In turn, the latter may be responsible for the cyclization through C–N or N–N bond formation, ultimately leading to **1** or **18**, respectively.

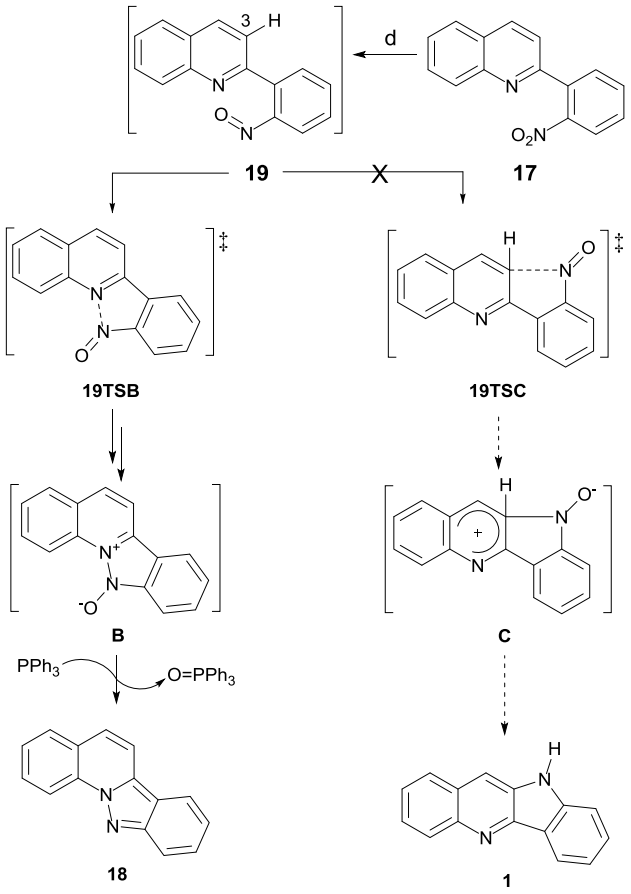
Thus, concerted insertion of the nitrene across the N—C-2 bond of the quinoline motif would afford a transition state intermediate like **ATS18**; in turn, the latter could collapse, undergoing a series of double bond shifts reminiscent of the classical 1,5-dipolar cyclisations, to furnish the aromatized indazole **18**. Following an analogous process, **ATS1** could be formed through nitrene insertion across the C-2—C-3 bond of the quinoline moiety to ultimately afford **1**.[24b]

In the alternative mechanism (Scheme 3), it was considered that the PPh_3-mediated reduction of **17** may give the nitroso derivative **19** as a reactive intermediate, which in turn may undergo cyclization by formation of either the C–N or N–N bond through the intermediacy of **B** or **C** (which could also undergo further double bond rearrangements and H-migration to give the related nitrones), affording the corresponding products **18** or **1**, respectively, after further abstraction of the oxygen by PPh_3.

Puzzlingly, when DFT calculations were performed, it was found that the natural product **1** would be thermodynamically favoured compared to **18** (ΔG= 19.49 kcal.mol^{-1}); hence, it was concluded that the isolation of the latter as the sole reaction product may obey to other factors.

Therefore, a more in-depth DFT study was carried out with the aim of achieving a better understanding of the outcome of the reaction, and the initial stages of both possible mechanistic routes were modelled, at a theory level B3LYP/6-311G** in toluene at the reaction temperature (383.15 K).

As depicted in Figure 2, it was observed that formation of the C–N bond involves loss of aromaticity of the quinoline system of **19** to afford the transition state **19TSC** ($\Delta G^{\ddagger}$ = 34.02 kcal.mol^{-1}) toward the intermediate **C** (ΔG = 30.48 kcal.mol^{-1}). Similarly, the N–N bond formation process in **19TSB** involves $\Delta G^{\ddagger}$ = 17.13 kcal.mol^{-1}, and the latter affords the intermediate **B**, which is essentially isoenergetic with the starting **19** (ΔG = 5.52 kcal.mol^{-1}).



Scheme 3. Proposed reaction mechanism toward the selective formation of **18** from **17**, involving the intermediacy of nitroso derivative **19**.

On the other hand, when formation of the nitrene **A** was analysed, it was found that **19TSA** requires $\Delta G^{\ddagger}$ = 30.99 kcal.mol^{-1}, being much more energetically expensive than **19TSB** (17.13 kcal.mol^{-1}), the transition state derived from the nitroso pathway. Despite the calculations revealed that the cyclic nitrone intermediate **B** (ΔG = 5.52 kcal.mol^{-1}) is 2.64 kcal.mol^{-1} less stable than the nitrene **A** (ΔG = 2.88 kcal.mol^{-1}), the energy of **19TSA** compared to **19TSB** suggests that the nitrene pathway may be comparatively less likely.

In fact, based on these results, it can be inferred that, unlike the path toward the indazole **18**, formation of the C–N bond leading to **1**, both via the nitrene and nitroso mechanisms, involves loss of aromatization; hence, the formation of the N–N bond should be favoured ($\Delta\Delta G^{\ddagger}$ = 16.89 kcal.mol^{-1}). Cyclization via the nitroso intermediate seems to be the most favourable alternative; however, formation of **18** through nitrene insertion into the N–C2 bond and further double bond rearrangement should not be discarded, especially in the presence of the molybdenum catalyst.

