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Total synthesis of bicyclomahanimbine by Cu(II)-promoted photoredox process†

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Since the isolation of carbazole alkaloids, the synthetic chemists have witnessed an upsurge in research of them due to their potential pharmacological properties. Our approach shows the total syntheses of five such biorelevant pyrano-[3,2*a*]-carbazole alkaloids, emphasizing biomimetic and innovative synthetic methodologies such as cascade reactions and strategic bond formations through sustainable electrochemical and photochemical conditions.

Introduction

Carbazole alkaloids, a prominent class of natural compounds, are renowned for their unique and wide biological effects, and have had a great impact on pharmaceutical research and development.[1–4] The curry tree (*Murraya koenigii*), a significant medicinal plant in Asia, is particularly notable for its abundance of biologically active carbazole alkaloids. It was from *Murraya koenigii* that Chakraborty *et al.* (1965) isolated the first carbazole (murrayanine, shows antibiotic properties) from a biological source.[5]

The foremost alkaloid component of *Murraya koenigii* is the monoterpenoid pyrano-[3,2-*a*]-carbazole, mahanimbine (Fig. 1); first isolated by Chakraborty *et al.* from the stem bark in 1966.[6] The structure elucidation was done by Narasimhan *et al.* later in 1968.[7] The 2*H*-chromene unit on mahanimbine indicates that its biosynthesis likely involves geranylation and subsequent cyclization of 2-hydroxy-3-methylcarbazole. Further annulations that transpire *in vivo* construct the bicyclic units that contribute to the structural variety of carbazoles found in this *Murraya* genus. Among them, curryanin (1969, Dutta *et al.*),[8] murrayazolinine (1973, Chakraborty *et al.*)[9] and feature pentacyclic scaffold whereas bicyclomahanimbine and isocyclomahanimbine (1969, Kapil *et al.*)[10] have hexacyclic heptane [3,2,0] core (Fig. 1).

Among these mahanimbine (**1**) has shown broad spectra of biological effects, primarily cytotoxic and antitumor properties against various cancer cell lines including CEM-SS, HL-60, MCF-7, P388, and HeLa.[11,12] It also exhibits anti-plasmodial (IC_{50} – 9.12 mM),[13] anti-HIV,[14] antioxidant,[3] anti-inflammatory,[3] and melanogenesis inhibitory activities,[15] highlighting its potential in pharmacology. Additionally, it lowers blood glucose levels by enhancing peripheral glucose uptake or stimulating pancreatic insulin secretion[4] underscoring its versatility to become a therapeutic agent and emphasizing its importance for further research and synthetic efforts. It was explored that, due to their parent skeleton (3-methylcarbazole), they exhibit potential biological activities, including antitumor, antibacterial, antiviral, and antifungal properties.[3,4] Adding methyl groups to biologically active molecules can alter their conformation, potentially enhancing their activity, as well as improving their hydrophilicity and solubility ('*Magic Methyl*' effect).[16]

The traditional methods for crafting the carbazole motifs or achieving subsequent annulations often rely on pre-functionalization steps, oxidants, metal catalysis or significantly high temperatures, which come with a number of disadvantages. These include the need for stoichiometric concentrations of oxidizers, and rather costly metal complexes

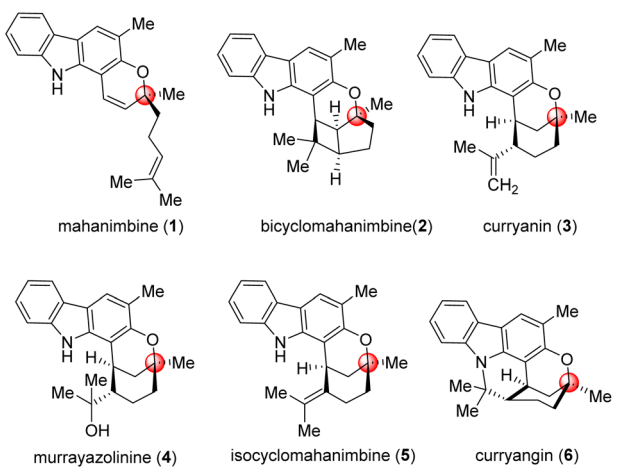

Fig. 1 Representatives of pyrano [3,2-*a*] carbazole alkaloids.

