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Intramolecular Imino Diels−Alder Approach to the Synthesis of the Aspidosperma Alkaloid from 3,5-Dibromo-2-pyrone†

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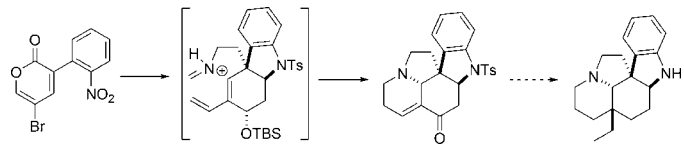
ABSTRACT



A new synthetic route to the key framework of aspidosperma alkaloid was devised from the cycloadduct of 3-(2-nitrophenyl)-5-bromo-2-pyrone via intramolecular imino Diels−Alder reaction.

Incorporated with a pentacyclic ABCDE framework in common, the aspidosperma alkaloid comprises one of the largest groups of indole alkaloids with more than 250 members (Figure 1).[1] The unique molecular architecture and

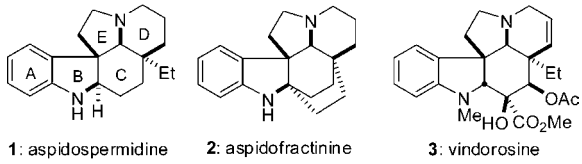


Figure 1. Selected examples of aspidosperma alkaloids.

a wide array of important biological activities featured by many of its members have led to intense investigation over the years. Aspidospermidine **1**, the parent compound of this alkaloid family, has attracted the most attention from the synthetic community because of its structural simplicity. Such interest has inspired the development of many efficient and elegant synthetic methods and strategies.[2]

As a part of our ongoing research program exploring the utility of 3,5-dibromo-2-pyrone and its derivatives as novel enophile synthons toward natural product synthesis,[3] we have recently envisaged that the Diels−Alder reaction of 3-aryl-5-bromo-2-pyrone could be a good starting point for the synthesis of aspidosperma alkaloids, as it provides necessary functional groups with correct orientation.

On the basis of the report by Büchi and co-workers showing the facile installation of the bridgehead C20 ethyl group of a similar enone system,[4] we envisioned the pentacyclic enone **4** would function as the common advanced

† Dedicated to the late Professor Chi Sun Hahn in admiration of his contributions to the organic chemistry of Korea.

(1) (a) Saxton, J. E. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1. (b) Saxton, J. E. *Indoles, Part 4: The Monoterpenoid Indole Alkaloids*; Wiley: Chichester, 1983.

(2) For a recent synthesis of aspidospermidine, see: (a) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159. (b) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831. (c) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. *J. Org. Chem.* **2005**, *70*, 10645. (d) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628. (e) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *23*, 2613. (f) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398. (g) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599. (h) Iyengar, R.; Schildknegt, K.; Aube, J. *Org. Lett.* **2000**, *2*, 1625. (i) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642. (j) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1: Org. Bio-Org. Chem.* **1999**, 995. (k) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523.

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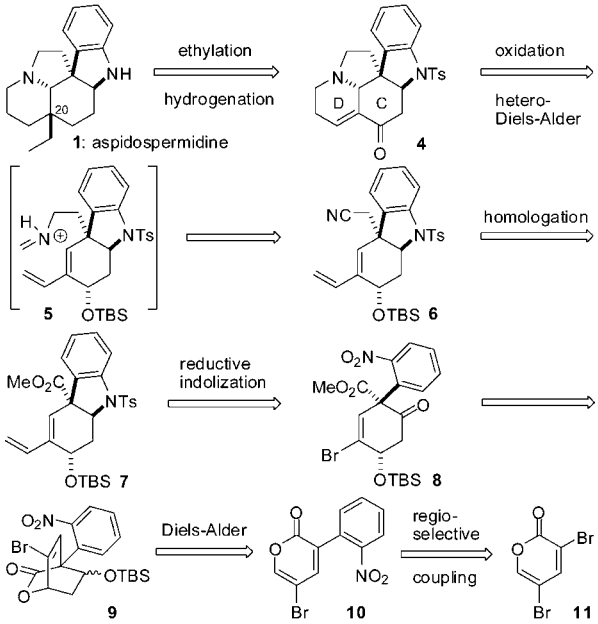
synthetic intermediate of not only aspidospermidine **1** but also aspidofractinine **2** and vindorosine **3** (Scheme 1).

