Natural Products

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Efficient Assembly of an Indole Alkaloid Skeleton by Cyclopropanation: Concise Total Synthesis of (±)-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 impressive biological activities, including significant anticancer 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-iminoethano-carbazole.[10]

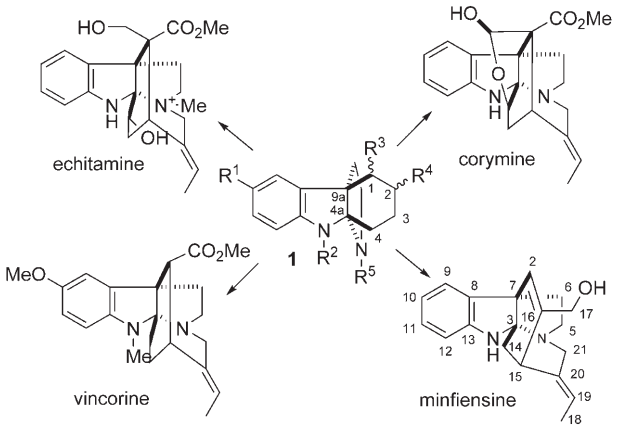
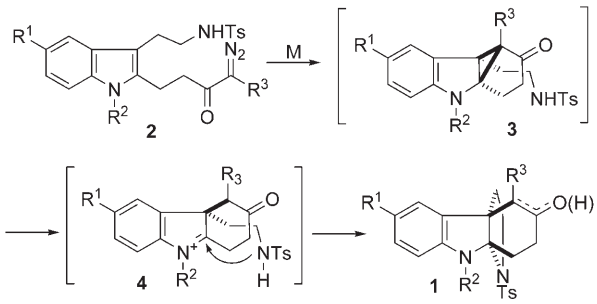


Figure 1. Representative indole alkaloids with a core tetrahydro-9a,4a-iminoethanocarbazole structure.

As a part of our studies on the synthesis of indole alkaloids,[11] we describe herein a concise total synthesis of (±)-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 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 (±)-minfiensine by palladium-catalyzed α-vinylation of the ketone.[12]



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

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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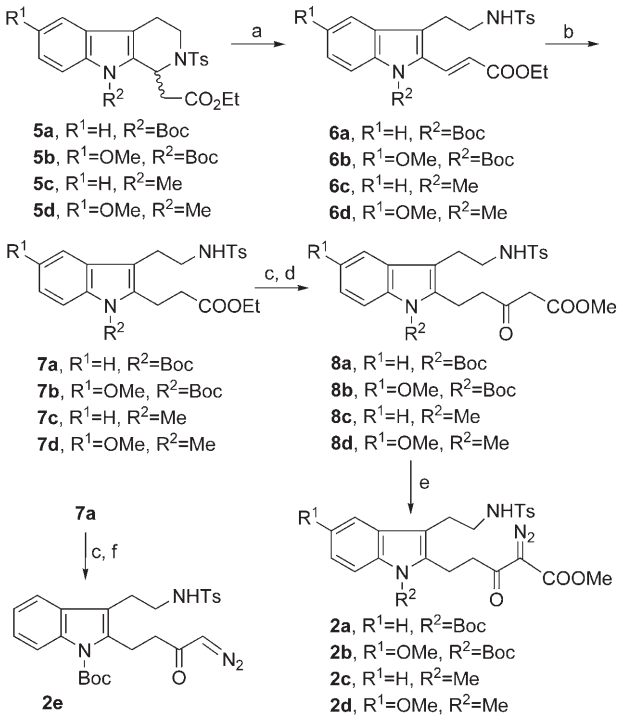
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

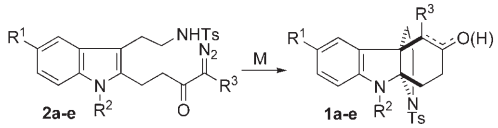


Scheme 2. Reagents and conditions: a) LiHMDS (1 M in THF, 1.5 equiv), THF, −40 °C, 10 h for **5a** and **5b**, NaH (1.2 equiv), DMF, RT, 2 h, for **5c** and **5d**; b) Pd/C (10 mol %), H_2 (1 atm), MeOH/THF 1:1, 24 h, **7a** (83 % from **5a**), **7b** (87 % from **5b**), **7c** (86 % from **5c**), **7d** (85 % from **5d**); c) LiOH (3 equiv), MeOH/THF/H_2O 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), CH_2Cl_2, 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), CH_3CN, 25 °C, 12 h, **2a** (86 %), **2b** (89 %), **2c** (83 %), **2d** (82 %); f) CH_2N_2 (10 equiv), Et_2O, 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 diazomethane.