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which can be hazardous or poisonous, limits functional group tolerance and also sometimes, the requirement for essential leaving groups, leading to significant reagent waste. Previous studies by various groups predominantly utilized such Pd-catalyzed cross-coupling reactions to synthesize the parent 2-hydroxy-3-methyl carbazole skeleton.[17–20] Furthermore, the sole documented method for converting mahanimbine into bicyclohamanimbine required sunlight irradiation over nearly a lunation and resulted only 45% yield.[17]

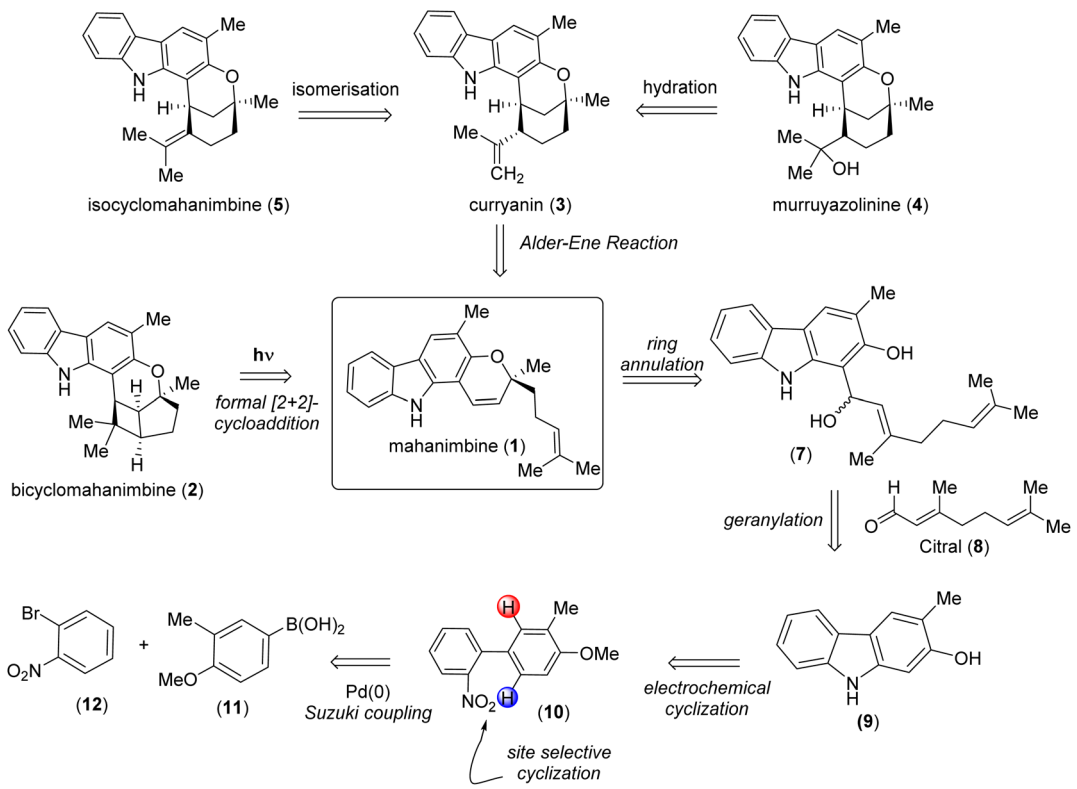
Thus, advancements in atom economics and improvement in environmental impact, reaction rate are much required. Hence, in our approach to synthesize pyrano-[3,2-*a*]-carbazole alkaloids, we reduced the usage of metal complexes wherever possible and utilized photo-redox chemistry as well as electrochemistry, which are 'green' substitutes in synthetic chemistry offering exceptional reaction paths and intrinsic safety. Correspondingly, the waste generation will significantly reduce.

