

Efficient Assembly of an Indole Alkaloid Skeleton by Cyclopropanation: Concise Total Synthesis of ($\pm$)-Minfiensine**

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Members of the akuammiline^[1] alkaloids such as echitamine,^[2] vincorine,^[3] and corymine,^[4] like indole alkaloid minfiensine,^[5] possess a highly congested pentacyclic ring system (Figure 1). These alkaloids exhibit a number of

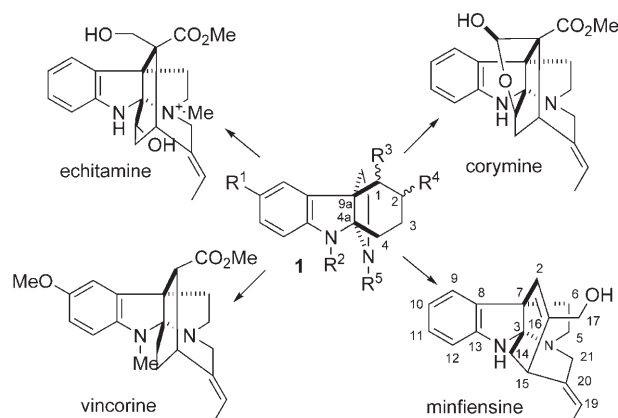
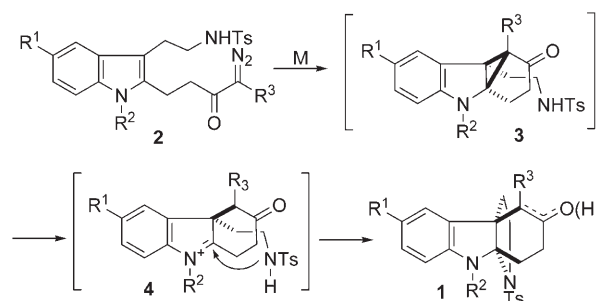


Figure 1. Representative indole alkaloids with a core tetrahydro-9a,4a-iminoethanocarbazole structure.

impressive biological activities, including significant anti-cancer activity.^[6] Although the first member of akuammiline alkaloids (echitamine) was characterized more than eighty years ago, only a few successful methods to synthesize the challenging tetracyclic subring system of 9a,4a-iminoethanocarbazole **1** are described^[7,8] because of the synthetic difficulties.^[9] In 2005, Overman and co-workers reported the first elegant synthesis of minfiensine by using an asymmetric Heck/iminium ion cyclization as the key step to assemble the tetracyclic platform of 3,4-dihydro-9a,4a-iminoethanocarbazole.^[10]

As a part of our studies on the synthesis of indole alkaloids,^[11] we describe herein a concise total synthesis of ($\pm$)-minfiensine that involves highly efficient construction of functionalized tetracyclic skeleton **1** through a three-step, one-pot cascade reaction including cyclopropanation, ring opening, and ring closure.

Scheme 1 outlines our synthetic design for a three-step, one-pot cascade reaction for the efficient assembly of tetracyclic skeleton **1**. Thus, the diazo decomposition of



Scheme 1. Three-step one-pot cascade reaction for the assembly of tetracyclic skeleton **1**. Ts = *p*-toluenesulfonyl.

diazo ketone **2** with appropriate R^1 , R^2 , and R^3 functional groups leads to the formation of cyclopropane intermediate **3**. The unstable cyclopropane ring in **3** is activated by an α -ketone and is prone to collapse to generate an indolenium cation (**4**), which is intramolecularly captured in situ by the sulfonamide group in **4** to create substituted tetracyclic **1**. Preinstallation of a ketone (or enol) functional group in **1** is beneficial to the formation of the fifth ring during the final steps of synthesis of ($\pm$)-minfiensine by palladium-catalyzed α -vinylation of the ketone.^[12]

