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COMMUNICATIONS

Published on Web 07/01/2005

# Sequential Catalytic Asymmetric Heck−Iminium Ion Cyclization: Enantioselective Total Synthesis of the *Strychnos* Alkaloid Minfiensine

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A variety of natural products containing the 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole (**1**) ring have been isolated from higher plants.[2] These alkaloids, exemplified by **2**−**4**, are comprised of tryptamine and monoterpene units, presumably being derived in nature by cyclization of corynantheine derivatives.[3] Several biological activities have been associated with these alkaloids, including promising anticancer activity.[2,4,5] A concise, enantioselective chemical synthesis entry to alkaloids, such as **2**−**4**, would allow further exploration of the pharmacology of this unique structural motif.[6]

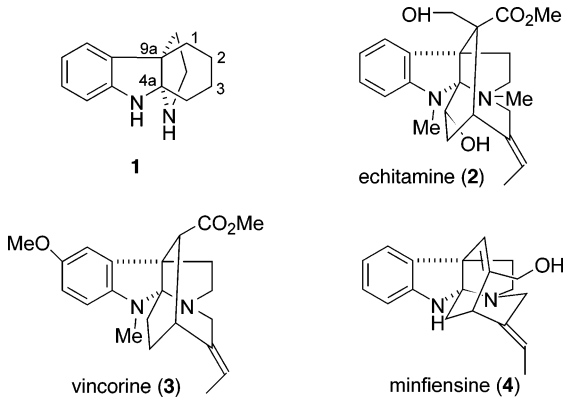
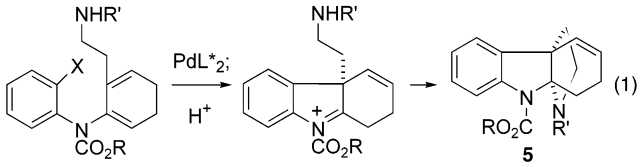


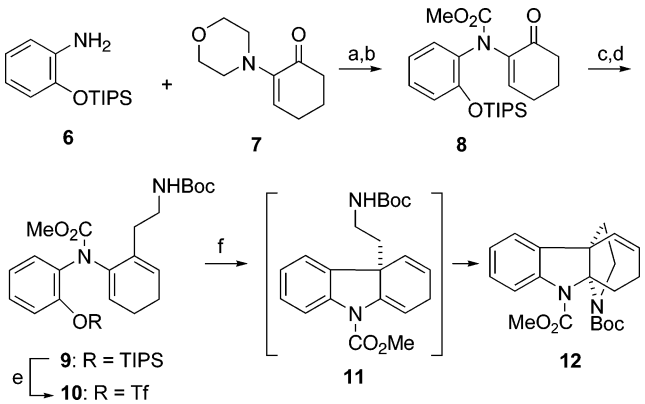

***Figure 1.*** Representative alkaloids containing a 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole ring system.

We saw (hydroiminoethano)carbazoles **1** having a 1,2 or 2,3 double bond as potentially versatile platforms for constructing alkaloids of this type, as stitching an ethylideneethano unit between the pyrrolidine nitrogen and C2 or C3 would form the pentacyclic ring systems found in these alkaloids. We furthermore perceived that the 4a*R*,9a*R* enantiomer **5** of these 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole intermediates might be directly assembled by the domino catalytic asymmetric Heck−*N*-acyliminium ion sequence posited in eq 1.[7] The development of this chemistry and its use to complete the first total synthesis of (+)-minfiensine (**4**)[8] is the subject of this communication.




The asymmetric construction of 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole **12** commenced with acid-catalyzed transamination[9] of the morpholine enamine **7**[10] of 1,2-cyclohexanedione with 2-siloxyaniline **6**[11] (Scheme 1). Selective protection of the nitrogen of the resulting enamine was complicated by competitive reaction of the cyclohexenone functionality. Useful selectivity was realized only when the sodium salt of the secondary enamine was allowed to react at −78 °C with methyl chloroformate, providing carbamate **8** in 52−60% yield. Elaboration of the enone functionality to a dienyl carbamate and introduction of the aminoethyl side chain were accomplished by initial enol triflation of **8** by reaction with sodium hexamethyldisilazide (NaHMDS) and 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent).[12] Suzuki cross-coupling of this dienyl triflate with the alkyl borane generated by hydroboration of *N*-vinyl-*tert*-butyl carbamate (**13**)[13] provided **9** in 60% overall yield.[14] In one step and 95% yield, the Heck cyclization precursor, aryl triflate **10**, was secured by reaction of silyl ether **9** at room temperature with CsF, $Cs_2CO_3$, and Comins' reagent.

