VIP Natural Product Synthesis

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Total Synthesis of (+)-Haplophytine**

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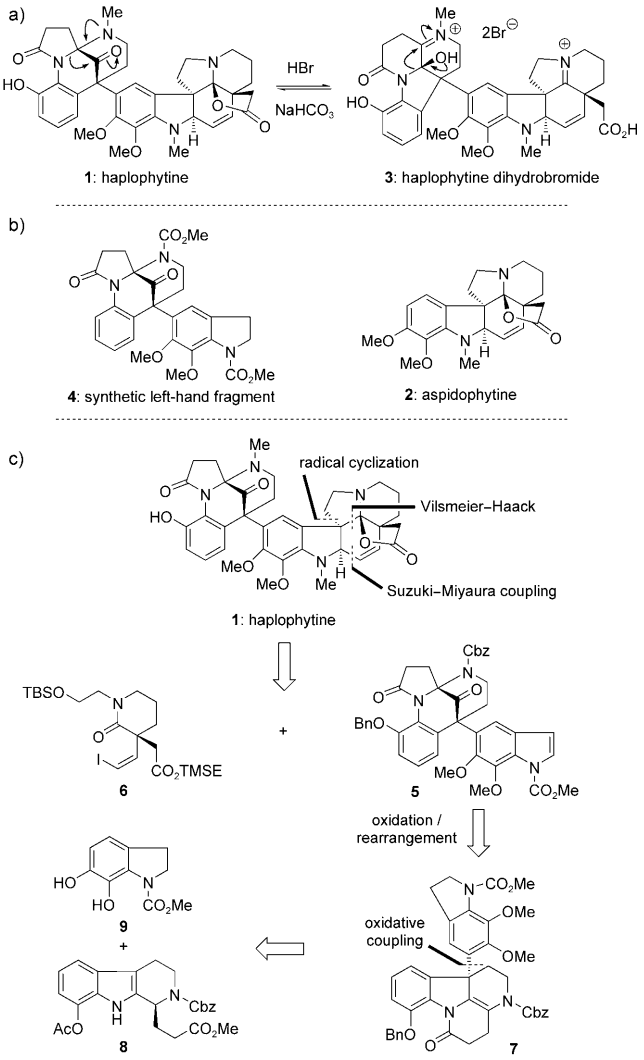
Despite the many impressive accomplishments in the field of total synthesis in recent years,[1] a number of natural products have proven stubbornly resistant to its advances.[2] Among them is haplophytine (**1**, Scheme 1 a), which has only very recently succumbed to synthesis following the elegant work of Fukuyama, Tokuyama and co-workers.[3] Haplophytine was first isolated by Snyder and co-workers in 1952, and identified as the principle bioactive component of the wild flower *Haplophyton cimicidum*,[4] valued for centuries by the Aztecs and subsequent settlers of Central America for its insecticidal properties. A heterodimeric indole alkaloid, haplophytine features a particularly complex polycyclic array of ten rings, six stereocenters (five of which are quaternary) and a highly congested carbon–carbon bond adjoining the two distinct halves of the molecule. The tetracyclic left-hand domain features a unique bridged ketone structure, while the right-hand domain consists of the naturally occurring aspidosperma alkaloid, aspidophytine (**2**, Scheme 1 b).[4,5] A complete appreciation of haplophytine's molecular structure was only reached some 21 years subsequent to its isolation, following extensive chemical degradation, spectroscopic, and X-ray crystallographic studies from the groups of Cava, Yates, and Zacharias,[6] which included identification of the dihydrobromide derivative **3** (Scheme 1 a). As depicted, this compound is formed through a unique acid-mediated skeletal rearrangement of the left-hand domain involving the 1,2-shift of an aminal C–N bond. Under basic conditions, however, this process can be reversed such as to return haplophytine through a complementary semi-pinacol type mechanism. As part of a program directed toward the total synthesis of haplophytine, we have previously demonstrated the suitability of this rearrangement as a means to construct the left-hand domain fragment **4** (Scheme 1 b).[7] A similar approach has been reported independently by Fukuyama and co-workers.[8] Our approach to aspidophytine,[5f] meanwhile, was specifically designed to complement that for **4**, in order to facilitate the total synthesis of haplophytine (**1**). Herein we wish to report the culmination of this work with our own asymmetric total synthesis of this historic synthetic target.