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Most likely, the preferential formation of **18** may stem from the higher nucleophilicity of the nitrogen atom compared to C-3.[24e] Calculations of FMOs were performed, noting that in the nitroso intermediate **19**, the LUMO is localized on the quinoline nitrogen atom. Noteworthy, these results also suggested that the assignment made by Ray and co-workers to the final product of their total synthesis of quindoline, should be revised.[22]

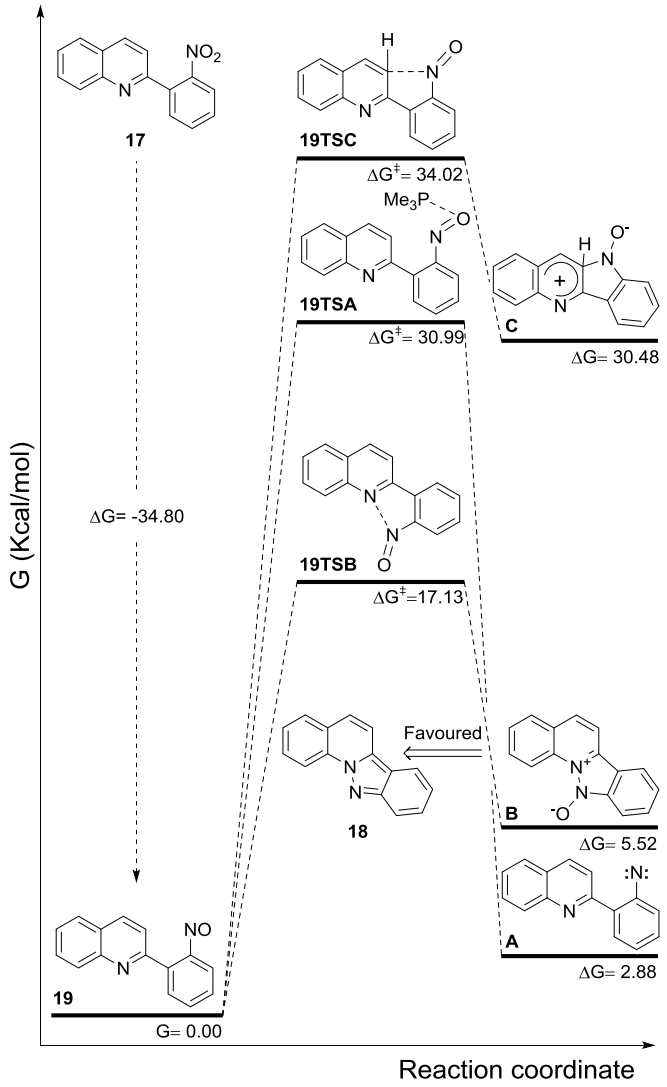


Figure 2. Energy diagram of some of the possible initial stages of the cyclization leading to indazole derivative **18**.

In view of the above results, the synthetic strategy was modified in order to include the installation of a cyclization directing group. In addition, the Friedländer approach was optimized with the aim to directly place the nitro group on the resulting quinoline and circumvent the rather moderate yields of **17** obtained in the previous $AgNO_3$-based nitration sequence.

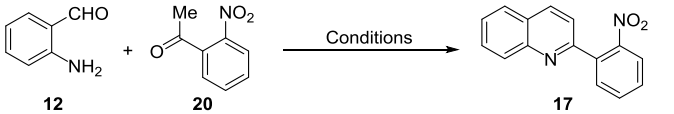
Therefore, the optimization of the Friedländer reaction between 2-nitroacetophenone (**20**) and 2-aminobenzaldehyde (**12**) toward the quinoline **17** was undertaken (Table 1),[17a] by first selecting the proper base, using EtOH as solvent. It was observed that sub-stoichiometric amounts of piperidine did not promote the reaction even under reflux (entry 1), whereas an unexpected and fruitless decomposition of the starting ketone took place in the presence of LiOH (entry 2).

On the other hand, it was found that Triton B and KOH (3.0 equiv.) performed quite similarly (entries 3 and 4), although the former required refluxing conditions. In a separate series of experiments, it was observed that the aldehyde **12**, which is considered unstable and prone to self-condensation, is rather stable in the ethanolic KOH solutions.

Next, the nature of the reaction medium was defined, employing KOH as base, at room temperature. It was observed that EtOH outperformed other alternatives, such as MeOH-H_2O and PEG 600 (entries 5-7). Notably, when the reaction was run in MeOH-H_2O the yield dropped to 17%, suggesting that the presence of water resulted in a significant deleterious effect on the reaction yields. On the other hand, when the transformation was executed in PEG 600, the ketone fully decomposed without affording the expected product. These results somehow revealed a lack of robustness of the transformation when performed with poorly stable precursors such as the aldehyde **12** and the nitroderivative **20**, and highlighted the importance of the solvent for its success.

Further, little performance differences were detected by lowering the temperature (entry 4 vs. entry 7) or the amount of KOH (entry 7 vs. entry 8). On the contrary, it was found that the refluxing condition proved detrimental to the product yields (entries 9 and 10).

Table 1. Optimization of the Friedländer reaction between **12** and **20**.[a]



12 **20** **17**

Run No.	Solvent	Base (equiv.)	Temp. (°C)	Time (h)	Yield (%)
1	EtOH	Piperidine (0.5)	reflux	48	s.m.[b]
2	EtOH	LiOH (0.5)	r.t.	96	dec.[c]
3	EtOH	Triton B (5.0)	reflux	24	34
4	EtOH	KOH (3.0)	55	21	32
5	MeOH-H_2O	KOH (3.0)	r.t.	96	17
6	PEG 600	KOH (3.0)	r.t.	72	dec.[c]
7	EtOH	KOH (3.0)	r.t.	48	36
8	EtOH	KOH (1.2)	r.t.	48	34
9	EtOH	KOH (2.4)	reflux	72	24
10	EtOH	KOH (5.0)	reflux	48	20.5
11	EtOH	KOH (0.7)	55	24	65[d]
12	EtOH	KOH (0.7)	r.t.	48	37[d]

[a]*Reaction conditions:* **12** (0.36 mmol), **20** (0.39 mmol), in solvent (3.5 mL). [b]No reaction. [c]Product decomposition was observed. [d]The ketone in EtOH was delivered *via* syringe pump in 12 h to an ethanolic solution of the aminoaldehyde and KOH.