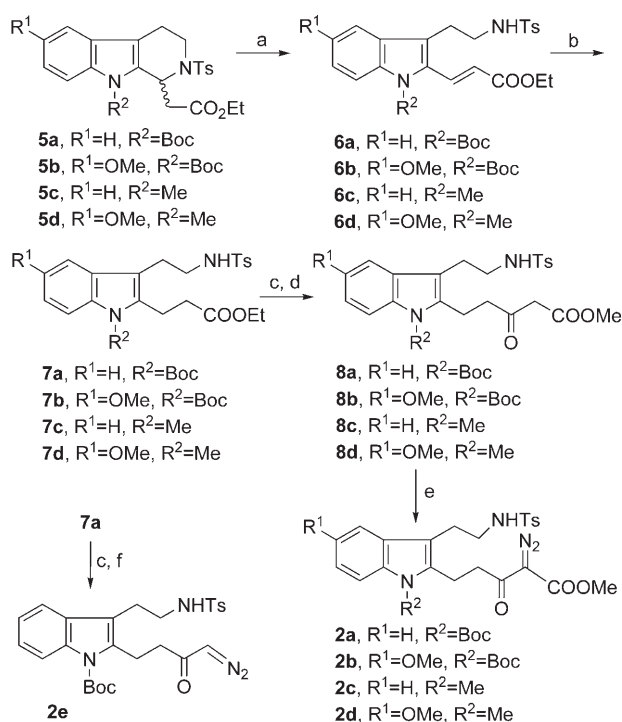
To perform the cascade reaction for assembly of tetracyclic **1**, diazo ketones **2a–e** needed to be prepared first (Scheme 2). Treatment of known *N*-Ts tetrahydrocarbolines **5a–d**^[13] with a strong base, such as LiHMDS or NaH, allowed the formation of *trans* α,β -unsaturated esters **6a–d**. The double bond in **6a–d** was then saturated with H_2 in the presence of Pd/C to provide esters **7a–d** in a 83–87% yield from **5a–d**. Expansion of the ester side chain was easily realized in two steps by hydrolysis of **7a–d** and then condensation with Meldrum's acid to give β -ketone esters **8a–d** in a 63–72% yield. α -Diazo β -ketone esters **2a–d** were prepared in a 82–89% yield by reacting **8a–d** with *p*-ABSA and Et_3N in MeCN, respectively. Similarly, α -diazo ketone **2e** was prepared in a 65% yield by hydrolysis of **7a** and

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Scheme 2. Reagents and conditions: a) LiHMDS (1 M in THF, 1.5 equiv), THF, −40°C, 10 h for **5a** and **5b**, NaH (1.2 equiv), DMF, RT, 2 h, for **5c** and **5d**; b) Pd/C (10 mol%), H₂ (1 atm), MeOH/THF 1:1, 24 h, **7a** (83% from **5a**), **7b** (87% from **5b**), **7c** (86% from **5c**), **7d** (85% from **5d**); c) LiOH (3 equiv), MeOH/THF/H₂O 1:1:0.2, 25°C, 2 h; d) DCC (1.1 equiv), DMAP (0.1 equiv), TEA (1.5 equiv), Meldrum's acid (1.5 equiv), CH₂Cl₂, 25°C, 20 h, then MeOH, reflux for 10 h, **8a** (72% from **7a**), **8b** (65% from **7b**), **8c** (63% from **7c**), **8d** (68% from **7d**); e) *p*-ABSA (1.1 equiv), TEA (3 equiv), CH₃CN, 25°C, 12 h, **2a** (86%), **2b** (89%), **2c** (83%), **2d** (82%); f) CH₂N₂ (10 equiv), Et₂O, 0°C → 25°C, 12 h, 65% from **7a**. Boc = *tert*-butylcarboxycarbonyl; LiHMDS = lithium hexamethyldisilazide; DCC = dicyclohexyl carbodiimide; DMAP = 4-dimethylaminopyridine; TEA = triethylamine; Meldrum's acid = isopropylidene malonate; *p*-ABSA = 4-acetamidobenzenesulphonyl azide.

subsequent condensation of the resulting acid with diazo-methane.

With diazo esters **2a–e** in hand, we next evaluated the efficiency of a variety of metal salts as catalysts in the three-step, one-pot cascade reaction (Table 1). Among the screened metal salts for the diazo decomposition reaction, only CuOTf gave a satisfying result in the model reaction of **2a**. Diazo decomposition of **2a–e** in CH₂Cl₂ in the presence of 5 mol % of CuOTf at room temperature provided tetracyclic products **1a–e** in moderate to high yields. The chemical structure of the reaction product was identified as either a single isomer of enol ester **1a–b** or as a two-isomer mixture of the β-keto ester and the enol ester (**1c–d**); the product structure was largely dependent on the R² substituent on nitrogen center of the indole. The fundamental architecture of product **1** was unambiguously confirmed by the two-dimensional NMR spectra analysis of **1a** and by the X-ray crystallographic analysis of *cis* β-hydroxyester **9a**,^[14] which was obtained by reduction of **1d** with NaBH₄ [Eq. (1) and Figure 2].