Scheme 1. Structures of haplophytine (**1**, a), haplophytine dihydrobromide (**3**, a), aspidophytine (**2**, b), synthetic left-hand fragment **4** (b) and our retrosynthetic analysis of haplophytine (**1**, c). Ac = acetyl, Bn = benzyl, Cbz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, TMSE = trimethylsilylethyl.

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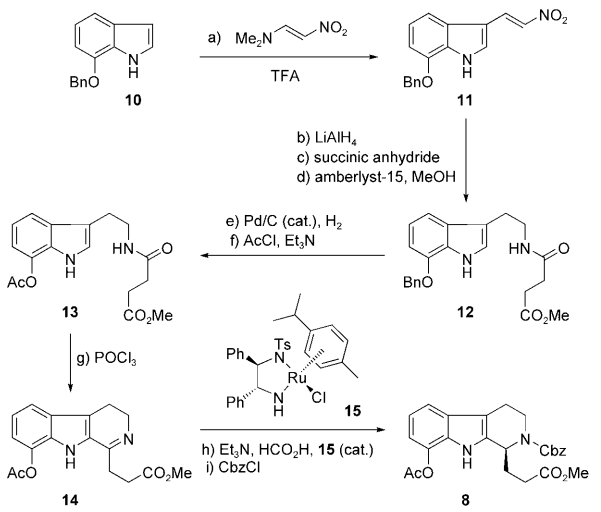
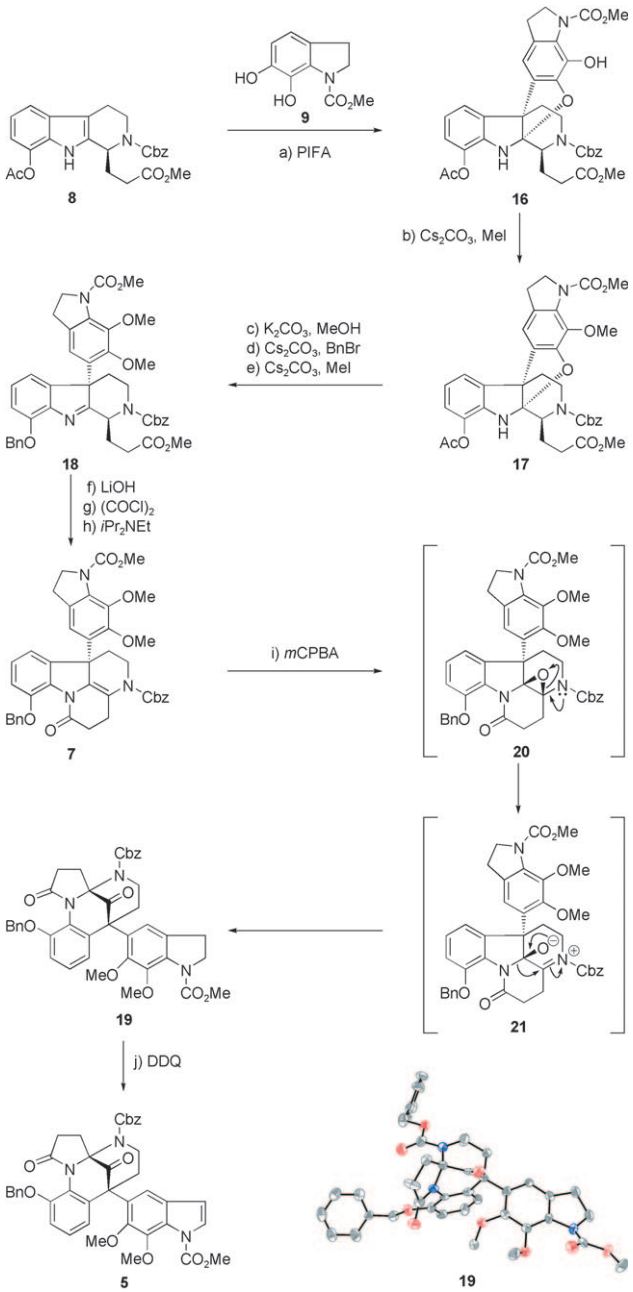
As shown in Scheme 1c, the right-hand aspidophytine domain was retrosynthetically excised to reveal indole **5** and vinyl iodide **6**, which would be annulated[5f] sequentially through Suzuki–Miyaura coupling,[9] a reductive Vilsmeier–Haack reaction,[10] and radical cyclization.[11] The left-hand domain of indole **5** would arise through the oxidative skeletal rearrangement of bis-enamine **7**,[7] which itself would derive from the oxidative coupling of enantiopure tetrahydro-β-carboline **8** and diphenol **9**.[7]

