Chemical Science

Cite this: DOI: 10.1039/c2sc20468a

www.rsc.org/chemicalscience

EDGE ARTICLE

Enantioselective total synthesis of (+)-ibophyllidine *via* an asymmetric phosphine-catalyzed [3 + 2] annulation†

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Received 18th April 2012, Accepted 19th May 2012
DOI: 10.1039/c2sc20468a

In this study we performed the total synthesis of the terpene indole alkaloid (+)-ibophyllidine through a pathway involving asymmetric phosphine catalysis, with our novel L-4-hydroxyproline-derived chiral phosphine mediating the key [3 + 2] annulation. Hydrogenation of the [3 + 2] adduct allowed the rapid formation of the stereochemically dense pyrrolidine ring of (+)-ibophyllidine in excellent yield with exceptionally high levels of both diastereo- and enantioselectivity. We constructed the remainder of the pentacyclic skeleton through an intramolecular alkylation and an intramolecular aza-Morita–Baylis–Hillman reaction.

Introduction

The ibophyllidines comprise a small family of terpene indole alkaloids sharing a fused pentacyclic framework, but varying in the substitution and stereochemistry at C20 (ibophyllidine numbering; Fig. 1). Derived biosynthetically from tryptamine and the iridoid terpene secologanin, the ibophyllidines share the A, B, C, and E rings that are conserved among skeletally similar aspidospermine and pseudoaspidospermidine alkaloids of the same origin (**2**, Fig. 1).[1] Although high levels of variation exist with respect to the D rings of these alkaloids, a unique variation found distinctly amid the ibophyllidines is the presence of a five-membered pyrrolidine ring in place of the more common six-membered piperidine. This characteristic architectural difference presumably arises as a result of biogenetic excision of a single carbon atom from the pandoline alkaloids through an oxidative cleavage process.[2] As a result, the five-membered D ring of the ibophyllidines represents an uncommon synthetic challenge among aspidospermine and pseudoaspidospermidine natural products. Arguably, the most demanding of this family, from a synthetic standpoint, is ibophyllidine. Originally isolated in 1976 from the plants *Tabernanthe iboga* and *T. subsessilis*, this alkaloid contains an all-*syn*-pyrrolidine nucleus that places the C20 ethyl group on the highly congested concave face of the cupped structure.[3] Despite the presence of this unique carbon skeleton, the ibophyllidines have received considerably less attention than their higher-carbon homologues.

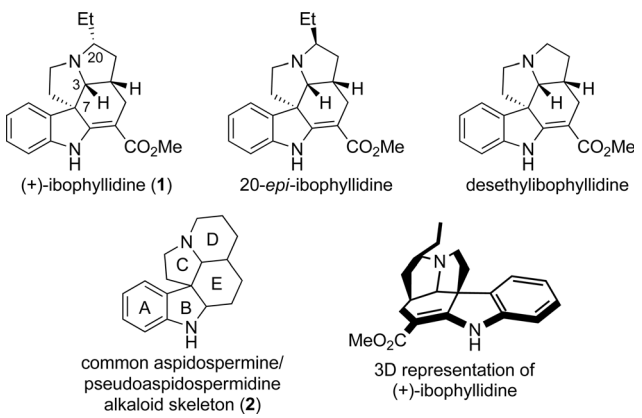

Fig. 1 Representative ibophyllidines and the aspidospermine/pseudoaspidospermidine alkaloid skeleton.