The above results suggested that EtOH and KOH were the most suitable solvent and base, respectively, and that the meagre overall yields attained (< 40%) were a result of side reactions involving the ketone **20**. In order to test this hypothesis, the ketone was dropwise fed into the system by means of a syringe pump, while keeping the reaction at 55°C to balance the reaction yield and process speed.

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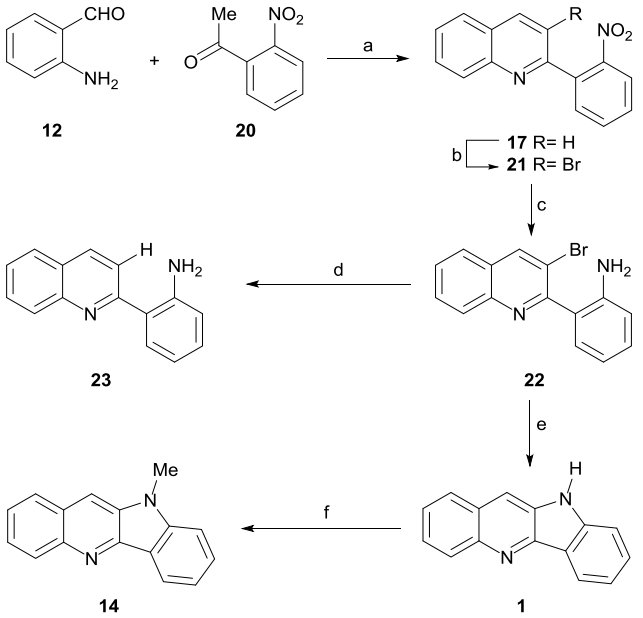
Under these conditions, the sought compound **17** was obtained in an improved 65% yield after 24 h (entry 11). Interestingly, this strategy failed to offer any significant performance improvement when the reaction was run at room temperature (entry 12 vs. entries 7 and 8).

After securing a robust and efficient supply of compound **17**, its bromination was examined (Scheme 4). Despite the efficiency of the available TBHP-based protocols for the halogenation of quinolines, it has been noted that the presence of substituents *ortho* to C-3 severely hinder the halogenation because lack of substitution of these positions is a requirement in the reaction mechanism.[25]

Therefore, alternatives were sought, observing that the exposure of **17** to NBS (5 equiv.) in AcOH at 150°C during 5 days gave 49% yield of **21**,[26a] whereas the use of the bromine/ pyridine reagent system in Cl_4C at reflux afforded the expected product **21** in an improved 78% yield.[26b-d] The latter was uneventfully reduced to the related aniline **22** in quantitative yield with iron chips as the reducing agent, in an hydro-alcoholic HCl medium.

With compound **22** in hand, its cyclization toward **1** by means of an amination of the halide moiety was next explored. Interestingly, however, despite the synthesis of heterocycles carrying the 5*H*-pyrido[3,2-*b*]indole motif is scarcely precedented,[23c] it was found that the amination of aromatic halides, a related transformation, has been recently performed under different conditions.



Scheme 4. *Reagents and conditions:* a) KOH, EtOH, 50°C, 24 h (65%); b) 1. Br_2, Cl_4C, reflux (closed vessel), 12 h; 2. pyridine, reflux, 48 h (78%); c) Fe^0, 0.1 N HCl, EtOH-H_2O, reflux, 4 h (100%); d) ^{t}BuOK, DMSO or MeCN, hυ (violet LED, 9 Watt, λ_{max} = 395 nm), rt, 6 h (**23**, > 90%); e) $Pd(MeCN)_2Cl_2$, dppf, ^{t}BuOK, THF, 100°C, 108 h (81%); f) Me_2CO_3, MeCN, DBU, 90°C (98%).

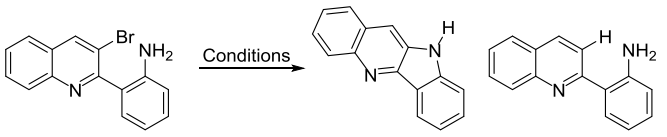
The four main alternatives include the classical aromatic nucleophilic substitution with strong bases, in the absence of transition metal catalysts, and a radical reaction under light promotion. Another couple of possibilities comprise the catalysis by palladium (Buchwald-Hartwig reaction) and copper (Ullmann-Goldberg aminations)[27a] complexes. Notably, copper-catalyzed reactions prevail among the intramolecular strategies toward carbazoles from halo-amino biphenyls,[27b] and ligand-free Ullmann reactions have also been reported.[27c,d]

In order to determine the best alternative to perform the cyclization, several conditions were explored (Table 2). In the first place, compound **22** was submitted to an aromatic nucleophilic substitution by treatment with ^{t}BuOK in DMSO,[28] resulting in the isolation of **1** in 56% yield (entry 1).

Encouraged by these results, a novel aromatic nucleophilic photo-stimulated substitution (SR_N1-based cyclization) was experimented, with ^{t}BuOK as base, in the presence of an array of violet LEDs (3 × 3 Watt, λ_{max} = 395 nm) as light source, at room temperature.[29] However, these conditions afforded chiefly (> 90% yield) the debrominated aniline **23**, most probably resulting from H-abstraction from the solvent by a halogen-deprived radical anion intermediate. Compound **23** was the exclusive product when MeCN was employed as the solvent, whereas minor amounts of the expected tetracycle **1** (< 5%) were observed when the starting material **22** was dissolved in DMSO.

In view of these results, and considering the low cost and scarce toxicity of copper reagents and its ability to accept rather inexpensive ligands, in contrast to the otherwise successful palladium-catalyzed Buchwald–Hartwig reaction, the cyclization through a Goldberg C-N cross-coupling reaction was explored next.