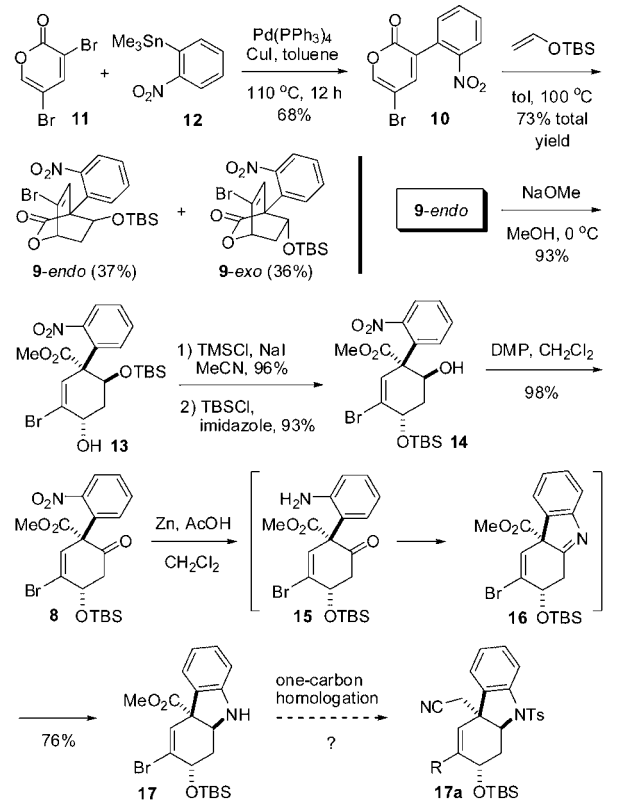
Scheme 1. Retrosynthesis of (±)-Aspidospermidine **1**



Further retrosynthetic disconnection of enone **4** led to nitrile **6**, revealing our key strategy: the construction of the indolizidine system (rings D and E, **6** → **4**) by the intramolecular imino Diels−Alder reaction of iminium intermediate **5**. The indole subunit of nitrile **6** would be readily installed from ketone **8** by the process involving the reduction of the aromatic nitro group and intramolecular reductive amination. The final elaboration called for the synthesis of bicyclolactone **9**, the cycloadduct of 3-(2-nitrophenyl)-5-bromo-2-pyrone **10** with silyl vinyl ether. The requisite 2-pyrone **10** should be accessed from 3,5-dibromo-2-pyrone **11** through a regioselective Stille coupling reaction.[5]

The Stille coupling reaction of 3,5-dibromo-2-pyrone **11** with aryltin **12** provided 3-(2-nitrophenyl)-5-bromo-2-pyrone **10** in 68% yield (Scheme 2). The Diels−Alder reaction of 2-pyrone **10** with TBS enol ether gave bicyclolactones **9**-*endo* and **9**-*exo* (1:1 ratio, 73% total yield).[6] The *endo*/*exo* isomers need not be separated because the stereogenic TBS ether group would be oxidized into ketone (vide infra). To facilitate structural characterization, however, each isomer was isolated and converted individually into ketone **8**, by following the sequence involving the basic methanolysis, protecting group relocation, and oxidation reaction. The resultant ketone **8** was then subjected to the Zn-mediated reduction process (**8** → **17**). The initially formed amine **15** was cyclized to imine **16** before the in situ follow-on reduction to indole **17** (76% total yield from **8**).[7]

Scheme 2. Synthesis of Indole **17**



As expected, subsequent one-carbon elongation (**17** → **17a**, Scheme 2) was quite difficult because of the high steric congestion at the benzylic quaternary carbon center, necessitating exploitation of many methods and tactics. On the basis of our previous results,[3b] methyl ester **17** was converted into neopentyl mesylate **19a** for the cyanation into nitrile **6** after the protection of the indole nitrogen and incorporation of the vinyl group (eq 1, Scheme 3). When heated with NaCN in DMSO at 70 °C,[8] however, mesylate **19a** mostly produced benzoazepine **21a**, presumed to form via the intramolecular Friedel−Craft-type alkylation reaction. No reaction was observed when mesylate **19b** or **19c** was used, even after a prolonged heating. The Wittig olefination reaction of aldehyde **23** also failed, implying once again the high steric hindrance (eq 2).

(3) For a recent review and selected articles, see: (a) Kim, H.-Y.; Cho, C.-G. *Prog. Heterocycl. Chem.* **2007**, *18*, 1. (b) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2008**, *10*, 601. (c) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. (d) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303. (e) Tam, T.; Cho, C.-G. *Org. Lett.* **2007**, *9*, 3391. (f) Shin, J.-T.; Hong, S.-C.; Shin, S.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3339. (g) Ryu, K.; Cho, Y.-S.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343. (h) Chung, S.-I.; Seo, J.; Cho, C.-G. *J. Org. Chem.* **2006**, *71*, 6701. (i) Shin, J.-T.; Shin, S.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 5857. (j) Pang, S.-J.; Min, S.-H.; Lee, H.; Cho, C.-G. *J. Org. Chem.* **2003**, *68*, 10191. Synthesis of **9**: (k) Cho, C.-G.; Kim, Y.-W.; Lim, Y.-K.; Park, J.-S.; Lee, H.; Koo, S. *J. Org. Chem.* **2002**, *67*, 290.

