A General Strategy to *Aspidosperma* Alkaloids: Efficient, Stereocontrolled Synthesis of Tabersonine

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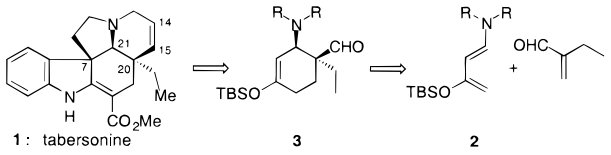
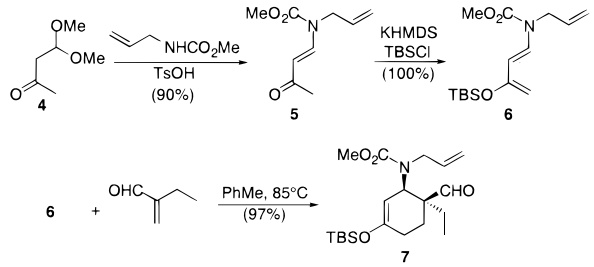
The *Aspidosperma* family comprises the largest group of indole alkaloids, with more than 250 compounds.[1] These alkaloids possess a complex pentacyclic skeleton that is conformationally rigid due to the cis relationship of the three contiguous stereocenters at C(7), C(21), and C(20) in the cyclohexenyl ring. The structural challenge posed by these alkaloids in conjunction with the potent pharmacological properties exhibited by several members has stimulated considerable effort directed toward their synthesis.[1] We describe here a conceptually new strategy to the *Aspidosperma* family of alkaloids,[1c] illustrated through a concise, highly stereocontrolled synthesis of tabersonine.

Isolated in 1954 from *Amsonia tabernaemontana*, tabersonine (**1**)[2] plays a central role in the biosynthesis of *Aspidosperma* alkaloids, serving as the biogenetic[1,3] (as well as synthetic)[4] predecessor of other members of the *Aspidosperma* family—most notably of vindoline, a key component of the clinically important antitumor agents vinblastine and vincristine.[5]



Our strategy to the *Aspidosperma* pentacycle is based on the recognition that control of the cis relationship between the amino group and C(15) on ring C is tantamount to solving all the stereochemical problems for these alkaloids. A particularly attractive solution for this stereocontrol was possible through a Diels−Alder reaction using our recently developed amino siloxy dienes.[6] Thus, the cycloaddition between ethacrolein and diene **2**

Scheme 1



was expected to give exclusively the endo cycloadduct **3**, in which the enol ether is poised for regioselective introduction of the required indole unit.[6a] What would be needed was the development of effective chemistry for the conversion of **3** to the *Aspidosperma* pentacycle.

The *N*-allyl-*N*-carbomethoxy diene **6** was chosen for the pivotal Diels−Alder reaction (Scheme 1). The carbomethoxy group was selected to temper the reactivity of the amino group, and the allyl group was chosen to provide a means to construct the piperidine ring. The condensation of commercially available acetylacetaldehyde dimethylacetal (**4**) with methyl *N*-(2-propenyl)carbamate in the presence of a catalytic amount of *p*-toluenesulfonic acid[7] in refluxing chloroform afforded vinylogous imide **5** in 90% yield. The treatment of a slight excess of the imide with KHMDS followed by quenching of the resulting enolate with TBSCl gave the desired diene (**6**) in quantitative yield, even on a multigram scale.[8] The cycloaddition reaction between diene **6** and ethacrolein proceeded with complete regiocontrol and excellent endo selectivity to yield adduct **7** in 97% yield.

Having achieved the cis relative stereochemistry required for *Aspidosperma* alkaloids, we then proceeded to construct the hexahydroquinoline ring system of these alkaloids using a ring-closing metathesis reaction.[9] The aldehyde was first converted into the desired vinylated compound **8** via a Wittig olefination (Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C; 85% yield). The critical ring-closing metathesis reaction was examined using both Grubbs's ruthenium[10] catalyst and Schrock's molybdenum[11] catalyst. Whereas both catalysts promoted the desired metathesis, the latter gave a cleaner, higher-yielding conversion to the product **9**, which was isolated in 88% yield.[12,13] It is worth noting that, despite its presence adjacent to the enol silyl ether, the amino group has remained intact.

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(4) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 155.

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(8) It was found that the use an excess of KHMDS (1.1 equiv), according to the general protocol described in ref 6a, resulted in partial isomerization of the double bond of the allyl group into an internal position.

(9) Recent reviews on olefin metathesis: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

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(12) Use of the Grubbs catalyst (7 mol %, CH_2Cl_2, 40 °C, 2 h) afforded **9** in 75% isolated yield.

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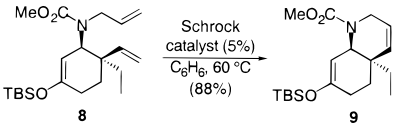
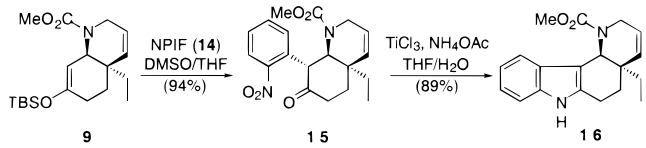


