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

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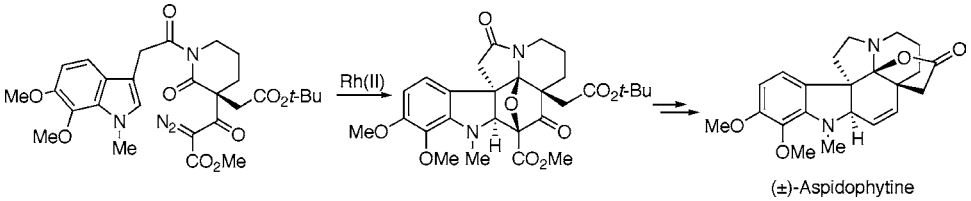
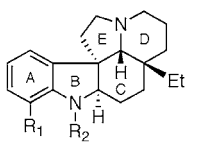
## ABSTRACT



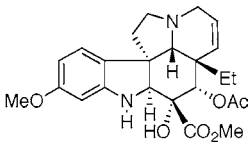

(±)-Aspidophytine

**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 variations 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]

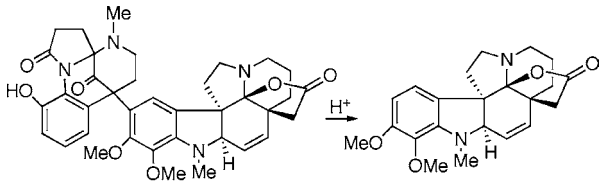



**1**; $R_1 = R_2 = H$ (Aspidospermidine)
**2**; $R_1 = OMe$; $R_2 = Ac$ (Aspidospermine)




**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 be not only 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




**4**; Haplophytine **5**; Aspidophytine

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

(1) Saxton, J. E. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1998; Vol. 51, pp 1−197.

(2) (a) Saxton, J. E. *Indoles, Part 4: The Monoterpenoid Indole Alkaloids*; Wiley: Chichester, 1983. (b) Herbert, R. B. In *The Monoterpenoid Indole Alkaloids*; Supplement to Vol. 25, part 4 of *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley: Chichester, 1994; Chapter 1. (c) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, 327 and references therein.

(3) For the first synthesis of aspidospermine and vindoline, see: (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (b) Ando, M.; Buchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880.

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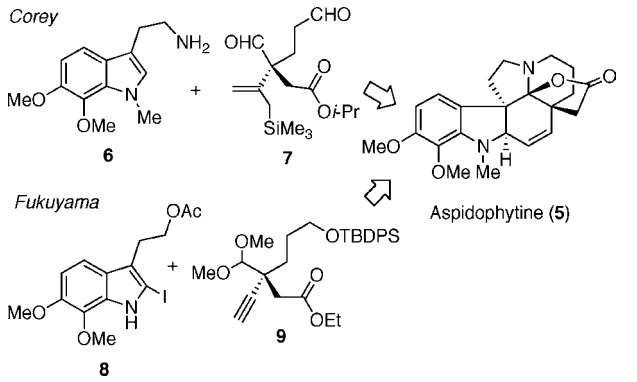
strategies. The Corey approach hinged on a creative cascade reaction between dialdehyde **7** and indole **6**, synthesized from vanillin acetate in 10 steps (Scheme 1). The Fukuyama group

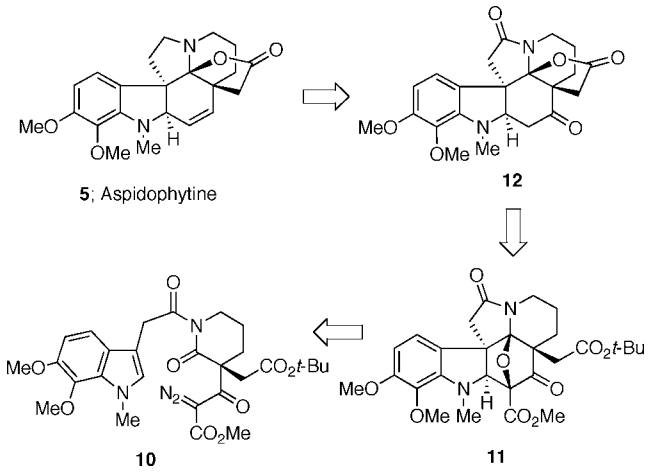
**Scheme 1**




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]

Our approach to aspidophytine was guided by a long-standing 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 $\pi$-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

**Scheme 2**




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.

