RECENT ADVANCES IN SYNTHETIC STRATEGIES FOR THE C4a,C9a-FUSED TETRACYCLIC HYDROCARBAZOLE CORE STRUCTURE OF MINFIENSINE AND RELATED AKUAMMILINE ALKALOIDS

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Abstract – The Strychnos alkaloid minfiensine and its analogs among the akuammiline alkaloids have a variety of biological activities, including anti-tumor and analgesic activities, and have therefore attracted considerable synthetic interest. Here we provide an overview of recent advances in methodologies for the construction of the characteristic tetracyclic hydrocarbazole core structure containing a fused pyrrolidine ring at C4a and C9a.

INTRODUCTION

The tetrahydrocarbazole 1 bearing a fused pyrrolidine ring at C4a and C9a forms the core structure of the Strychnos alkaloid minfiensine (2)1-4 and its analogs among the akuammiline alkaloids, such as vincorine (3),5-7 echitamine (4)8 and corymine (5) (Figure 1).9,10 These alkaloids have various biological activities, including anti-tumor11 and analgesic activities.12-14 These activities, together with the complex structures including a characteristic cage-like motif, have attracted the interest of synthetic chemists.15

In 2005, Overman and co-workers reported the first total synthesis of minfiensine (2) with tetracyclic hydrocarbazole 9 as a key intermediate (Scheme 1).1 They employed an enantioselective intramolecular Heck reaction of 6 followed by iminium ion mediated intramolecular cyclization of amine to construct the corresponding tetracyclic hydrocarbazole 9, which lead them to the synthesis of 2. In the report, Overman mentioned about the utility of the tetracyclic hydrocarbazole 9 for constructing those types of alkaloids. Since then, most synthetic works on 2 and the structurally related akuammiline alkaloids have been focused on the construction of the characteristic tetracyclic hydrocarbazole core, such as 9.16-18
Here, we review recent advances in methodologies for the construction of the C4a,C9a-fused tetracyclic hydrocarbazole skeleton (1).

The core structure 1 possesses an all-carbon quaternary stereogenic center at C4a and an N,N-aminal at C9a (Figure 2), and synthetic approaches reported so far can be categorized into three main types: 1) intramolecular alkylation, 2) [3+2] cycloaddition, and 3) dearomatization of phenols. The intramolecular alkylation approach is straightforward and has been widely explored by utilizing tryptamine derivatives 10 with a side chain bearing an electrophilic moiety at C2 in the indole for cascade construction of the quaternary carbon center at C4a and the N,N-aminal moiety at C9a. In the case of the [3+2] cycloaddition approach, the new bond at C4a and C9a can be constructed in a single step by the reaction of tricyclic indole derivatives 11 with three-atom components such as aziridine 12. In the third approach, researchers have focused on dearomatization of diarylamine 13 with phenols and subsequent intramolecular nucleophilic conjugate addition to the resulting enone. In the following sections, we review advances in each of these three main approaches, as well as some additional strategies.

**Figure 1.** Structures of the *Strychnos* alkaloid minfiensine (2) and analogous akuammiline alkaloids having a C4a,C9a-fused tetracyclic hydrocarbazole motif

**Scheme 1.** First total synthesis of (+)-minfiensine (2) through a construction of tetracyclic carbazole 9 by Overman’s group
Figure 2. Main synthetic strategies for the construction of C4a,C9a-fused tetracyclic hydrocarbazoles

INTRAMOLECULAR ALKYLATION
The C3 position in indoles is strongly nucleophilic. In the case of indoles substituted at this position, dearomatization of the pyrrole ring occurs by nucleophilic reaction at C3, generating a highly electrophilic iminium cation. By applying this strategy to tryptamine derivatives, a multiple ring system can be constructed via a cascade reaction, and this is a powerful approach for construction of the tetracyclic hydrocarbazole skeleton.

Yang and co-workers synthesized tetracyclic hydrocarbazoles from tryptamine derivative 14 bearing an allylic alcohol moiety by employing an iridium catalyst. They employed Carreira’s chiral phosphoramidite ligand (S)-15 with Zn(OTf)2 as a promoter in the presence of the iridium catalyst, resulting in nucleophilic attack at C3 to generate the π-allyl cation 16, followed by nucleophilic addition of the amine to the subsequently formed iminium cation 17 (Scheme 2). The reaction affords a mixture of anti and syn products in good yield with high enantioselectivity. This reaction was applied to the synthesis of tetrahydrofuran-fused tetracyclic hydrocarbazole 20, leading to the first total synthesis of the akuammiline alkaloid (-)-aspidophylline A (21) by the same group.

