Natural Product Synthesis

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Enantioselective Total Synthesis of (−)-Minovincine in Nine Chemical Steps: An Approach to Ketone Activation in Cascade Catalysis**

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Since its isolation in 1962, (−)-minovincine[1] (**1**, Figure 1) has garnered considerable interest within the chemical synthesis community because of its characteristic spiroindoline framework, a common structural feature found among a number of high-profile natural products derived from the *Aspidosperma*, *Kopsia*, and *Catharanthus* genre.[2] Indeed, this structural core has led to (−)-minovincine being described as a "biogenetic turntable" between the vindolinine and kopsinine classes of isolates,[3a,b] and has provided the impetus over several decades for a number of racemic total syntheses of this biosynthetic linchpin. At the present time, however, no asymmetric total synthesis of (−)-minovincine has been reported,[4] a surprising fact given the range of catalytic technologies which have been developed to forge this broadly represented spiroindoline framework. Herein, we detail the first enantioselective total synthesis of (−)-minovincine in only nine chemical steps using a novel organocascade[5] catalysis transformation which incorporates an enantioselective Diels–Alder cycloaddition/β-elimination/conjugate addition sequence.[6] Central to the development of this new catalysis cascade has been the identification of ketone substrates and amine catalysts which combine to provide direct access to the key functional and architectural elements found in (−)-minovincine.

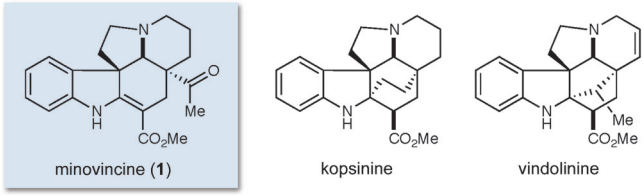

Figure 1. Apocynaceae alkaloids—common pentacyclic framework.

We were initially drawn to (−)-minovincine on the basis of its 1) benchmark spiroindoline framework, which is broadly represented across a large range of *Aspidosperma*, *Kopsia*, and *Catharanthus* isolates; and 2) the exocyclic ketone substituent which is not common within these alkaloid families.[2] Previous studies conducted by our group have revealed that similar tetracycles are readily constructed by iminium-activated organocascade catalysis protocols which involve enantioselective [4+2] cycloaddition of 2-vinyl indoles with an unsaturated aldehyde partner.[6] We questioned whether this strategy might be extended to ketone dienophiles, such as 3-butyn-2-one, thereby providing direct access to the exocyclic ketone present in (−)-minovincine and several other natural alkaloids. Despite their apparent similarities on paper, aldehydes and ketones exhibit markedly different behavior in organocatalytic processes, and the latter have historically posed a significant challenge in amine-catalyzed Diels–Alder and cascade catalysis reactions (Figure 2).[7] More specifically, ketones typically exhibit

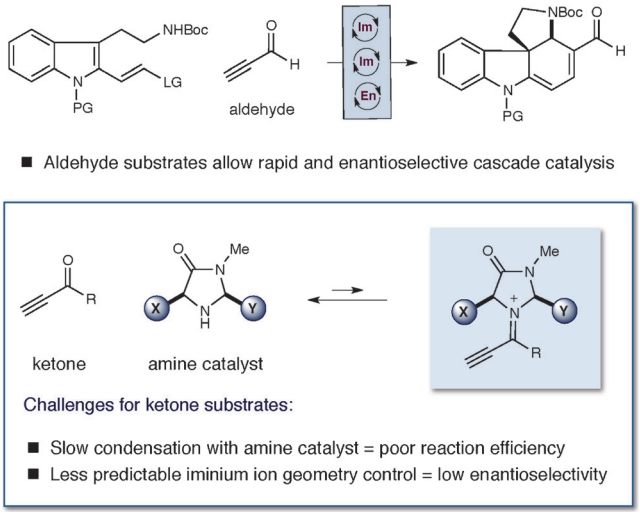

Figure 2. Issues with ketone substrates in organocatalytic cascades. Boc = *tert*-butoxycarbonyl, PG = protecting group, LG = leaving group.

1) attenuated reactivity towards condensation with secondary amines in comparison to their formyl counterparts—a limitation that can dramatically impact overall reaction efficiency; and 2) they are prone to nonselective iminium geometry formation with amine catalysts, a loss of organizational control which often leads to diminished enantioselectivity in the critical bond-forming step. As such, we were intrigued by the possibility of expanding the scope of organocascade catalysis to include this more challenging family of carbonyl groups while developing a concise route to (−)-minovincine.

