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

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Received May 9, 2006

ORGANIC LETTERS 2006 Vol. 8, No. 15 3275-3278





A new strategy for the synthesis of (\pm) -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}



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



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.

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 chemistry¹⁰ to construct indole **8** from vanillin acetate (11 steps), followed by a

(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.

(5) Yates, P.; MacLachlan, F. N.; Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Cava, M. P.; Behforouz, M.; Lakshmikantham, M. V.; Ziegler, W. J. Am. Chem. Soc. **1973**, 95, 7842.

(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.

(7) (a) Cava, M. P.; Talapatra, S. K.; Nomura, K.; Weisbach, J. A.; Douglas, B.; Shoop, E. C. *Chem. Ind. (London)* **1963**, 1242. (b) Cava, M. P.; Talapatra, S. K.; Yates, P.; Rosenberger, M.; Szabo, A. G.; Douglas, B.; Raffuaf, R. F.; Shoop, E. C.; Weisbach, J. A. *Chem. Ind. (London)* **1963**, 1875. (c) Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Yates, P.; Zacharias, D. E.; Jeffrey, G. A.; Douglas, B.; Kirkpatrick, J. L.; Weisbach, J. A. *J. Am. Chem. Soc.* **1967**, *89*, 3061.

(8) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. J. Am. Chem. Soc. 1999, 121, 6771.

(9) (a) Sumi, S.; Matsumoto, S.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891. (b) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2003**, *59*, 8571.

(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. Syntett **2001**, 1403. (d) Kobayashi, S.; Peng, G.; Fukuyama, T. Tetrahedron Lett. **1999**, 40, 1519. (e) Kobayashi, S.; Ueda, T.; Fukuyama, T. Syntett **2000**, 883.

Sonogashira coupling¹¹ 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 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.

(14) Boger and co-workers have recently described an alternate approach to onium ylides based on a [4+2]-cycloaddition of 1,3,4-oxadiazoles followed by a thermal extrusion of nitrogen and have elegantly exploited this chemistry for the construction of a variety of aspidosperma alkaloid targets. See: Choi, Y.; Ishikawa, H.; Velcicky, J.; Elliott, G. I.; Miller, M. M.; Boger, D. L. *Org. Lett.* **2005**, *7*, 4539 and references therein.

(15) (a) Padwa, A.; Price, A. T. J. Org. Chem. 1995, 60, 6258. (b) Padwa,
A.; Price, A. T. J. Org. Chem. 1998, 63, 556. (c) Mejía-Oneto, J. M.; Padwa,
A. Org. Lett. 2004, 6, 3241. (d) Padwa, A.; Lynch, S. M.; Mejía-Oneto, J.
M.; Zhang, H. J. Org. Chem. 2005, 70, 2206.

⁽¹¹⁾ Sonogashira, K.; Tohda, Y.; Hagihara, N. Tetrahedron Lett. 1975, 16, 4467.

⁽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.

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 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 ring¹⁶ which was easily converted to **16** by N-methylation with CH₃I (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).



The ethyl ester portion of **18** was converted to the methyl 3-oxopropanoate group using a modified Masamune proce-

dure¹⁷ to furnish β -keto ester **19** in 54% overall yield. Finally, the requisite α -diazo lactam **20** was easily obtained using standard diazo transfer conditions¹⁸ 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 BF₃. OEt₂ 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



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** ($\mathbf{R} = \mathbf{H}$) 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

^{(16) (}a) Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 1037. (b) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (c) Aubert, K. M.; Heathcock, C. H. J. Org. Chem. **1999**, *64*, 16.

⁽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.



hydroxyl groups next to the keto group were sequentially removed to produce compound **27**. Treatment of **23** with MgI₂ 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 migration²² 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/NEt₃ afforded the corresponding acetate which was subsequently reduced using SmI₂ 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(Ph₃P)₄ and *n*-Bu₃SnH 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'Bu)₃/ⁿBu₃SnH reduction²⁵ 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 (\pm) -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.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (GM 059384) and the National Science Foundation (CHE-0450779). We wish to thank Professor Tohru Fukuyama and Dr. Hidetoshi Tokuyama (University of Tokyo) for an authentic sample of aspidophytine for comparison purposes.

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.

OL061137I

⁽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.

⁽²⁴⁾ Čurphey, T. J. J. Örg. Chem. 2002, 67, 6461.

⁽²⁵⁾ Raucher, S.; Klein, P. Tetrahedron Lett. 1980, 21, 4061.