A similar type of dearomative cyclization of tryptamine derivatives with allyl carbonate 22a was reported by Jiao and co-workers, who utilized the diphosphine ligand (S,S)-23 with a dihydro-9,10-ethanoanthracene backbone in the presence of a palladium catalyst to obtain tetracyclic hydrocarbazole 26a via π-allylpalladium cation 24 (Scheme 3). In this reaction, the intramolecular nucleophilic addition of the amine to the iminium cation intermediate 25 gave 26a in 91% yield with 89%
Substituents on the aromatic ring in the indole affect the enantioselectivity of the reaction. High enantioselectivity was obtained when an electron-donating group was present on the aromatic ring, such as in 26b and 26c, while the enantioselectivity was decreased to 22-76% ee in the case of an electron-withdrawing group on the aromatic ring, such as in 26d and 26e. The same group reported the total synthesis of (+)-minfiensine \( (2) \) from the tetracyclic hydrocarbazole 26a.

Scheme 2. Enantioselective construction of tetracyclic hydrocarbazole 18 via iridium-catalyzed enantioselective cyclization of indole 14, leading to a total synthesis of (-)-aspidophylline A \( (21) \) (Yang’s group)
Scheme 3. Enantioselective construction of tetracyclic hydrocarbazoles 26 via palladium-catalyzed enantioselective cyclization of indole 22, leading to a total synthesis of (+)-minfiensine (2) (Jiao’s group)

In 2017, Wang and co-workers reported a synthesis of tetracyclic hydrocarbazoles 29 from tryptamine derivatives 27 bearing an alkynyl group via 6-exo-dig cyclization of an iminium cation by utilizing chiral phosphoric acid (S)-28 bearing a 9-anthryl group at the 3,3’ position together with a complex of Ag(I) and phosphoric acid (Scheme 4). In this reaction, tetracyclic hydrocarbazoles 29 were obtained in up to 99% yield with 96% ee. DFT calculations suggested that hydrogen-bonding interaction between oxygen of phosphoric acid and NH of indole is crucial to stabilize the transition state (TS-1).
A similar type of activation of alkynes using Ag(I) for the construction of the tetracyclic hydrocarbazole skeleton was reported by Unsworth and co-workers (Scheme 5).\textsuperscript{26,27} The 6-\textit{endo-dig} cyclization of ynnone 32 proceeded under similar conditions to those reported by Wang, and various tetracyclic hydrocarbazoles 35 were obtained in high yield with high enantioselectivity. The enantioselectivity of the products increased as the bulkiness of the R group was increased (35a-35c). An ynnone moiety in the substrate 32 is crucial to obtain the product in high yield with high enantioselectivity. The cyclized product 36, obtained from the corresponding propargyl alcohol, was produced in a low yield of 20%, and with only 40% ee. The ynones 32 was prepared from the tryptamine derivatives 30 by radical alkylation followed by treatment with alkynyl Grignard agents. With the three-steps simple manipulation, a variety of tetracyclic hydrocarbazoles were synthesized.

**Scheme 4.** Enantioselective construction of tetracyclic hydrocarbazole 29 via Ag(I) promoted 6-\textit{exo-dig} cyclization of 27 (Wang’s group)

In 2017, Snyder and co-workers synthesized tetracyclic hydrocarbazole 39 from tetrahydro-β-carboline 37 (Scheme 6).\textsuperscript{28} They employed 6-\textit{endo-dig} cyclization of the alkyne moiety in 37 by utilizing a catalytic amount of AuPPh\textsubscript{3}Cl and a stoichiometric amount of AgSbF\textsubscript{6}, and obtained the cyclized product 38 in 59% yield. Skeletal rearrangement of 38 under microwave irradiation in the presence of a base furnished tetracyclic hydrocarbazole 39 in 62% yield.
Scheme 5. Enantioselective construction of tetracyclic hydrocarbazole 35 from yrones 32 via Ag(I) promoted cyclization (Unsworth’s group)

Scheme 6. Construction of tetracyclic hydrocarbazole 39 using Ag(I)-catalyzed cyclization followed by skeletal rearrangement (Snyder’s group)
The double bond at C2-C3 in indoles can undergo cycloaddition reaction, and indole derivatives with fused ring structures can be synthesized by applying a cycloaddition reaction strategy using C3-substituted indoles. For example, tetracyclic hydrocarbazoles can be constructed by employing [3+2] cycloaddition reaction of tricyclic indole derivatives with appropriate ethylamine units. Aziridines, aza-oxyallyl cations, and acetamide acrylates have been applied as ethylamine units for this purpose.

Aziridine is a synthetically useful aminoethyl group equivalent, which is introduced by means of nucleophilic ring-opening reaction. In 2015, Zhao and co-workers developed a formal [3+2] cycloaddition of indole with aziridines to construct tetracyclic hydrocarbazole (Scheme 7). The formal [3+2] cycloaddition reaction of tricyclic indole 40 and aziridine 41 was carried out in the presence of Pd(PhCN)2Cl2 to generate tetracyclic hydrocarbazole 42 in 62% yield. In this reaction, Pd(II), which has a Lewis-acidic nature, activates aziridine by interacting with nitrogen (intermediate 43a or 43b) to promote the nucleophilic addition of indole at C3 to aziridine with ring-opening to generate iminium cation intermediate 44. Then, intramolecular cyclization of the amino group in 44 affords 42.

