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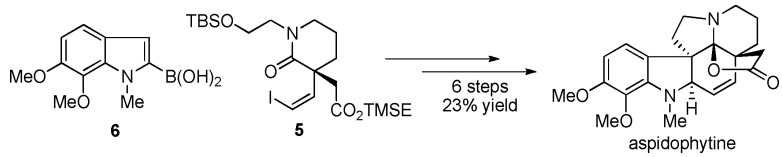

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A Concise Asymmetric Total Synthesis of Aspidophytine

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The structure of the dimeric indole alkaloid haplophytine (**1**, Figure 1) was first disclosed in 1973 by the groups of Cava and Yates,[1] having been isolated from the dried leaves of *Haplophyton cimicidum* over 20 years previously.[2] Acid-mediated degradation of haplophytine led to the isolation of its right-hand constituent, aspidophytine (**2**), an aspidospermine-type alkaloid distinguished by a *C*,*D*-ring-fused lactone.[3] Owing both to its appealing structure and importance as a probable biosynthetic (and thus potential synthetic) precursor to haplophytine, a number of total syntheses of aspidophytine have been reported,[4] beginning with Corey's memorable conquest in 1999.[4a] As part of ongoing studies in our laboratory toward a total synthesis of haplophytine, for which we have recently reported the construction of a left-hand domain fragment,[5] we now wish to disclose a concise stereocontrolled approach to the accompanying aspidophytine domain.

Our approach is outlined retrosynthetically in Scheme 1. We envisaged that the congested aspidophytine skeleton could arise through sequential annulation of the *D*-ring to a suitably substituted indole, exploiting varying modes of reactivity. Thus, oxidative lactonization[4a] (**3**,a, Scheme 1) would be carried out at a late stage, subsequent to closure of the *E*-ring through a 5-*exo*-trig radical process (**3**,b, Scheme 1), designed to exploit the *C*-ring olefin and indoline nitrogen as an effective radical trap.[6] Formation of the *C*-ring itself would exploit the nucleophilicity of the electron-rich indole through a reductive Vilsmeier−Haack-type process (**4**,c, Scheme 1),[7] while the final bond adjoining the key building blocks **5** and **6** was to be forged by Suzuki coupling (**4**,d, Scheme 1).[8] Notably, substrate-based stereocontrol would be relied upon throughout, templated for by the chiral vinyl iodide **5**.

A straightforward chiral auxiliary approach was developed for the preparation of **5**, which commenced with *N*-alkylation of *δ*-valerolactam (**7**) with iodide **8**[9] (Scheme 2). Acylation with the methyl-(*R*)-lactate derivative **9**[10] then afforded the chiral *β*-ketoamide **10** in high yield (89%). Installation of the crucial quaternary stereocenter was then effected by alkylation of **10** with bromide **11**, which furnished a 4:1 mixture of adducts, from which the desired product **12** could be isolated in good yield (66%) after chromatographic purification. The stereochemical outcome of this reaction was confirmed by X-ray crystallographic analysis of the lactone derivative **13** (see ORTEP drawing, Figure 2)[11] and is in accord with that observed for the aldol reactions of related lactate-derived ketones.[12] Following hydrogenolysis of the benzyl ether,[13] the lactate auxiliary could be efficiently cleaved through a reduction/oxidative glycol cleavage process to deliver aldehyde **14** (65%, two steps). Finally, Stork−Wittig homologation[14] of **14** afforded the targeted vinyl iodide **5** as a single geometric isomer in excellent yield (88%, 23% over six steps from **7**). This short sequence proved most robust and made multigram quantities of this pivotal building block readily accessible.