The potential of mahanimbine (**1**) as a versatile intermediate for accessing diverse monoterpenoid pyrano-[3,2-*a*]-carbazole alkaloids, we developed a synthetic strategy centered on this compound. Inspired by biosynthetic pathways, we explored a sustainable formal [2 + 2]-cycloaddition approach to construct the bicyclomahanimbine (**2**) skeleton. Here, toxic reagents can be superseded by using photoredox catalysis for ring annulation. Constructing curryanin (**3**) can also be facilitated by using an Alder-ene type reaction on mahanimbine (**1**). Subsequent regioselective hydration of curryanin (**3**) can lead to the formation of murruyazolinine (**4**). Furthermore, isocyclomahanimbine (**5**) can be achieved through the isomerization of curryanin (**3**). Therefore, the synthesis of mahanimbine (**1**) serves as a crucial starting point in our synthetic strategy (Scheme 1).

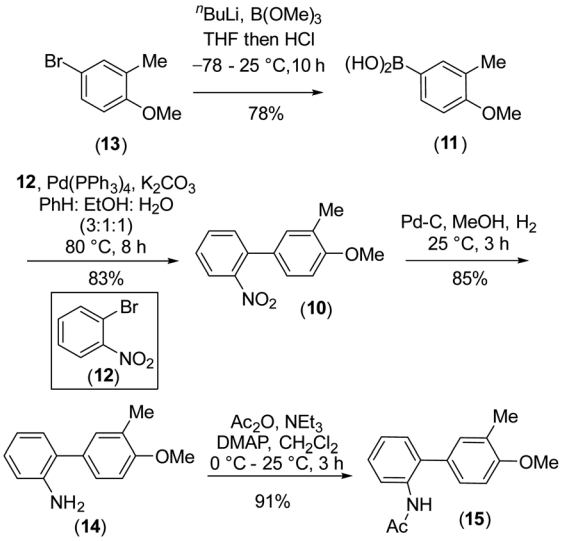
To design the 2*H*-chromene ring on mahanimbine (**1**), we envisaged the established biomimetic geranylation protocol for pyran annulation on 2-hydroxy-3-methylcarbazole (**9**). Sustainable and cost-effective electrochemical C–N bond formation was hypothesized to craft the carbazole motif.[21] To construct the C–C bond, Suzuki–Miyaura coupling has been chosen. Therefore, the synthesis begins with commercially available 4-bromo-2-methylanisole (**13**) (Scheme 2).

Our experimental approach commenced by treating 4-bromo-2-methylanisole (**13**) with ^{n}BuLi for metal-halogen exchange, followed by quenching of the generated aryl lithium species with $B(OMe)_3$ and subsequent acidic work-up. This process yielded 4-methoxy *m*-tolyl boronic acid (**11**), which underwent a Pd(0)-catalyzed Suzuki–Miyaura coupling[22] with readily available 2-bromonitrobenzene (**12**) to form compound (**10**). After forming the C–C bond, the nitro group on (**10**) was fully reduced to an amino group with Pd/C-occluded H_2 (Scheme 2). Subsequently, we attempted electrochemical oxidation to construct the carbazole scaffold from compound (**14**). Due to their susceptibility towards side reactions,[23] we implemented a constant potential protocol.

However, this approach was unsuccessful. Since the use of amidyl radicals as reactive intermediates has been extensively studied and is closely linked to cyclization reactions,[25] we then explored same dehydrogenative electrochemical reaction, protecting the amino group with various electron-withdrawing



Scheme 1 Divergent retrosynthetic analysis of pyrano-[3,2-*a*] carbazole alkaloids using mahanimbine (**1**) as the precursor.

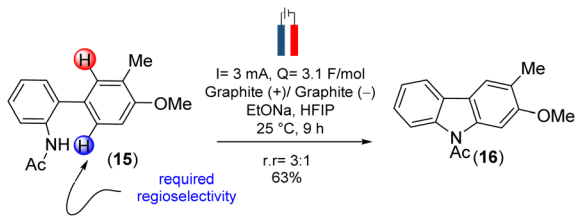


Scheme 2 Generation of carbazole precursor biphenyl compound (**10**) for electrochemical cyclization.