Table 2. Cyclization of the bromoaniline derivative **22**.[a]



Run No.	Solvent	Catalyst/Additive (equiv.)	Base (equiv.)	Temp. (°C)[a]	Time (h)	Yield of **1** (%)	Yield of **23** (%)
1	DMSO	-	^{t}BuOK (3.0)	130	48	56	-
2	DMSO	Violet LED	^{t}BuOK (2.0)	r.t.	6	< 5	90
3	MeCN	Violet LED	^{t}BuOK (2.0)	r.t.	6	-	91
4	DMF	CuI (0.1); L-proline (0.2)	Na_2CO_3 (2.0)	110	48	45[b]	-
5	THF	$Pd(MeCN)_2Cl_2$ (0.1); dppf (0.047)	^{t}BuOK (2.0)	100	108	81	-
6	THF	$Pd(MeCN)_2Cl_2$ (0.1); dtbpf (0.047)	^{t}BuOK (2.0)	100	24	62	23
7	$PhCH_3$ THF	$Pd(OAc)_2$ (0.1); Xantphos (0.1)	Cs_2CO_3 (0.6)	121	168	57[c]	-

[a]The reactions were performed in closed vessels at the informed temperatures. [b]Starting material (12%) was also recovered. [c]Starting material (36%) was also recovered.

The transformation was performed in DMF, with L-proline as ligand and Na_2CO_3 as base.[30] The reaction was run at 110°C, and was still exhibiting the presence of the starting material after 48 h, when it afforded a moderate 45% corrected yield of quindoline, along with a complex mixture of unidentified decomposition products (entry 4). The intermolecular amination of 3-bromopyridines under Ullmann-Goldberg conditions,[31a,b] has few and scattered

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precedents. Most of the successful examples of this transformation have relied on the Buchwald-Hartwig reaction.[31c-f] A plausible explanation to these statistics is that, in general, the Ullmann-Goldberg reaction proceeds well with electron-rich aryl halides, whereas the Buchwald–Hartwig amination gives best yields with electron-poor aryl halides.

Therefore, compound **22** was exposed to Buchwald-Hartwig conditions. Although an insightful literature search revealed the successful use of a stoichiometric quantity of $Pd(PPh_3)_4$, for a similar transformation,[32a-c] it also demonstrated that catalytic amounts of palladium salts have been employed along with chelating ligands to afford high product yields.

Hence, the performances of dppf,[32d] dtbpf and the more rigid xantphos as ligands were explored. The former couple of reactions were executed in the presence of ^{t}BuOK as the base, whereas Cs_2CO_3 was employed in the third case. The best result (81% yield of **1**) was achieved with dppf (entry 5), after 4.5 days of reaction.

However, in the presence of the more reactive dtbpf complex (entry 6) the transformation was less efficient and the cyclized product was isolated in 62% yield, along with some debrominated product (23% yield). On the other hand, the yield of **1** dropped to 57% when xantphos was employed as palladium ligand (entry 7). In the latter case, the reaction did not come to an end even after 168 h of refluxing **22** in a PhMe/THF mixture, and 12% starting material was recovered.

The transformation of quindoline (**1**) into the widely known cryptolepine (**2**) has been achieved a number of times, employing MeI or Me_2SO_4 as methylating agents. On the contrary, the synthesis of its regioisomer, the antifungal and renal vasodilator[33a,b] 10-methylquindoline (**14**) has few only precedents, but has been performed with the same toxic alkylating agents, under different conditions.[33b,f] The use of *N*-methyl precursors for this purpose has also been disclosed.[34] Therefore, by analogy with our previous work, and in order to provide an eco-conscious alternative, a solution of compound **1** in MeCN was exposed to dimethyl carbonate as methylating reagent under DBU promotion, cleanly affording the expected compound **14** in 98% yield.[11c]

The synthesis of authentic samples of natural products and related compounds, as well as the careful analysis of their spectra has helped us to suggest corrections to structural or spectroscopic assignment errors.[10c,11c,35] Hence, the final products **1** and **14**, as well as their relevant synthetic intermediates and side products (**18** and **23**), were unequivocally characterized by spectroscopic means.

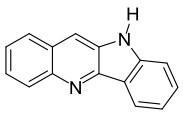
In addition, the ^{13}C NMR spectral data of the synthetic "quindoline" (Comp. **Q**) reported by Ray and co-workers[22] were examined for similarity, against the spectral information of authentic compounds **1** and **18**, employing the total absolute error criterion ($\Sigma|\Delta\delta|$). This parameter, which is the sum of the absolute differences among the chemical shifts of the individual atoms of the molecules being compared, is usually employed as a primary metric in spectral comparisons and for purposes of identity assessment.[36]

It was observed (Table 3) that the $\Sigma|\Delta\delta|$ values of the comparison between Comp. **Q** and reported spectra of both, natural and synthetic quindoline, including the currently synthesized heterocycle were rather high ($\Sigma|\Delta\delta|$ = 34.0-34.9 ppm). The same was observed when the data of Comp. **Q** were compared with those of the indazole derivative **18** ($\Sigma|\Delta\delta|$ = 21.5-22.2 ppm).

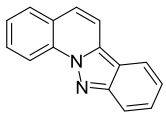
Interestingly, however, when the two most incongruous signals (greyed in Table 3) were removed from the comparison, the spectrum of Comp. **Q** turned to be more akin to that of the indazole derivative **18** ($\Sigma|\Delta\delta|$ = 1.5-2.0 ppm) than to **1** ($\Sigma|\Delta\delta|$ = 33.1-33.8 ppm), suggesting that the synthesis reported by the group of Ray might have furnished compound **18** instead of quindoline (**1**). Strikingly, we have previously found another identity misassignment within the area of the indoloquinolines.[11c]

On the other hand, the comparison between the synthesized quindoline and literature data gave low values of $\Sigma|\Delta\delta|$ (0.2 and 1.3 ppm), indicating the strong agreement of the results for the previously synthesized heterocycle[33d,37] as well as for the indoloquinoline alkaloid isolated from natural sources.[13] The same degree of agreement was observed for the synthetic compounds **18** ($\Sigma|\Delta\delta|$ = 1.1 ppm) and for **14**.[33b,33f]

Table 3. ^{13}C NMR chemical shift comparison among Comp. **Q**, quindoline (**1**, natural and synthetic), and indazolo[2,3*a*]quinoline (**18**).



