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Nine-Step Enantioselective Total Synthesis of (+)-Minfiensine

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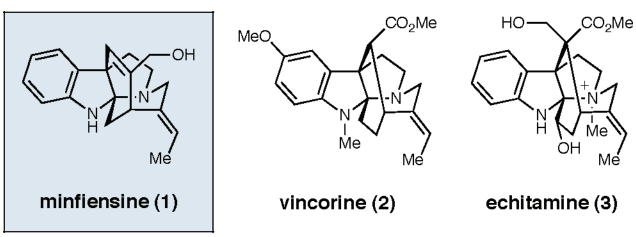
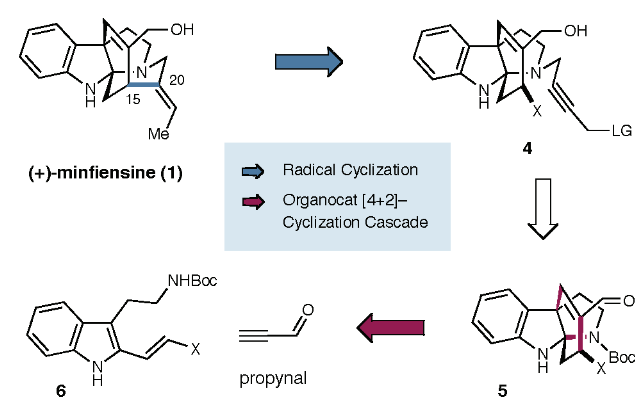
Over the last 50 years, the *Strychnos* alkaloids have become recognized as a family of molecular benchmarks, used to calibrate the utility of new complexity-generating reactions or novel synthetic strategies.[1] In this context, minfiensine (**1**),[2] a structurally unique isolation product from *Strychnos minfiensis*, has received considerable attention from the chemical synthesis community,[3] culminating recently in the highly elegant (and first) enantioselective total synthesis by Overman and co-workers.[3a] Minfiensine is characterized by an embedded 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole moiety, a tetracyclic core that is also found among related akuammiline alkaloids vincorine (**2**) and echitamine (**3**).[4] In this communication, we document a new organocatalytic Diels−Alder/amine cyclization sequence that allows rapid and enantioselective access to this tetracyclic carbazole framework using only an amine catalyst, propynal, and a simple tryptamine derivative. Moreover, we elaborate upon this new asymmetric protocol to achieve a nine-step total synthesis of minfiensine beginning from commercial materials.



Design Plan

As outlined in Scheme 1, we envisioned two key steps that would allow rapid access to the complete pentacyclic topography of minfiensine. From a disconnection approach, we assumed the fifth and final ring of the natural product might be forged via a 6-*exo*-dig cyclization between an allylic radical and a pendent alkyne **4**, a carbon−carbon bond union that would also create the requisite stereogenicity at C(15) and the exocyclic olefin at C(20).[5] As for our second key step, we hypothesized that the structurally complex pyrroloindoline tetracycle **5** might arise directly from vinyl indole **6** via a cascade reaction that would incorporate an organocatalytic Diels−Alder cycloaddition, enamine to iminium isomerization, and an amine cyclization sequence.[6] More specifically, we proposed that condensation of secondary amine catalyst **7** with propynal should generate an activated iminium ion with the acetylenic group being partitioned away from the bulky *t*-butyl substituent of the catalyst framework (Scheme 2, **TS-A**). In this conformation, the aryl ring would shield the top face of the reactive alkyne, facilitating an *endo*-selective[7] Diels−Alder cycloaddition with 2-vinylindole **8** in a regioselective manner to produce the tricyclic diene **9**. Protonation of the enamine moiety would then give rise to an iminium ion **10**, facilitating a 5-*exo* amine heterocyclization to deliver the tetracyclic pyrroloindoline **11**. As a key design element, the dienyl substructure of indole **8** incorporates a 1-methyl sulfide substituent, a moiety that we hoped would accelerate the Diels−Alder

