Natural Products

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Total Synthesis of (+)-Minfiensine: Construction of the Tetracyclic Core Structure by an Asymmetric Cascade Cyclization

*Ze-Xin Zhang, Si-Cong Chen, and Lei Jiao**

Abstract: *A new method for one-step construction of the tetracyclic core structure of the indole alkaloid (+)-minfiensine was developed utilizing a palladium-catalyzed asymmetric indole dearomatization/iminium cyclization cascade. An efficient total synthesis of (+)-minfiensine was realized using this strategy. The present method enables access to the common core structure of a series of monoterpene indole alkaloids, such as vincorine, echitamine, and aspidosphylline A.*

Monoterpene indole alkaloids constitute a large category of natural products.[1] Among them, an array of *strychnos* and *akuammiline* alkaloids are quite attractive because of their unique cagelike structure and promising biological activity (Figure 1).[1,2] These natural products share a common core

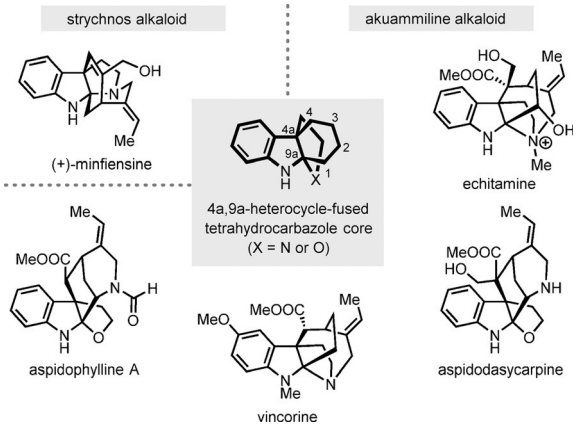
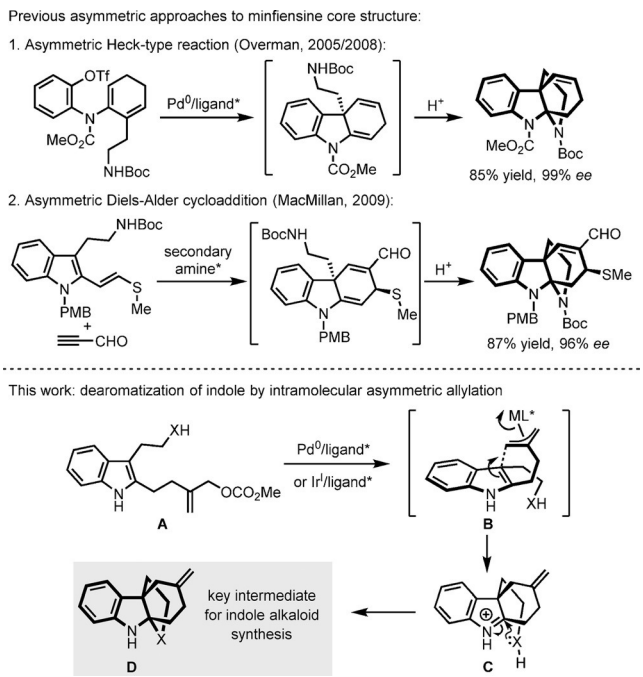


Figure 1. Representative *strychnos* and *akuammiline* alkaloids and their common core structure.

structure, the 4a,9a-heterocycle-fused tetrahydrocarbazole skeleton, which bears two adjacent quaternary stereocenters. To address the synthetic challenges posed by these complex alkaloids, the development of strategies for efficient asymmetric assembly of the core structure is in demand.

During the past decade, these monoterpene indole alkaloids attracted much research interest from the synthetic community. As a result, a large number of total syntheses have been reported.[3–5] However, the strategies that rendered efficient asymmetric syntheses are still limited.[3a,b,d,4d,5b,c] For instance, for a representative member in these alkaloids, (+)-minfiensine, only two catalytic asymmetric methods have been reported to date for achieving its total synthesis (Scheme 1).[3a,b,d] Given the effort devoted to the syntheses of these important alkaloids, the discovery of efficient and flexible new strategies for asymmetric assembly of the core framework would promote advances in this field.