Table 1: Yields of the cascade reaction of diazo ketone **2**.^[a]

Table 1. Yields of the catalytic reaction of chiral ketone **2a-e**.

Reaction scheme showing the conversion of ketone **2a-e** to enol **1a-e** using reagent **M**. The structures show substituents R^1 , R^2 , and R^3 .

	R^1	R^2	R^3	Salts	Yield of 1 [%] ^[b]	Ratio ^[c] of ketone:enol
2a	H	Boc	COOMe	CuI	0	
2a	H	Boc	COOMe	[Cu(acac) ₂]	0	
2a	H	Boc	COOMe	Rh(OAc) ₂	8 (1a)	0:1
2a	H	Boc	COOMe	[Cu(MeCN) ₄] ⁺ PF ₆ ⁻	15 (1a)	0:1
2a	H	Boc	COOMe	Cu(OTf) ₂	25 (1a)	0:1
2a	H	Boc	COOMe	CuOTf	50 (1a)	0:1
2b	MeO	Boc	COOMe	CuOTf	52 (1b)	0:1
2c	H	Me	COOMe	CuOTf	81 (1c)	1:30
2d	MeO	Me	COOMe	CuOTf	82 (1d)	1:5
2e	H	Boc	H	CuOTf	42 (1e)	1:0

[a] Reaction conditions: metal salt (0.05 equiv), and CH₂Cl₂ as the solvent. [b] Yield of isolated product. [c] Determined from ¹H NMR analysis.

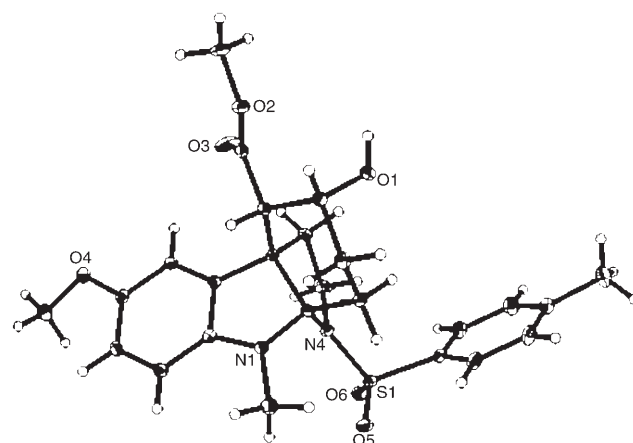
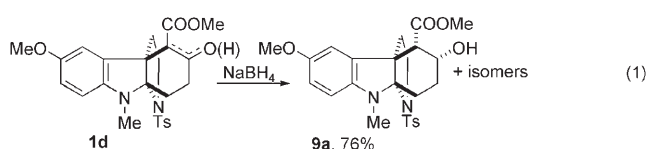
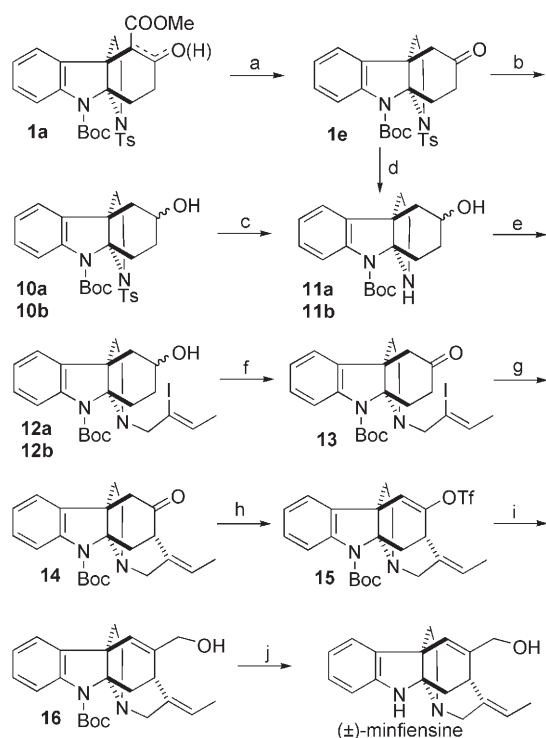


Figure 2. ORTEP diagram of **9a**.