Of the existing strategies for constructing the ibophyllidine skeleton, perhaps the most elegant is the use of a biomimetically inspired Diels–Alder reaction of an *in situ*-generated secodine-analogue (**3**, Scheme 1). First implemented by Kuehne and Bohnert, and later by Das *et al.*, the key cyclization in this concise route exhibited high levels of stereospecificity with regard to the C20 ethyl group. Cyclization was found, however, to occur *via* the diene approaching opposite the C20 ethyl substituent, generating 20-*epi*-ibophyllidine (**4**) exclusively.[4,5] In an alternative strategy, the Bonjoch group attempted a key Fischer indolization on a bicyclic ketone bearing all of the D ring stereochemistry (**5** → **6** + **6′**), but obtained poor selectivity (ratio of **6** : **6′** = 1 : 4.5).[6] In fact, the four reported total syntheses of ibophyllidine have all been accomplished utilizing a singular tactical blueprint based on a variation of Kuehne and Bohnert's original Diels–Alder strategy. The key cyclizations in these routes led to A-B-C-E tetracycles (**7a–d** → **8a–d**), as opposed to the 20-*epi*-ibophyllidine (**4**) skeleton. This strategy allows late-stage closure of the D ring through condensation between the C

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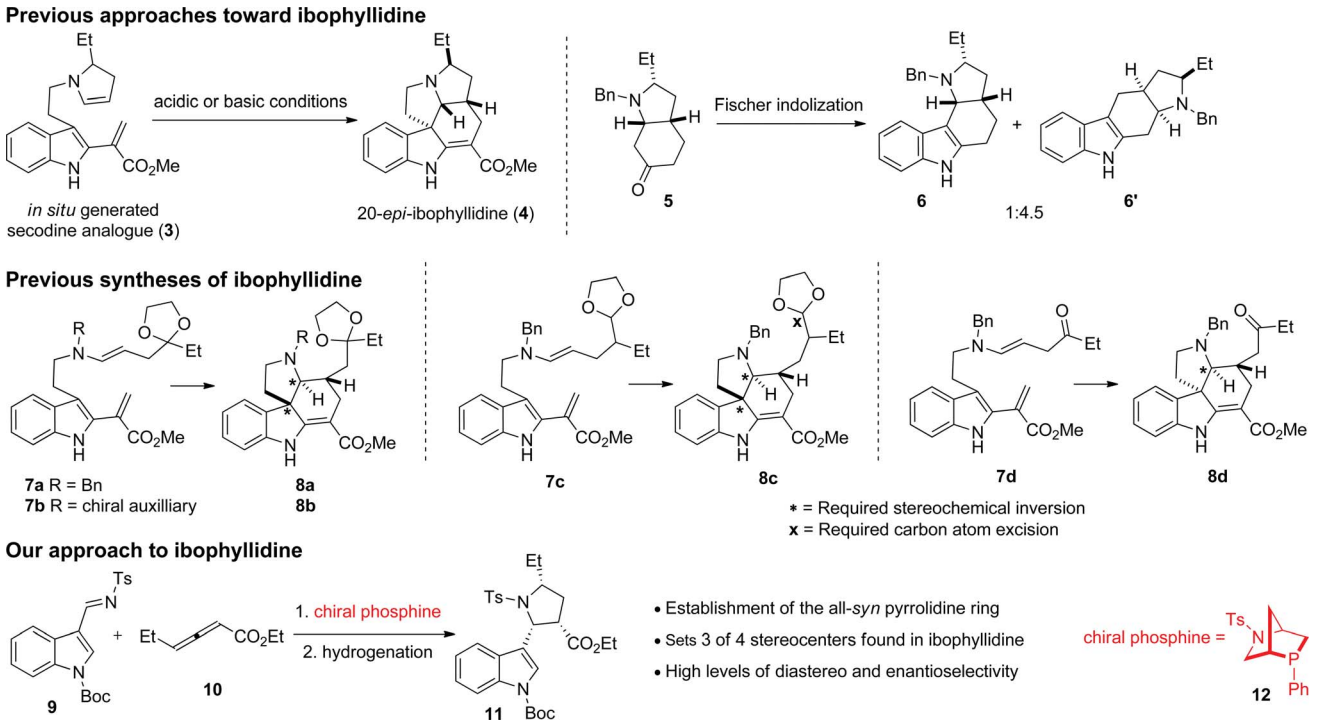
† Electronic supplementary information (ESI) available: Experimental details and spectral data of new compounds. See DOI: 10.1039/c2sc20468a