The preparation of **8** commenced with the conversion of commercially available 7-benzyloxyindole (**10**) to nitroalkene **11** (Scheme 2, 50%).[12] Reduction with $LiAlH_4$ to the corresponding tryptamine followed by acylation with succinic anhydride and methylation provided methyl ester **12** (92% over three steps). To facilitate the forthcoming oxidative coupling with diphenol **9**, the benzyl ether of **12** was replaced with an acetate group to provide **13** (see below). Ring closure under modified Bischler–Napieralski conditions ($POCl_3$, DMPU)[13] then afforded the rather labile imine **14**, which was immediately subjected to asymmetric Noyori reduction[14] employing the ruthenium catalyst **15**, and, subsequently, Cbz protection to deliver the targeted fragment **8** in 35% over three steps, and in >95% *ee*.[15]

With tetrahydro-β-carboline **8** secured, its coupling with diphenol **9** and formation of perhaps the singularly most difficult bond bridging the two halves of the target molecule



Scheme 2. Construction of tetrahydro-β-carboline **8**. Reagents and conditions: a) 1-dimethylamino-2-nitroethylene (1.0 equiv), TFA (2.0 equiv), CH_2Cl_2, 23 °C, 0.5 h, 50%; b) $LiAlH_4$ (5.0 equiv), THF, 0 °C→reflux, 3 h; c) succinic anhydride (1.04 equiv), CH_2Cl_2, 23 °C, 2 h; d) amberlyst-15 (20% wt/wt), MeOH, reflux, 4 h, 92% over three steps; e) Pd/C (10% wt/wt, 0.05 equiv), H_2 (1 atm), MeOH/THF (1:1), 23 °C, 8 h; f) AcCl (1.4 equiv), Et_3N (2.0 equiv), THF, −78→23 °C, 2.5 h, 79% over two steps; g) $POCl_3$ (8.0 equiv), DMPU, 23 °C, 2 h; h) **15** (0.03 equiv), HCO_2H/Et_3N (5:2), DMF, 23 °C, 0.5 h; i) CbzCl (2.8 equiv), Et_3N (3.4 equiv), CH_2Cl_2, −78→23 °C, 9 h, 35% over three steps. DMF = *N*,*N*′-dimethylformamide DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, TFA = trifluoroacetic acid, THF = tetrahydrofuran.