1



18

Synthetic Ref.[22]	Synthetic Ref.[33d,37]	Natural Ref.[13]	Synthetic This work	Synthetic This work	Synthetic Ref.[23b]
Comp. **Q** DMSO-d_6	**1** in DMSO-d_6	**1** in DMSO-d_6	**1** in DMSO-d_6	**18** in $CDCl_3$	**18** in $CDCl_3$
148.9	145.7	145.7	145.7	149.2	149.1
144.0	144.0	144.1	144.0	134.1	134.0
142.4	143.3	143.4	143.3	132.3	132.2
129.5	132.4	132.5	132.4	129.4	129.3
128.4	129.7	129.8	129.7	128.5	128.3
128.1	128.6	128.8	128.7	127.9	127.9
126.1	127.5	127.6	127.5	126.0	125.9
125.2	126.7	126.8	126.7	125.1	125.1
123.3	126.0	126.1	126.0	123.0	123.0
120.8	124.8	124.9	124.8	120.7	120.6
119.7	121.4	121.4	121.3	119.6	119.6
117.1	121.0	121.0	121.0	117.1	117.0
116.7	119.3	119.4	119.3	116.7	116.6
116.4	113.0	113.1	113.0	116.5	116.5
115.5	111.5	111.6	111.5	115.5	115.4
$\Sigma\|\Delta\delta\|^a$	34.0	34.9	34.0	21.5	22.2
$\Sigma\|\Delta\delta\|^b$	33.1	33.8	33.1	**1.5**	**2.0**
$\Sigma\|\Delta\delta\|^c$	**1.3**	**0.2**	-	1.1	-

[a]Total absolute error with regards to Comp. **Q**. All resonances considered. [b]Total absolute error with regards to Comp. **Q**. Resonances in grey were not considered. [c]Total absolute error of synthetic **1** and **18** from this work against literature data for the corresponding compounds.

Conclusions

In conclusion, we have developed a short, straightforward and efficient strategy for the total synthesis of quindoline (1), a natural indoloquinoline alkaloid (5 steps, 39% overall yield from 15; 4 steps, 40% overall yield from commercial 12) and its 10-methyl derivative 14. The sequence involved a Friedländer quinoline synthesis to

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access a suitable 2-arylquinoline precursor and a Buchwald-Hartwig intramolecular cyclization to build the remainder five-member ring. The intermediate stages included a C-3 bromination to direct and facilitate cyclization and a highly selective iron-mediated nitro reduction step. The highly selective *N*-methylation of **1** toward the unnatural tetracycle **14** was accomplished by reaction with dimethyl carbonate under DBU promotion.

With authentic samples of indazolo[2,3-*a*]quinoline (**18**) and quindoline (**1**) in hand, this study also demonstrated that a previous claim related to the total synthesis of **1** through the triethylphosphite-mediated cyclization of **17** may be incorrect presumably due to the lack of a directing group, and that the structure of the so obtained product should be reassigned to **18**. DFT calculations were also performed to establish the most plausible mechanism for the latter transformation.

Finally, it is worth noting that the strategy toward quindoline is modular and does not resort to the use of protecting groups. Hence, analogs of the natural product could be readily accessed from differently substituted 2-aminobenzaldehydes and 2-nitro acetophenones. Hence, this contribution may also promote the synthesis of complex analogs of this natural heterocycle.

Experimental

General information

All the reactions were carried out under dry Nitrogen or Argon atmospheres, employing oven-dried glassware. Anhydrous DMF was obtained by heating the PA grade product over BaO for 4 h, followed by distillation under reduced pressure; anhydrous pyridine was prepared by sequential storage of the product for 7 days on NaOH pellets and atmospheric pressure distillation; anhydrous MeCN and anhydrous DMSO were prepared by reflux of the commercial product over CaH_2, followed by distillation.

Anhydrous CCl_4 and anhydrous 1,2-dichlorobenzene were obtained by a 4 h reflux of the PA product over P_2O_5, followed by distillation. Anhydrous toluene was obtained by reflux over sodium to which benzophenone was added, followed by distillation from the deep-blue sodium benzophenone ketyl.

Anhydrous EtOH was obtained by refluxing the PA product over magnesium turnings to which a crystal of iodine was added, and distilling the solvent from the thus formed magnesium ethoxide. Anhydrous solvents were stored in dry Young ampoules. All other reagents were used as received.

Flash column chromatographies were executed with Merck's silica gel 60 H. The elutions were carried out with hexane/EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques. All new compounds gave single spots on TLC plates (silica gel 60 GF_{254}) run in different hexane/EtOAc solvent systems.

The chromatographic spots were detected by exposure to 254 nm UV light, followed by spraying with Dragendorff reagent (Munier and Macheboeuf modification),[38] or with ethanolic *p*-anisaldehyde/sulfuric acid reagent. The plates were carefully heated after spraying, for improving selectivity.

Apparatus

The melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are reported uncorrected. The IR spectra were recorded with a Shimadzu Prestige 21 spectrophotometer, as solid dispersions in KBr disks.