Scheme 1 Summary of strategies that have been used to synthesize ibophyllidine and our unique approach.

ring's secondary amino group and a pendant ketone unit, followed by setting of the troublesome C20 stereocenter through hydrogenation of the resultant imine/enamine. To date, this strategy remains the only successful one for the synthesis of ibophyllidine, with tactical variances occurring only with respect to the exact structure of the acyclic secodine analogue and the method of its formation. Each of these cases, however, required stereochemical inversion at one or more of the stereocenters at the C/E ring juncture. First disclosed by Kuehne and Bohnert, this approach generated the desired A-B-C-E ring system, but required full epimerization at C3 and C7 in order to access ibophyllidine (**7a** → **8a**; Scheme 1).[4] In a similar approach developed during a study aimed at advancing a common intermediate to a number of related aspidosperma alkaloids, the synthesis still required epimerization of the C3 and C7 centers and, in this case, also necessitated excision of the additional carbon atom that was positioned to allow access to other targets (**7c** → **8c**).[7] In 2007, Kalaus *et al.* reported a similar tactic nearly paralleling Kuehne and Bohnert's studies that necessitated inversion of stereochemistry at C3 after formation of the C and E rings (**7d** → **8d**).[8] Although the required stereochemical inversions were implemented efficiently in each of these cases, they exemplify the inherent challenges in controlling the relative stereochemistry around the pyrrolidine ring of ibophyllidine.[9]

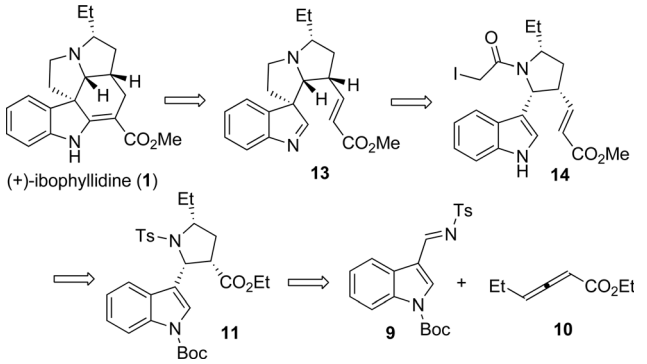
Kuehne and Bohnert's original synthesis was later modified to prepare optically active (+)-ibophyllidine, with the absolute configuration controlled using a bulky ferrocenyl chiral auxiliary (**7b** → **8b**). The key annulation resulted in a modest 5 : 1 dr with respect to the auxiliary; to date, this synthesis has been the only one reported for non-racemic ibophyllidine.[10]

Although a number of other methods exist for building the ibophyllidine skeleton, they have typically been employed only in the synthesis of desethylibophyllidine and they do not address the difficulties associated with the introduction of the additional C20 stereocenter.[11] Therefore, synthesis of the ibophyllidine alkaloids, in particular ibophyllidine, with selective introduction of the stereochemistry about the D ring as well as control over the absolute configuration, remains a considerable challenge.

Results and discussion

As part of a research program dedicated to investigating the reactivity of electron-deficient π systems under the influence of nucleophilic phosphine catalysts,[12] we have developed a powerful method for the *syn*-selective formation of 1,2,3,5-tetrasubstituted pyrroline rings.[13] Recently, we have employed this approach with our novel *trans*-L-4-hydroxyproline-derived chiral phosphine **12** to obtain products with high yields and ee's.[14,15] We suspected that this method could be implemented to set the relative stereochemistry between the indole nucleus and the daunting C20 ethyl group, while a subsequent diastereoselective hydrogenation would effect formation of the third asymmetric center about the D ring of ibophyllidine (**9** + **10** → **11**; Scheme 1). This unique pathway directly addresses the challenge of D ring stereocontrol and starkly contrasts the existing syntheses by focusing on early stage formation of this ring with an emphasis on high diastereo- and enantioselectivity.

