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# Regiocontrol in an Intramolecular Schmidt Reaction: Total Synthesis of (+)-Aspidospermidine

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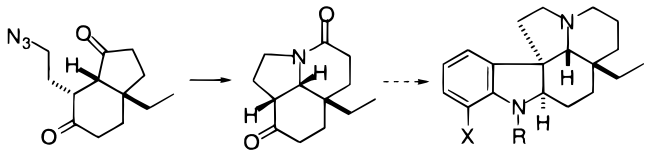
## ABSTRACT



**A total synthesis of (+)-aspidospermidine (1) is described, featuring an intramolecular Schmidt reaction as the key step. The effects of stereochemistry and protecting group status on the regio- and chemoselectivity of this reaction were examined.**

The intramolecular Schmidt reaction is a versatile tool for the synthesis of fused, nitrogen-containing heterocycles.[1] As part of a program to explore the use of this reaction in total synthesis, we chose the pentacyclic alkaloid aspidospermidine (**1**) as an initial entry into this interesting class of natural products.[2] The total synthesis of (±)-aspidospermine by Stork and Dolfini was an important achievement in alkaloid chemistry.[3] This work established that all of the stereocenters in the final target were responsive to a single, nonepimerizable quaternary center in ketone **2** (C-22, Scheme 1). We sought to utilize this finding in an asymmetric approach that would focus on the enantioselective formation of this center.[4] Further motivation was provided by the opportunity to examine a challenging intramolecular Schmidt reaction, in which selectivity for insertion into only one of two regioisomeric ketones is required for the preparation of a key tricyclic lactam **4**. In this paper, we describe a route to (+)-aspidospermidine (**1**) using these general strategies that additionally uncovered some unexpected features of intramolecular Schmidt chemistry.

The key step for the preparation of enantiomerically

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(4) Asymmetric total syntheses of aspidospermidine: (a) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517−521. (b) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292−2303. (c) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855−6861. In addition, an asymmetric approach to the Stork tricyclic intermediate **2** has been reported: (d) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673−4676.

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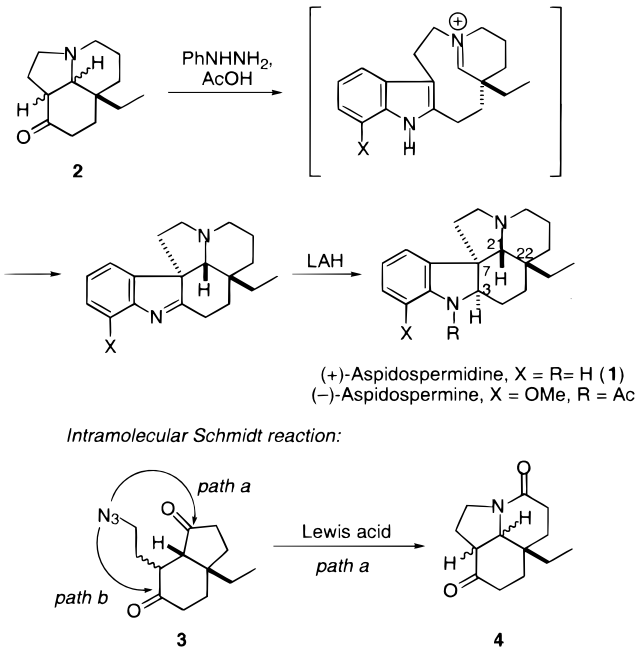
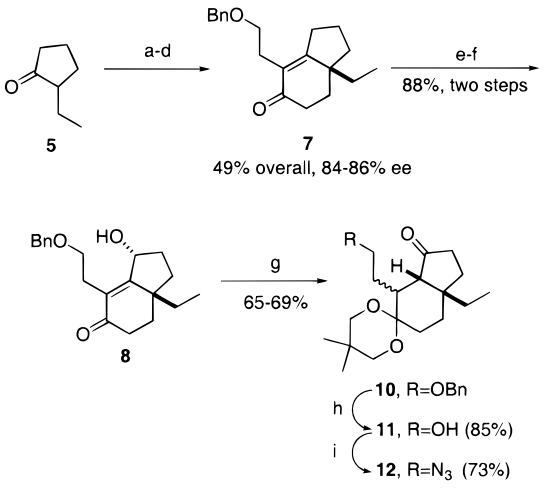
**Scheme 1**




enriched enone **7** was a deracemizing imine alkylation protocol as introduced by d'Angelo (Scheme 2).[5] The best results were obtained by carrying out the initial Michael addition step in the presence of fused $ZnCl_2$.[6] In this way, treatment of the α-methylbenzylidene imine of **5** with 6-(benzyloxy)hex-1-ene-3-one (**6**)[7] gave enone **7** in ca. 85% ee, with simple recrystallization of a later intermediate ultimately providing a convenient entry into an enantiomerically pure synthesis. The introduction of $\gamma$-oxidation was

