

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

Peng Wen Tan,^[a,b] Jayasree Seayad^{*[b]} and Darren J. Dixon^{*[a]}

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]

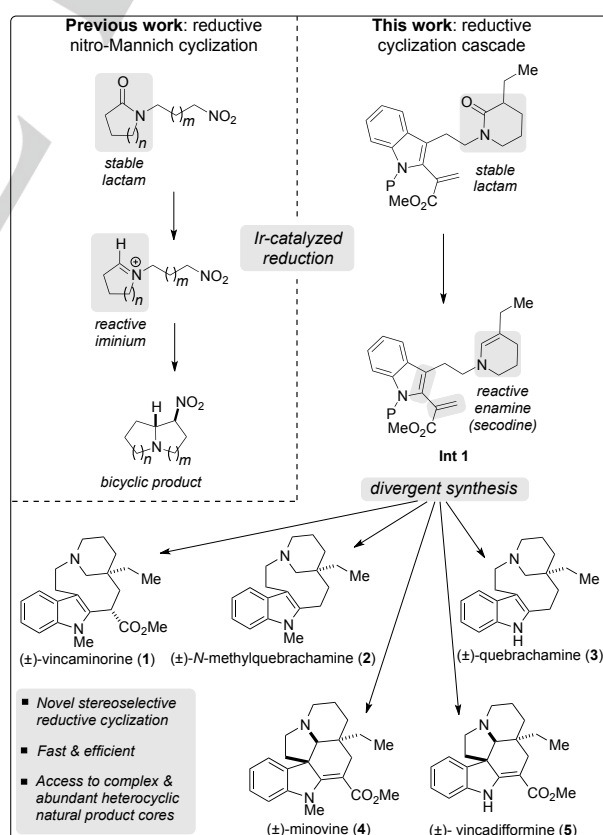


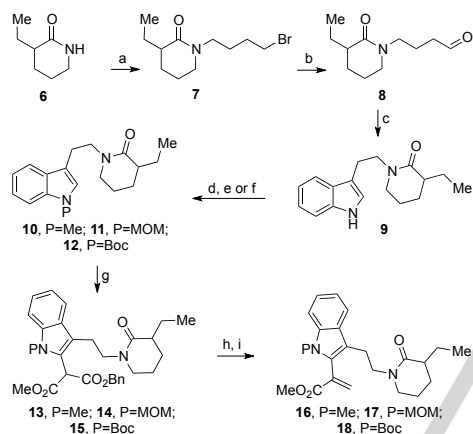
Figure 1. Divergent synthesis of *aspidosperma*-type alkaloids *via* Ir-catalyzed reductive generation of reactive enamine intermediates from lactams

[a] Mr. P. W. Tan and Prof. Dr. D. J. Dixon
Department of Chemistry, Chemistry Research Laboratory,
University of Oxford, 12 Mansfield Road, Oxford, UK
E-mail: darren.dixon@chem.ox.ac.uk

[b] Dr. J. Seayad
Organic Chemistry, Institute of Chemical and Engineering Sciences,
8 Biomedical Grove, Neuros, #07-01, Singapore 138665, Singapore
E-mail: jayasree_seayad@ices.a-star.edu.sg

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.



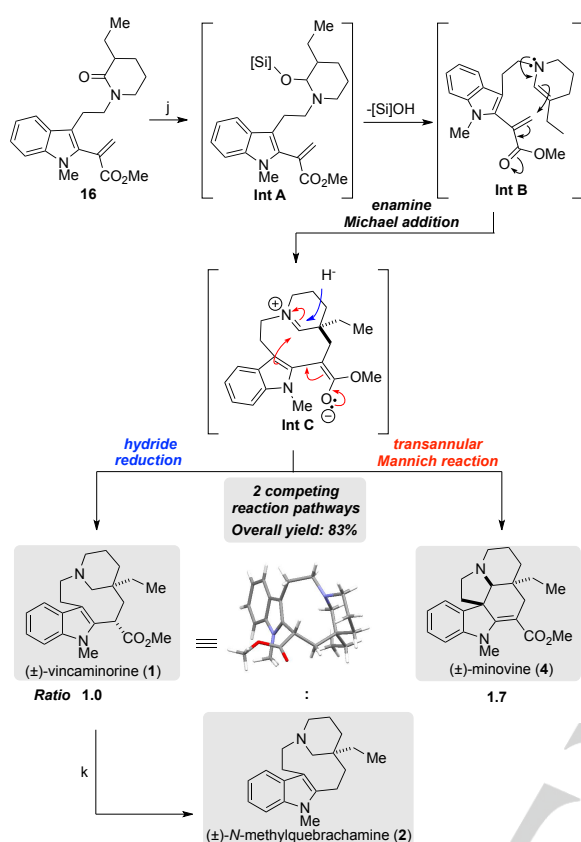
Scheme 1. Synthesis of lactam **16**, **17** & **18**: a) NaH, 1,4-dibromobutane, THF:DMF (5:1), RT, 18 h, 80%; (b) NMO, DMSO, RT, 18 h, 60%; (c) Phenylhydrazine, HCl, 4% H₂SO₄ (aq): DMA (1:1), 110 °C, 2h, 62%; (d) MeI, NaH, THF, RT, 3 h, 95%; (e) MOMCl, NaH, THF:DMF (2:1), 0 °C, 2 h, 89%; (f) Boc₂O, NEt₃, DMAP, CH₂Cl₂, RT, 1.5 h, 95% (g) [Ru(bpy)₃Cl₂], 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).