Scheme 1. Previous asymmetric syntheses of (+)-minfiensine and the designed asymmetric cascade cyclization strategy. Boc = *tert*-butoxycarbonyl, PMB = *para*-methoxybenzyl.

We sought to develop a new and straightforward approach to (+)-minfiensine based on the catalytic asymmetric dearomatization of indole (Scheme 1). It is envisioned that intramolecular asymmetric allylic substitution of the indole substrate **A** gives the intermediate **C**, which upon in situ trapping of the generated iminium ion[3a–d,g,6,8f] affords the tetracycle **D**, having the desired core structure. The advantage of this design is that the exocyclic C=C bond formed by allylic alkylation largely facilitates creation of the hydroxymethyl functionality in (+)-minfiensine. To our surprise, although palladium-[7] and iridium-catalyzed[8] asymmetric allylic alkylations of indole have been well established,[9] very little effort was made to utilize the synthetic power of those protocols in

[*] Z.-X. Zhang, S.-C. Chen, Prof. Dr. L. Jiao
Center of Basic Molecular Science (CBMS)
Department of Chemistry, Tsinghua University
Beijing 100084 (China)
E-mail: Leijiao@mail.tsinghua.edu.cn

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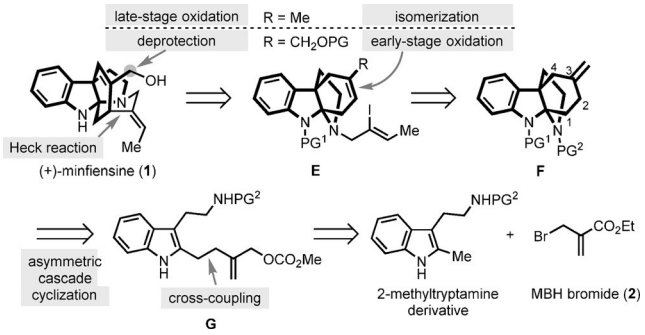
the synthesis of these unique indole alkaloids.[10] Since the reaction pattern (formation of an exocyclic C=C bond) has not been explored in transition metal catalyzed indole dearomatization reactions, the challenges for the designed asymmetric cascade cyclization are: 1) to realize an efficient synthesis of the multifunctional 2,3-disubstituted indole substrate **A**; and 2) to search for a suitable catalyst/ligand combination leading to both high yield and high enantioselectivity for this new reaction pattern.

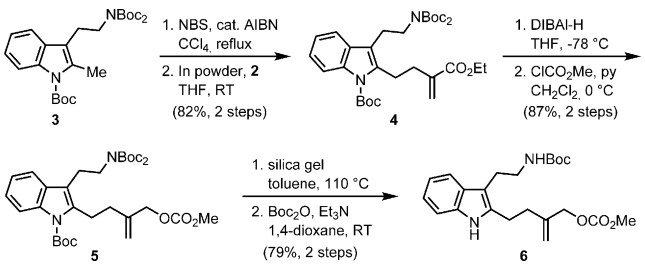
On the basis of the designed asymmetric cascade cyclization, we conducted a retrosynthetic analysis of (+)-minfiensine (**1**; Scheme 2). Different from most previous synthetic routes which utilized cross-coupling with a one-carbon synthon to install the hydroxymethyl group,[3a–c,e–h] we envisioned making use of the exocyclic C=C bond for hydroxylmethyl formation. In this way, two slightly different synthetic routes were planned. One features a late-stage oxidation (R = Me in **E**), in which the C2-alkene connection is made by a Heck-type reaction and the hydroxy group is installed by an allylic C–H oxidation. The other features an early-stage oxidation (R = protected hydroxylmethyl in **E**), in which the methylidene group in cyclization product **F** is converted into an allylic alcohol, and the last ring is established by a similar Heck-type process. The designed asymmetric cascade cyclization could produce **F** from **G**, which could be prepared by cross-coupling a protected 2-methyltryptamine and the bromide **2**.



Scheme 2. Retrosynthetic analysis of (+)-minfiensine. PG = protecting group.