(4) For some select methods to synthesize the pentacyclic framework of aspidospermidine (**1**), see: (a) Camerman, A.; Camerman, N.; Kutney, J. P.; Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, 637. (b) Harley-Mason, J.; Kaplan, M. *J. Chem. Soc., Chem. Commun.* **1967**, 915. (c) Laronze, J.-Y.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, 491. (d) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. (e) Gallagher, T.; Magnus, P.; Huffman, J. *J. Am. Chem. Soc.* **1982**, *104*, 1140. (f) Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953. (g) Mandal, S. B.; Giri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, *53*, 4236. (h) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673. (i) Node, M.; Nagasawa, H.; Fugi, K. *J. Org. Chem.* **1990**, *55*, 517. (j) Le Menez, P.; Kunesch, N.; Lui, S.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 2915. (k) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292. (l) Wenkert, E.; Lui, S. *J. Org. Chem.* **1994**, *59*, 7677. (m) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882. (n) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855. (o) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995. (p) Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625. (q) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642. (r) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599. (s) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628. (t) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2613. (u) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398. (v) Gnecco, D.; Vázquez, E.; Galindo, A.; Terán, J. L.; Bernès, S.; Enríquez, R. G. *Arkivoc* **2003**, *11*, 185. (w) Tanino, H.; Fukuishi, T.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, *60*, 3273. (x) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, *3*, 213.

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(6) (a) Saxton, J. E. *Alkaloids* **1965**, *8*, 673. (b) Cheng, P.-T.; Nyburg, S. C.; MacLachlan, F. N.; Yates, P. *Can. J. Chem.* **1976**, *54*, 726.

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(10) (a) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (b) Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. *Synthesis* **2000**, 429. (c) Tokuyama, H.; Watanabe, M.; Hayashi, Y.; Kurokawa, T.; Peng, G.; Fukuyama, T. *Synlett* **2001**, 1403. (d) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519. (e) Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, 883.

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(12) For some leading references, see: (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (c) Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121. (d) Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933. (e) Padwa, A.; Brodney, M. A.; Lynch, S. M.; Rashatasakhon, P.; Wang, Q.; Zhang, H. *J. Org. Chem.* **2004**, *69*, 3735.

(13) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998.

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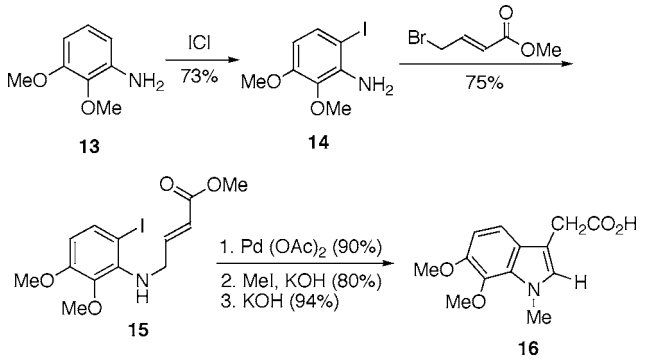
Construction of the required α-diazo imide **10** entailed the synthesis of two building blocks, the substituted 2-(indol-3-yl)acetic acid **16** and the diazo lactam **20**. The preparation of **16** was carried out in five steps in 36% overall yield starting from aniline **13** and is summarized in Scheme 3.

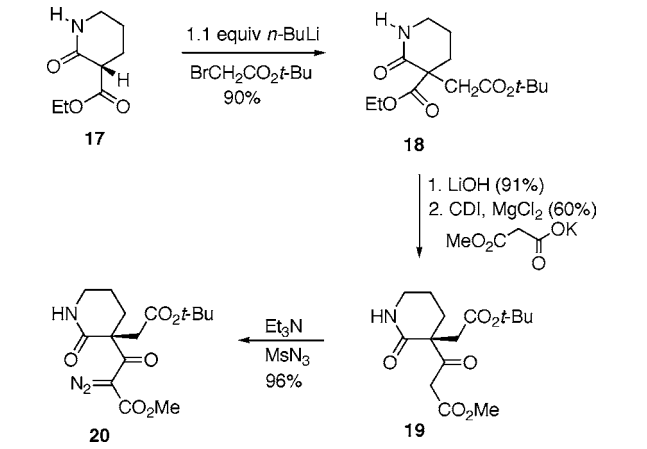
**Scheme 3**




Commercially available aniline **13** was iodinated using ICl (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 *tert*-butyl bromoacetate to give lactam **18** in 80% yield (Scheme 4).