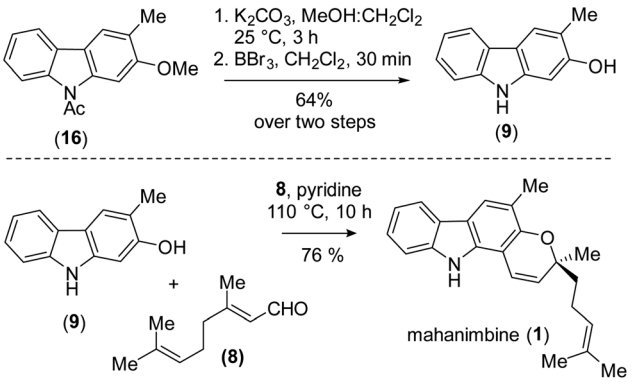
groups.[26,27] Notably, when the amino group was protected with an acetyl group (as in **15**), the desired C–N bond formation (see, carbazole **16**) occurred with a yield of 73% ($r:r = 3:1$) (Scheme 3) [for detailed optimization, see the ESI† for details].

Having ample quantities of carbazole (**16**) available, we proceeded with alkaline hydrolysis of amide followed by phenolic ether cleavage using BBr_3. These set of reactions provided the biological carbazole precursor, 2-hydroxy-3-methylcarbazole (**9**). Now, to construct the 2*H*-chromene motif, we accomplished base-mediated cascade pyran-ring annulation[28] with an established C_{10}-building block such as citral (**8**), over the previously reported Lewis-acid mediated cyclization [which yielded only 74% using $Ti(O^iPr)_4$].[15] After exhaustive optimization, we found that refluxing the phenolic compound (**9**) in pyridine solvent in the presence of 10 equiv. citral (**8**) yielded mahanimbine (**1**) with an impressive yield of 76% (Scheme 4). The tentative mechanism for the formation of mahanimbine (**1**) from a reaction of carbazole **9** with citral (see, ESI for details†).

In 2013, Knölker group[17] subjected mahanimbine (**1**) to prolonged exposure to sunlight. After 26.5 days, they isolated bicyclomahanimbine (**2**) with a yield of 45%. With utilization of 5 mol% $FeCl_3$, Tan group also achieved this conversion but only with 42% yield.[29] Hence, our focus was also into expediting the synthesis of bicyclomahanimbine (**2**) within a significantly



Scheme 3 Sustainable dehydrogenative electrochemical C–N bond formation to construct the carbazole scaffold.

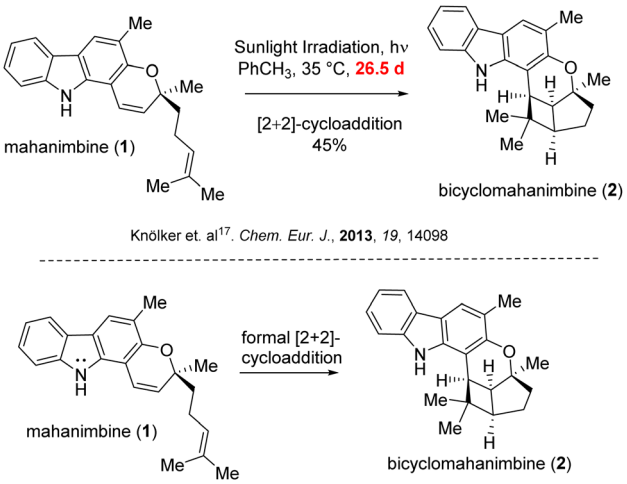


Scheme 4 Biomimetic synthesis of mahanimbine (**1**).