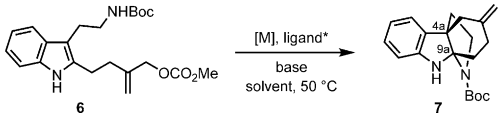
The synthesis commenced with the coupling of the 2-methyltryptamine derivative **3**[11] and bromide **2** (Scheme 3). It was found that the reaction between the bromomethyl derivative of **3** and the allyl indium reagent derived from **2** was most effective for the synthesis of **4**.[12] Reduction of the ester group and subsequent esterification produced the allyl carbonate **5** smoothly. Global deprotection of **5** using silica gel[13] and reprotection of the amine group afforded the desired cyclization precursor **6**.

The key asymmetric cascade cyclization was tested under different reaction conditions (Table 1). Catalyst/ligand combinations which were previously reported to be efficient for dearomative asymmetric allylic alkylation of indoles were employed.[7,8] It was found that the designed cascade cyclization indeed took place to produce the tetracyclic product **7**



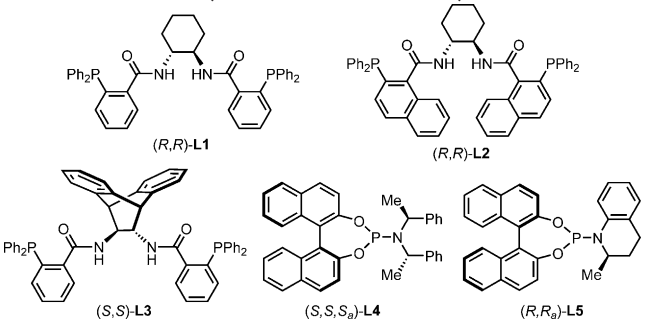
Scheme 3. Synthesis of the cyclization precursor **6**. AIBN = 2,2′-azobis(2-methylpropionitrile), DIBAl-H = diisobutylaluminium hydride, NBS = *N*-bromosuccinimide, THF = tetrahydrofuran.

Table 1: Optimization of reaction conditions.[a]



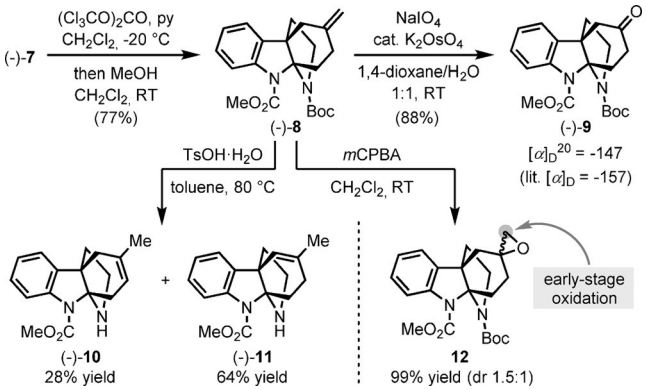
Entry	[M]	Ligand	Yield [%][b]	*ee* [%][c]	Config.[d]
1	$[Pd_2(dba)_3]$	(*R*,*R*)-**L1**	67	53	(4a*R*,9a*R*)
2	$[Pd_2(dba)_3]$	(*R*,*R*)-**L2**	71	72	(4a*R*,9a*R*)
3	$[Pd_2(dba)_3]$	(*S*,*S*)-**L3**	91	89	(4a*S*,9a*S*)
4	$[\{Ir(COD)Cl\}_2]$	(*S*,*S*,*S*$_a$)-**L4**	5	23	(4a*R*,9a*R*)
5	$[\{Ir(COD)Cl\}_2]$	(*R*,*R*$_a$)-**L5**	61	68	(4a*R*,9a*R*)

[a] Reaction conditions for palladium-catalyzed reactions: **6** (0.1 mmol), $[Pd_2(dba)_3]$ (2 mol%), ligand (4.5 mol%), K_2CO_3 (2 equiv) in anhydrous toluene (2 mL), 50°C for 12 h; reaction conditions for iridium-catalyzed reactions: **6** (0.1 mmol), $[\{Ir(COD)Cl\}_2]$ (5 mol%), ligand (10 mol%), Cs_2CO_3 (2 equiv) in anhydrous THF (2 mL), 50°C for 12 h (catalyst was prepared by *n*$PrNH_2$ activation). [b] Yields of products isolated after flash column chromatography. [c] Enantiomeric excess were determined by chiral-phase HPLC. [d] Absolute configuration of the major enantiomer. The absolute configuration was determined by chemical correlation; see Scheme 4. COD = 1,5-cyclooctadiene, dba = dibenzylideneacetone.