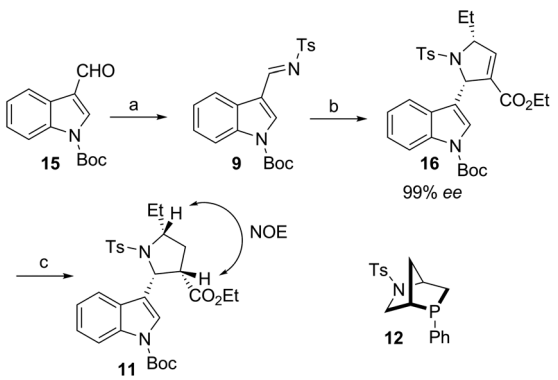
In the retrosynthetic sense, we envisioned (+)-ibophyllidine (**1**) as being derived from the highly functionalized all-*syn*-pyrrolidine **14** by way of intramolecular alkylation at the C3 position of the indole followed by an aza-Morita–Baylis–Hillman reaction onto the newly formed spirocyclic indolenine **13**, to establish the C and E rings, respectively (Scheme 2). The cyclization precursor **14** would be derived from the less-elaborated pyrrolidine **11**. We



Scheme 2 Retrosynthetic analysis of (+)-ibophyllidine based on a phosphine-catalyzed [3 + 2] annulation.

planned for this key intermediate to be readily accessible in two steps from the *N*-tosyl imine **9** and the allenoate **10** by way of an asymmetric [3 + 2] annulation, followed by diastereoselective hydrogenation of the resultant pyrroline double bond.

Our synthetic campaign commenced (Scheme 3) with an exploration of the key [3 + 2] annulation between the known allenoate **10** and the *N*-tosyl imine **9**, prepared in 90% yield by condensation of *p*-toluenesulfonamide with *N*-Boc-indole-3-aldehyde (**15**). Next, we applied our novel P-chiral [2.2.1]bicyclic phosphine **12**, derived from *trans*-L-4-hydroxyproline, to the annulation. The reaction proceeded exceedingly well, forming the desired pyrroline in 99% yield and 99% ee after 1 h at room temperature when employing 30 mol% of the catalyst.[16] Decreasing the catalyst loading to 10 mol% had no effect on enantioselectivity, but the reaction took 4 h to reach completion and provided a slightly decreased yield of 93%. This practical procedure (at 10 mol% catalyst loading) allowed the preparation of the optically pure pyrroline **16** on a multigram scale. As an example of the utility of this reaction, the annulation performed on an approximately 30 g scale proceeded in 94% yield and 97% ee. While efficiently controlling the absolute configuration of the two newly formed stereocenters, it should also be noted that the high diastereoselectivity of this process quickly sets the *syn* relationship between the C20 ethyl group and the indole nucleus—an inherently difficult process in the previous syntheses

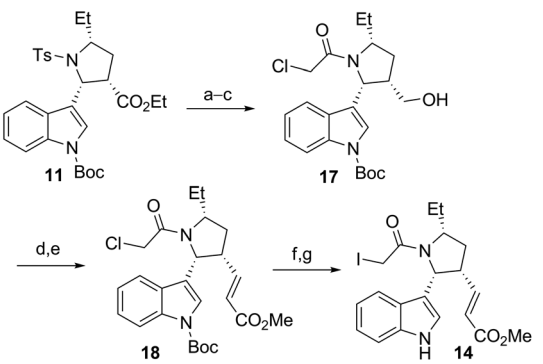


Scheme 3 Synthesis of the key pyrrolidine **11**: (a) *p*-toluenesulfonamide, $TiCl_4$, Et_3N, CH_2Cl_2, 0 °C to rt, 90%; (b) allenoate **10**, 10 mol% chiral phosphine **12**, benzene, 93%, 99% ee; (c) RANEY® Ni, THF, H_2 (200 psi), 80%.