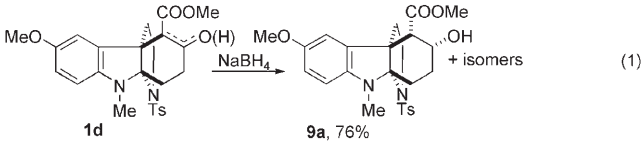
With diazo esters **2a–e** in hand, we next evaluated the efficiency of a variety of metal salts as catalysts in the three-step, one-pot cascade reaction (Table 1). Among the screened metal salts for the diazo decomposition reaction, only CuOTf gave a satisfying result in the model reaction of **2a**. Diazo decomposition of **2a–e** in CH_2Cl_2 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 R^2 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 $NaBH_4$ [Eq. (1) and Figure 2].

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



	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 CH_2Cl_2 as the solvent. [b] Yield of isolated product. [c] Determined from ^1H NMR analysis.



(1)

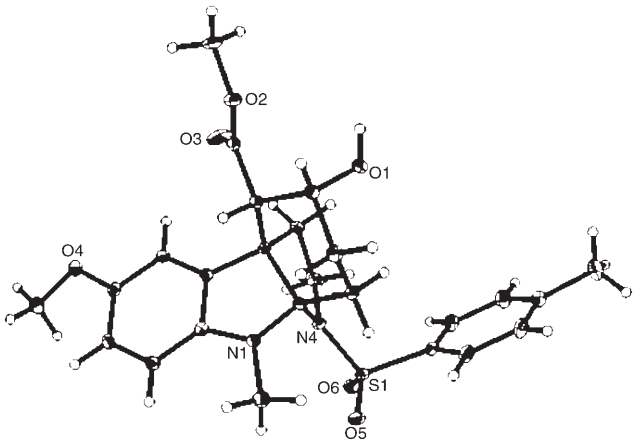
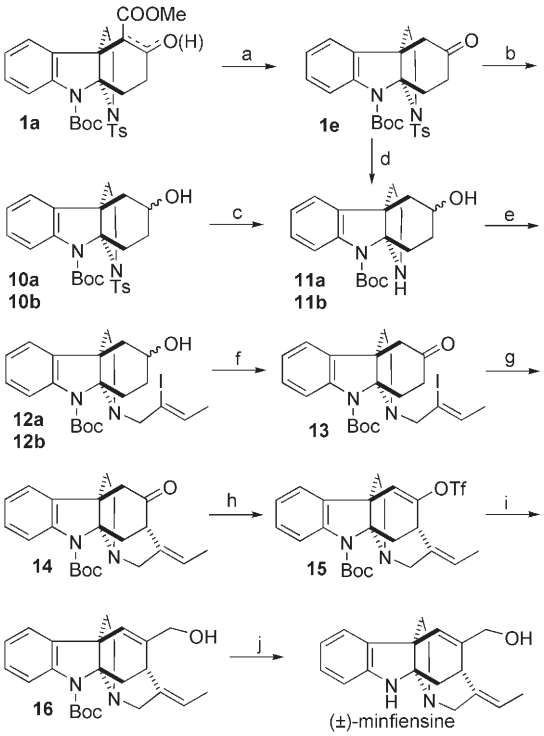


Figure 2. ORTEP diagram of **9a**.