enantioselectively. Modest yields and enantioselectivities were achieved with the combination of palladium(0) and the Trost-type diphosphine ligands (*R*,*R*)-**L1**[14] and (*R*,*R*)-**L2**[15] bearing a diaminocyclohexane (DACH) backbone (entries 1 and 2), while the ligand (*S*,*S*)-**L3**[13] with a dihydro-9,10-ethanoanthracene (ANDEN) backbone provided both good yield and satisfactory enantioselectivity (entry 3). However, the iridium(I)-based catalytic systems[8] afforded only moderate results (entries 4 and 5).

We then started to make further steps for the synthesis of (+)-minfiensine (Scheme 4). Treatment of **7** by triphosgene/py and then MeOH protected the aniline NH with a methoxycarbonyl group to form (−)-**8**. Following the late-stage

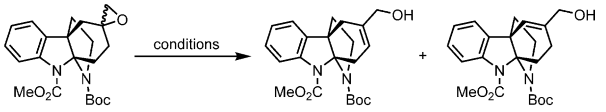


Scheme 4. Further transformations of the cyclization product **7**. *m*CPBA = *meta*-chloroperbenzoic acid, Ts = 4-toluenesulfonyl.

oxidation strategy, the isomerization of the exocyclic C=C bond in (−)-**8** was performed. However, under acidic olefin isomerization conditions[16] the undesired regioisomer (−)-**11** was obtained as the major product, and attempts to optimize this isomerization failed. Thus we switched to the early-stage oxidation strategy. Treatment of (−)-**8** with *m*CPBA afforded the epoxide **12** in excellent yield (as a mixture of two diastereoisomers), in which the methylene carbon atom was set to the correct oxidation state.

At this stage we set out to explore the conditions for epoxide ring-opening to approach the allylic alcohol intermediate. It was found that the regioselectivity of the ring-opening reaction highly depends on the reagents used (Table 2). Treatment of epoxide **12** with TMSOTf/DBU[3f]

Table 2: Ring-opening reaction of the epoxide **12**.

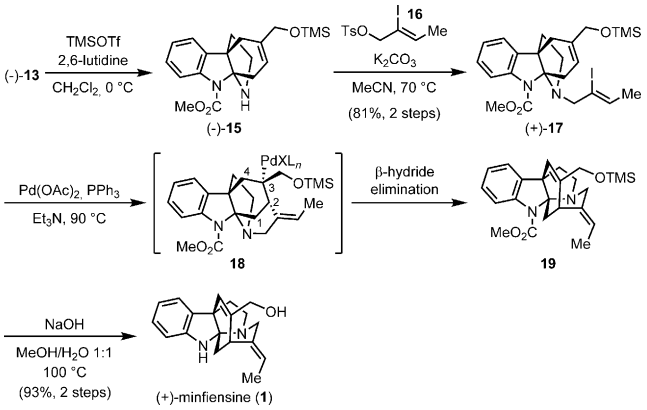


Entry	Reaction conditions	**13**/**14**[a]	Yield [%][b]
1	TMSOTf, DBU, CH_2Cl_2, −40 °C to RT, 24 h	18:82	11[c]
2	$Al(OiPr)_3$, toluene, reflux, 12 h	66:34	69
3	TMP-$AlMe_2$, toluene, 0 °C, 2 h	97:3	93

[a] Determined by ^{1}H NMR spectroscopy. [b] Combined yield of **13** and **14** isolated after flash column chromatography. [c] Most of **12** was recovered. TMP = 2,2,6,6-tetramethylpiperidinyl. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMS = trimethylsilyl.

led to only minor conversion, and the undesired regioisomer **14** was the major product (entry 1). To increase the selectivity by favoring proton abstraction at the less hindered C2 of the ring system, a sterically hindered Lewis acid/base pair, $Al(OiPr)_3$ was employed.[17] Gratifyingly, improved yield and regioselectivity were observed (entry 2). Finally, the use of TMP-$AlMe_2$ further increased steric hindrance and led to satisfactory yield and perfect regioselectivity (entry 3).[18] This crucial step, in combination with the epoxidation reaction, efficiently created the desired hydroxymethyl moiety and enabled the final ring closure.