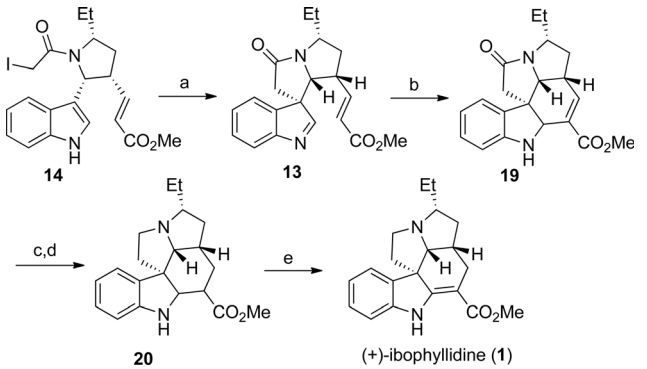
of ibophyllidine. Having developed an efficient route toward multigram quantities of the necessary tricycle **16**, we next investigated the hydrogenation of the pyrroline double bond. After significant experimentation, we found that treating the pyrroline with RANEY® Ni in THF under 200 psi of H_2 yielded the desired all-*syn*-pyrrolidine **11** in 80% isolated yield; we established this relative stereochemistry through observation of an NOE between the protons at the 3 and 5 positions of the pyrrolidine ring.[17]

Having successfully established the congested stereochemical arrangement about the ibophyllidine D ring, we then used conventional functional group transformations to elaborate the key pyrrolidine into the desired cyclization precursor **14** (Scheme 4). We used $LiAlH_4$ to reduce the ester group of compound **11** and then employed Mg powder under sonication for reductive cleavage of the tosyl amide; we treated the resulting crude amino alcohol with chloroacetyl chloride to provide the chloroacetamide **17** in 78% yield over three steps.[18] Sequential Swern oxidation of **17** and Horner–Wadsworth–Emmons olefination proceeded in 98 and 76% yields, respectively, furnishing the α,β-unsaturated ester **18**, the Boc group of which was cleaved in toluene under reflux in the presence of silica gel. The crude material obtained after filtration and removal of the volatiles was re-dissolved in acetone and reacted under Finkelstein conditions to provide the iodide **14** in 94% over two steps.

With access to the cyclization precursor **14**, we explored the transformations necessary to form the C and E rings (Scheme 5). The use of reactive haloamides to form the C ring of aspidosperma and related alkaloids, by way of an intramolecular alkylation, is well established, having been first demonstrated by Heathcock and Toczko in the synthesis of (±)-aspidospermidine.[19,20] Accordingly, we found that activation of the iodide with silver trifluoromethanesulfonate, along with added base, facilitated the desired spirocyclization, delivering the spirocyclic indolenine **13**. For formation of the E ring, we drew inspiration from Andrade's recent exploits regarding a similar intramolecular aza-Morita–Baylis–Hillman reaction.[20,21] We were delighted to discover that addition of the highly nucleophilic and sterically undemanding trimethylphosphine to a solution of the



Scheme 4 Elaboration of the pyrrolidine **11** to the cyclization precursor **14**: (a) $LiAlH_4$, THF, 0 °C to rt; (b) Mg powder, THF–MeOH (9 : 1), sonication; (c) chloroacetyl chloride, THF, Et_3N, 0 °C, 78% (three steps); (d) oxalyl chloride, DMSO, −78 °C, then Et_3N, 98%; (e) methyl diethylphosphonoacetate, NaHMDS, THF, −78 °C, 76%; (f) SiO_2, toluene, reflux; (g) NaI, acetone, reflux, 94% (2 steps).



Scheme 5 Completing the synthesis of (+)-ibophyllidine: (a) AgOTf, Et_3N, toluene, 0 °C to rt; (b) Me_3P, benzene–MeOH (14 : 1), 80% (two steps); (c) Lawesson's reagent, benzene, reflux; (d) RANEY® Ni, THF, H_2 (200 psi), 90% (two steps); (e) Dess–Martin periodinane, CH_2Cl_2, 51%.

indolenine **13** in benzene, with methanol as an additive, promoted the desired intramolecular aza-Morita–Baylis–Hillman reaction, yielding the desired pentacycle **19** in 80% yield over two steps.[22,23]