***Scheme 1*** [a]




[a] Reagents: (a) *p*-TsOH, PhH, 50 °C (95%); (b) $ClCO_2Me$, NaHMDS, THF, −78 °C (52−60%); (c) Comins' reagent, NaHMDS, THF, −78 °C (82%); (d) 9-BBN, **13**, THF; $PdCl_2$(dppf)·DCM, THF, rt; $H_2O_2$, 0 °C (72%); (e) CsF, $Cs_2CO_3$, Comins' reagent, DMF, rt (95%); (f) $Pd(OAc)_2$, **14**, PMP, PhMe, 170 °C; $CF_3CO_2H$, $CH_2Cl_2$, 0 °C (75%).

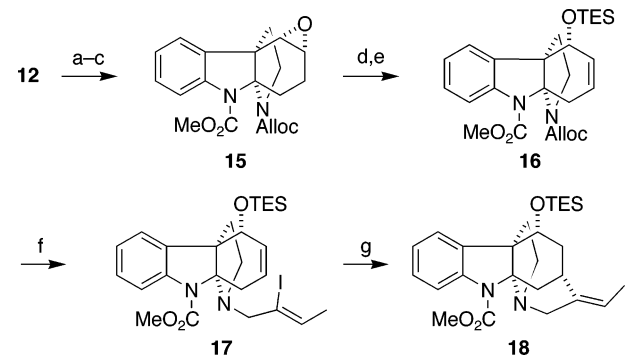
Initial survey experiments showed that the pivotal asymmetric Heck cyclization of **10** could be realized with several chiral enantiopure ligands.[15] The Pfaltz ligand, (*S*)-4-*tert*-butyl-2-[2-(diphenylphosphinyl)phenyl]-4,5-dihydrooxazole (**14**),[16] proved optimal, providing tricyclic dienyl carbamate **11** in ca. 85% yield and 99% ee. However, asymmetric Heck cyclization of **10** was slow, requiring more than 70 h at 100 °C to reach completion. Fortunately, this conversion could be accomplished in 30 min with no erosion in enantioselectivity at 170 °C in a microwave reactor.[17] Upon addition of excess trifluoroacetic acid to the crude Heck product, the one-pot reaction sequence was completed to furnish (dihydroiminoethano)carbazole **12** in 75% overall yield.[18,19]

The elaboration of dihydrocarbazole **12** to the pentacyclic ring system of minfiensine is summarized in Scheme 2. Epoxidation of **12** with *m*-chloroperoxybenzoic acid provided the corresponding α-epoxide in 87% yield.[20] Because of the propensity of the aminal fragment to open under acidic conditions,[21] the *tert*-butoxycarbonyl (Boc) protecting group had to be exchanged for an allyloxycarbonyl (Alloc) group prior to transforming the epoxide to an allylic



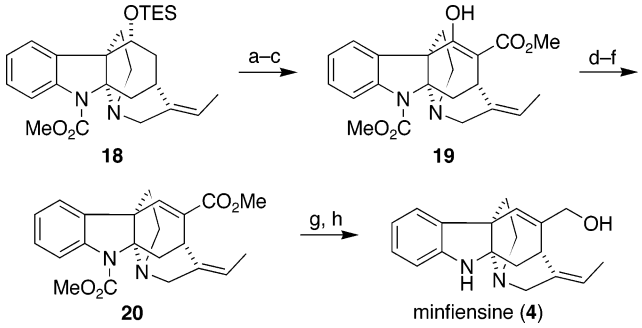
10.1021/ja0533895 CCC: $30.25 

***Scheme 2*** [a]




[a] Reagents: (a) *m*-CPBA, $CH_2Cl_2$, 0 °C → rt (87%); (b) $CF_3CO_2H$, 0 °C → rt (98%); (c) $CH_2{=}CHCH_2OCOCl$, $K_2CO_3$, rt (92%); (d) $(PhSe)_2$, $NaBH_4$, THF/MeOH, 70 °C; $H_2O_2$, 0 → 70 °C (83%); (e) TESCl, imidazole, $CH_2Cl_2$, rt (90%); (f) $Pd(PPh_3)_4$, pyrrolidine, THF, rt; (*Z*)-2-iodo-2-butenyl tosylate, $K_2CO_3$, MeCN, 70 °C (96%); (g) $Pd(OAc)_2$, $K_2CO_3$, $Bu_4NCl$, $NaO_2CH$, DMF, 80 °C (80%).

***Scheme 3*** [a]




[a] Reagents: (a) TBAF, THF, rt (100%); (b) DMP, $CH_2Cl_2$, rt (99%); (c) $CNCO_2Me$, LiHMDS, THF, −78 °C (71%); (d) $NaBH_4$, MeOH/THF, 0 °C (60%); (e) BzOTf, pyridine, $CH_2Cl_2$, 60 °C (100%); (f) KHMDS, THF, −78 °C (83%); (g) $LiAlH_4$, THF, −20 °C (89%); (h) NaOH, MeOH/$H_2O$, 100 °C (95%).

alcohol.[22] This former conversion was accomplished in standard fashion to deliver *N*-Alloc derivative **15** in 78% overall yield from precursor **12**. Opening of epoxide **15** by reaction with sodium phenylselenide, followed by hydrogen peroxide-induced elimination,[23] formed the corresponding allylic alcohol, which upon silyl protection, gave allylic silyl ether **16** in 75% overall yield. Alloc deprotection, followed by alkylation of the resulting secondary amine with (*Z*)-2-iodo-2-butenyl tosylate,[24] then delivered vinyl iodide **17** in 96% yield. Using Heck reaction conditions introduced by Jeffery[25] and a reductive trap ($NaO_2CH$), iodide **17** was converted to pentacyclic diamine **18** in 80% yield.