(4) Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299.

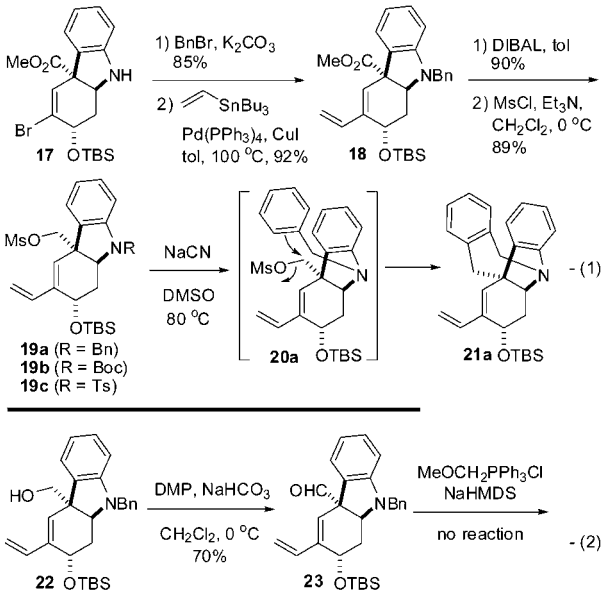
(5) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc.* **2003**, *125*, 14288.

(6) Kim, W.-S.; Lee, J.-H.; Kang, J.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 1683.

(7) The isolated **9**-*exo* was subjected to the same reaction sequence to provide **17** in slightly lower overall yield.

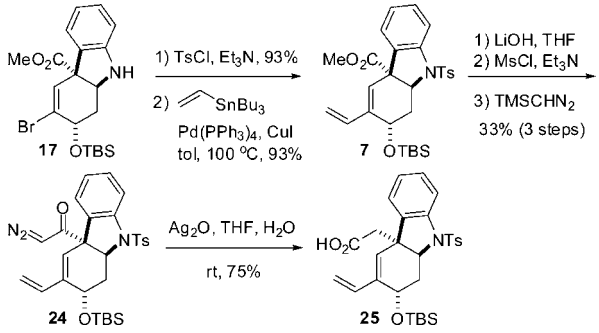
(8) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2007**, *9*, 1461.

Scheme 3. Attempted One-Carbon Homologation Reactions



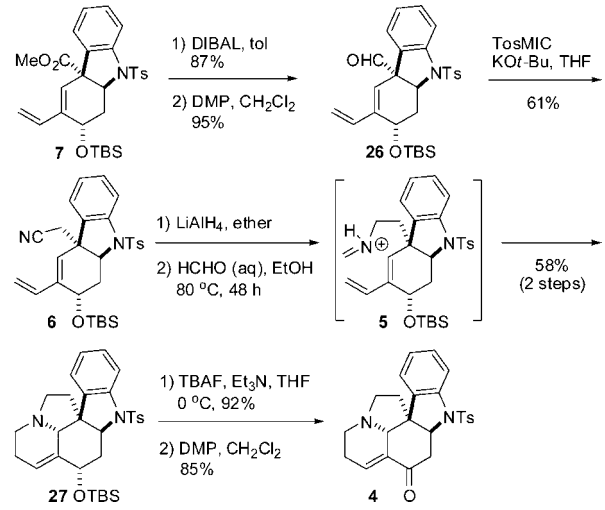
With an Arndt−Eistert homologation in que,[9] ester **17** was transformed to **7**, prior to the hydrolysis into the corresponding carboxylic acid (Scheme 4). Sequential treatment with mesyl chloride followed by a displacement reaction with TMS diazomethane afforded α-diazo ketone **24** in moderate total yield (33%, 3 steps). Silver oxide mediated decomposition of α-diazo ketone provided the much desired one-carbon extended carboxylic acid **25** in 75% yield.[10]

Scheme 4. Arndt−Eistert Homologation



Later, we found that the van Leusen TosMIC homologation approach[11] was more effective in our system, affording nitrile **6** in 61% yield from aldehyde **26** (Scheme 5). Similar homologation of aldehyde **26** under the Nicolaou conditions also gave nitrile **6** but in much lower total yield.[12] Reduction of the cyano group to amine followed by heating with aqueous formaldehyde effected the intramolecular imino Diels−Alder reaction to provide **27** in 51% total yield from nitrile **6**.[13] Desilylation and oxidation furnished the key pentacyclic enone **4** in good total yield.

Scheme 5. Synthesis of Pentacyclic Enone **4**



In summary, we have devised a new synthetic route to enone **4**, the key framework of aspidosperma alkaloid, from 3,5-dibromo-2-pyrone via an intramolecular imino Diels−Alder reaction.

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Supporting Information Available: Details of experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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