Natural Products

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Total Syntheses of (+)-Haplophytine**

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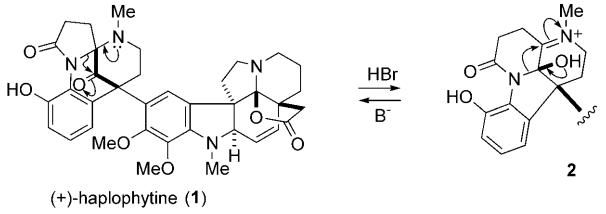
alkaloids · natural products · total synthesis

In memory of Charles Mioskowski

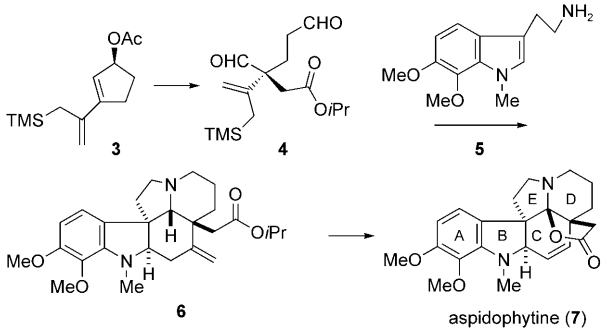
Haplophytine (**1**) is a heterodimeric alkaloid found in the leaves of the Mexican plant *Haplophyton cimicidum*. Haplophytine possesses an intriguing complex skeleton which can be subdivided into two domains: a left-hand domain made of a tetracyclic heterocycle, which includes a bridged ketone, and a right-hand indolic domain known as aspidophitine, which incorporates a fused lactone. The two domains are connected at a quaternary carbon center. Upon exposure to HBr, haplophytine undergoes a unique 1,2-rearrangement leading to the imminium compound **2** (Scheme 1). This process is reversible under mildly basic conditions by a



Scheme 1. Semipinacol rearrangement of haplophytine (**1**).

semipinacol-type rearrangement. Aspidophytine is itself obtained by acidic cleavage of haplophytine and is the assumed biosynthetic precursor of the latter with five total syntheses already reported.[1–5] No synthesis of the left-hand domain of haphophytine is available to date despite numerous attempts,[6] and it is only very recently that Fukuyama, Tokuyama et al. successfully achieved the challenging first total synthesis of haplophytine,[7] followed soon after by the second reported total synthesis by the research group of Nicolaou and Chen.[8]

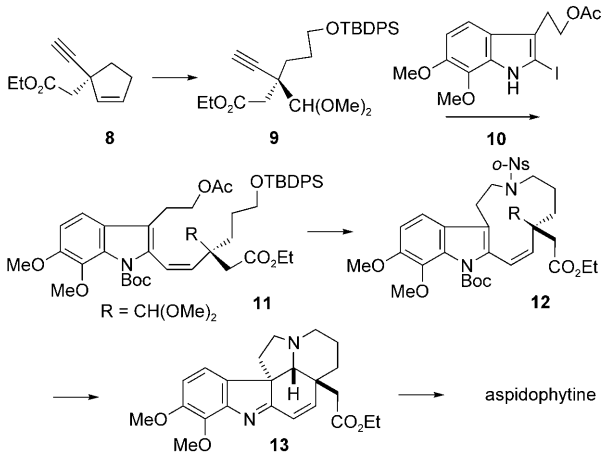
The first total synthesis of aspidophytine (**7**) was completed by the Corey group in 1999;[1] their approach is based on a cascade reaction between tryptamine **5** and chiral dialdehyde **4** (Scheme 2). The enantioselective synthesis of the latter was achieved through an Ireland–Claisen rearrangement of the optically active vinyl acetate **3**, resulting from a Corey–Bakshi–Shibata (CBS) reduction of the corresponding



Scheme 2. Synthetic pathway devised by the Corey group. TMS = trimethylsilyl.

enone. Oxidative cleavage of the intracyclic double bond provided access to dialdehyde **4**. The crucial step of the synthesis was the simultaneous construction of the CDE rings by amination of both aldehydes and cyclization, leading to pentacyclic ester **6**. The lactone ring of the aspidophytine skeleton was introduced by oxidative lactonization, and the intracyclic double bond by oxidative cleavage of the *exo* methylene. The resulting ketone was trapped as an enol triflate and deoxygenated to give aspidophytine (**7**).