**Scheme 2**

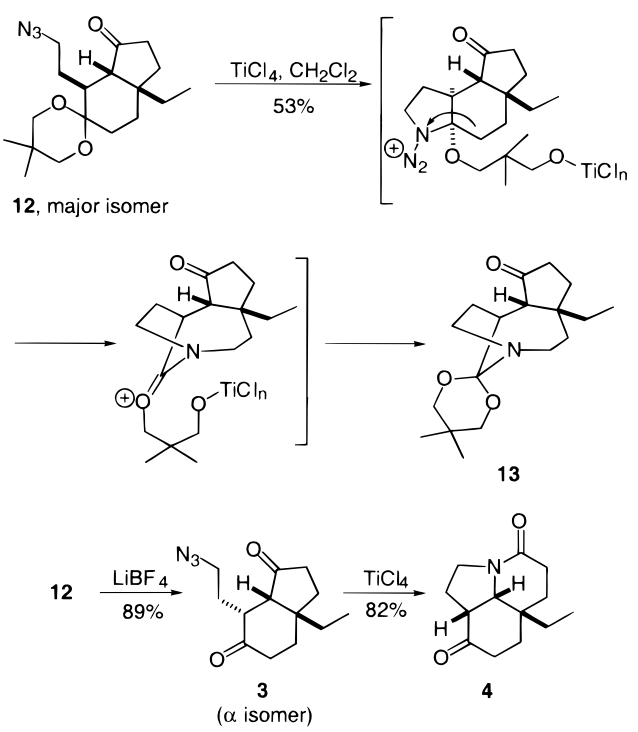



[a] Reagents and conditions: (a) (*S*)-α-methylbenzylamine; (b) 6-(benzyloxy)hex-1-en-3-one (**6**), HQ, $ZnCl_2$, $Et_2O$, reflux; (c) 10% aq AcOH; (d) NaOMe, MeOH, reflux; (e) isopropenyl acetate; (f) Oxone, acetone; (g) bis(trimethylsilyl)neopentyl glycol (**9**), TMSOTf, $CH_2Cl_2$, 0 °C→ rt; (h) $H_2$, 10% Pd/C; (i) $HN_3$, $PPh_3$, DEAD, PhH, 0 °C→ rt.

achieved by first converting the enone to its dienol acetate followed by treatment with Oxone to give **8** in 88% yield over two steps. Early versions of the synthesis entailed multistep routes to oxidize the alcohol, reduce the double bond, and accomplish side chain functionalization. In addition, difficulties were encountered in the seemingly simple displacement by azide in saturated diketo chlorides related to **8**.[8] The route was significantly improved by the simple, expedient ketalization of the C-3 carbonyl (aspidospermidine numbering). In this reaction, olefin migration was followed by tautomerization to **10** (formed as 12:1 mixture of $\beta$/α side chain stereoisomers), accomplishing formal $\gamma$-oxidation and double bond "reduction" in a single step. This material was readily converted, without further ado, to the corresponding azide by debenzylation and a Mitsunobu reaction.

The stage was now set for the key heterocycle-forming reaction (Scheme 3). It was expected that an intramolecular

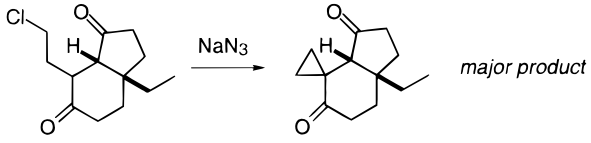
**Scheme 3**




Schmidt reaction in **12** would occur at the uniquely unprotected carbonyl group. However, treatment of **12** afforded only **13**, which involved Lewis acid activation of the ketal,

(7) Synthesized from 1,4-butanediol by monobenzylation, PCC oxidation, vinyl Grignard addition, and Jones oxidation.