shortened timeframe. As hypothesized, we explored various photocatalytic optimization strategies (Table 1) for synthesizing bicyclo-[3,2,0] heptane system in bicyclomahanimbine (**2**) from mahanimbine (**1**). The most successful approach involved using $Cu(OTf)_2$ as a catalyst (10 mol%) in diethyl ether solvent under the irradiation of a 500 W Na-lamp, achieving a maximum yield of 87%. Under visible light, $Cu(OTf)_2$ undergoes excitation[30] and subsequent abstraction of an electron from the nitrogen atom of mahanimbine (**1**), forms a cation radical intermediate and ultimately Cu(II) reduces to Cu(I). The intermediate then undergoes electronic rearrangement, resulting in the formation of a five-membered ring, with the radical stabilizing at a tertiary position. Concurrently, a four-membered ring forms adjacent to the fused five-membered ring, with a radical cation generated at the nitrogen center. Subsequently, the Cu(I) species donates an electron, oxidizing the nitrogen radical cation intermediate resulting in the formation of bicyclomahanimbine (**2**) *via* a formal [2 + 2]-cycloaddition and regenerating $Cu(OTf)_2$ in the process (Scheme 5).

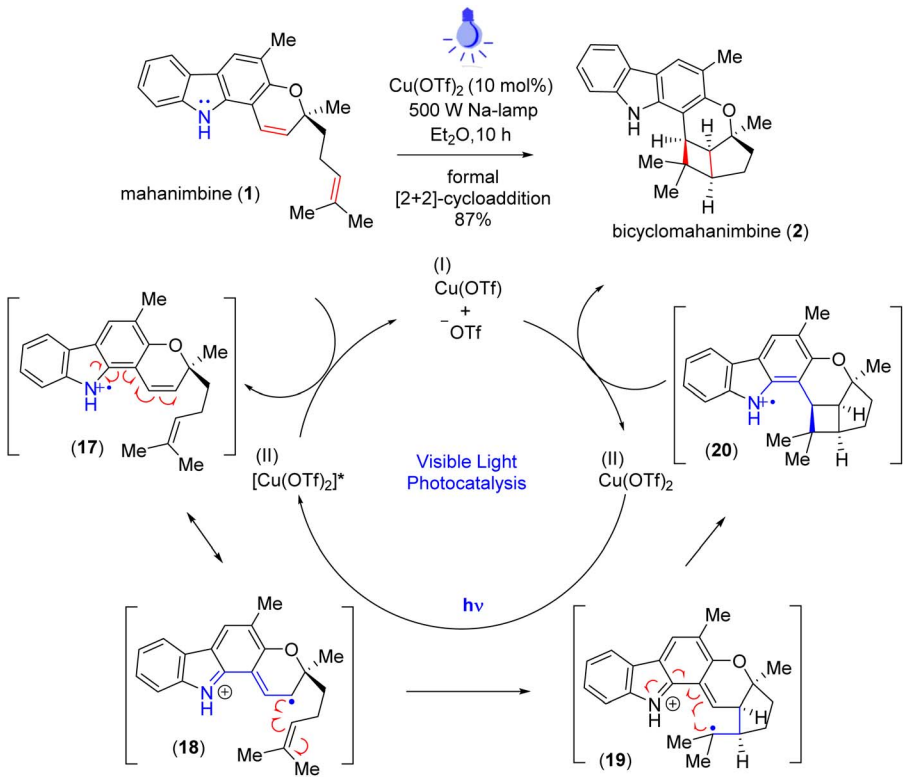
Conversion of mahanimbine (**1**) into curryanin (**3**) using camphor sulfonic acid (CSA) as a Brønsted acid has previously been accomplished by the Knölker group.[17] However, their procedure had few drawbacks as being time-consuming, nevertheless prone to generating side-products which could have reduced the output.[17] In this regard, Sarpong *et al.* achieved 99% yield in the reaction under the same conditions with a desmethylated mahanimbine analog; however, it still required 41.5 hours.[20] To reduce such time-consumption, we employed CSA in toluene medium under sodium light conditions. Within 24 hours of reaction time, we successfully acquired our intended product compound (**3**) with a striking yield of 93% (Scheme 6). Following the synthesis pathway, to design murrayazolinine (**4**), we first reacted the olefin on curryanin (**3**) with m-CPBA. Subsequently, the generated epoxide compound (**21**) was charged with $LiAlH_4$-mediated S_N2-reaction for epoxy-ring opening. These sequential reactions resulted in the regioselective hydration of the olefin, which ultimately led to murrayazolinine (**4**) with an excellent yield of 76.5% over two steps (Scheme 6). Then, instead of directly attempting the isomerization of curryanin (**3**), we chose to proceed with dehydration of murrayazolinine (**4**). This approach aimed to favor the formation of the more substituted olefin, which is the