The NMR spectra were acquired at 300.13 (^{1}H) or 75.48 (^{13}C) MHz on a Bruker Avance spectrometer in $CDCl_3$, unless stated otherwise. The peak for $CHCl_3$ in $CDCl_3$ (δ_H = 7.26 ppm), and the signal of $CDCl_3$ (δ_C = 77.0 ppm) were used as the corresponding internal standards. Chemical shifts are reported in parts per million on the δ scale and *J*-values are given in Hertz. In special cases, selective TOCSY and 2D-NMR experiments (COSY, HMBC and HMQC) were also employed. Pairs of signals marked with asterisk (*) indicate that their assignments may be exchanged. The high-resolution mass spectra were obtained from UMYMFOR (Buenos Aires, Argentina) with a Bruker MicroTOF-Q II instrument. Detection of the ions was performed in electrospray ionization, positive ion mode.

2-(2-Nitrophenyl)quinoline (17)

Powdered KOH (11.8 mg, 0.21 mmol) was added to a solution of 2-aminobenzaldehyde (**12**, 35 mg, 0.29 mmol, 1 equiv.) in EtOH (1 mL) and the system was stirred at room temperature until its complete dissolution. Under stirring, the mixture was heated at 55 °C and treated with a solution of 2-nitroacetophenone (**20**, 53.1 mg, 0.32 mmol, 1.1 equiv.) in EtOH (1 mL) delivered over 12 h through a syringe pump. Once the addition of **20** was complete, the reaction was stirred until completion, when it was concentrated under reduced pressure. Brine (15 mL) was added to the residue and the products were extracted with EtOAc (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by chromatography to give the desired quinoline **17** (47 mg, 65%), as a yellow solid, mp 115–117 °C (Lit.:[21a] 116–117 °C). *Rf* = 0.47 (hexane–EtOAc = 7 : 3) . IR (KBr, υ): 3063, 2953, 2872, 2850, 1595, 1537, 1504, 1485, 1425, 1352, 1315, 1033, 943, 850, 831, 781, 760, 744, 710, 653 and 621 cm^{-1}. ^{1}H NMR δ 7.54 (d, 1H, *J* = 8.5, H-3), 7.56-7.62 (m, 2H, H-4' and H-6), 7.68-7.78 (m, 2H, H-5' and H-7), 7.73 (d, 1H, *J* = 8.2, H-6'), 7.87 (d, 1H, *J* = 8.2, H-5), 8.00 (d, 1H, *J* = 8.6, H-3'), 8.11 (d, 1H, *J* = 8.5, H-8) and 8.25 (d, 1H, *J* = 8.3, H-4). ^{13}C NMR δ 120.6 (C-3), 129.7 (C-8), 127.1 (C-6), 127.2 (C-4a), 127.6 (C-5), 129.4 (C-4'), 129.7 (C-8), 130.0 (C-5'),* 131.6 (C-6'), 132.7 (C-7),* 135.9 (C-1'), 136.8 (C-4), 148.0 (C-8a), 149.2 (C-2') and 155.6 (C-2).

3-bromo-2-(2-nitrophenyl)quinoline (21)

A solution of bromine (28 µL, 0.55 mmol, 4 equiv.) in CCl_4 (0.5 mL) was added dropwise to a solution of the quinoline **17** (34 mg, 0.136 mmol, 1 equiv.) in anhydrous CCl_4 (0.5 mL). The mixture was heated at reflux for 12 h, when a solution of pyridine (11 µL, 0.14 mmol, 1.03 equiv.) in CCl_4 (1 mL) was added and the system was heated under reflux for 48 h. Brine (10 mL) was added and the reaction products were extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue afforded **21** (35 mg, 78%) as a brownish solid, mp 105–107 °C. *Rf* = 0.50 (hexane–EtOAc = 7 : 3). IR (KBr, υ): 3100, 2955, 2918, 2849, 2357, 1730,

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1614, 1587, 1574, 1537, 1526, 1487, 1454, 1398, 1346, 1298, 1259, 1063, 1038, 957, 852, 785, 719 and 696 cm^{-1}. ^1H NMR δ 7.55 (dd, 1H, *J* = 1.5 and 7.4, H-6'), 7.61 (ddd, 1H, *J* = 1.3, 6.8 and 8.0, H-6), 7.65 (ddd, 1H, *J* = 1.4, 7.6 and 8.0, H-4'), 7.76 (dt, 1H, *J* = 1.4 and 8.6, H-7), 7.78 (dt, 1H, *J* = 1.3 and 7.9, H-5'), 7.81 (bd, 1H, *J* = 7.7, H-5), 8.06 (d, 1H, *J* = 8.5, H-8), 8.26 (dd, 1H, *J* = 1.2 and 8.3, H-3') and 8.46 (s, 1H, H-4). ^{13}C NMR δ 117.0 (C-3), 124.6 (C-3'), 126.7 (C-5), 127.9 (C-6), 128.5 (C-4a), 129.4 (C-8), 129.8 (C-4'), 130.3 (C-7), 131.7 (C-6'), 133.8 (C-5'), 135.8 (C-1'), 138.9 (C-4), 146.3 (C-8a), 147.6 (C-2') and 156.5 (C-2). HRMS (ESI-TOF): Found *m/z*: 328.9919; $C_{15}H_{10}BrN_2O_2$ ($[M+H]^+$) requires *m/z*: 328.9920.

