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Application of the Rh(II)-Cyclization/Cycloaddition Cascade for the Total Synthesis of (±)-Aspidophytine

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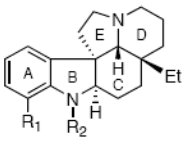
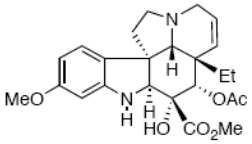
Abstract

A new strategy for the synthesis of (±)-aspidophytine has been developed and is based on a Rh(II)-catalyzed cyclization/dipolar-cycloaddition sequence. The resulting [3+2]-cycloadduct undergoes an efficient Lewis acid mediated cascade that rapidly provides the complete skeleton of aspidophytine. The synthesis also features a mild decarbomethoxylation reaction.

The *Aspidosperma* alkaloids occupy a central place in natural product chemistry because of their wide range of complex structural variation and diverse biological activity.[1] This family of indole alkaloids contains over 250 members that share in their molecular structure a common pentacyclic ABCDE framework, with the C-ring being of critical importance because all six stereocenters and most of the functionalities are located in this ring.[2] Individual members differ mainly in functionality and stereochemistry. Over the years, efficient and elegant routes to this molecular framework have been developed.[3,4]



1; $R_1 = R_2 = H$ (Aspidospermidine)
2; R_1 = OMe; R_2 = Ac (Aspidospermine)



3; Vindoline

In 1973, Cava and Yates reported on the structural determination of haplophytine (**4**), a dimeric indole alkaloid isolated from the leaves of *Haplophyton cimicidum*.[5,6] Acid cleavage of haplophytine (**4**) led to aspidophytine (**5**),[7] a lactonic aspidospermine type of alkaloid which has been suggested to not only be a biosynthetic precursor of **4** but also a possible intermediate to be used in its synthesis.[8,9] Because of its intriguing structure, aspidophytine has attracted the attention of two major research groups. In 1999 Corey *et al*[8] and four years later Fukuyama *et al*[9] accomplished the synthesis of aspidophytine utilizing completely different strategies. The Corey approach hinged on a creative cascade reaction between dialdehyde **7** and indole **6**, synthesized from vanillin acetate in 10 steps (Scheme 1). The Fukuyama group used their signature radical cascade chemistry[10] to construct indole **8** from vanillin acetate (11 steps), followed by a Sonogashira coupling[11] with alkyne **9** and then an effective amine-aldehyde condensation cascade to furnish the aspidosperma skeleton[9].

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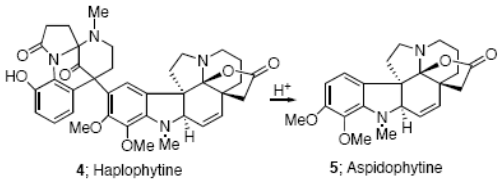

4; Haplophytine **5**; Aspidophytine

Our approach to aspidophytine was guided by a longstanding interest in developing new applications of the *Rh(II)-cyclization/cycloaddition cascade* for the synthesis of complex natural products, particularly alkaloids.[12] The generation of onium ylides by a transition-metal promoted cyclization reaction has emerged in recent years as an important and efficient method for the assembly of ring systems that are difficult to prepare by other means.[13,14] In earlier work from our laboratory we had described the formation of push-pull dipoles from the Rh (II)-catalyzed reaction of α-diazo imides and noted that a smooth intramolecular 1,3-dipolar cycloaddition occurred across both alkenyl and heteroaromatic π-bonds to provide novel pentacyclic compounds in good yield and in a stereocontrolled fashion.[15] Our plan for the synthesis of aspidophytine is shown in retrosynthetic format in Scheme 2 and is centered upon the construction of the key cycloadduct **11** by making use of α-diazo imide **10**. The successful completion of this synthesis demonstrates the utility of this cascade methodology for the construction of complex indole-containing natural products.