(\pm)-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 alkylbromide 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 1-benzyl 3-methyl 2-bromomalonate occurred smoothly to obtain **13** in 82% yield.^[14] Finally, debenzoylation of the benzyl ester via Pd-catalyzed hydrogenolysis, followed by decarboxylative Mannich reaction occurred efficiently to give 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. 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 (\pm)-minovine (**4**) (Scheme 2).^[16] However, during our initial attempts no observable (\pm)-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 SI for details). Pleasingly, it was observed that the addition of silica gel^[17] facilitated the direct formation of the target alkaloid, (\pm)-minovine (**4**). Serendipitously, another skeletally distinct alkaloid, (\pm)-vincaminorine (**1**) was also formed as a single diastereomer in the reaction vessel (**4:1** = 1.7: 1.0, combined yield = 83%). Presumably (\pm)-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 (\pm)-vincaminorine (**1**) was unambiguously determined by single crystal X-ray diffraction. (\pm)-vincaminorine (**1**) was further treated with 6*N* HCl (aq) to undergo acid hydrolysis/ decarboxylation to furnish (\pm)-*N*-methylquebrachamine (**2**).

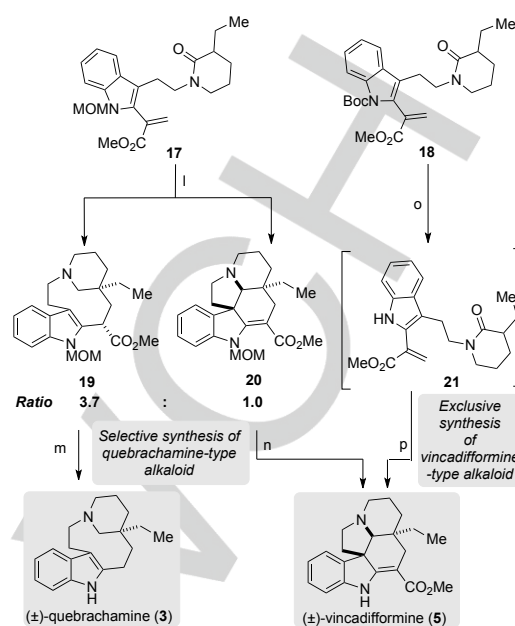
Thereafter, our attention shifted to generating non-methylated *aspidosperma*-type alkaloids by applying the same synthetic strategy to MOM-protected lactam intermediate **17** (Scheme 3). The synthesis of **17** was straightforward and although the key transformation, the Ir-catalyzed reduction of lactam **16** 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



Scheme 2. Divergent synthesis of (±)-vincaminorine (**1**), (±)-minovine (**4**) and (±)-N-methylquebrachamine (**2**): j) $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (1 mol%), TMS (2 eq), toluene, RT, 10 min, subsequent addition of SiO_2 , -78°C to RT, 1 h, (**4**): 52%, (**1**): 31%; k) 6N HCl, 90°C , 2 h, 61%.

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 and subjected to the same Ir-catalyzed reduction conditions (Scheme 3). As the lactam **21** was relatively unstable towards attempted 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, (±)-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.

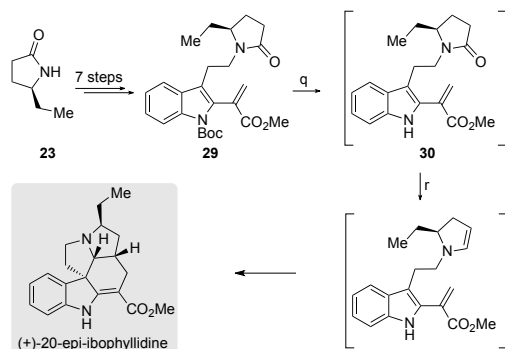


Scheme 3. Divergent synthesis of (±)-quebrachamine (**3**) and (±)-vincadifformine (**5**): l) $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (1 mol%), TMS (2 eq), toluene, RT, 10 min, subsequent addition of SiO_2 , -78°C to 0°C to RT, 2 h, (**20**): 14%, (**19**): 52 %; m) 3N HCl, MeOH, 55°C , 48h, 71%; n) 1N HCl, MeOH, RT, 20 min, 84%; o) TFA, Me_2S , CH_2Cl_2 , RT, 1 h; p) $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (1 mol%), TMS (2 eq), toluene, RT, 1 h, 44% (over 2 steps).

