

Alkaloid Synthesis

International Edition: DOI: 10.1002/anie.201605503
German Edition: DOI: 10.1002/ange.201605503**Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates**

Peng Wen Tan, Jayasree Seayad,* and Darren J. Dixon*

Abstract: A new approach for the divergent total syntheses of (±)-vincaminorine, (±)-N-methylquebrachamine, (±)-quebrachamine, (±)-minovine and (±)-vincadifformine, each in less than 10 linear steps starting from a single δ-lactam building block, is reported. Key to our route design is the late-stage generation of reactive enamine functionality from stable indole-linked δ-lactams via a highly chemoselective iridium(I)-catalyzed reduction. The efficiently formed secodine intermediates subsequently undergo either a formal Diels–Alder cycloaddition or a competitive Michael addition/reduction to access aspidosperma-type alkaloids in excellent diastereoselectivities. Product selectivity could be controlled by changing the indole N-protecting group in the reductive cyclization precursors. An asymmetric variant of this synthetic strategy for the synthesis of (+)-20-epi-ibophyllidine is also described.

Monoterpene indole alkaloids are a diverse class of natural products that is comprised of at least 2000 members. They possess inherent structural complexity and a range of important biological activities that qualifies a number of them to be ideal candidates for anti-cancer, anti-malarial and anti-arrhythmic agents.^[1] As a result, these natural products have inspired the synthetic community to devise innovative and elegant approaches that allow their efficient synthesis.^[2] Interestingly, and despite the many successful synthetic approaches already reported, recent efforts have shifted towards demonstrating unified, general and concise strategies that enable collective syntheses of a range of structurally related natural products. For example, Zhu and co-workers reported an elegant approach that involved the synthesis of cyclopentene intermediates which would then undergo an integrated oxidation/reduction/cyclization (iORC) sequence to access a range of monoterpene indole alkaloids.^[3] Oguri and co-workers established an artificial divergent synthesis that allowed access to ene-yne substrates that underwent a dihydropyridine (DHP) cyclization to a key intermediate that could be transformed into terpenoid indole alkaloids of

skeletally distinct scaffolds.^[4] Similarly, Movassaghi et al. demonstrated a versatile double-cyclization strategy that generated a complex diiminium ion intermediate that could be readily converted into a series of related aspidosperma alkaloids.^[5] Furthermore, MacMillan et al. developed an organocatalytic route to access an enantioenriched tetracyclic spiroindoline molecular scaffold, and from it elegantly diversified to a series of common alkaloid natural products.^[6]

Stimulated by these well-designed and well-executed approaches, we set out to devise a synthetic route that could furnish a range of related, yet structurally diverse, monoterpene indole alkaloid natural products from easily accessible substrates in a concise fashion. In particular, we were attracted to the possibility of generating and trapping reactive enamine intermediates from stable lactam substrates via a chemoselective partial reduction/elimination sequence. Our hope was that the enamine could act as an electron-rich nucleophile/dienophile and be readily intercepted by a strategically placed diene to afford pentacyclic natural products such as minovine and vincadifformine via a formal Diels–Alder reaction. Recent work from our group had indeed demonstrated the feasibility of generating and trapping reactive iminium ions—via enamine intermediates—from nitroalkyl-linked lactam starting materials in a reductive nitro-Mannich cyclization cascade using Vaska's catalyst in the presence of a silane terminal reductant.^[7,8]

Our synthetic plan was well-founded; employing enamine derivatives as synthetic intermediates towards alkaloid natural product target molecules has been of great interest to the synthetic community.^[9] In the early 1960s, Wenkert and Scott proposed that aspidosperma and iboga alkaloids were biogenetically derived from enamine intermediates, via intramolecular Diels–Alder type reactions.^[10] This hypothesis was subsequently supported by labelling experiments and various synthetic approaches that employed the high reactivity of the secodine intermediate (**Int 1**, Figure 1) formed in situ from acyclic precursors to obtain the aspidosperma alkaloids such as vincadifformine.^[11]

Herein we wish to report a new strategy which provides a short and divergent synthetic route to several vincadifformine-type, quebrachamine-type and iboga-type alkaloids. Our new approach features a key late-stage generation of reactive enamine functionality from stable indole-linked δ-lactams via a highly chemoselective iridium(I) catalyzed reduction.