2'-(3-Bromoquinolin-2-yl)aniline (22)[23c]

Iron powder (24 mg, 0.41 mmol, 1.37 equiv.) was added to a stirred solution of **21** (35 mg, 0.1 mmol, 1 equiv.) in EtOH 96° (2 mL). The mixture was treated with a solution of 0.1M HCl (0.052 mL, 5.2 µmol) and heated under reflux for 4 h. Then, EtOAc was added and the solids were removed by filtration. The filtrate was washed with a saturated $NaHCO_3$ solution and concentrated under reduced pressure to give **22** (31.7 mg, 100%) as a yellow solid, mp 140–142 °C. *Rf* = 0.43 (hexane‑EtOAc = 7 : 3). IR (KBr, υ): 3428, 3331, 2918, 2849, 1732, 1714, 1694, 1568, 1485, 1250, 925, 783, 762 and 754 cm^{-1}. ^1H NMR δ 4.20 (bs, 2H, $w_{1/2}$ = 65, NH_2), 6.84 (d, 1H, *J* = 8.0, H-3'), 6.86 (ddd, 1H, *J* = 1.7, 7.6 and 8.0, H-5'), 7.24 (dt, 1H, *J* = 1.7 and 8.0, H-4'), 7.36 (dd, 1H, *J* = 1.7 and 7.6, H-6'), 7.58 (dt, 1H, *J* = 1.1 and 7.6, H-6), 7.74 (ddd, 1H, *J* = 1.4, 6.9 and 8.6, H-7), 7.78 (d, 1H, *J* = 8.7, H-5), 8.08 (d, 1H, *J* = 8.4, H-8) and 8.54 (s, 1H, H-4). ^{13}C NMR δ 116.8 (C-3'), 118.0 (C-5'), 118.2 (C-3), 124.8 (C-1'), 126.5 (C-5), 127.6 (C-6), 128.2 (C-4a), 129.2 (C-8), 130.0 (C-4'), 130.1 (C-7), 130.8 (C-6'), 140.5 (C-4), 144.4 (C-2'), 146.4 (C-8a) and 157.4 (C-2).

Indazolo[2,3-*a*]quinoline (18)

Method A: A stirred solution of **17** (20 mg, 0.08 mmol, 1 equiv.) in 1,2-dichlorobenzene (2 mL) under argon was treated with PPh_3 (65 mg, 0.248 mmol, 1.55 equiv.) and the reaction mixture was refluxed for 4 d in a sealed tube. After concentration under reduced pressure, the residue was subjected to chromatography to give pure **18** (9.2 mg, 53%) as a yellow solid, mp 98–101 °C (Lit.:[23a,b] 98 °C), along with some starting material (2.2 mg), raising the yield of **18** to 60% (based on recovered starting material, brsm). *Rf* = 0.75 (hexane‑EtOAc = 7 : 3).

Method B: A stirred solution of **17** (20 mg, 0.08 mmol) in PhMe (1 mL) under argon was exposed to PPh_3 (50 mg, 0.19 mmol) and $MoO_2Cl_2(dmf)_2$ (2.8 mg, 0.008 mmol). The reaction mixture was refluxed for 72 h in a sealed tube. After removal of the solvent under reduced pressure, the residue was subjected to chromatography to give pure **18** (12.8 mg, 73%).

Method C: A solution of **17** (20 mg, 0.08 mmol) in distilled $P(OMe)_3$ (0.5 mL) was refluxed for 2 d in a sealed tube. Then, Na_2CO_3 was added and the system was further stirred for 1.5 h, when the reaction products were extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue afforded **18** (17.5 mg, 100%) as a yellow solid. IR (KBr, υ): 3055, 3034, 2367, 2344, 1636, 1609, 1558, 1541, 1477, 1450, 1433, 1393, 1354, 1308, 1233, 1179, 1140, 1103, 961, 930, 837, 802, 760, 746, 729, 714, 690 and 638 cm^{-1}. ^1H NMR δ 7.27 (ddd, 1H, *J* = 0.8, 6.7 and 8.3, H-5'), 7.56 (ddd, 1H, *J* = 1.2, 6.7 and 8.9, H-4'), 7.60 (ddd, 1H, *J* = 1.1, 7.1 and 8.0, H-6), 7.65 (d, 1H, *J* = 9.1, H-4), 7.80 (ddd, 1H, *J* = 1.4, 7.2 and 8.5, H-7), 7.92 (dd, 1H, *J* = 1.3 and 8.0, H-5), 7.98 (dt, 1H, *J* = 0.9 and 8.7, H-3'), 7.99 (d, 1H, *J* = 9.1, H-3) 8.08 (dt, 1H, *J* = 1.0 and 8.3, H-6') and 8.95 (dd, 1H, *J* = 0.5 and 8.5, H-8). ^{13}C NMR δ 115.6 (C-3), 116.6 (C-3'), 116.8 (C-6a'), 117.2 (C-8), 119.7 (C-6'), 120.8 (C-5'), 123.1 (C-4), 125.2 (C-4a), 126.1 (C-6), 128.0 (C-4'), 128.5 (C-5), 129.5 (C-7), 132.4 (C-2), 134.2 (C-8a) and 149.2 (C-2').

2'-(Quinolin-2-yl)aniline (23)

A solution of **22** (15 mg, 0.05 mmol, 1 equiv.) in anhydrous and degassed MeCN (2 mL) was treated with ^{t}BuOK (12 mg, 0.1 mmol, 2 equiv.). The reaction mixture was flushed with nitrogen and irradiated at room temperature with violet LED light (3 × 3W, λ_{max} = 395 nm) during 48 h. Then, the reaction was quenched with saturated NH_4Cl (5 mL) and the mixture was extracted with EtOAc (3 × 30 mL), the organic extract was washed with water (2 × 5 mL), dried over Na_2SO_4 and purified through column chromatography, to afford **23** (10 mg, 91%), as a yellow solid, mp 145–147 °C (Lit.:[21b] 153 °C). *Rf* = 0.67 (hexane‑EtOAc = 7 : 3). ^1H NMR δ 3.64 (bs, 2H, $w_{1/2}$ = 22, NH_2), 6.86 (d, 1H, *J* = 7.6, H-3'), 6.87 (t, 1H, *J* = 7.6, H-5'), 7.24 (dt, 1H, *J* = 1.3, 7.6, H-4'), 7.55 (bdd, 1H, *J* = 7.9, 8.3, H-6), 7.70 (dd, 1H, *J* = 1.3, 7.6, H-6'), 7.74 (ddd, 1H, *J* = 1.3, 7.9, 8.3, H-7), 7.84 (dd, 1H, *J* = 1.3, 8.3, H-5), 7.87 (d, 1H, *J* = 8.8, H-3), 8.10 (bd, 1H, *J* = 8.3, H-8) and 8.26 (d, 1H, *J* = 8.8, H-4). ^{13}C NMR δ 117.8 (C-3'), 118.2 (C-5'), 120.6 (C-3), 121.6 (C-1'), 126.4 (C-4a), 126.5 (C-6), 127.5 (C-5), 128.3 (C-8), 129.9 (C-6'), 130.0 (C-7), 130.6 (C-4'), 137.3 (C-4), 146.2 (C-8a), 146.5 (C-2') and 158.8 (C-2). The use of DMSO as solvent afforded quite similar yields of **23** (90%), along with minor amounts (< 5%) of **1**.