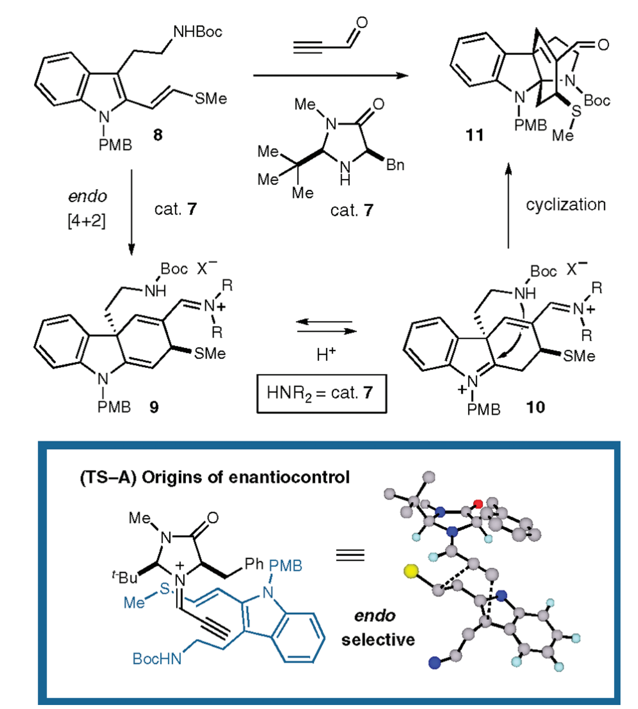
Scheme 1. Retrosynthetic Approach to Minfiensine Pentacycle



cycloaddition while providing a latent handle for radical formation,[8] as required in the final ring-forming step.

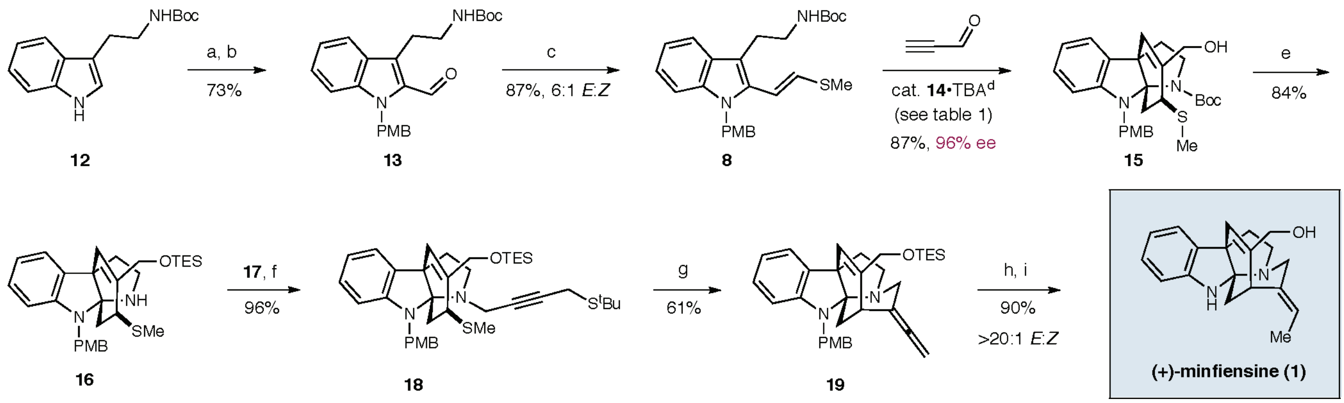
Synthesis of the minfiensine core began with production of the requisite [4 + 2] cycloaddition substrate **8** in three steps from commercial materials using the standard procedures outlined in Scheme 3. With this material in hand, we were able to examine the pivotal Diels−Alder-cyclization cascade in detail. As shown in Table 1, we were delighted to find that subjection of 2-vinylindole **8** to propynal in the presence of imidazolidinone catalyst **7** produced the desired tetracycle **15**, albeit with moderate selectivity (entry 1,

Scheme 2. Enantioselective Catalytic Cascade Sequence to Core



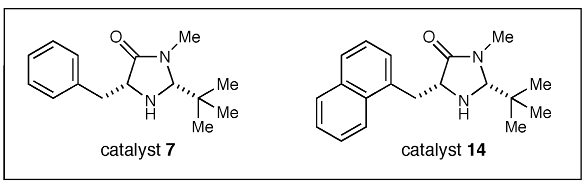
 10.1021/ja906472m CCC: $40.75

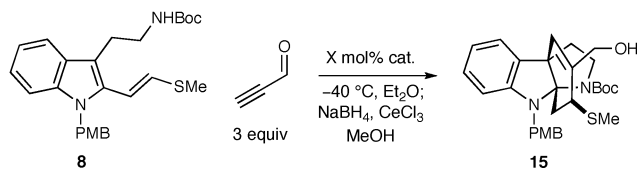
Scheme 3. Nine-Step Total Synthesis of Minfiensine (**1**)[a]