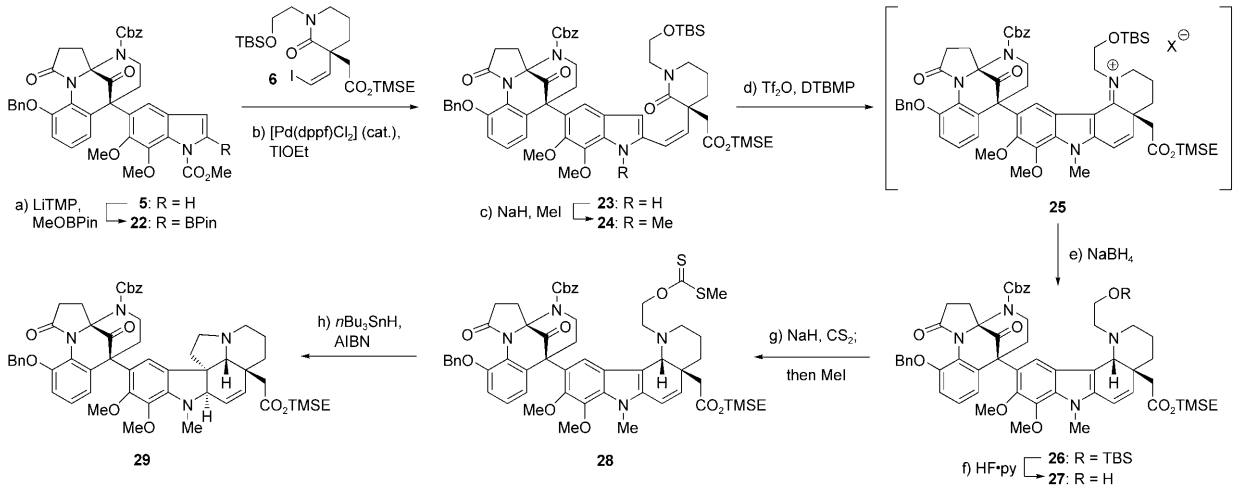
Scheme 3. Construction of indole fragment **5** and ORTEP drawing of compound **19**. Reagents and conditions: a) **8** (2.0 equiv), **9** (1.0 equiv), PIFA (1.1 equiv), MeCN, −30 °C, 36 h, then 23 °C, 1 h, 23% [based on 25% conversion of **8** (the more valuable component), or 11.5% based on **9** (the less valuable component)]; b) Cs_2CO_3 (3.0 equiv), MeI (5.0 equiv), DMF, 23 °C, 2 h, 76%; c) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 20 min; d) Cs_2CO_3 (3.0 equiv), BnBr (1.2 equiv), DMF, 23 °C, 1 h, 70% over two steps; e) Cs_2CO_3 (5.0 equiv), MeI (30 equiv), DMF, 23 °C, 12 h, 65%; f) LiOH (2.0 M aq.)/EtOH (1:1), 23 °C, 20 min; g) $(COCl)_2$ (5.0 equiv), DMF (cat.), PhH, 0 °C, 0.5 h; h) iPr_2NEt (10 equiv), PhH, 0→23 °C, 1 h, 60% over three steps; i) *m*CPBA (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, −5 °C, 12 h, 78%; j) DDQ (5.0 equiv), PhH, 75 °C, 12 h, 63%. PIFA = phenyliodine-bis-trifluoroacetate, PhH = benzene, *m*CPBA = *meta*-chloroperoxybenzoic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

was at hand (Scheme 3). Employing our previously described method,[7] treatment of a mixture of **8** and **9** with PIFA (1.1 equiv) in MeCN at −30 °C for 36 h effected the desired coupling and provided the propellane-like hexacycle **16** in 23 % yield, based on 25 % conversion of **8** [the more valuable component, or 11.5 % based on **9** (the less valuable component)].[16] Whilst the reaction could not be driven to completion, tetrahydro-β-carboline **8** was successively recycled to provide sufficient throughput of material for completion of the synthesis. The excellent diastereoselectivity observed for acetate **8** (d.r. > 20:1) was in stark contrast to that for the corresponding benzyl ether *N*-methyl carboxylate, which proceeded to give only a 5:1 mixture of diastereomers, presumably reflecting a subtle electronic effect (see Supporting Information).