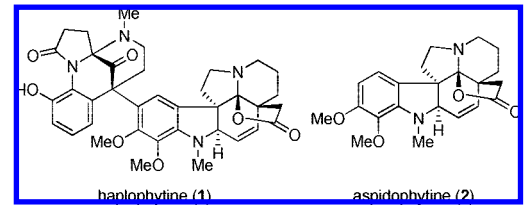
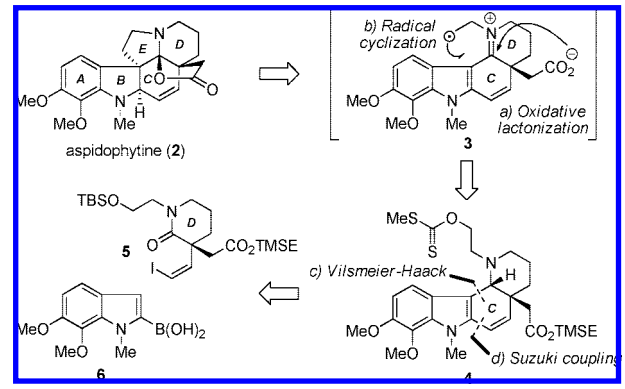
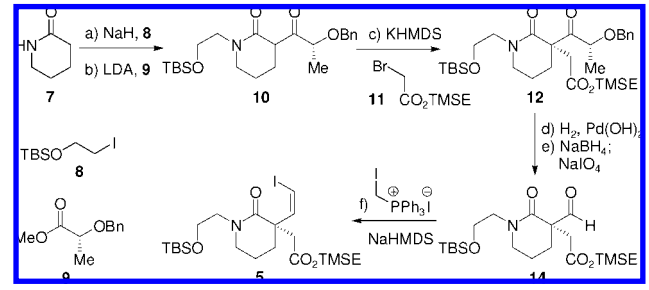


Figure 1. Structures of haplophytine (**1**) and aspidophytine (**2**).

Scheme 1. Retrosynthetic Analysis of Aspidophytine



Scheme 2. Preparation of Vinyl Iodide **5**[a]



[a] Reagents and conditions: (a) NaH, DMF, 25 °C; **8**, 4 h, 68%; (b) LDA, THF; **9**, −78 °C, 2 h, 89%; (c) KHMDS, **11**, DME, −78 → −30 °C, 12 h, 66%; (d) H_2, $Pd(OH)_2$ (cat.), EtOAc, 25 °C, 4 h, 82%; (e) $NaBH_4$, MeOH, 0 °C, 15 min; $NaIO_4$, MeOH/pH 7 buffer (3:1), 25 °C, 2 h, 79%; (f) NaHMDS, $Ph_3PCH_2I_2$, THF, −78 °C, 30 min, 88%.

The coupling partner for vinyl iodide **5**, boronic acid **6**, was itself prepared from the known indole **15**[4a] (69%, Scheme 3). Smooth union of the key fragments **5** and **6** was brought about through Suzuki coupling, which furnished the targeted amide **16** in excellent yield (86%). Treatment of **16** with Tf_2O initiated a rapid 6-*exo*-trig cyclization to generate the *C*-ring and, following rearomatization, the isolable iminium species **17**, which was reduced with $NaBH_4$ to provide the tetracyclic piperidine **18** as essentially a single diastereomer in excellent yield (88%). While exposure of the

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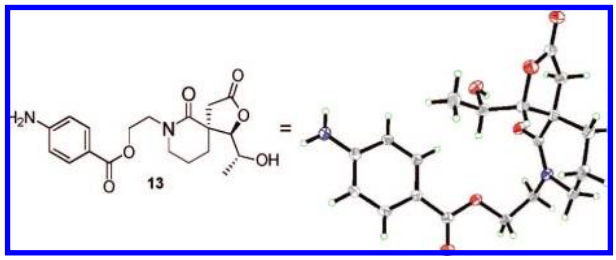
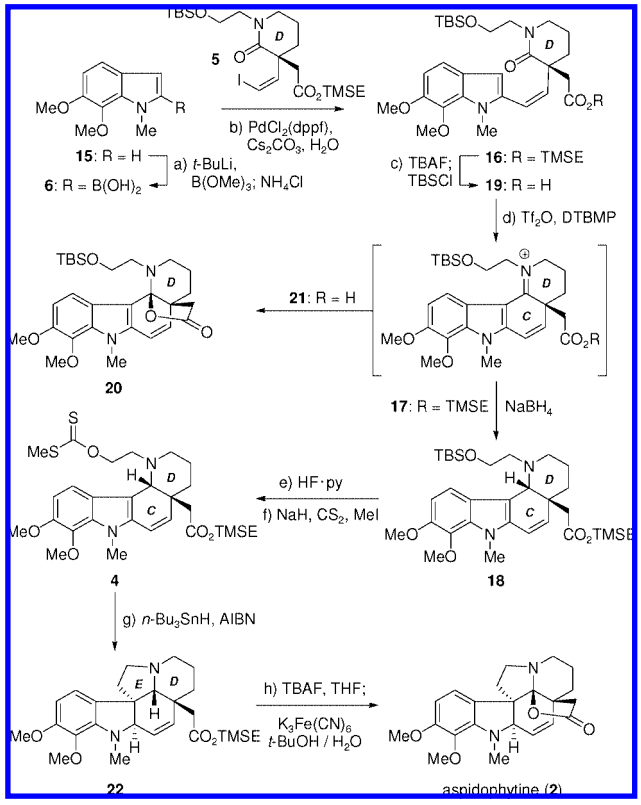