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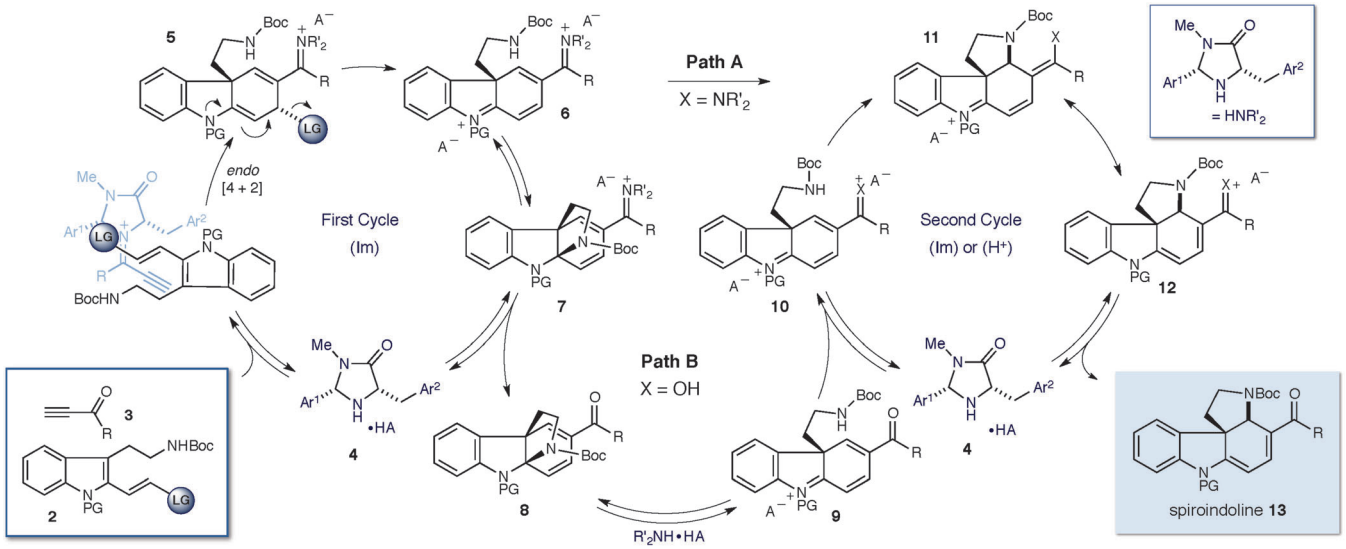


Scheme 1. Proposed mechanism for [4+2] cycloaddition/β-elimination/hetero-conjugate addition organocascade sequence.

The pathway for the proposed organocascade sequence involves a series of catalytic cycles outlined in Scheme 1. In the first cycle, condensation between 3-butyn-2-one (**3**, R = Me) and amine catalyst **4** would transiently generate a LUMO-lowered unsaturated iminium ion poised to undergo [4+2] cycloaddition with vinyl indole **2**.[8] We hypothesized that incorporation of a suitable leaving group on the terminus of the diene would result in facile β-elimination, thus delivering indolinium ion **6**. At this stage, 5-*exo*-heterocyclization of the pendent amine onto the α,β-unsaturated iminium moiety would directly yield tetracycle **11** (Path A), which, after hydrolysis, would deliver spiroindoline **13** and regenerate the amine catalyst. Based on previous studies, we recognized the possibility of an alternative second cycle in which indolinium trapping by the pendent amine would furnish pyrroloindoline **8** (Path B), an isolable intermediate when propynal is utilized as the dienophile (R = H). Importantly, we have demonstrated that this aldehyde undergoes facile conversion into the desired spiroindoline **13** (R = H) in the presence of the tribromoacetic acid salt of *N*-methyl **4** (incapable of undergoing iminium ion formation), thus illustrating the feasibility of Brønsted acid catalysis as an operative pathway in this organocascade sequence.[6] As a key stereocontrol element, we hypothesized that condensation of 3-butyn-2-one with the imidazolidinone catalyst would lead to an iminium ion geometry wherein the acetylenic functionality of the conjugated system is projected towards the benzylic unit on the catalyst scaffold (enabling stabilizing cation–π interactions between the pendent arene and the terminal alkyne). In this geometry, the catalyst substituents effectively shield one π-face of the iminium ion, thereby ensuring that *endo*-selective Diels–Alder cycloaddition[8,9] occurs from the opposing trajectory (**TS-A**, Figure 3), a feature that should induce high levels of enantiocontrol.