With the pentacyclic framework in place, all that remained was reduction of the lactam and migration of the double bond into conjugation with the indoline nitrogen atom. Although we failed in our cursory attempts to isomerize the olefinic bond of **19** to form the desired vinylogous urethane, we found that thioamide formation with Lawesson's reagent, followed by reductive desulfurization with RANEY® nickel to deoxygenate the amide, concomitantly reduced the double bond, leading to dihydroibophyllidine (**20**) as a single diastereoisomer.[24,25] We suspected that oxidation of the indoline unit of **20** to the corresponding indolenine would result in facile tautomerization to (+)-ibophyllidine. To this end, we investigated a number of oxidants [DDQ,[26] Pd/C,[27] $(PhSeO)_2$,[28] *tert*-butyl hypochlorite,[29] MnO_2,[30] *N*-*tert*-butylbenzenesulfinimidoyl chloride,[31] IBX,[32] PhIO[33]], but none resulted in any detectable (+)-ibophyllidine. Oxidation under Swern conditions provided some of the target structure, but it was isolated in low yield as the minor component of an inseparable mixture with an unidentified side product.[34] Much to our surprise, treating compound **20** with the Dess–Martin periodinane led to formation of (+)-ibophyllidine in 51% yield,[35] with spectroscopic data consistent with those reported in the literature.[3,8,10]

Conclusions

We have completed the first enantioselective total synthesis of (+)-ibophyllidine in 15 steps and 13% overall yield from *N*-Boc-indole-3-aldehyde. The key transformation is our recently developed asymmetric [3 + 2] annulation, here performed between 4-ethyl-2,3-butadienoate and the *N*-tosyl-aldimine derived from *N*-Boc-indole-3-aldehyde. Diastereoselective hydrogenation of the [3 + 2] adduct provided rapid access to the synthetically challenging all-*syn*-pyrrolidine ring of ibophyllidine, with exceptional levels of stereochemical control. Our strategy not only circumvents some of the difficulties typically associated with constructing the stereochemistry around the D ring of (+)-ibophyllidine but also resulted in the first total synthesis of (+)-ibophyllidine utilizing asymmetric catalysis. This approach is also the first non-formal total synthesis of a complex natural product to employ phosphine-catalyzed [3 + 2] annulation between activated imines and electron-deficient allenes.

Acknowledgements

This study was supported by the NIH (O.K.: R01GM071779 and P41GM081282), the NSF (equipment grant CHE-1048804), and the National Center for Research Sources (S10RR025631).

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14 Full disclosure of the chiral phosphine **12**, including its preparation and the substrate scope of [3 + 2] annulations between *N*-sulfonyl

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17 See the ESI† for a discussion of the hydrogenation, including the various conditions employed and the optimization of the reaction using RANEY® Ni.
18 During various trials, we observed the formation of some of the bis-acylation product derived from N- and O-acylation. In these instances, the O-acetyl group could be selectively cleaved in quantitative yield through treatment with a methanolic suspension of K_2CO_3 (see ESI† for details).
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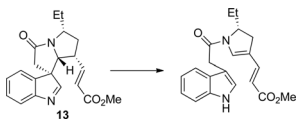
21 Treatment of the spirocyclic indolenine **13** under Andrade's conditions (DBU, toluene) resultedin clean conversion to a C ring fragmentation product, with no observed formation of the pentacycle **19**. We suspect that the added steric bulk adjacent to the enoate double bond prohibited addition of DBU in favor of deprotonation at the C3 position of the pyrrolidine ring, followed by C ring fragmentation and restoration of the aromatic indole nucleus (see ESI† for details). Although we also screened other amines known to catalyze Morita–Baylis–Hillman reactions, none led to the desired pentacycle, with fragmentation being the dominant pathway in each case.



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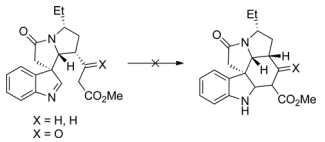

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