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 SI for details). Subsequent N-Boc deprotection 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.

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 chemoselective 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.



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

Acknowledgements

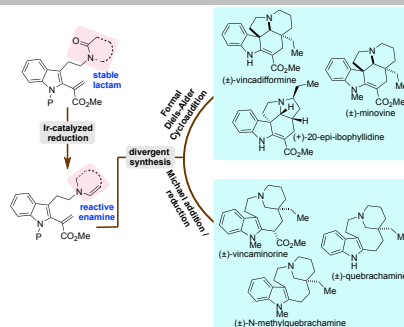
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Keywords: Lactam • enamine • iridium catalyzed reduction • aspidosperma alkaloid • total synthesis

- [1] a) S. E. Malawista, H. Sato, K. G. Bensch, *Science* **1968**, 160, 770; b) R. I. Owellen, C. A. Hartke, R. M. Dickerson, F. O. Haines, *Cancer Res.* **1976**, 36, 1499; c) H. L. Pearce, *In The Alkaloids* (Eds.: A. Brossi, M. Suffness), Academic: San Diego, **1990**, 37, 145; d) B. Gigant, C. G. Wang, R. B. G. Ravelli, F. Roussi, M. O. Steinmetz, P. A. Curmi, A. Sobel, M. Knossow, *Nature* **2005**, 435, 519; e) F. Gueritte, J. Fahy, *The vinca Alkaloids, Anticancer agents from natural products* (Eds.: D. J. C. Newman, G. M. Kingston), Taylor & Francis group, New York, **2005**.
- [2] Selected examples: a) J. P. Kutney, U. Bunzlirepp, K. K. Chan, J. P. D. Souza, Y. Fujise, T. Honda, J. Katsube, F. K. Klein, A. Leutwiler, S. Morehead, M. Rohr, B. R. Worth, *J. Am. Chem. Soc.* **1978**, 100, 4220; b) S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2001**, 124, 2137; c) S. A. Kozmin, T. Iwama, Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, 124, 4628; d) H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi, D. L. Boger, *J. Am. Chem. Soc.* **2006**, 128, 10596; e) I. Coldham, A. J. M. Burrell, L. E. White, H. Adams, N. Oram, *Angew. Chem. Int. Ed.* **2007**, 46, 6159; *Angew. Chem.* **2007**, 119, 6271; f) E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, 131, 943; g) F. De Simone, J. Gertsch, J. Waser, *Angew. Chem. Int. Ed.* **2010**, 49, 5767; *Angew. Chem.* **2010**, 122, 5903; h) D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, 132, 3685; i) L. McMurray, E. M. Beck, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2012**, 51, 9288; *Angew. Chem.* **2012**, 124, 9422; j) R. Frei, D. Staedler, A. Raja, R. Franke, F. Sasse, S. Gerber-Lemaire, J. Waser, *Angew. Chem. Int. Ed.* **2013**, 52, 13373; *Angew. Chem.* **2013**, 125, 13615; k) R. Yang, F. G. Qiu, *Angew. Chem. Int. Ed.* **2013**, 52, 6015; *Angew. Chem.* **2013**, 125, 6131; l) X.-L. Shen, R.-R. Zhao, M.-J. Mo, F.-Z. Peng, H.-B. Zhang, Z.-H. Shao, *J. Org. Chem.* **2014**, 79, 2473.
- [3] O. Wagnieres, Z. Xu, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2014**, 136, 15102.
- [4] H. Mizoguchi, H. Oikawa, H. Oguri, *Nat. Chem.* **2014**, 6, 57.
- [5] M. Mewald, J. W. Medley, M. Movassaghi, *Angew. Chem. Int. Ed.* **2014**, 53, 11634; *Angew. Chem.* **2014**, 126, 5903.
- [6] S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. Macmillan, *Nature*, **2011**, 475, 183.
- [7] A. W. Gregory, A. Chambers, A. Hawkins, P. Jakubec, D. J. Dixon, *Chem. Eur. J.* **2015**, 21, 111.
- [8] Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto, H. Nagashima, *Chem. Commun.* **2009**, 1574.
- [9] Selected reviews: a) M. E. Kuehne, *Synthesis* **1970**, 10, 510; b) P. W. Hickmott, *Tetrahedron* **1982**, 38, 1975; c) A. G. Cook, *Enamines: Synthesis, Structure, and Reactions*, 2nd Ed, Marcel Dekker: New York, **1988**.