Scheme 7. Construction of tetracyclic hydrocarbazole 42 via formal [3+2] cycloaddition reaction of 40 with aziridine 41 in the presence of Pd(II) catalyst (Zhao’s group)
A similar formal [3+2] cycloaddition of tricyclic indole 45 with aziridine 47 was reported by Xiao and co-workers (Scheme 8). In this reaction, indole 45 was activated with triethylborane and potassium tert-butoxide, and the resulting borate 46 underwent nucleophilic addition at C3 with allylaziridine 47, followed by cyclization to furnish tetracyclic hydrocarbazole 48 in 38% yield with 2:1 dr.

Scheme 8. Construction of tetracyclic hydrocarbazole 48 via formal [3+2] cycloaddition, using indole 45 and allylaziridine 47 (Xiao’s group)

Liao and co-workers reported a formal [3+2] cycloaddition of tricyclic indole 49 with aza-oxyallyl cation 51, generated in situ from α-bromo amide 50 by reaction with potassium carbonate, to construct tetracyclic hydrocarbazole 52 (Scheme 9a). This led to a total synthesis of minfiensine (2) from tricyclic indole 53 via tetracyclic hydrocarbazole 55 (Scheme 9b).

Andrus and co-workers developed a synthesis of tetracyclic hydrocarbazole 57 from tricyclic indole 49 and acetamide acrylate 56 with an isoxazolidinone-type chiral auxiliary via an exo-selective formal [3+2] cycloaddition in the presence of the Lewis acid SnCl₄ (Scheme 10). In this reaction, acetamide acrylate is activated by tin chloride through bidentate coordination, and nucleophilic attack of indole proceeds from the less hindered side (TS-2). However, the regioselectivity was low (1.6:1 exo/endo).

DEAROMATIZATION OF PHENOLS
Dearomatization of para-substituted phenols provides 2,5-cyclohexadienones, which are reactive electrophiles that have been applied widely in the synthesis of natural products, as well as pharmaceuticals. This approach was successfully adopted to synthesize tetracyclic hydrocarbazole by utilizing diarylamine derivatives bearing a phenol group. Dearomatization of the diarylamines was performed with palladium catalysts or hypervalent iodine reagents.
Scheme 9. a) Construction of tetracyclic hydrocarbazole 52 via formal [3+2] cycloaddition reaction of tricyclic indole 49 and aza-oxyallyl cation 51 (Liao’s group). b) Total synthesis of minfiensine (2) based on the formal [3+2] cycloaddition reaction by the same group.

Scheme 10. Construction of tetracyclic hydrocarbazole 57 from tricyclic indole 49 and acetamide acrylate 56 via formal [3+2] cycloaddition reaction (Andrus’ group).
Tang and co-workers reported a synthesis of tetracyclic hydrocarbazole 65 via palladium-catalyzed asymmetric dearomative cyclization of diarylamine 58 followed by intramolecular cyclization of allylic alcohol 63 derived from dienone 60 (Scheme 11). Specifically, they performed palladium-catalyzed asymmetric dearomative cyclization of diarylamine of 58 to obtain dienone 60 in 63% yield with 90% ee. The less hindered olefin in 60 was selectively reduced under hydrogenolysis conditions in the presence of PdCl₂ catalyst and the exo-olefin was installed by aldol condensation using paraformaldehyde with Triton B. Upon conversion of 60 into allyl alcohol 63, intramolecular cyclization took place simultaneously to generate tetracyclic hydrocarbazole 65. Several further steps afforded 66, which is identical to Overman’s intermediate for their group’s synthesis of minfiensine (2).²

In 2020, our group reported a synthesis of tetracyclic hydrocarbazole 70 from dienone 68, which was obtained from oxidative dearomative cyclization of diarylamine 67 with hypervalent iodine agent (Scheme 12). Specifically, oxidative dearomative cyclization of diarylamine 67 bearing an ethylamino group using diacetoxy iodobenzene (PIDA) in hexafluoro-2-propanol (HFIP) afforded dienone 68 in 40% yield. The aza-Michael reaction products at C9a 71 and C4 72 were each selectively obtained from 68 under different acidic conditions (TFA and HCl, respectively). The product 72 corresponds to the core structure of Aspidosperma monoterpene indole alkaloids such as aspidospermidine (73).⁴⁶-⁴⁸

OTHER APPROACHES
In addition to the above three synthetic approaches to tetracyclic carbazoles, some other strategies, i.e., aza-pinacol rearrangement, photo-redox catalyst-mediated reaction, and asymmetric addition reaction with a copper catalyst, have also been developed.