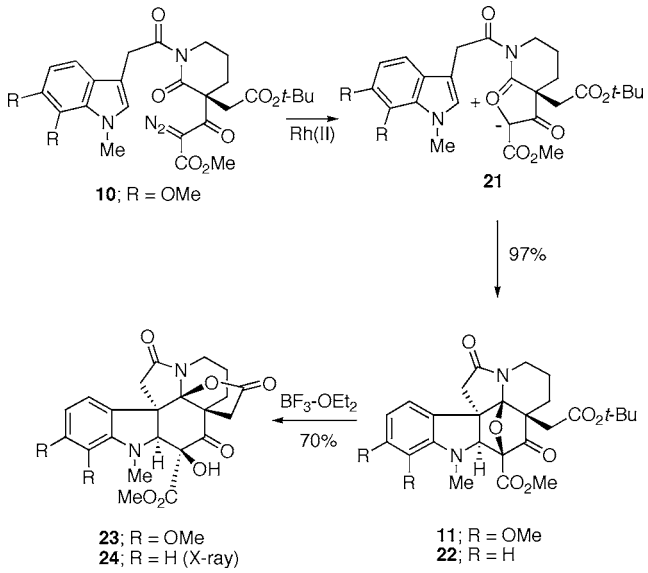
**Scheme 4**




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 $(COCl)_2$ and allowing the resulting acid chloride to react with the stable *N*-H diazo lactam in the presence of 4 Å 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 *tert*-butyl ester (Scheme 5). Loss of isobutylene from the resulting oxonium

**Scheme 5**




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

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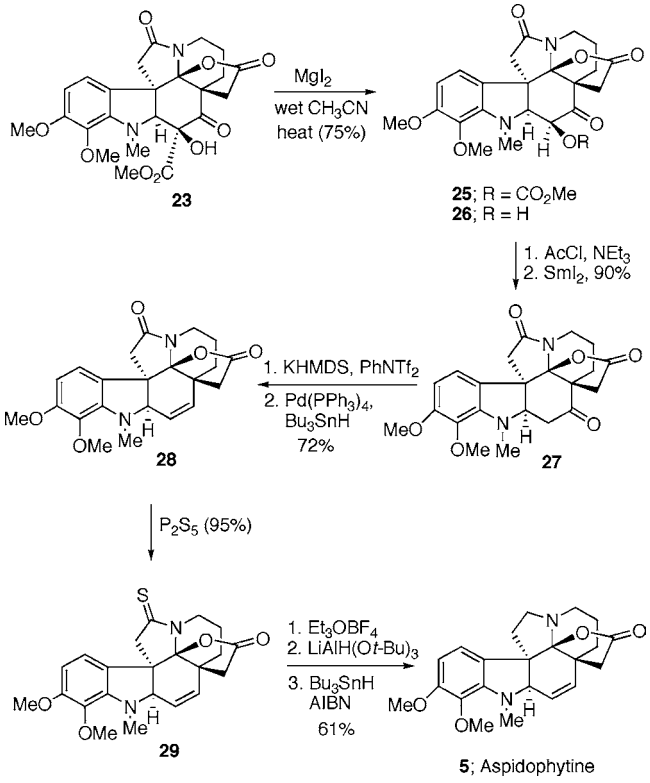
(17) Brooks, D. W.; Lu, D. L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.

(18) (a) Regitz, M. *Chem. Ber.* **1966**, *99*, 3128. (b) Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth.* **1973**, *5*, 179.

(19) In contrast to a 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 *tert*-butyl ester functionality blocks the endo approach thereby resulting in cycloaddition taking place from the less-congested exo face.

**Scheme 6**




hydroxyl groups next to the keto group were sequentially removed 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. Although 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 a 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 $LiAlH(O^tBu)_3/^nBu_3SnH$ 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.

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**Supporting Information Available:** Spectroscopic data and experimental details for the preparation of all new compounds together with an ORTEP drawing for compounds **24** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(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, U.K.

(21) For a review of dealkoxycarbonylations, see: Krapcho, A. P. *Synthesis* **1982**, 805 and 893.

(22) For some related examples, see: (a) Rubin, M. B.; Inbar, S. *Tetrahedron Lett.* **1977**, 1037. (b) Davis, F. A.; Clark, C.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1994**, *59*, 1184.

(23) Structure **25** was established on the basis of an X-ray crystal structure analysis. A more detailed study of this unusual rearrangement is currently underway in our laboratory.

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