Construction of the required α-diazo imide **10** entailed the synthesis of two building blocks, the substituted 2-(indol-3-yl)acetic acid **16** and the diazo lactam **20**. The preparation of **16** was carried out in five steps in 36% overall yield starting from aniline **13** and is summarized in Scheme 3. Commercially available aniline **13** was iodinated using IC1 (73%) and the resulting iodoaniline **14** was subsequently alkylated with methyl bromocrotonate to give the secondary amine **15** in 75% yield based on recovered starting material. Intramolecular Heck cyclization (90%) of **15** afforded the expected indole ring[16] which was easily converted to **16** by *N*-methylation with CH_3I (80%) followed by a subsequent hydrolysis step (94%).

Preparation of the diazo lactam unit **20** commenced with commercially available δ-valerolactam **17** which was deprotonated with excess base and allowed to react with *t*-butyl bromoacetate to give lactam **18** in 80% yield (Scheme 4). The ethyl ester portion of **18** was converted to the methyl 3-oxopropanoate group using a modified Masamune procedure[17] to furnish β-keto ester **19** in 54% overall yield. Finally, the requisite α-diazo lactam **20** was easily obtained using standard diazo transfer conditions[18] and was isolated in 96% yield.

At this point we joined the two synthesized fragments by treating acid **16** with $(COC1)_2$ and allowing the resulting acid chloride to react with the stable *N*-H diazo lactam in the presence of 4A° molecular sieves. The desired α-diazo imide **10** was obtained in 92% yield. Formation of the push-pull dipole **21** was achieved by reaction of **10** with $Rh_2(OAc)_4$, which afforded a rhodium carbenoid species that readily underwent cyclization onto the neighboring imido carbonyl to form the carbonyl ylide dipole **21**.[12]

Subsequent intramolecular cycloaddition across the tethered indolyl group furnished cycloadduct **11** in 97% yield.[19] The acid lability of cycloadduct **11** was exploited in the next step of the synthesis. Treatment of **11** with a Lewis acid such as $BF_3{\cdot}OEt_2$ resulted in cleavage of the oxabicyclic ring and formation of a transient *N*-acyl iminium ion which was captured by the adjacent carbonyl group of the *t*-butyl ester (Scheme 5). Loss of isobutylene from the resulting oxonium ion resulted in the isolation of **23** in 70% yield. The relative stereochemistry of **23** was assigned on the basis of its spectroscopic properties which were essentially identical to the related ring opened product **24** (R=H) whose structure was confirmed by a single-crystal X-ray analysis.[20]

The completion of the synthesis of aspidophytine (**5**) from **23** is outlined in Scheme 6. First, the carbomethoxy and hydroxyl groups next to the keto group were sequentially removed so as to produce compound **27**. Treatment of **23** with MgI_2 in refluxing acetonitrile containing a small quantity of water resulted in the formation of alcohol **26** in 75% yield. While a cursory analysis of the conditions suggests a Krapcho dealkoxycarbonylation reaction,[21] the isolation of carbonate **25** from the reaction is more consistent with an unexpected carbomethoxy group migration[22] to the adjacent hydroxyl group followed by further reaction of the carbonate with halide ion and loss of CO_2 to give **26**.[23] Acetylation of **26** with acetyl chloride/NEt_3 afforded the corresponding acetate which was subsequently reduced using SmI_2 to give **27** in 90% yield from both steps. The carbonyl group of **27** was transformed into the corresponding enol triflate which, upon treatment with $Pd(Ph_3P)_4$ and *n*-Bu_3SnH according to Corey's experimental conditions,[8] gave **28** (72%). Treatment of **28** with P_2S_5 furnished thiolactam **29** in 95% yield.[24] Although not investigated in detail, our attempts to reduce **29** with Raney-Ni were not successful. Instead, *S*-ethylation of thiolactam **29** with Meerwein's reagent followed by LiAlH(O*t*-Bu)$_3$/n-Bu_3SnH reduction[25] provided (±)-aspidophytine (**5**) in 61% yield from **29**. Confirmation of the structure was obtained by comparison of the spectral data with that of an authentic sample of aspidophytine provided by Professor Fukuyama.