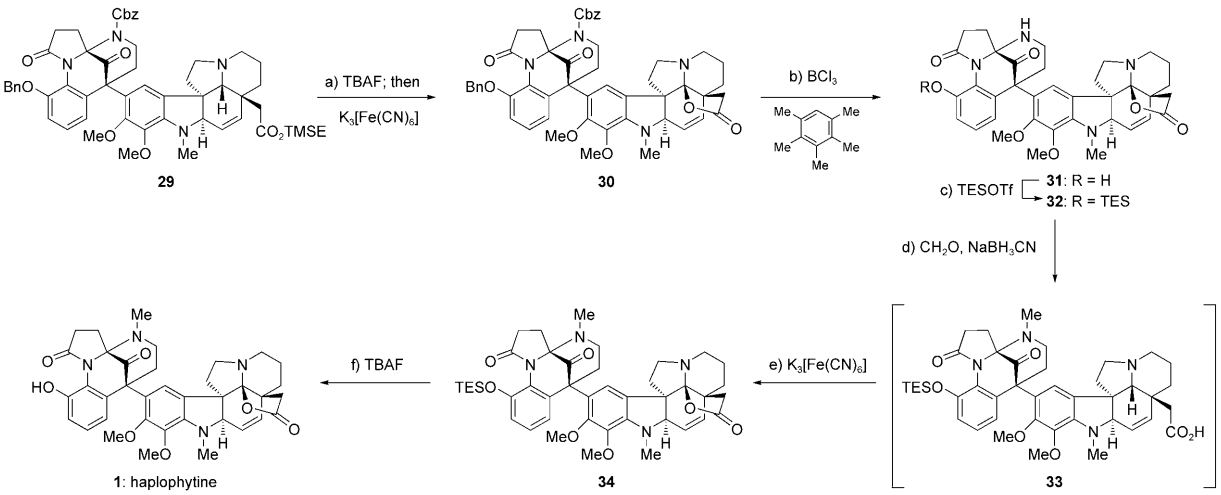
Advancement of **16** to the skeletal rearrangement substrate **7** commenced with selective phenolic methylation to provide **17**, whose acetate group was then methanolyzed and replaced with a benzyl group. Rupture of the superfluous *N*,*O*-acetal and methylation of the ensuing phenol was accomplished through treatment with an excess of Cs_2CO_3 (5.0 equiv) and MeI (30 equiv) in DMF, which afforded imine **18** in 65 % yield over three steps. Finally, ester saponification with LiOH, followed by acid chloride formation [$(COCl)_2$] and treatment with iPr_2NEt, afforded the hexacyclic bisenamine **7** in 60 % overall yield from imine **18**. The bisenamine **7** was now set to undergo oxidation and rearrangement to the appropriate haplophytine framework. Following our previously developed procedure,[7] treatment of **7** with *m*CPBA in CH_2Cl_2 at −5 °C smoothly afforded the rearranged crystalline ketone **19** [m.p. = 182–183 °C (CH_2Cl_2/EtOH); see ORTEP drawing,[17] Scheme 3] in 78 % yield, presumably through intermediates **20** and **21**. The targeted indole **5** was then finally accessed in 63 % yield through oxidation of indoline **19** with DDQ.

With the left-hand substructure of haplophytine secured, coupling of **5** to the aspidophytine domain precursor vinyl iodide **6** by palladium-mediated cross-coupling was now required. Extensive optimization was necessary to identify appropriate means for this coupling, which was complicated by the lability of a range of indole C-2 derivatives (**5**, for example, R = $SnMe_3$/$B(OH)_2$/I, Scheme 4) and accompanying lithiation/reaction of the left-hand domain lactam in their preparation. Ultimately, it was found that lithiation of indole **5** with LiTMP in the presence of B-methoxy-pinacolatoborane in THF at −100 °C for 15 min provided the relatively stable pinacol borane **22** (Scheme 4), which was submitted without purification to Suzuki–Miyaura coupling[9] with vinyl iodide **6**. Accordingly, treatment of **22** with [Pd(dppf)Cl_2], Ph_3As, and TlOEt in anhydrous DMSO effected the desired coupling together with fortuitous cleavage of the methyl carbamate, providing adduct **23** in 67 % yield. In particular, the use of TlOEt in combination with DMSO proved critical to the success of this reaction, enabling the rate of coupling to compete effectively with the otherwise rather facile process of proto-deborylation.