(±)-Minovine (**4**) was chosen as our initial synthetic target. The synthesis of the key lactam intermediate **16** began with alkylation of 3-ethyl-2-piperidone **6** with 1,4-dibromobutane to furnish lactam **7** (Scheme 1). The N-linked alkyl-

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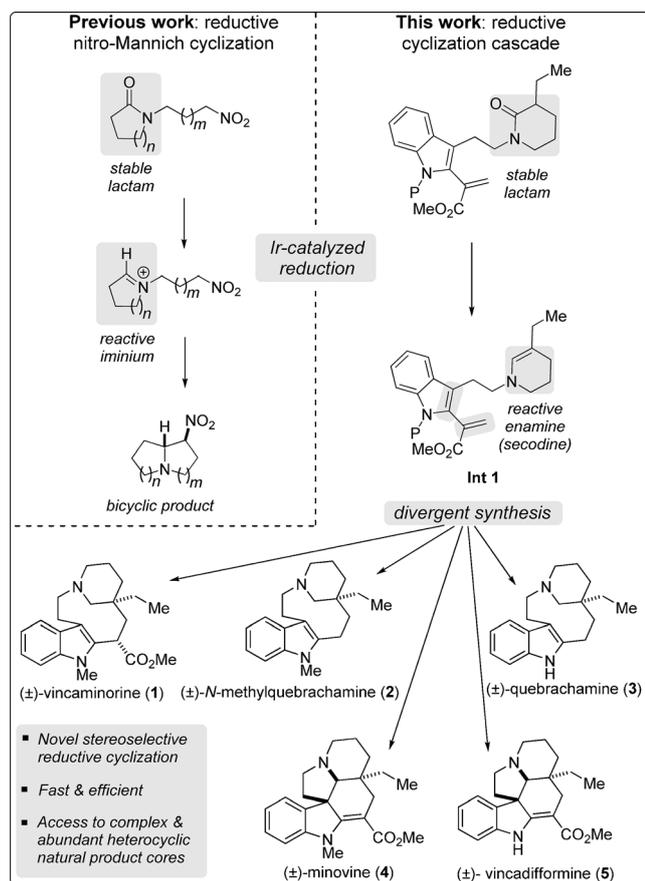
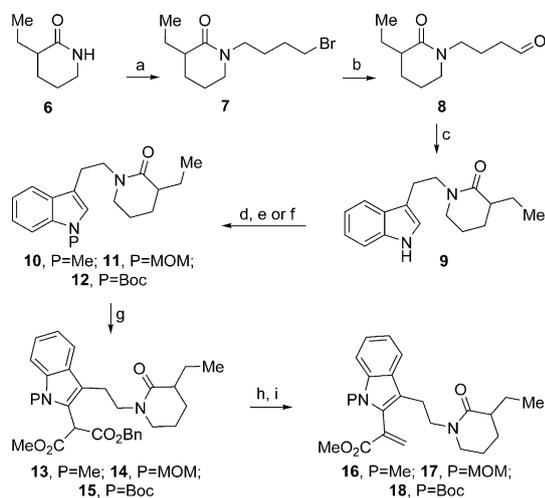


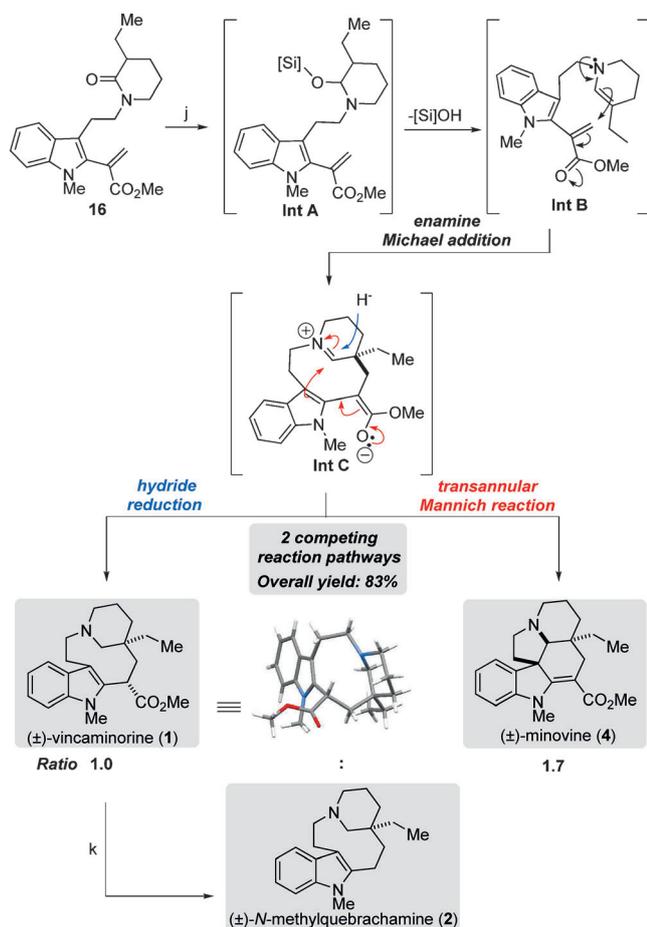
Figure 1. Divergent synthesis of aspidosperma-type alkaloids via Ir-catalyzed reductive generation of reactive enamine intermediates from lactams.