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 $NaBH_4$, 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), H_2O (2 equiv), DMSO, 130 °C, 7 h, 87%; b) $NaBH_4$ (1 equiv), MeOH, RT, 98%; c) Na/naphthalenide (10 equiv), THF, −78 °C, 1 h, 95%; d) Na/Hg amalgam (60 equiv), NaH_2PO_4 (2 equiv), MeOH, reflux, 24 h, 63% (**11b**); e) (*Z*)-2-iodo-2-butenyl mesylate, K_2CO_3, CH_3CN, 70 °C, 24 h, 82%; f) Dess–Martin reagent (1 equiv), CH_2Cl_2, 25 °C, 30 min, 90%; g) $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.5 equiv), Bu_4NBr (1 equiv), K_2CO_3 (4 equiv), DMF/H_2O (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(PPh_3)$_4$] (0.1 equiv), Bu_3SnCH_2OH (4 equiv), LiCl (40 equiv), dioxane, MW (200 mA), 1 h, 85%; j) TMSOTf (4.5 equiv), CH_2Cl_2, 0 °C, 10 min, 83%. Tf = trifluoromethanesulfonyl; Dess–Martin reagent = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; Comins' reagent = 2-[*N*,*N*-bis(trifluoromethyl-lsulfonyl)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*-butylcarboxycarbonyl (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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[1] For a review on akuammiline alkaloids, see: A. Ramírez, S. García-Rubio, *Curr. Med. Chem.* **2003**, *10*, 1891.
[2] a) H. Manohar, S. Ramaseshan, *Tetrahedron Lett.* **1961**, *22*, 814; b) J. A. Goodson, *J. Chem. Soc.* **1932**, *134*, 2626; c) J. A. Goodson, T. A. Henry, *J. Chem. Soc.* **1925**, *127*, 1640.
[3] a) A. M. Morfaux, P. Mouton, G. Massiot, L. Le Men-Oliver, *Phytochemistry* **1992**, *31*, 1079; b) J. Mokrý, L. Dúbravková, P. Šefčovič, *Experientia* **1962**, *18*, 564.
[4] B. Proksa, D. Uhrin, E. Grossmann, Z. Votický, *Planta Med.* **1987**, *53*, 120.
[5] G. Massiot, P. Thépenier, M.-J. Jacquier, L. L. Men-Oliver, C. Delaude, *Heterocycles* **1989**, *29*, 1435.
[6] a) M. S. Baliga et al., *Toxicol. Lett.* **2004**, *151*, 317; b) V. Saraswathi, V. Subramanian, S. Govindasamy, *Cancer Biochem. Biophys.* **1999**, *17*, 79; c) A. Maier, C. Maul, M. Zerlin, S. Grabley, R. Thiericke, *J. Antibiot.* **1999**, *52*, 952; d) V. Saraswathi, S. Subramanian, N. Ramamoorthy, V. Mathuram, S. Govindasamy, *Med. Sci. Res.* **1997**, *25*, 167; e) P. Leewanich, M. Tohda, K. Matsumoto, S. Subhadhirasakul, H. Takayama, N. Aimi, H. Watanabe, *Eur. J. Pharmacol.* **1997**, *332*, 321; f) P. Leewanich, M. Tohda, K. Matsumoto, S. Subhadhirasakul, H. Takayama, N. Aimi, H. Watanabe, *Biol. Pharm. Bull.* **1996**, *19*, 394; g) P. Kamarajan, N. Sekar, S. Govindasamy, *Med. Sci. Res.* **1995**, *23*, 237.
[7] D. B. Grotjahn, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1990**, *112*, 5653.
[8] J. Lévy, J. Sapi, J. Y. Laronze, D. Royer, L. Toupet, *Synlett* **1992**, 601.
[9] a) L. J. Dolby, S. J. Nelson, *J. Org. Chem.* **1973**, *38*, 2882; b) L. J. Dolby, Z. Esfandiari, *J. Org. Chem.* **1972**, *37*, 43.
[10] A. B. Dounay, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2005**, *127*, 10186. After submission of this manuscript, the second-generation synthesis of minfiensine in 6.5% overall yield and 15 steps was reported by Overman and co-workers: A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2008**, DOI: 10.1021/ja800163y.
[11] a) H. Song, J. Yang, Y. Qin, *Org. Lett.* **2006**, *8*, 6011; b) J. Yang, H. Song, X. Xiao, J. Wang, Y. Qin, *Org. Lett.* **2006**, *8*, 2187; c) J. Yang, H.-X. Wu, L.-Q. Shen, Y. Qin, *J. Am. Chem. Soc.* **2007**, *129*, 13794.
[12] a) D. Solé, X. Urbaneja, J. Bonjoch, *Adv. Synth. Catal.* **2004**, *346*, 1646; b) D. Solé, E. Peidró, J. Bonjoch, *Org. Lett.* **2000**, *2*, 2225; c) E. Piers, J. Renaud, *J. Org. Chem.* **1993**, *58*, 11; d) E. Piers, P. C. Marais, *J. Org. Chem.* **1990**, *55*, 3454.

[13] a) P. D. Bailey, S. P. Hollinshead, *Tetrahedron Lett.* **1987**, *28*, 2879; b) P. D. Bailey, S. P. Hollinshead, Z. Dauter, *J. Chem. Soc. Chem. Commun.* **1985**, 1507; c) J. Vercauteren, C. Lavaud, J. Lévy, G. Massiot, *J. Org. Chem.* **1984**, *49*, 2278. Modifications to the original procedure for the preparation of **5c** and **5d** were made, see the Supporting Information.

[14] A colorless crystal of **9a** ($C_{25}H_{30}N_2O_6S_1$, m.p. 168–170 °C) for the X-ray analysis was obtained by recrystallization from EtOH. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 663298 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey, W. P. Stephens, *J. Org. Chem.* **1978**, *43*, 138.

[16] a) H. Zhou, X. B. Liao, W. Y. Yin, J. Ma, J. M. Cook, *J. Org. Chem.* **2006**, *71*, 251; b) J. M. Yu, X. Z. Wearing, J. M. Cook, *J. Org. Chem.* **2005**, *70*, 3963; c) H. Zhou, X. B. Liao, J. M. Cook, *Org. Lett.* **2004**, *6*, 249; d) J. M. Yu, T. Wang, X. X. Liu, J. Deschamps, J. Flippen-Anderson, X. B. Liao, J. M. Cook, *J. Org. Chem.* **2003**, *68*, 7565; e) T. Wang, J. M. Cook, *Org. Lett.* **2000**, *2*, 2057.

[17] W. J. Scott, J. K. Still, *J. Am. Chem. Soc.* **1986**, *108*, 3033.

[18] The synthetic sample has identical ^1H and ^{13}C NMR spectra to that of the natural minfiensine provided by G. Massiot and a synthetic sample provided by L. E. Overman.