(8) For example, attempted azidation of the intermediate shown below resulted in cyclopropane formation as the major product. In addition, it did not prove feasible to open this cyclopropane with azide in a subsequent step.

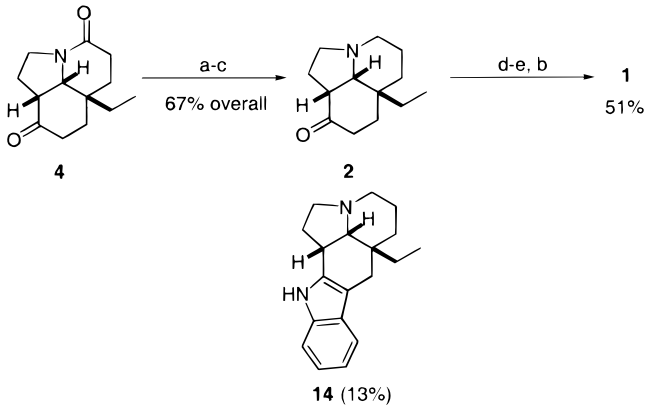


followed by attack of azide and *migration of the less-substituted carbon to nitrogen*. Although intramolecular reactions of alkyl azides with ketals had been previously established,[9] this reaction marked the first time that (1) such a reaction with a ketal prevailed over addition to ketone and (2) that a bridged nitrogen ring system was observed in this chemistry. We hypothesized that this mode of reaction was favored because of the trans disposition of the azidoethyl substituent and the cyclopentantone carbonyl in structure **12**; further evidence of this was obtained through an X-ray crystallographic structure of compound **13**, which confirmed the stereochemical assignment as shown.

Previous work had established that simple intramolecular Schmidt reactions are more facile when there are four atoms between the azide and carbonyl groups rather than three.[1a,f] This would translate into selective reaction of the desired carbonyl in the case of unprotected **12** (i.e., path a in Scheme 1). Furthermore, it was expected that revealing the C-3 carbonyl in **3** would permit isomerization of the side chain into the requisite α position. Thus, deketalization ($LiBF_4$) gave diketo azide **3**; NMR analysis revealed that deprotection was accompanied by substantial epimerization in favor of the desired isomer (1:10 $\beta/\alpha$). As proposed, the intramolecular Schmidt reaction then proceeded smoothly to give tricyclic lactam **4** as a single diastereomer in 82% yield and 84% ee. The enantiomerically enriched lactam was then recrystallized from EtOAc/hexanes (50% overall yield after recrystallization) to enantiomeric purity (≥99% ee, Chiralcel OD, 10% EtOH/hexanes).

As reported for a related lactam,[3a] this material did not prove amenable to a direct Fisher indole synthesis and so was converted in a three-step process to the corresponding ketoamine by selective protection of the ketone carbonyl, followed by a reduction/deprotection sequence (Scheme 4). The synthesis was then completed by invoking Stork's classic Fischer indolization to afford (+)-aspidospermidine (51% overall yield from **2**) accompanied by 13% of a side product **14** (which arises from the less-substituted enamine regioisomer). It is worth noting that the reported yields of similar Fisher indole processes using 2-methoxyphenylhydrazine on ketones such as **2** are variable (and in some cases unreported),[3a,10] and accordingly this step has often been circumvented in approaches to this series of alkaloids.[2−4] Spectral data ($^1H$ and $^{13}C$ NMR, IR, MS), mp (118−119 °C), and specific rotation of aspidospermidine ($[\alpha]_D = 20.6$ (*c* 0.64, EtOH)) were fully consistent with reported values[11] (mp 119.5−121 °C, $[\alpha]_D = 21$ (EtOH)).

**Scheme 4**




[a] Reagents and conditions: (a) **9**, TMSOTf, $CH_2Cl_2$, 0 °C→ rt; (b) LAH, THF, reflux; (c) $LiBF_4$, aq $CH_3CN$, reflux; (d) $PhNHNH_2$; (e) AcOH, reflux.

In summary, a total synthesis of (+)-aspidospermidine has been completed. Noteworthy steps include the protection/oxidation state adjustment reaction leading to ketal **10**, and the regioselective Schmidt reaction of diketone **3**. The latter reaction, in particular, shows that high selectivity for reaction with a given ketone can be obtained without recourse to protecting group chemistry. Indeed, Lewis acid activation of a "protected" analogue of **3** led to a hitherto unobserved mode of Schmidt reactivity, which is itself worthy of additional study.

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