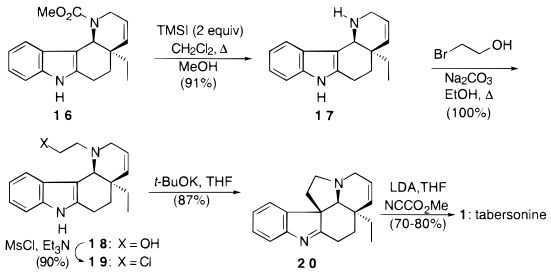
The regiocontrolled installation of the indole unit on bicycle **9** proved challenging. Most of the available methods for indole synthesis involve the reaction of a ketone with a suitable aryl partner and, consequently, do not always provide predictable control of the regiochemistry. Having unsuccessfully examined a few of these procedures,[14−17] we decided to develop an indole synthesis that took advantage of the regiospecifically formed enol silyl ether present in **9**. Building on the precedent provided by Chen and Koser,[18] we prepared *o*-nitrophenylphenyliodonium fluoride (NPIF),[19] with the expectation that the more electron deficient nitrophenyl group would react with the enol silyl ether. In the event, treatment of a solution of enol ether **9** with NPIF cleanly generated the desired α-arylated ketone **15** in 94% yield, as the single diastereomer shown (Scheme 2). Reduction[20] of the nitro group using $TiCl_3$ gave the desired, regiospecifically generated indole **16** in 89% yield.

What was required for the end game leading to the *Aspidosperma* skeleton was introduction of the two carbons for the pyrrolidine ring that is in a spiro arrangement to the indole. Although this construction is precedented in the *Aspidosperma* alkaloids area,[21] the yields for this transformation have been variable. The methyl carbamate group was first removed by the reaction of **16** with trimethylsilyl iodide in refluxing CH_2Cl_2, followed by a methanol quench to hydrolyze the labile silyl carbamate.[22,23] Alkylation of the resulting secondary amine with a 10-fold excess of bromoethanol in the presence of sodium carbonate in refluxing ethanol for 18 h afforded the desired tertiary amine **18** in quantitative yield (Scheme 3).[24]

Scheme 2



Scheme 3



The final cyclization required the conversion of the hydroxy group in **18** into a leaving group, followed by a base-mediated intramolecular nucleophilic displacement by the indole anion.[21] Interestingly, activation of the alcohol of **18** using mesyl chloride gave not the expected mesylate but the corresponding chloride (**19**), presumably arising via the aziridinium ion.[25] On reaction with *t*-BuOK in THF, chloride **19** was efficiently converted to didehydroaspidospermidine **20**,[26] a common late-stage intermediate to several *Aspidosperma* alkaloids.[1] Deprotonation of **20** with LDA in THF followed by acylation with Mander's reagent[27] gave cleanly the C-acylated product, tabersonine (**1**), in 70−80% yield.[28,29]

In summary, we have described here a novel, highly stereocontrolled route to *Aspidosperma* alkaloids. The strategy was illustrated through the total synthesis of (±)-tabersonine, which was achieved in 12 steps and ca. 30% overall yield, the highest reported to date. The synthesis illustrates (a) the complete regioselectivity and excellent endo selectivity possible with 1-amino-3-siloxy-1,3-butadienes, which have been developed in our laboratory, (b) the use of an olefin metathesis reaction to construct the *cis*-hexahydroquinoline ring system, having the double bond correctly positioned for these alkaloids, and (c) a novel indole synthesis based on the regiospecific *ortho*-nitrophenylation of an enol silyl ether.

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Supporting Information Available: Experimental procedures and compound characterization data, including copies of NMR spectra for all new compounds (36 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(13) The structure of **9** was established by a combination of the DQF COSY and NOESY experiments. The cis stereochemistry of the hexahydroquinoline system was confirmed by the strong NOE cross-peaks between the proton adjacent to the nitrogen and the methylene unit of the ethyl group.

(14) For example, see: (a) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676. (b) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Berkeley, W. C. *J. Am. Chem. Soc.* **1974**, *96*, 5495.

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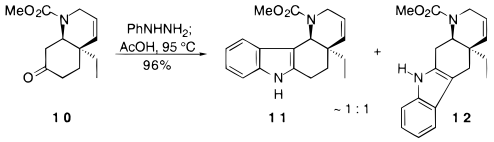
(16) Fischer Indole synthesis: Robinson, B. *The Fischer Indole Synthesis*; J. Wiley & Sons: New York, 1982.

(17) For example, when ketone **10**, obtained from hydrolysis of **9** (1.2 M HCl, THF/H_2O, 96%), was subjected to Fischer indolization procedure ((a) $PhNHNH_2$·HCl, Na_2CO_3, EtOH; (b) AcOH, 95 °C), it produced both regioisomeric tetracycles in 96% yield in approximately a 1:1 ratio.



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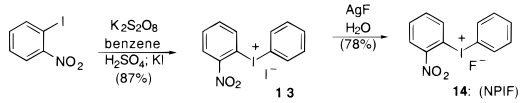
(19) Birman, V. B.; Kozmin, S. A., unpublished results. NPIF was prepared according to the scheme shown below. The full details of this preparation and its application to indole synthesis will be reported separately.



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(22) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.

(23) (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.

(24) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, S. *J. Org. Chem.* **1989**, *54*, 5591.

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(26) This two-step process was also carried out in one step, albeit less reproducibly, using Rubiralta's recently reported conditions (ref 22). Thus, simply treating alcohol **18** with TsCl and *t*-BuOK in THF at room temperature gave directly the desired didehydroaspidospermidine **20** in up to 51% isolated yield, with ca. 70% conversion of the starting material.

(27) (a) Mander, L. N. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol. 5, p 3465. (b) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256 and references therein.

(28) Acylation using methyl chloroformate gave the C-acylated product in 37% isolated yield, along with an appreciable amount of the N-acylated compound. For a precedent, see ref 2f.

(29) The 500-MHz ^1H NMR and 125-MHz ^{13}C NMR spectra of our synthetic sample of tabersonine were identical to those previously reported in the literature. See: (a) refs 2d and 2e. (b) Wen, R.; Laronze J.-Y.; Lévy, J. *Heterocycles* **1984**, *22*, 1061.