- [10] a) E. Wenkert, *J. Am. Chem. Soc.*, **1962**, 84, 98; b) A. A. Qureshi, A. I. Scott, *Chem. Commun. (London)*, **1968**, 947; c) A. I. Scott, *Bioorg. Chem.*, **1974**, 3, 398.
- [11] a) F. E. Ziegler, E. B. Spitzner, *J. Am. Chem. Soc.* **1973**, 95, 7146; b) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, C. L. Kirkemo, *J. Org. Chem.* **1979**, 44, 1063; c) M. E. Kuehne, D. M. Roland, R. Hafter, *J. Org. Chem.* **1978**, 43, 3705; d) M. E. Kuehne, J. A. Huebner, T. H. Matsko, *J. Org. Chem.* **1979**, 44, 2477; e) M. E. Kuehne, J. C. Bohnert, *J. Org. Chem.* **1981**, 46, 3443; f) M. E. Kuehne, F. J. Okuniewicz, C. L. Kirkemo, J. C. Bohnert, *J. Org. Chem.* **1982**, 47, 1335; g) M. E. Kuehne, D. E. Podhorez, *J. Org. Chem.* **1985**, 50, 924; h) M.-C. Barsi, B. C. Das, J.-L. Fourrey and R. Sundaramoorthi, *J. Chem. Soc., Chem. Commun.*, **1985**, 88; i) G. Kalaus, M. Kiss, M. Kajtar-Peredy, J. Brlick, L. Szabo, C. Szantay, *Heterocycles* **1985**, 23, 2783; j) J. P. Brennan, J. E. Saxton, *Tetrahedron* **1986**, 42, 6719; (k) S. Jegham, J.-L. Fourrey, B. C. Das, *Tetrahedron Lett.*, **1989**, 30, 1959; l) S. Kobayashi, G. Peng, T. Fukuyama, *Tet. Lett.* **1999**, 40, 1519; m) S. Kobayashi, T. Ueda, T. Fukuyama, *Synlett* **2000**, 883; n) S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, 124, 2137; o) Y. Han-ya, H. Tokuyama, T. Fukuyama, *Angew. Chem. Int. Ed.* **2011**, 50, 4884; *Angew. Chem.* **2011**, 123, 4986.
- [12] a) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, W. M. Weaver, *J. Am. Chem. Soc.* **1957**, 79, 6562; b) N. Kornblum, W. J. Jones, G. J. Anderson, *J. Am. Chem. Soc.* **1959**, 81, 4113; c) P. Dave, H.-S. Byun, R. Engel, *Syn. Commun.* **1986**, 16, 1343.
- [13] Selected examples on the application of Fischer indole synthesis in total synthesis: a) J. Bonjoch, J. Catena, N. Valls, *J. Org. Chem.* **1996**, 61, 7106; b) R. Iyengar, K. Schildknegt, J. Aube, *Org. Lett.* **2000**, 2, 1625; c) C. W. Roberson, K. A. Woerpel, *J. Am. Chem. Soc.* **2002**, 124, 11342; d) T. Gan, R. Liu, P. Yu, S. Zhao, J. M. Cook, *J. Org. Chem.* **1997**, 62, 9298.
- [14] L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2010**, 12, 3104.
- [15] R. Kuwano, M. Takahashi, Y. Ito, *Tetrahedron Lett.* **1998**, 39, 1017.
- [16] Concerted Diels-Alder reaction pathway cannot be ruled at this stage of investigation.
- [17] Selected examples on silica gel promoted reactions: a) Q. Ding, B. Cao, Z. Zong, Y. Peng, *J. Comb. Chem.* **2010**, 12, 370; b) C.-Y. Ho, S. Roy, Y.-M. Chen, K. Chen, *J. Chin. Chem. Soc.* **2012**, 59, 940; c) Y. Zhou, C.-X. Zhuo, Q. Gu, S.-L. You, *Adv. Synth. Catal.* **2015**, 357, 912; d) A. Sagar, V. N. Babu, D. S. Sharada, *RSC Adv.* **2015**, 5, 29066; e) Y.-H. Zhang, M.-Y. Wu, W.-C. Huang, *RSC Adv.* **2015**, 5, 105825.
- [18] J. P. Kutney, C. Ehret, V. R. Nelson, D. C. Wigfield, *J. Am. Chem. Soc.* **1968**, 90, 5929.
- [19] The *N*-Boc protected lactam derivative **18** was subjected to the same Ir-catalyzed reduction conditions (See SI for details). In this case only 13% of reductive cyclization product **22** was obtained; the remainder of the mass was largely over-reduced lactam and importantly no formal *Diels-Alder* product was observed.

COMMUNICATION

A novel synthetic strategy for the divergent synthesis of different classes of Aspidosperma alkaloids featuring as the key step 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, is described.



Peng Wen Tan,^[a,b] Jayasree Seayad^{*(b)}
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