The synthesis of aspidophytine developed by Fukuyama et al. involved the optically pure acetylene unit **9**, which was derived from chiral ester **8** (Scheme 3).[2] The latter was prepared in a few steps by Claisen–Johnson rearrangement of



Scheme 3. Synthetic pathway devised by the Fukuyama group. Boc = *tert*-butoxycarbonyl, *o*-NS = nitrobenzenesulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

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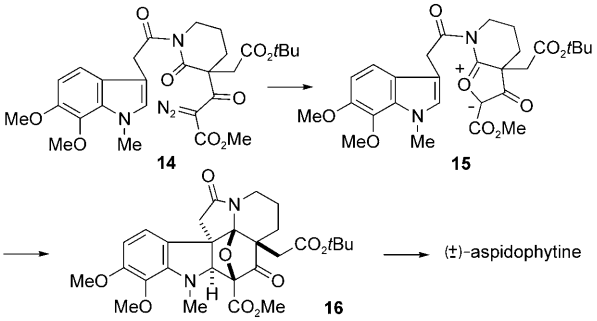
the corresponding allylic alcohol, which was derived from lipase-mediated kinetic resolution of the racemate. In previous work, the team of Fukuyama had developed a methology for the efficient radical synthesis of indoles.[9] They used the same strategy for the construction of iodinated indole **10**, which was coupled to acetylene **9** using a Sonogashira process. Selective partial reduction of the alkyne afforded the *cis* olefin **11**. The nitrogen group (*o*-Ns-amide) was introduced by double Mitsunobu reaction (→**12**), and the CDE-ring aspidosperma skeleton of **13** was built by an intramolecular Mannich-type reaction after deprotection of the aldehyde, secondary amine, and indole. Finally, methylation of the indole nitrogen, saponification of the ester side chain, and oxidative lactonization furnished aspidophitine.

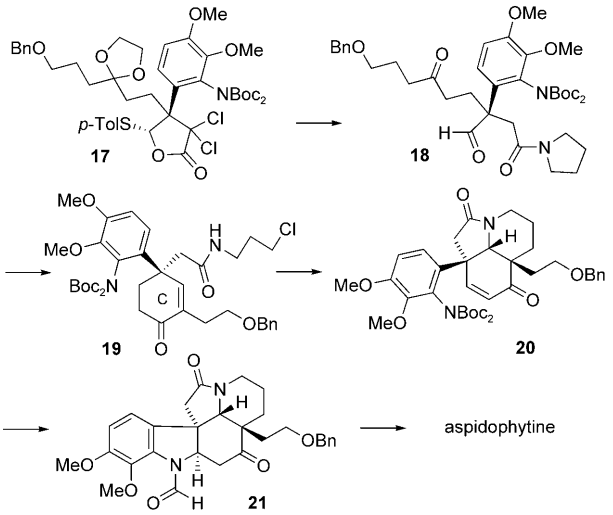
The key step of the approach to aspidophytine developed by Padwa et al.[3] was guided by their long-standing interest in rhodium-catalyzed tandem cyclization/dipolar cycloaddition sequences for the synthesis of natural products. Accordingly, the reaction of **14** with $Rh_2(OAc)_4$ led to a transient carbenoid species that underwent addition to the neighboring imido carbonyl oxygen (Scheme 4). Subsequent intramolecular 1,3-dipolar cycloaddition of carbonyl ylide **15** with the indole



Scheme 4. Synthetic pathway developed by the Padwa group.

nucleus furnished the aspidospermine core **16** in nearly quantitative yield. Completion of the synthesis was realized by construction of the fused lactone under Lewis acidic conditions, which proceeded with concomitant opening of the oxabicyclic ring and loss of the *tert*-butyl ester. The lower methyl ester and the adjacent hydroxy group were then removed, and the C-ring carbonyl group was transformed into an enol triflate and deoxygenated. (±)-Aspidophytine was finally obtained by reduction of the E-ring lactam.