To evaluate the key organocascade sequence, a series of halide- or selenium-bearing vinyl indoles were prepared by a straightforward, three-step protocol (Scheme 2). More

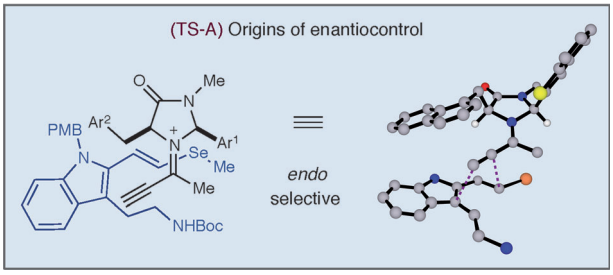
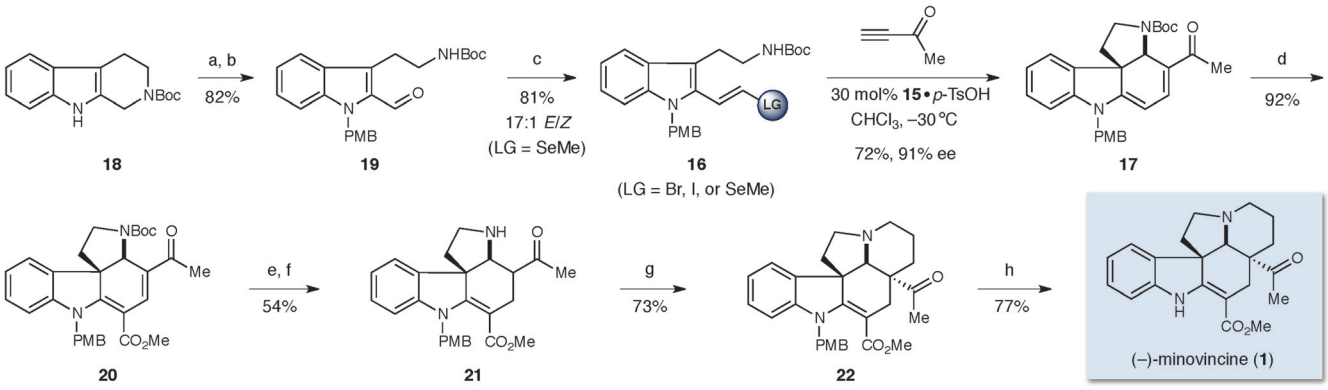


Figure 3. Proposed stereochemical model for cascade Diels–Alder. PMB = *para*-methoxybenzyl.

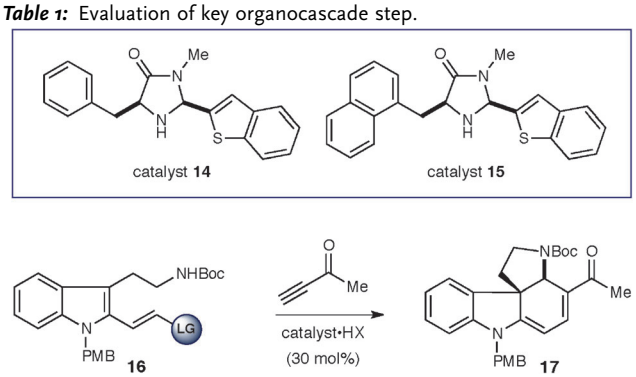
specifically, *N* indole protection of commercially available tetrahydro-β-carboline derivative **18** was followed by selenium-dioxide-mediated oxidation[10] and subsequent olefination to afford diene **16** as the vinyl bromide, iodide, or selenide.

As illustrated in Table 1, our initial attempts to construct spiroindoline **17** by our proposed organocascade sequence using the vinyl bromide derivative of **16** were unsuccessful (entry 1). However, employing the indole vinyl iodide derivative in conjunction with the camphorsulfonic acid salt of catalyst **14** (known to efficiently condense with cyclic ketones to form enamines)[11] produced the desired tetracycle, albeit with low yield and enantioselectivity (entry 2). To our delight, further investigation revealed that use of the vinyl selenide system afforded **17** in a promising 45% yield and 36% *ee* (entry 3). The reaction medium was also critical with respect to obtaining high levels of asymmetric induction, as demonstrated by the implementation of chloroform (entry 4). Further improvements in enantioselectivity were achieved by increasing the size of the pendent aromatic unit on the catalyst framework, thus presumably allowing greater facial shielding of the transient iminium ion (entry 5). Finally, a pronounced acid co-catalyst effect was identified, wherein changing from camphorsulfonic acid[12] to *p*-toluenesulfonic