Scheme 1. Synthesis of lactam **16**, **17** and **18**: a) NaH, 1,4-dibromobutane, THF:DMF (5:1), RT, 18 h, 80%; b) NMO, DMSO, RT, 18 h, 60%; c) Phenylhydrazine-HCl, 4% H₂SO₄(aq)/DMA (1:1), 110 °C, 2 h, 62%; d) MeI, NaH, THF, RT, 3 h, 95%; e) MOMCl, NaH, THF:DMF (2:1), 0 °C, 2 h, 89%; f) Boc₂O, NEt₃, DMAP, CH₂Cl₂, RT, 1.5 h, 95%; g) [Ru(bpy)₃]Cl₂, 1-benzyl-3-methyl-2-bromomalonate, 4-methoxyphenylamine, blue LEDs, DMF, RT, 12 h, **13**: 82%; **14**: 66%; **15**: 89%; h) Pd/C, H₂, EtOH, RT, 1 h; i) CH₂=O, HNMe₂·HCl, NaOAc, AcOH, RT, 4 h, **16**: 55%; **17**: 55%; **18**: 82% (over 2 steps).

bromide was then readily converted to its corresponding aldehyde **8** via a Kornblum oxidation.^[12] The construction of the indole functionality proceeded successfully by Stork's modification of the Fischer indole synthesis^[13] of aldehyde **8** with phenylhydrazine-HCl. After methylating the indolyl nitrogen to afford **10**, Stephenson's photoredox-catalyzed direct C–H functionalization at C2 of the indole adduct **10** with benzyl methyl bromomalonate occurred smoothly to obtain **13** in 82% yield.^[14] Finally, debenzoylation of the benzyl ester via Pd-catalyzed hydrogenolysis, followed by a decarboxylative Mannich reaction gave the desired enamine precursor—stable lactam **16**—in 55% yield over two steps.