The conversion of pentacyclic intermediate **18** to (+)-minfiensine (**4**) is adumbrated in Scheme 3. Using standard chemistry, $\beta$-ketoester **19** was secured in 70% overall yield.[26] Transformation of this intermediate to $\alpha,\beta$-unsaturated ester **20** was accomplished by reaction with $NaBH_4$ to provide the corresponding $\beta$-hydroxyester in 60% yield (70% based on consumed **19**). Benzoylation of this product[27] and reaction with KHMDS in THF at −78 °C supplied unsaturated ester **20** in 83% yield. Reduction of this $\alpha,\beta$-unsaturated ester with $LiAlH_4$, and subsequent removal of the carbamate protecting group with NaOH, provided (+)-minfiensine (**4**), $[\alpha]^{23}_D$ +125 (*c* 0.82, $CHCl_3$), in 85% overall yield.[28]

In summary, a concise catalytic asymmetric chemical synthesis entry to alkaloids containing the 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole (**1**) moiety is reported. The central step in this sequence is a sequential catalytic asymmetric Heck−*N*-acyliminium ion cyclization of dienyl carbamate triflate **10** to deliver enantiopure 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole (**12**). This intermediate and related intermediates containing a 2,3 double bond should be versatile precursors for constructing a variety of pentacyclic indole alkaloids containing the (hydroiminoethano)-carbazole fragment. The enantioselective total synthesis of (+)-minfiensine (**4**) reported herein provides the first verification of this total synthesis strategy.

**Acknowledgment.** Financial support from the NIH Heart, Lung and Blood Institute (HL-25854) and postdoctoral fellowship support for A.B.D. (CA94471) and A.D.W. (CA108197) from the NIH National Cancer Institute is gratefully acknowledged. We thank Professor Georges Massiot for copies of NMR spectra of natural minfiensine.

**Supporting Information Available:** Experimental details for key steps and $^1H$ and $^{13}C$ spectra of new compounds (48 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Current address: Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105.

(2) For a recent review, see: Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 14, pp 163−236.

(3) Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151−157.

(4) Ramírez, A.; Garcia-Rubío, S. *Curr. Med. Chem.* **2003**, *10*, 1891−1915.

(5) For example, the antitumor potential of echitamine has received considerable study in India. See: Saraswathi, V.; Mathuram, V.; Subramanian, S.; Govindasamy, S. *Cancer Biochem. Biophys.* **1999**, *17*, 79−88.

(6) No total syntheses in this area have been recorded.[2,4]

(7) Catalytic asymmetric Heck cyclizations have been proven to have wide utility for constructing quaternary carbon stereocenters of natural products. See: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963.

(8) Massiot, G.; Thépenier, P.; Jacquier, M.; Le Men-Olivier, L.; Delaude, C. *Heterocycles* **1989**, *29*, 1435−1438.

(9) Polozov, G. I.; Tishchenko, I. G. *USSR Vestn. Belorus. Un-ta, Ser. 2* **1986**, *1*, 67−69.

(10) Ohashi, M.; Takahashi, T.; Inoue, S.; Sato, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1892−1896.

(11) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507−6511.

(12) Comins, D.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(13) Hart, R. *Bull. Soc. Chim. Belg.* **1956**, *65*, 291−296.

(14) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743−8744.

(15) The use of BINAP as the ligand resulted in extensive double bond migration to form the fully conjugated dienyl carbamate.

(16) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200−202.

(17) For a review of microwave assisted synthesis, see: Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(18) Intermediate **11** can be isolated and converted to **12** in a separate step; the overall yield in this case was 74%.

(19) Absolute configuration was secured by single-crystal X-ray analysis of a heavy atom derivative.

(20) The $\beta$-epoxide is isolated in 10% yield.

(21) Fritz, v. H.; Fischer, O. *Tetrahedron* **1964**, *20*, 1737−1753.

(22) Attempted acidic cleavage of the Boc protecting group at the allylic alcohol stage led to fragmentation of the six-membered ring.

(23) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699.

(24) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695−1698.

(25) (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667−2670. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130.

(26) Attempts to directly introduce the methyl ester by carbonylative trapping of the alkylpalladium intermediate generated from Heck cyclization of **17** have proven unsuccessful thus far.

(27) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875−3880.

(28) A rotation of $[\alpha]^{23}_D$ +134 (*c* 0.82, $CHCl_3$) is reported for natural minfiensine.[8]

JA0533895