Figure 2. ORTEP view of **13** (Thermal ellipsoids at 30% probability).[11]

Scheme 3. Fragment Coupling and Elaboration to Aspidophytine[a]



[a] Reagents and conditions: (a) *t*-BuLi, THF, 25 °C, 1 h; $B(OMe)_3$, 30 min, 69%; (b) **5**, $PdCl_2(dppf)$, Cs_2CO_3, DMF/H_2O (10:1), 25 °C, 12 h, 86%; (c) TBAF, THF, 25 °C, 2 h; TBSCl, imid, CH_2Cl_2, 25 °C, 1 h; NH_4Cl (59%); (d) Tf_2O, DTBMP, CH_2Cl_2, 25 °C, 30 min; $NaBH_4$, MeOH, 0 °C, 15 min, 88%, >95:5 d.r.; (e) HF·py, THF, 25 °C, 1 h; (f) NaH, CS_2, THF, −78 → 25 °C, 1 h; MeI, 83% (two steps); (g) *n*-Bu_3SnH, AIBN (cat.), PhH, 85 °C, 58%; (h) TBAF, THF, 25 °C, 12 h; $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH/H_2O (1:2), 25 °C, 63%.

corresponding carboxylic acid (**19**) to analogous conditions provided the lactone **20** directly (*via* **21**) through a tandem cyclization process, this compound proved too labile to be advanced to the natural product, presumably due to the interaction of the electron-rich indole with the rather sensitive *N*,*O*-acetal.

Chemoselective desilylation of **18** with HF·py provided the corresponding alcohol, which was converted to the alkyl radical precursor, xanthate **4** (83%, two steps), in readiness for the crucial radical cyclization. In the event, heating a mixture of **4**, *n*-Bu_3SnH (3 equiv.), and a catalytic amount (0.1 equiv.) of AIBN to 85 °C in benzene for 2 h effected smooth *E*-ring closure, providing a 3:1 mixture of pentacyclic, allyl-radical reduction regioisomers,[15] from which the desired product **22** was isolated as a single diastereomer in a respectable 58% yield. With the requisite aspidospermine core now in place, all that remained to complete the total synthesis of aspidophytine was installation of the lactone. Significant improvement to reported yields for this type of transformation[4b] was realized by employing a single-pot TBAF-mediated ester hydrolysis/oxidative lactonization[4a] protocol, which furnished synthetic aspidophytine in good yield (63%). All spectral data for the synthetic material were identical to those published.[4]

In summary, we have accomplished a concise and efficient total synthesis of aspidophytine, proceeding in 5% yield over the longest linear sequence of 12 steps, which compares most favorably with previous syntheses. Notably, the rapid assembly of the pentacyclic aspidospermine framework through sequential annulation of the *D*-ring to the indole nucleus imparts a high degree of convergency to this approach, which should make it particularly amenable to a total synthesis of haplophytine. Further studies toward this end will be reported in due course.

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Supporting Information Available: Experimental procedures, abbreviations, and compound characterization (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) See the Supporting Information for the preparation of **13**. CCDC 697197 contains the supplementary crystallographic data for **13** and is available free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
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