The transformation of the intermediate (−)-**13** into (+)-minfiensine was rather straightforward (Scheme 5). First, the N-Boc group was removed by TMSOTf/2,6-lutidine to afford the intermediate (−)-**15**,[19] in which the hydroxy group was converted into the TMS ether simultaneously.



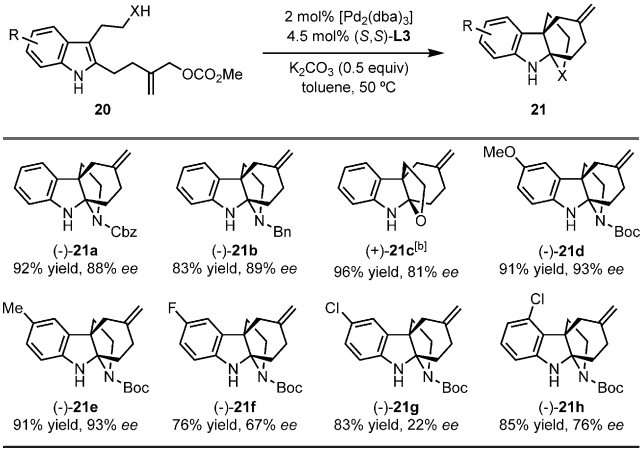
Scheme 5. Construction of the final ring and completion of the total synthesis.

Subsequent N-alkylation using the crude (−)-**15** with tosylate **16**[20] introduced the iodoallyl side chain to afford intermediate (+)-**17**. Second, a Heck-type reaction[21] established the last ring by connecting the side chain with C2 of the tetracyclic core, thus leading to the intermediate **18**. Then β-hydride elimination occurred to form the intermediate **19** bearing an endocyclic olefin. Finally, treatment of the crude **19** with NaOH in $MeOH/H_2O$ removed the CO_2Me protecting group[3e] as well as the TMS ether to produce (+)-minfiensine in an excellent yield.

Having completed the total synthesis of (+)-minfiensine, we expected that the present asymmetric cascade cyclization could be utilized to construct more related ring systems. In this line, a series of tryptamine and tryptophol derivatives bearing a branched allyl carbonate moiety were prepared and tested under the optimal reaction conditions (Table 3). It was found that, different N-substituents on the substrates gave similarly good yields and enantioselectivities (products **21a** and **21b**). In particular, a secondary amine functionality is compatible with the cascade cyclization reaction, though an amine is considered a good nucleophile for transition-metal π-allyl complexes.[22] The tryptophol derivative **20c** could also undergo the asymmetric cascade cyclization to afford the product **21c** in excellent yield, albeit with slightly diminished enantioselectivity. In contrast, the electronic nature of the indole core seemed to have a major impact on the enantioselectivity (products **21d–h**), which is not common in related indole asymmetric allylic alkylation reactions.[7b] In general, the present asymmetric cascade cyclization strategy constructs related tetracyclic ring systems, thus enabling its further application in the syntheses of other indole alkaloids.

In summary, total synthesis of (+)-minfiensine was achieved by employing a new strategy which features an indium-mediated cross-coupling, a palladium-catalyzed asymmetric cascade cyclization, and a palladium-catalyzed intra-

Table 3: Scope of the asymmetric cyclization reaction.[a]



[a] Reaction conditions: **20** (1 equiv), $[Pd_2(dba)_3]$ (2 mol%), (*S*,*S*)-**L3** (4.5 mol%), K_2CO_3 (0.5 equiv) in anhydrous toluene (0.1 M), 50°C for 12 h. Yields of products isolated after flash column chromatography. [b] $[Pd_2(dba)_3]$ (5 mol%), (*R*,*R*)-**L3** (12.5 mol%), and K_2CO_3 (2 equiv) were used.

molecular Heck-type reaction. Starting from commercially available 2-methyltryptamine, the synthetic route consists of 15 steps (11 column separations) with an overall yield of 21%. The developed asymmetric cascade cyclization represents a new method for efficient construction of the polycyclic skeleton of (+)-minfiensine and several *akuammiline* alkaloids. Related synthetic studies are ongoing.

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Keywords: alkaloids · cyclizations · natural products · palladium · total synthesis

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