Table 1 Optimization table for formal [2 + 2]-cycloaddition to craft bicyclomahanimbine (**2**)

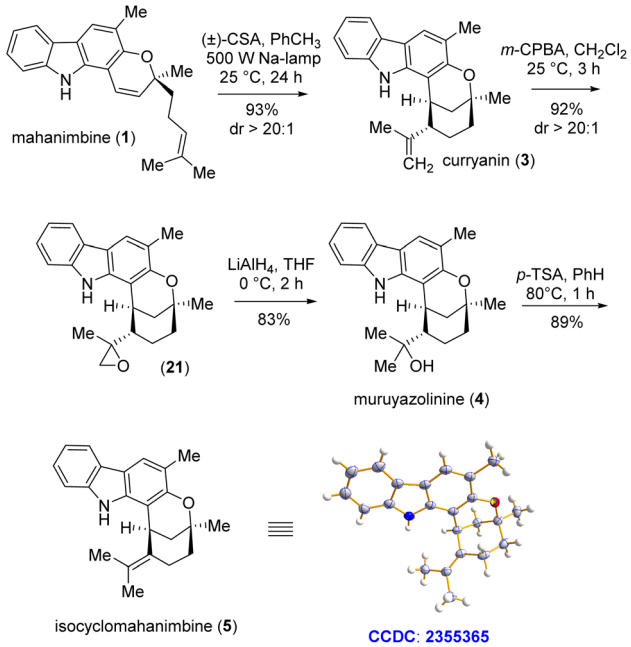


Entry	Reagent	Solvent	Lamp	Time	Yield[a,b]
1 (ref. 24)	LDA	THF	Tungsten bulb	5 h	ND
2	*fac*-Ir(ppy)$_3$	MeOH	456 nm LED	10 h	32%
3	—	Et_2O	500 W Na-lamp	3 d	NR
4	Cu(OTf)$_2$ (10 mol%)	Et_2O	500 W Na-lamp	10 h	87%

[a] Optimization reactions were carried out on 0.33 mmol of substrate. [b] Yields are isolated after column chromatography.



Scheme 5 Proposed mechanism of visible-light photocatalysis for the synthesis of bicyclomahanimbine (**2**).



Scheme 6 End-game synthesis of curryanin (3) and conversion to murrayazolinine (4) and isocyclomahanimbine (5).

thermodynamically controlled product, namely isocyclomahanimbine (5). Catalytic *para*-toluenesulfonic acid (20 mol%) in benzene under reflux conditions was employed to carry out this dehydration and after 1 hour of reaction time, we successfully isolated the crystalline form of the natural product isocyclomahanimbine (5) with 89% yield (Scheme 6).

Conclusions

In summary, to achieve complex monoterpenoid pyrano-[3,2-*a*]-carbazole alkaloids, this approach not only enhances the efficiency of the synthesis but also aligns with principles of sustainability and environmental responsibility redressing the drawbacks of previous reports. Key highlights include the successful application of photoredox and electrochemical methods for efficient bond formations, as well as the regioselective hydration and dehydration strategies to access different structural motifs. The use of $Cu(OTf)_2$ played crucial roles in the photoredox process controlling reaction outcomes with excellent yields. Overall, the synthetic approach demonstrated a blend of modern sustainable methodologies and traditional organic chemistry techniques, showcasing the importance of innovation and optimization in natural product synthesis.

Experimental

Synthetic procedures and full characterization data are provided in the ESI.†

Data availability

Experimental details and spectral analysis are available free of charge from the ESI† available with this article.

Conflicts of interest

There are no conflicts to declare.

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