The synthetic scheme leading to aspidophytine developed by the Marino group[4] is described here starting from the advanced chiral lactone intermediate **17**, which was obtained by reacting dichloroketene with the appropriate (*S*)-vinylsulfoxide (Scheme 5). This process, also known as the Marino annulation reaction, enantiospecifically set the quarternary carbon center of lactone **17**. After dechlorination, deprotection of the ketal, and ring opening of the lactone (→**18**), the latent C-ring of aspidophitine was built by intramolecular aldol condensation. The pyrrolidine amide was converted to 3-chloropropylamide **19**, and the tricyclic CDE-ring core structure was introduced by a tandem conjugate addition–alkylation sequence. Further elaboration consisted of oxida-

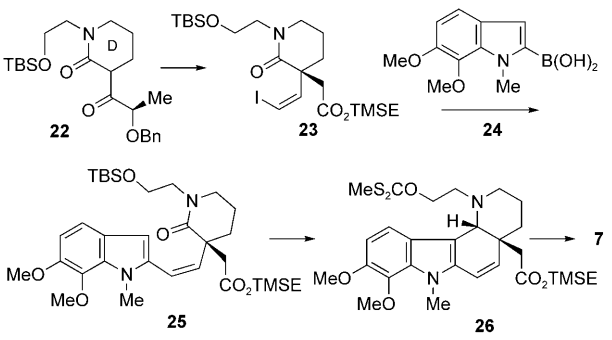


Scheme 5. Synthetic pathway developed by the Marino group. Bn = benzyl, *p*-Tol = *para*-tolyl.

tion of the C-ring to give enone **20**, removal of the two Boc protecting groups of the aniline derivative, N-formylation, and intramolecular conjugate addition of the latter to form the indolic B-ring (→**21**). The C-ring ketone was then transformed into a C–C double bond using the same sequence as in Corey's and Padwa's syntheses of aspidophitine. Deprotection of the side-chain primary alcohol, followed by oxidation afforded the carboxylic precursor of the lactone. The two amide groups were then reduced, and oxidative lactonization finally provided aspidophitine.

The synthesis of aspidophytine reported by the Nicolaou group commenced with the construction of the D-ring using a chiral lactate auxiliary (Scheme 6).[5] Thus, alkylation of **22** with the appropriate bromoacetate permitted the introduction of the quaternary stereocenter in a diastereoselective fashion. The lactate auxiliary was then transformed into an aldehyde by a reduction/oxidative cleavage sequence, and the vinyl iodide of **23** introduced by Stork–Wittig homologation.

Suzuki coupling of **23** with indole boronic acid **24** furnished target amide **25**, whose Vilsmeyer–Haack-type cyclization (triflic anhydride/$NaBH_4$) induced efficient C-ring closure (88% yield). The TBS protecting group of piperidine **25** was removed with HF·pyridine and the resulting primary

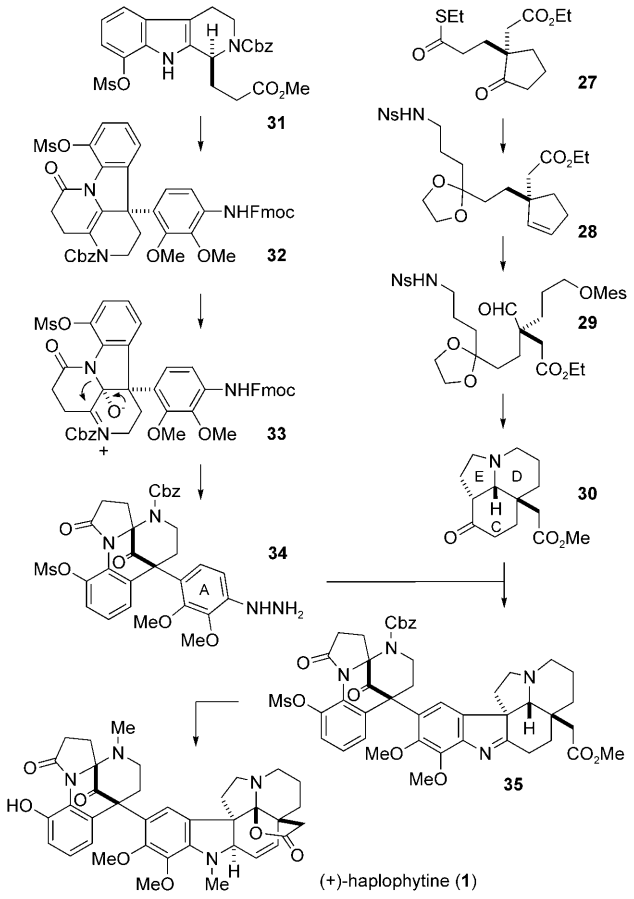


Scheme 6. Synthetic pathway reported by the Nicolaou group. TMSE = 2-(trimethylsilyl)ethyl, TBS = *tert*-butyldimethylsilyl.