Successful construction of tetracyclic skeletons **1a–e** provided us with a good opportunity to begin the synthesis of indole alkaloids with a skeleton of type **1**. To demonstrate the usefulness of these skeletons with versatile functional groups, **1a** and **1e** were used as starting materials for the synthesis of (±)-minfiensine. As shown in Scheme 3, the α-methyl ester in **1a** was readily removed by using standard Krapcho conditions^[15] to give **1e** with an 87% yield. Initial experiments to remove the Ts group in **1e** led to decomposition of the skeleton under acidic conditions. After reduction of the ketone in **1e** with NaBH₄, the resulting mixture (without purification) of the two separable diastereomers **10a** and **10b** (7:4 ratio) was treated with Na/



Scheme 3. Reagents and conditions: a) LiCl (2 equiv), H₂O (2 equiv), DMSO, 130 °C, 7 h, 87%; b) NaBH₄ (1 equiv), MeOH, RT, 98%; c) Na/naphthalenide (10 equiv), THF, –78 °C, 1 h, 95%; d) Na/Hg amalgam (60 equiv), NaH₂PO₄ (2 equiv), MeOH, reflux, 24 h, 63% (**11b**); e) (Z)-2-iodo-2-butenyl mesylate, K₂CO₃, CH₃CN, 70 °C, 24 h, 82%; f) Dess–Martin reagent (1 equiv), CH₂Cl₂, 25 °C, 30 min, 90%; g) Pd(OAc)₂ (0.05 equiv), PPh₃ (0.5 equiv), Bu₄NBr (1 equiv), K₂CO₃ (4 equiv), DMF/H₂O (10:1), 70 °C, 12 h, 60%; h) Comins' reagent (2 equiv), NaHMDS (1 M in THF, 2 equiv), THF, –78 °C, 20 min, 88%; i) [Pd-(PPh₃)₄] (0.1 equiv), Bu₃SnCH₂OH (4 equiv), LiCl (40 equiv), dioxane, MW (200 mW), 1 h, 85%; j) TMSOTf (4.5 equiv), CH₂Cl₂, 0 °C, 10 min, 83%. Tf = trifluoromethanesulfonyl; Dess–Martin reagent = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one; Comins' reagent = 2-[N,N-bis(trifluoromethyl-sulfonyl)amino]-5-chloropyridine; NaHMDS = sodium hexamethyldisilazide; TMSOTf = trimethylsilyl trifluoromethanesulfonate.

naphthalenide at –78 °C in THF to produce a mixture of separable amines **11a** and **11b** in a 93% yield from **1e**. Importantly, the above two-step procedure of the ketone reduction and the removal of the Ts group could be simplified to a one-step reaction by using a large excess of Na/Hg amalgam to provide single diastereomer **11b** in 63% yield. Alkylation of **11a** and **11b** with (Z)-2-iodo-2-butenyl mesylate and subsequent oxidation with the Dess–Martin reagent afforded ketone **13** in 74% yield over two steps. Palladium-catalyzed intramolecular α -vinylation of ketone **13**, by using conditions improved by Cook and co-workers,^[16] facilitated the formation of the fifth ring to give pentacyclic **14** in 60% yield. Conversion of the ketone functional group of **14** into an enol triflate was realized by reaction of **14** with Comins' reagent under strong basic conditions to provide **15** in 88% yield. Replacement of the triflate group with a hydroxymethyl group by microwave assisted Still cross-coupling^[17] with tri-*n*-butylstannylmethanol and the removal of the *tert*-butylcar-

boxycarbonyl (Boc) group with TMSOTf led to the total synthesis of (±)-minfiensine.^[18]

In summary, we have developed a highly efficient method for the assembly of tetracyclic skeleton **1** with readily manipulated functional groups. The usefulness and efficiency of the newly developed methodology was demonstrated by the completion of a concise total synthesis of highly congested (±)-minfiensine with a 4% overall yield in 12 steps from tetrahydrocarboline **5a**. Synthesis of members of the akuammiline alkaloids by using synthesized tetracyclic skeleton **1** are under investigation and the results will be reported in due course.

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