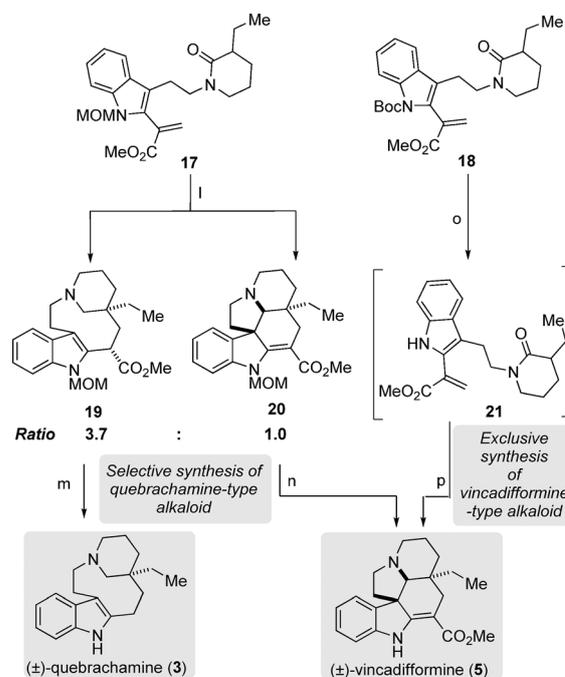
With the desired indole-linked lactam **16** in hand, the key Ir-catalyzed reduction–cycloaddition sequence was investigated. To our delight, the chemoselective Ir-catalyzed reduction of the lactam moiety in the presence of the α,β -unsaturated ester occurred smoothly to give the corresponding enamine (**Int B**), via presumed siloxy intermediate (**Int A**),^[15] as confirmed by ¹H NMR spectroscopy. On the basis of Wenkert's hypothesis, this reactive secodine intermediate was expected to undergo a formal Diels–Alder reaction via a two-stage intramolecular enamine conjugate addition on the acrylate moiety followed by a transannular Mannich reaction of the iminium species (**Int C**) to form (±)-minovine (**4**) (Scheme 2).^[16] However, during our initial attempts no observable (±)-minovine (**4**) was detected under ambient reaction conditions. We anticipated that the addition of a Lewis acid or hydrogen bond-donor promoter would enhance the electrophilicity of the acrylate moiety to facilitate the nucleophilic addition step (see the Supporting Information for details). Pleasingly, it was observed that the addition of silica gel^[17] facilitated the direct formation of the target alkaloid, (±)-minovine (**4**). Serendipitously, another skeletally distinct alkaloid, (±)-vincaminorine (**1**) was also formed as a single diastereomer in the reaction vessel (**4:1** = 1.7: 1.0, combined yield = 83%). Presumably (±)-vincaminorine (**1**) was formed by a competing Ir-catalyzed reduction of the iminium intermediate (**Int C**) resulting from the initial Michael addition of the enamine to the α,β -unsaturated ester. In 1968, Wigfield and co-workers^[18] postulated a biosynthetic sequence that invoked a common secodine type enamine intermediate as the source of quebrachamine-type and vincadifformine-type alkaloids via independent pathways. To the best of our knowledge, this here is the first evidence demonstrating the feasibility of such a sequence to form divergently these alkaloids from a common enamine intermediate. Furthermore, from a synthetic viewpoint, such an enamine Michael addition/reduction sequence in a single pot is also the first example of its kind. Thus the results of this intriguing one-pot reaction sequence not only support the hypothesis of the secodine intermediate undergoing a formal Diels–Alder cycloaddition reaction pathway to give vincadifformine-type alkaloids but also provide invaluable insights into its stepwise nature and the potential biogenesis of skeletally distinct quebrachamine-type alkaloids. Due to the lack of full characterization data available in the literature, the stereochemical configuration of the (±)-vincaminorine (**1**) was unambiguously determined by single-crystal X-ray diffraction. (±)-Vincaminorine (**1**) was further treated with



6 N HCl (aq) to undergo acid hydrolysis/ decarboxylation to furnish (\pm)-*N*-methylquebrachamine (**2**).

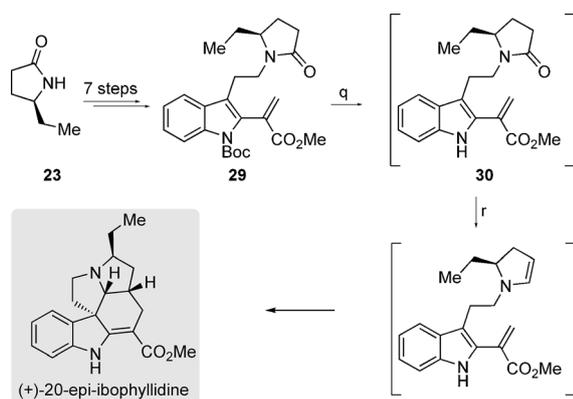
Thereafter, our attention shifted to generating non-methylated aspidosperma-type alkaloids by applying the same synthetic strategy to MOM-protected lactam intermediate **17** (Scheme 3). The synthesis of **17** was straightforward and although the key transformation, the Ir-catalyzed reduction to attain the secodine intermediate, proceeded without incident, it is interesting to note that the Michael addition/iminium reduction product **19** was obtained in larger proportion than the formal Diels–Alder cycloaddition product **20** (**19**:**20** = 3.7:1.0) (Scheme 3). Subsequent treatment of product **19** and **20** with dilute hydrochloric acid generated (\pm)-quebrachamine (**3**) and (\pm)-vincadifformine (**5**) with 71% and 84% yields, respectively.