N-Methylation of indole **23** then provided **24**, a compound in line with our previous synthesis of aspidophytine.[5f] Accordingly, treatment of lactam **24** with Tf_2O smoothly provided the iminium salt **25**, which was rapidly reduced with $NaBH_4$ at low temperature (−78 °C, 2 min) in order to circumvent accompanying ketone reduction. This delivered piperidine **26** as essentially a single diastereomer in good yield (76 %). Selective desilylation of **26** (HF·py) followed by conversion of the ensuing primary alcohol (**27**) to xanthate ester **28** (NaH, CS_2 and MeI; 70 % yield over two steps) set the stage for the final carbon–carbon bond formation through radical cyclization. In the event, heating a mixture of xanthate **28** and nBu_3SnH (3.0 equiv) in the presence of AIBN (1.0 equiv) delivered nonacycle **29** as a single diastereoisomer



Scheme 4. Preparation of nonacycle **29**. Reagents and conditions: a) LiTMP (0.67 M in THF, 4.0 equiv), MeOBPin (5.0 equiv), THF, −100 °C, 15 min; b) **6** (1.5 equiv), [Pd(dppf)Cl_2] (0.2 equiv), Ph_3As (0.5 equiv), TlOEt (3.0 equiv), DMSO, 23 °C, 1 h, 67 % over two steps; c) NaH (3.0 equiv), MeI (7.0 equiv), DMF, 23 °C, 0.5 h, 87 %; d) Tf_2O (2.0 equiv), DTBMP (3.0 equiv), CH_2Cl_2, 23 °C, 0.5 h; e) $NaBH_4$ (1.5 equiv), CH_2Cl_2/MeOH (2:1), −78 °C, 2 min, 76 % over two steps; f) HF·py (excess), THF, 23 °C, 0.5 h; g) NaH (3.0 equiv), CS_2 (34 equiv), THF, 0→23 °C, 1 h; then MeI (26 equiv), 23 °C, 1 h, 70 % for the two steps; h) nBu_3SnH (3.0 equiv), AIBN (1.0 equiv), PhH, 85 °C, 2 h, 32 %. AIBN = 2,2′-azobisisobutyronitrile, DMSO = dimethylsulfoxide, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, Pin = 2,3-dimethylbutane-2,3-diolate, py = pyridine, Tf = trifluoromethanesulfonyl, TMP = 2,2,6,6-tetramethylpiperidine.



Scheme 5. Completion of the total synthesis of (+)-haplophytine; a) TBAF (1.0 M in THF, 5.0 equiv), THF, 23 °C, 2 h; then $K_3[Fe(CN)_6]$ (10 equiv), $NaHCO_3$ (20 equiv), *t*BuOH/H_2O (1:2), 0.5 h, 71%; b) BCl_3 (1.0 M in CH_2Cl_2, 10 equiv), pentamethylbenzene (5.0 equiv), CH_2Cl_2, 0 °C, 1 h, 58%; c) TESOTf (5.0 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2, 23 °C, 0.5 h, 68%; d) CH_2O (37% aq., excess), $NaBH_3CN$ (5.0 equiv), AcOH (20 equiv), MeOH, 23 °C, 0.5 h; e) $K_3[Fe(CN)_6]$ (10 equiv), $NaHCO_3$ (20 equiv), THF/*t*BuOH/H_2O (1:1:2), 23 °C, 15 min; f) TBAF (1.0 M in THF, 10 equiv), THF, 23 °C, 0.5 h, 42% over three steps. TBAF = tetra-*n*-butyl ammonium fluoride, TES = triethylsilyl.

in 32% yield. The rather moderate yield for this reaction is thought to relate to increased hindrance to cyclization relative to aspidophytine imposed by the left-hand domain,[5f] implied by the isolation of significant amounts of the deoxygenated, yet uncyclized compound corresponding to **28**.