alcohol converted to the alkyl radical precursor, xanthate **26**. Upon heating **26** in the presence of Bu_3SnH/azobis isobutyronitrile, deoxygenation and 5-*exo*-trig radical cyclization led to smooth E-ring closure. As in most of the previous syntheses of aspidophytine, the final step consisted of the introduction of the lactone ring using the Corey's oxidative process. The 12-step linear sequence of Nicolaou's synthesis compares most favorably with other syntheses.

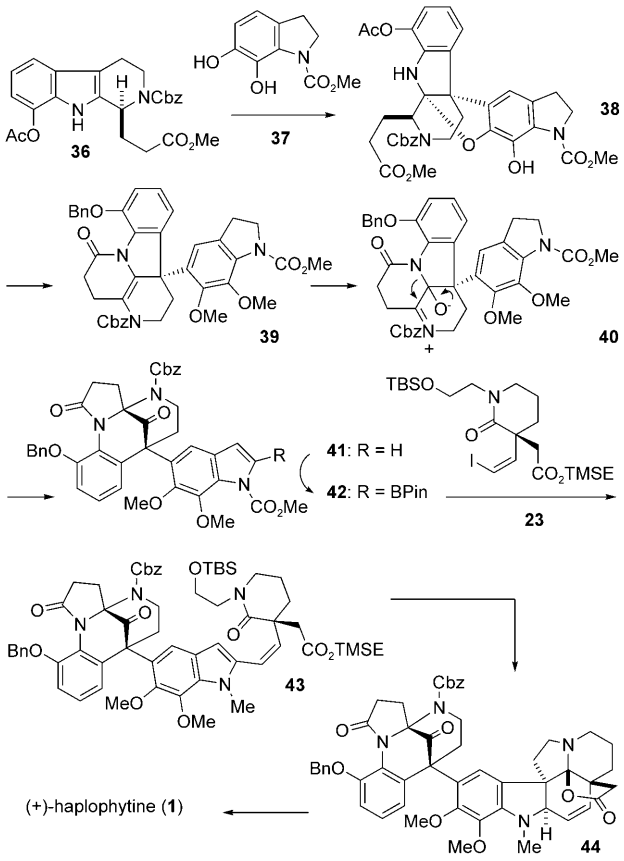
The convergent synthetic scheme leading to haplophytine proposed by the Fukuyama and Tokuyama groups[7] did not rely on the synthesis of aspidophytine previously reported by Fukuyama et al.[2]. One of the main synthetic problems to be solved was the connection of the left-hand segment to the indole moiety of aspidophytine. To this end, their approach was based on the synthesis of the haplophytine left-hand portion **34** already incorporating the aromatic ring of the central indole and in parallel, the construction of the CDE-ring fragment **30** of aspidophytine; the two building blocks were united at a later stage of the synthesis (Scheme 7).

The CDE-ring aspidosperma core **30** was elaborated from **27**, which was derived from asymmetric Michael addition of a cyclic β-ketoester to a thioacrylate. The thioester group was used to elongate the side chain, and the resulting ketone was protected as a dioxolane. The cyclopentanone functionality was also transformed into an olefin by a reduction/β elimination sequence (→**28**). Ozonolysis of the cyclopentene and reduction of the produced aldehydes afforded a diol; subsequent activation of the less hindered hydroxy group and oxidation of the remaining alcohol led to intermediate **29**. Substitution of the mesylate by the Ns-amide permitted the initial closure of an 11-membered ring before Mannich cyclization. After hydrolysis of the ketal, saponifcation of the ester, and removal of the Ns protecting group, the CDE-ring skeleton of aspidophytine was assembled by intramolecular Mannich-type reaction. The tricyclic ketone **30** was obtained after reesterification of the carboxylic side chain. The strategy that was used for the elaboration of the left-hand segment of haplophytine is based on the well-established HBr-triggered pinacol-type rearrangement of **1** illustrated in Scheme 1. As the process is reversible under basic conditions, the target compound for the construction of the left-hand segment of halophytine was the transient hemiaminal **33**. The 1,2-rearrangement of **33** was to provide access to the tetracyclic bridged ketone **34**. The synthesis of the left-hand segment is described starting from optically active tetrahydro-β-carboline **31**, which was prepared by Noyori asymmetric reduction of the corresponding dihydro-β-carboline. Tetrahydrocarboline **31** was transformed to an iodoindolenine and arylated with protected 2,3-dimethoxyaniline. The aryl group was introduced diastereoselectively (2:1 ratio) to be later connected to the right-hand domain and to set up the central indole. After formation of the lactam ring of **32**, the key rearrangement step was initiated by epoxidation (with *meta*-chloroperbenzoic acid) of the diaminoethene moiety. The epoxide underwent spontaneous ring-opening leading to hemiaminal **33**, which rearranged into the expected bridged ketone. The protected aniline was converted to hydrazine **34** and submitted to Fisher indole synthesis with the tricyclic ketone **30**. The resulting imine **35** was converted to the conjugated imine, the CBz group removed, and the imine reduced. After methylation of the two secondary amines, haplophytine was finally obtained after hydrolysis of the mesylate and ester, whose oxidative lactonization afforded **1**.