The changing selectivity between the formal Diels–Alder product and the Michael addition/ reduction product as a result of the nature of substituent on the indolyl nitrogen was interesting and synthetically relevant. The results suggested that decreasing the electron density of the indole moiety reduced the rate of second cyclization relative to reduction by hydride. To probe this further, we proceeded to



examine if the absence of a protecting group (P) on the indolyl nitrogen would also influence the outcome of the reaction.^[19] Consequently, the unprotected precursor **21** was synthesized from **18** by treatment with trifluoroacetic acid. (Scheme 3). As the lactam **21** was relatively unstable towards attempted chromatographic purification, it was then immediately subjected to the Ir-catalyzed reduction conditions. In this case however, the reaction proceeded directly—without the addition of any silica gel mediator—to give exclusively the formal Diels–Alder product, (\pm)-vincadifformine (**5**), with a yield of 44% over 2 steps. Overall, this study demonstrated that manipulation of the intrinsic electron density of the indole moiety through varying the substituent on the indolyl nitrogen atom could influence the selectivity of the reductive cyclization cascade towards either the vincadifformine-type alkaloids or quebrachamine-type alkaloids.

Finally, the versatility of our synthetic strategy was further demonstrated by expanding its scope towards the synthesis of enantiomerically pure monoterpene indole alkaloid, (+)-20-*epi*-ibophyllidine,^[11e,h,k] beginning with the γ -lactam derivative (*S*)-5-ethylpyrrolidin-2-one, **23** (Scheme 4). Thus, **23** was converted into the stable lactam intermediate **29** by similar synthetic steps to those described in Scheme 1 (see the Supporting Information for details). Subsequent *N*-Boc protection of **29** to the precursor **30** followed by the Ir-catalyzed reduction proceeded smoothly without the aid of any silica gel promoter, to generate the formal Diels–Alder product, (+)-20-*epi*-ibophyllidine as a single diastereomer.



Scheme 4. Synthesis of (+)-20-epi-ibophyllidine: q) TFA, Me₂S, CH₂Cl₂, RT, 1 h; r) IrCl(CO)(PPh₃)₂ (1 mol%), TMDS (2 equiv), toluene, RT, 1 h, 40% (over 2 steps).

In conclusion, we have developed an expeditious and divergent reaction sequence to aspidosperma-type alkaloids (±)-vincaminorine, (±)-*N*-methylquebrachamine, (±)-quebrachamine, (±)-minovine and (±)-vincadifformine in excellent diastereoselectivities. Strategically, the route relied on the late-stage generation of reactive enamine functionality from stable indole-linked delta lactams via a highly chemo-selective iridium(I)-catalyzed reduction. This secodine intermediate could subsequently undergo either a formal Diels–Alder cycloaddition or Michael addition/reduction to provide the target products. This study demonstrated that subtle modifications of the indole lactam precursors could control the preference of the secodine intermediate to undergo either of the two reaction pathways. Furthermore, we have demonstrated the versatility of our synthetic approach by applying it to an asymmetric synthesis of iboga-type alkaloid (+)-20-epi-ibophyllidine, starting from γ -lactam, (*S*)-5-ethylpyrrolidin-2-one **23**. Investigations into the development of an enantioselective variant of this iridium(I)-catalyzed reductive cyclization sequence are currently ongoing and will be disclosed in due course.

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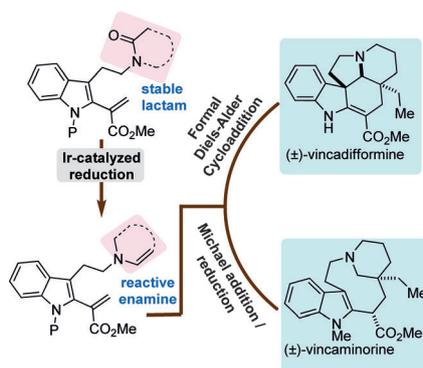


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Expeditious and Divergent Total
Syntheses of Aspidosperma Alkaloids
Exploiting Iridium(I)-Catalyzed
Generation of Reactive Enamine
Intermediates



Which way to go? A novel synthetic strategy for the divergent synthesis of different classes of aspidosperma alkaloids is described. Key step is the highly chemoselective iridium(I)-catalyzed reduction of cyclic lactams to enamine intermediates, followed by either a highly diastereoselective formal Diels–Alder reaction or a competitive Michael addition/reduction (see scheme; two examples shown).