10*H*-Indolo[3,2-*b*]quinoline (quindoline, 1)

A mixture of $Pd(MeCN)_2Cl_2$ (2.6 mg, 0.01 mmol, 0.1 equiv.) and dppf (26 mg, 0.047 mmol, 0.47 equiv.), in anhydrous THF (1 mL) was stirred for 18 h at rt. Then, compound **22** (30 mg, 0.1 mmol, 1 equiv.) was added, and the reaction mixture was stirred for 1 h at rt. After that, ^{t}BuOK was added (22 mg, 0.2 mmol, 2 equiv.), the tube was sealed and system was heated for 108 h at 100 °C. Then, the reaction mixture was filtered through Celite®, the solvent was evaporated under reduced pressure, and the crude product was purified by chromatography to afford pure **1** (17.7 mg, 81%) as a yellow solid, mp 201–203 °C (Lit.:[4d] 200–203 °C). *Rf* = 0.33 (hexane‑EtOAc = 7 : 3). IR (KBr, υ): 3063, 2955, 2924, 2853, 2351, 1732, 1715, 1643, 1614, 1568, 1557, 1454, 1396, 1371, 1337, 1261, 1223, 1142, 1109, 1070, 1018, 798 and 746 cm^{-1}. ^1H NMR δ 7.35 (t, *J* = 7.7, H-7), 7.46 (d, *J* = 8.1, H-9), 7.54 (ddd, *J* = 1.2, 6.8, 8.3 H-2), 7.60 (ddd, *J* = 1.2, 7.7, 8.1, H-8), 7.67 (ddd, *J* = 1.7, 6.8, 8.6, H-3), 7.94 (d, *J* = 8.3, H-1), 8.04 (s, H-11), 8.11 (bs, NH, $w_{1/2}$= 7.5), 8.33 (d, *J* = 8.6, H-4) and 8.55 (d, *J*= 7.7, H-6). ^{13}C NMR δ 110.9 (C-9), 113.1 (C-11), 120.4 (C-7), 120.5 (C-5b), 122.2 (C-6), 125.3 (C-2), 126.7 (C-3), 127.0 (C11a), 127.2 (C-1), 129.2 (C-4), 129.8 (C-8), 132.4 (C-10a), 143.6 (C-9a), 144.4 (C-4a) and 146.5 (C-5a).

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10-Methylquindoline (14)

A solution of **1** (14 mg, 0.064 mmol, 1 equiv.), DBU (8 µL, 0.064 mmol, 1 equiv.) and DMF (25 µL, 0.323 mmol, 5 equiv.) in DMC (0.125 mL, 1.485 mmol, >20 equiv., excess) was stirred at 90 °C until complete conversion of the starting material was verified by TLC. After evaporation of the volatiles, the residue was chromatographed to give **14** (14.8 mg, 98%), as a yellow solid, mp 117–119 °C (Lit.:[33b,33d] 115-116 °C; 110-112 °C). *Rf* = 0.55 (hexane-EtOAc = 7 : 3). IR (KBr, υ): 2916, 2849, 2320, 1715, 1609, 1531, 1456, 1344, 1260, 1121 and 746 cm^{-1}. ^1H NMR δ 3.88 (s, 3H, NMe), 7.34 (t, 1H, *J* = 7.6, H-7), 7.42 (d, 1H, *J* = 8.2, H-9), 7.55 (ddd, 1H, *J* = 1.1, 6.7, 8.2, H-2), 7.63-7.70 (m, 2H, H-3, H-8), 7.93 (s, 1H, H-11), 7.97 (dd, 1H, *J* = 1.1, 8.2, H-1), 8.34 (d, 1H, *J* = 8.6, H-4) and 8.56 (d, 1H, *J* = 7.6, H-6). ^{13}C NMR δ 29.1 (NMe), 108.4 (C-9), 110.7 (C-11), 119.7 (C-7), 121.5 (C-5b), 122.1 (C-6), 125.3 (C-2), 126.2 (C-3), 126.8 (C-11a), 127.1 (C-1), 129.2 (C-4), 129.7 (C-8), 134.1 (C-10a), 144.0 (C-4a), 145.0 (C-9a) and 146.0 (C-5a).

Conflicts of interest

There are no conflicts to declare.

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A concise Friedländer/Buchwald-Hartwig approach to the total synthesis of quindoline, a bioactive natural indoloquinoline alkaloid, and toward the unnatural 10-methylquindoline

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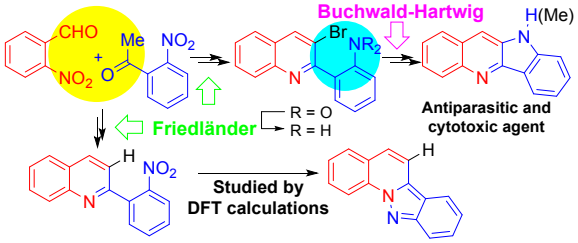
Friedländer and Buchwald-Hartwig reactions were used sequentially to achieve an efficient total synthesis of quindoline and a new synthesis of the unnatural 10-methylquindoline. DFT calculations were employed to explain the outcome of a failed key transformation.



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