With the entire carbon skeleton of haplophytine in place, completion of the total synthesis required lactone formation, and deprotection/*N*-methylation of the left-hand nitrogen atom. The flexibility of our end-game was narrowed, however, by an inability to remove the benzyl and Cbz groups without concomitant removal of the TMSE ester. As such, lactone formation was first carried out, through a sequence involving desilylation with TBAF followed by in situ treatment of the resulting carboxylic acid with $K_3[Fe(CN)_6]$, to afford smoothly the desired decacyclic lactone **30** (71% yield, Scheme 5). Removal of the benzyl and Cbz protecting groups was then achieved through treatment with BCl_3 in the presence of pentamethylbenzene,[18] which cleanly provided desmethyl haplophytine **31**. Unfortunately, direct access to haplophytine by *N*-methylation of **31** was hampered by the basicity of the tertiary amine, rapid quaternization of which was encountered with all electrophilic methylation reagents tested.

Following extensive investigation, it was found that selective silylation of the free phenol (**32**) was necessary to enable *N*-methylation under reductive amination conditions. Whilst this also led to reduction of the *N*,*O*-acetal, providing the carboxylic acid **33**, in situ reoxidation with $K_3[Fe(CN)_6]$ returned lactone **34**. Finally, desilylation of **34** with TBAF provided haplophytine (**1**) in 42% overall yield from **32**. All physical properties (^1H and ^{13}C NMR spectra, IR, MS, and $[\alpha]_D$) of synthetic haplophytine (**1**) were in accordance with those obtained from a sample of the natural substance.[19]

In summary, a total synthesis of (+)-haplophytine has been achieved, demonstrating the power of modern synthetic methods for providing solutions to long standing problems in natural product synthesis.

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Keywords: aminal rearrangement · natural products · radical cyclization · Suzuki–Miyaura coupling · total synthesis

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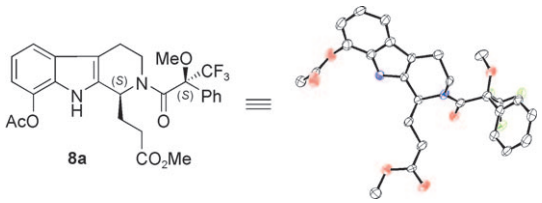
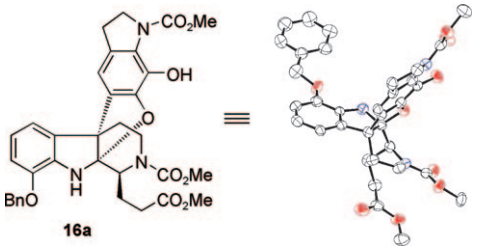
[15] The absolute configuration of **8** was confirmed through the preparation (see the Supporting Information) and X-ray crystallographic analysis of the Mosher amide derivative **8a** (m.p. = 131–132 °C, CH_2Cl_2/hexanes, see ORTEP drawing below). CCDC 706349 contains the supplementary crystallographic data for **8a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[16] The structural identity of **16** was confirmed by its conversion to a compound prepared independently from the related benzyl ether **16a** (m.p. = 144–145 °C, EtOAc/hexanes), the major isomer obtained from an analogous oxidative coupling reaction, which proved sufficiently crystalline for X-ray crystallographic analysis (see ORTEP drawing below). See the supporting information for further details. CCDC 730565 contains the supplementary crystallographic data for **16a**.





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