Scheme 7. Synthetic pathway to haplophytine devised by the Fukuyama and Tokuyama groups. Cbz = benzyloxycarbonyl, Fmoc = 9-fluorenylmethyloxycarbonyl, Ms = methanesulfonyl, Ns = 2-nitrobenzenesulfonyl.

Soon after the report of Fukuyama, Tokuyama et al. on the first total synthesis of haplophytine, Nicolaou, Chen et al. described their own approach to this complex alkaloid.[8] Their strategy was inspired by the previous work of the Nicolaou research group on the synthesis of aspidophytine[5] and truncated left domain of haplophytine.[6] Their synthesis of haplophytine started from enantiopure tetrahydro-β-carboline **36**, which was prepared by the same sequence as for **31** (see above). Treatment of **36** and diphenol **37** with hypervalent phenyliodobis(trifluoroacetate) led to hexacycle **38** with high diastereoselectivity (d.r. > 20:1; Scheme 8). The remaining OH group was methylated and the acetate replaced with a benzyl group, before the N,O-acetal was cleaved under basic conditions. The resulting phenol was methylated, and bis(enamine) **39** was obtained by saponification of the methyl ester, activation of the resulting carboxylic acid, and ring closure. The stage was thus set for the key oxidative rearrangement to produce the left portion of haplophytine: epoxidation of **39** with *meta*-chloroperbenzoic acid led to hemiaminal **40**, whose skeletal rearrangement afforded the characteristic bridged ketone of the left domain.



Scheme 8. Synthetic route to haplophytine by Nicolaou, Chen et al.

Subsequent oxidation of the indoline ring produced indole **41**, which was further converted into pinacol borane **42** for the ensuing Suzuki–Miyaura coupling with vinyl iodide **23**. The coupling with the right-hand fragment proceeded with concomitant deprotection of the indole, which was N-methylated to provide **43**. The following steps resemble those of the synthesis of aspidophytine by Nicolaou et al.,[5] with sequential construction of the C and E rings of the aspidophytine backbone. Hence, a Vilsmeier–Haack reaction permitted closure of the C ring, and elaboration of the E ring was achieved by desilylation of the primary alcohol, its conversion into a xanthate, and radical addition to the indole. The fused lactone was then introduced by desilylation of the carboxylic acid side chain and oxidative lactonization to give **44**.

The final steps of the synthesis consisted of removal of the benzyl and Cbz protecting groups and methylation of the resulting desmethylhaplophytine. However, reductive amination of the piperidine first required silylation of the newly debenzylated phenol. The reductive conditions also proved detrimental to the lactone, which was converted back into the starting carboxylic acid. The latter was hence oxidatively relactonized, and haplophytine **1** was finally obtained after deprotection of the phenol.

The pioneering synthesis of aspidophytine by Corey et al. paved the way for the synthesis, a decade later, of haplophytine by the Fukuyama and Tokuyama groups. The synthetic approach that has been put in place tackles remarkable challenges, in particular the tricky problem of connecting the two indole alkaloid precursors and the elegant construction of the tetracyclic left-hand domain of haplophytine using the inherent oxidative skeletal rearrangement.

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