In conclusion, a concise total synthesis of (±)-aspidophytine was achieved featuring a *Rh(II)-cyclization/cycloaddition cascade* of a suitably substituted α-diazo imide as the key step. We are currently refining this strategy and further applying the methodology toward other aspidosperma alkaloids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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19. In contrast to previous finding,[15] the *exo*-cycloadducts **11** and **22** were the exclusive products isolated from the Rh(II)-catalyzed reaction. We assume that the bulky *t*-butyl ester functionality blocks the *endo*-approach thereby resulting in cycloaddition taking place from the less congested *exo*-face.
20. The authors have deposited coordinates for structure **24** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, B2 1EZ, UK.
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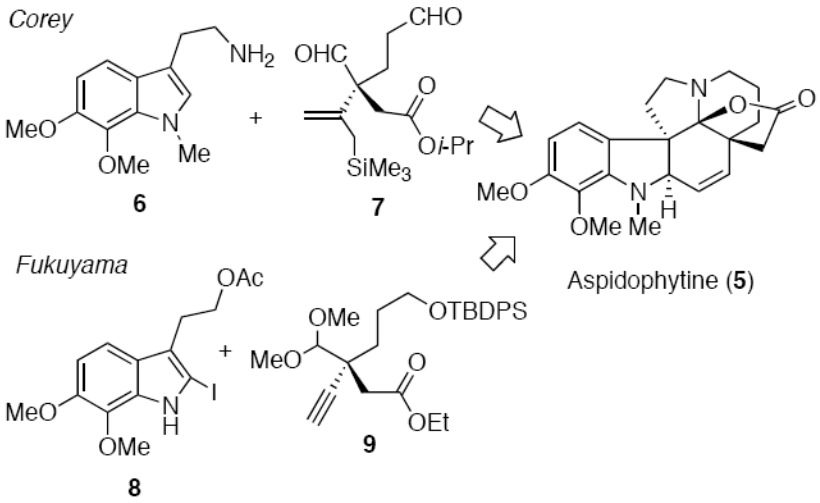
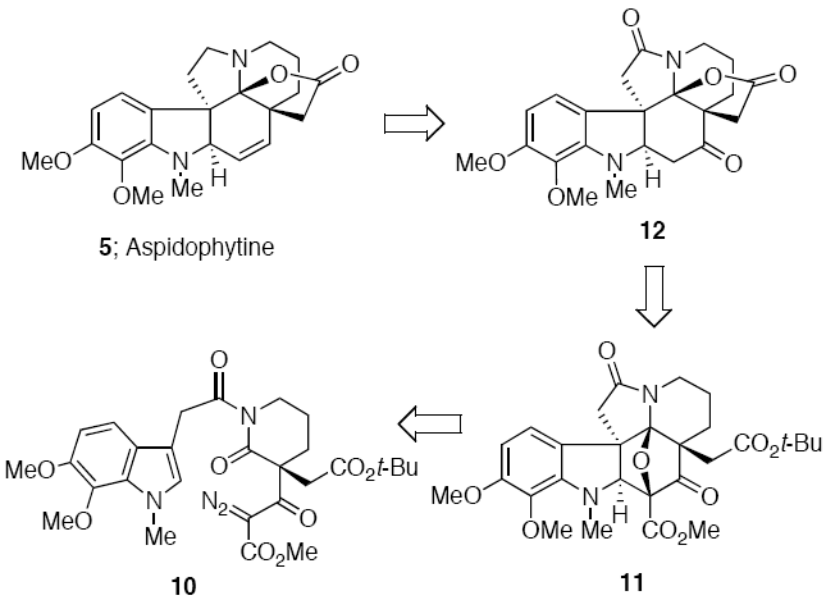
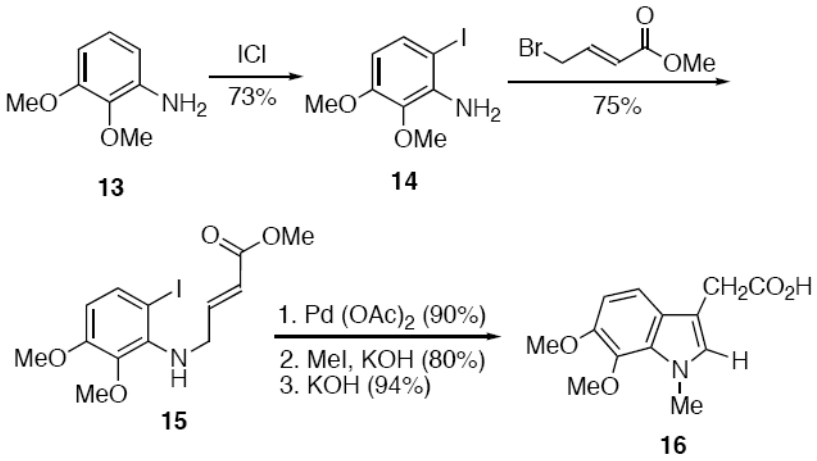