[a] Reagents and Conditions: (a) NaH, PMBCl, DMF, 0 °C. (b) *n*-BuLi, THF, −78 °C; then DMF, −78 °C to rt. (c) $(EtO)_2P(O)CH_2SMe$, NaH, THF, 0 °C to rt. (d) Table 1, entry 3. (e) TESOTf, MeCN, 0 °C. (f) 4-(*tert*-Butylthio)but-2-ynal (**17**), $NaBH(OAc)_3$, CH_2Cl_2, rt. (g) 3 equiv of *t*-Bu_3SnH, 0.3 equiv AIBN, toluene, 110 °C. (h) Pd/C, H_2, THF, −15 °C; >20:1 *E*/*Z* selectivity. (i) PhSH, TFA, rt.

Table 1. Organocatalytic Diels−Alder-Cascade Cyclization Studies





entry	catalyst · HA	mol %	time (h)	% yield[a]	% ee[b]
1	**7**·TFA	20	12	84	75
2	**7**·TBA	20	12	81	88
3[c]	**14**·TBA	15	24	87[d]	96
4	**14**·TBA	10	48	83	94
5	**14**·TBA	5	72	80	94

[a] Yield determined by ^1H NMR with internal standard. [b] Enantiomeric excess determined by chiral SFC analysis. [c] At −50 °C. [d] Isolated yield.

75% ee). A catalyst structure evaluation revealed that the 1-naphthyl substituted catalyst **14** in conjunction with tribromoacetic acid (TBA) cocatalyst provided superior levels of yield and enantioselectivity, presumably due to the extended shielding effect of the naphthyl ring in the [4 + 2] transition state (entry 3, 87% yield, 96% ee). It is important to note that catalyst loadings as low as 5 mol % were sufficient to effect the cascade while maintaining high levels of reaction efficiency (entries 4 and 5, 80% yield, 94% ee).

Subsequent conversion of the pyrroloindoline tetracycle **15** to minfiensine (**1**) was achieved in a five-step sequence as shown in Scheme 3. Simultaneous *N*-Boc deprotection and primary alcohol protection were performed by exposure of carbamate **15** to TESOTf in acetonitrile at 0 °C to afford silyl ether **16** in 84% yield. Reductive amination of secondary amine **16** with butynal *t*-butyl sulfide **17** was readily accomplished with $NaBH(OAc)_3$ in CH_2Cl_2 to render the requisite radical cyclization substrate **18** in 96% yield. At this stage, we were surprised to find that all attempts to forge the final piperidine ring of minfiensine via alkyne radical cyclization were unsuccessful using prototypical conditions (AIBN, Bu_3SnH).[9] However, replacement of Bu_3SnH with the more bulky *t*-Bu_3SnH[10] (with AIBN in refluxing toluene) cleanly afforded the allene **19** in 61% yield.[11,12] Next, we envisioned that regio- and diastereoselective allene hydrogenation would provide the *trans*-ethylidene subunit that is commonly found throughout the *Strychnos* alkaloid family. In the event, we were pleased to find that the proposed reduction could be realized via subjection of allene **19** to 10% Pd/C and H_2 in THF at −15 °C to give the desired *trans*-ethylidene with greater than 20:1 *E*/*Z* selectivity.[13] Finally, a global deprotection using neat TFA at room temperature delivered (+)-minfiensine (**1**) in 90% yield, a substance that was identical in all respects to the natural isolate.

In summary, the total synthesis of (+)-minfiensine (**1**) was completed in nine steps and 21% overall yield from commercial materials. Prominent features of this synthesis include (i) a new cascade organocatalysis sequence to build the central tetracyclic pyrroloindoline framework and (ii) a 6-*exo*-dig radical cyclization to forge the final piperidinyl ring system.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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