Scheme 2. Total synthesis of (−)-minovincine: a) NaH, PMBCl, DMF, 0 °C, 94%; b) SeO_2, 95:5 1,4-dioxane/H_2O, 100 °C, 87%; c) LG = Br: $[(PPh_3)CH_2Br]Br$, *t*BuOK, THF, −78 °C, 21%; LG = I: $CrCl_2$, CHI_3, THF, 0 °C, 50%; LG = SeMe: $(EtO)_2P(O)CH_2SeMe$, KHMDS, [18]crown-6, −78 °C to RT, 81%; d) *N*-iodosuccinimide, $[Pd(PhCN)_2Cl_2]$ (10 mol%), Et_3N, MeOH, MeCN, CO (1 atm), 60 °C, 92%; e) L-Selectride, THF, −78 to 0 °C, 75%; f) $(Me)_3SiI$, Et_3N, CH_2Cl_2, 0 °C, 72%; g) 1,3-diiodopropane, $NaHCO_3$, DMF, 35 °C; then *t*BuOK, *t*BuOH, RT, 73%; h) 1:1 TFA/CH_2Cl_2, 0 °C to RT, 77%. DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazide, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

Table 1: Evaluation of key organocascade step.



Entry[a]	Catalyst·HX	LG	Solvent	Yield [%][b]	*ee* [%][c]
1	**14**·(+)-CSA	Br	CH_2Cl_2	0	–
2	**14**·(+)-CSA	I	CH_2Cl_2	15	24
3	**14**·(+)-CSA	SeMe	CH_2Cl_2	45	36
4	**14**·(+)-CSA	SeMe	$CHCl_3$	36	79
5	**15**·(+)-CSA	SeMe	$CHCl_3$	38	95
6	**15**·*p*-TSA	SeMe	$CHCl_3$	72	91

[a] Reactions for entries 1–4 performed at −20 °C; reactions for entries 5 and 6 performed at −30 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. CSA = camphorsulfonic acid, LG = leaving group, TSA = toluenesulfonic acid.

acid provided the desired spiroindoline in 72% yield while maintaining excellent levels of enantioselectivity (entry 6).

Having established our optimal ketone activation cascade catalysis sequence, and with the enantioenriched tetracyclic core **17** in hand, we next focused upon completing the natural product synthesis in an expeditious fashion (Scheme 2). With the goal of installing the requisite (−)-minovincine ester group, we exposed **17** to a variety of traditional acylating agents (i.e. phosgene, methyl chloroformate, etc.), however, with little success. Fortunately, the palladium-catalyzed carbomethoxylation of the dienylogous amide in the presence of carbon monoxide and methanol proceeded smoothly to afford vinylogous carbamate **20** in excellent yield (92%).[13] Regioselective 1,4-conjugate reduction of the resulting α,β,γ,δ-unsaturated ketone was accomplished with the aid of the sterically demanding reducing agent L-Selectride,[14] followed by Lewis acid mediated Boc removal to deliver β-amino ketone **21** in 54% yield over two steps.[15] Closure of the final ring was achieved through *N* alkylation with 1,3-diiodopropane and treatment with potassium *tert*-butoxide to provide the natural product in its protected form in 73% yield as a single diastereomer. Finally, removal of the *para*-methoxybenzyl group from the indoline nitrogen atom afforded (−)-minovincine in 77% yield for the final step, and in 13% overall yield for the nine-step sequence.[16] Synthetic (−)-minovincine was found to be identical in all spectroscopic respects to the natural isolate.

In summary, the first enantioselective total synthesis of (−)-minovincine has been completed in nine chemical steps and 13% overall yield from commercial materials. A prominent feature of this synthesis involves an organocatalytic Diels–Alder/β-elimination/conjugate addition cascade to rapidly construct the tetracyclic framework of (−)-minovincine in a highly enantioselective manner. This total synthesis exemplifies the capacity of ketone dienophiles to be viable substrates for iminium catalysis in the context of complex target settings.

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[15] Variable-temperature NMR studies suggested a rotameric mixture of the reduced product as a single diastereomer (see the Supporting Information). The amine **21** was obtained as a single diastereomer.

[16] A slight decrease in enantiomeric excess between **17** (91% *ee*) and (−)-minovincine (86% *ee*) was observed upon completion of the synthesis.