Zu and co-workers reported the synthesis of tetracyclic hydrocarbazole 76 by means of aza-pinacol rearrangement of spiroindoline 74 (Scheme 13). They subjected the tertiary alcohol 74 bearing an aminoethyl group to aza-pinacol rearrangement in the presence of trifluoroacetic acid. The resulting tricyclic indolenines 75 cyclized immediately to afford the tetracyclic hydrocarbazoles 76 in up to 95% yield. This strategy was successfully applied for the synthesis of Overman and Qiu’s intermediate 80 for minfiensine (2)²,5⁰ from 77 via indolenine 79.
Scheme 11. Enantioselective synthesis of tetracyclic hydrocarbazole 65 via dearomative cyclization of diarylamine with phenols, leading to a formal total synthesis of (-)-minfiensine (2) (Tang’s group)

Scheme 12. Synthesis of tetracyclic hydrocarbazoles 71 and 72 by regioselective aza-Michael reaction of dienone 68 obtained via oxidative dearomative cyclization of diarylamine 67 (Nagasawa’s group)
Scheme 13. a) Synthesis of tetracyclic hydrocarbazole 76 through aza-pinacol rearrangement, leading to a formal total synthesis of minfiensine (2) (Zu’s group)

The same authors reported an asymmetric version of the aza-pinacol rearrangement by using chiral phosphoric acid (R)-82, derived from a SPINOL, and obtained tetracyclic hydrocarbazoles 85 with high enantioselectivity (Scheme 14). The reaction proceeds via an aza-ortho-xylylene intermediate 83, and the catalyst presumably coordinates with NH and iminium cation through electrostatic interaction to control the transition state of the reaction. Application of this reaction to a substrate containing acetonide 86 afforded tetracyclic hydrocarbazole 90 in 74% yield with 97% ee through the aza-pinacol rearrangement product 87 via isomerization and 1,2-hydride transfer.

Zheng and co-workers reported a photo-redox catalyst-mediated cascade reaction for the synthesis of tetracyclic hydrocarbazole 94 (Scheme 15). The ruthenium photo-redox catalyst-mediated reaction of 91 afforded tetracyclic hydrocarbazole 94 in up to 71% yield under blue LED irradiation conditions via formation of a benzyl cation intermediate 92, followed by a 1,2-alkyl shift in intermediate 93. Pivalic anhydride is mandatory for the reaction to trap generated water, as well as to keep the medium acidic.
Scheme 14. Enantioselective synthesis of tetracyclic hydrocarbazoles 85 and 90 via asymmetric aza-pinacol rearrangement in the presence of the chiral phosphoric acid catalyst (R)-82 (Zu’s group)

Scheme 15. Synthesis of tetracyclic hydrocarbazole 94 from 91 via photoredox catalyst-mediated spiro-cyclization followed by 1,2-alkyl rearrangement (Zheng’s group)
In 2020, Li and co-workers achieved total syntheses of five kinds of akuammiline alkaloids, including (+)-corymine (5) and (-)-deformylcorymine (102), from tetracyclic hydrocarbazole 101 as a common key intermediate (Scheme 16). They employed Stoltz’s enantioselective alkylation of bromooxindole 95 to introduce malonic diester, obtaining oxindole 97 bearing the all-carbon quaternary stereogenic center at C3 in 65% yield with 91% ee. After single recrystallization of 97, the resulting enantiomerically pure 97 (>99% ee) was converted to 98, which was cyclized with sodium ethoxide. In this reaction, p-thiocresol was added successively in one pot to deprotect the Ns group, affording aminal 100 in 66% yield.

**Scheme 16.** Total syntheses of (+)-corymine (5), (-)-deformylcorymine (102), and other akuammiline alkaloids from tetracyclic hydrocarbazole 101 as a common key intermediate (Li’s group)
Then, syntheses of (+)-corymine (5) and (-)-deformylcorymine (102) were accomplished via tetracyclic hydrocarbazole 101. This strategy was extended to the synthesis of other akuammiline alkaloids: (-)-10-demethoxyvincorine (103), (-)-3-epi-dihydrocorymine-17-acetate (104), and (-)-2(S)-cathafoline (105).

SUMMARY AND OUTLOOK
In this review, we cover recent advances in synthetic strategies for C4a,C9a-fused tetracyclic hydrocarbazole, which is the core structure of akuammiline alkaloids and the Strychnos alkaloid minfiensine. These strategies are grouped according to the context of the construction of the all-carbon quaternary stereogenic center at C4a and N,N-aminal moiety at C9a. All the methodologies are still being actively investigated with the aim of synthesizing tetracyclic hydrocarbazoles on a multi-gram scale, in order to investigate the potential of compounds containing this structure as drug candidates.

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