Scheme 1.



Scheme 2.



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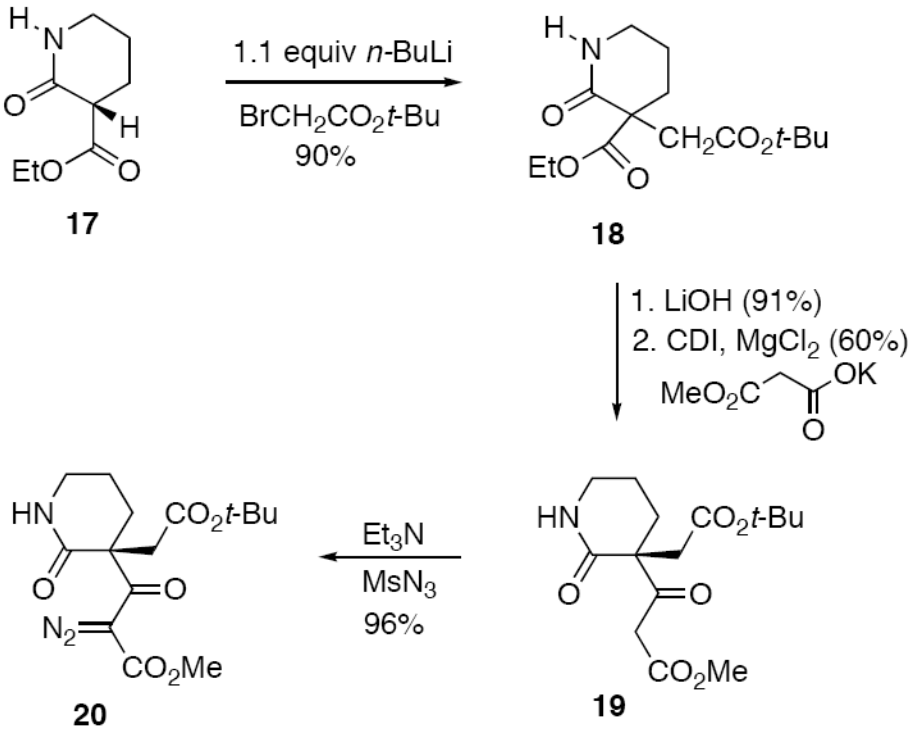

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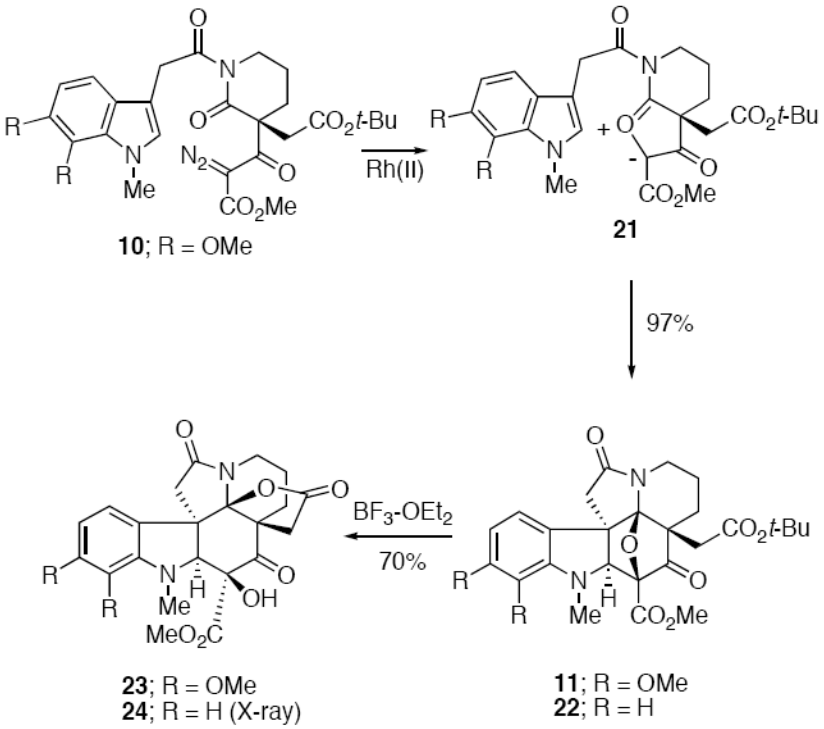
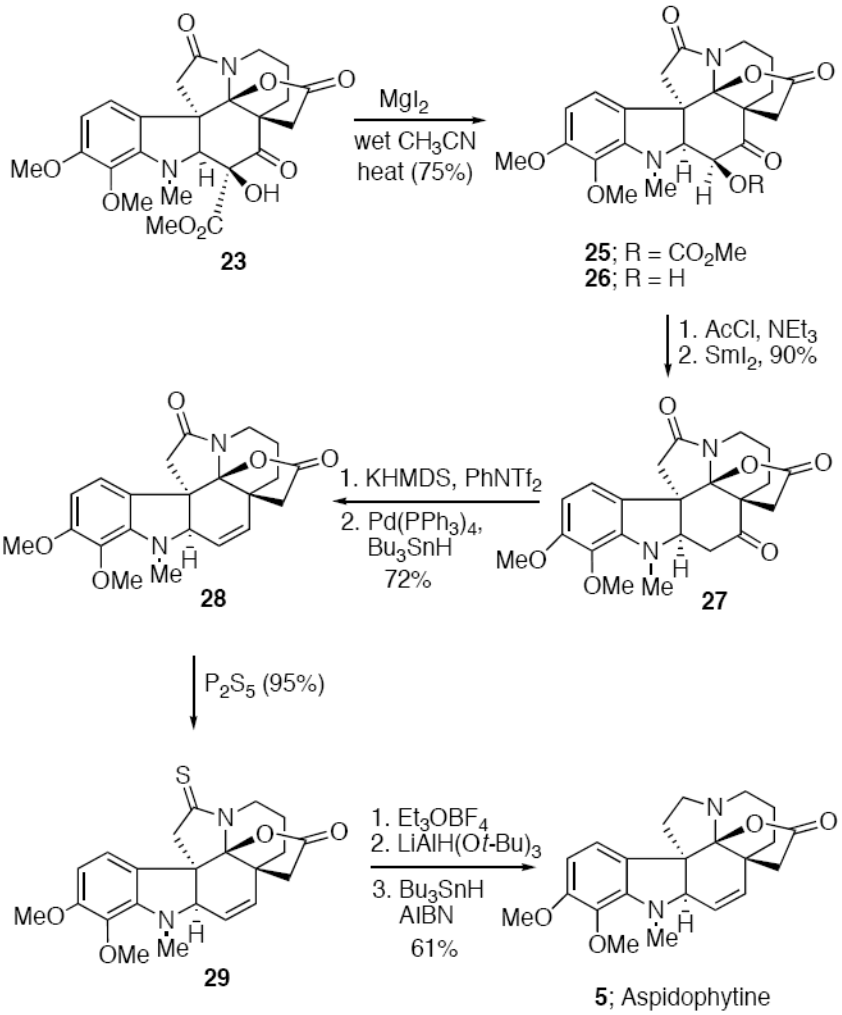


Scheme 5.



Scheme 6.