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# Revisiting a Classic Approach to the *Aspidosperma* Alkaloids: An Intramolecular Schmidt Reaction Mediated Synthesis of (+)-Aspidospermidine

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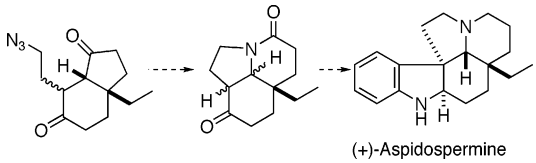
*Received June 14, 2005*

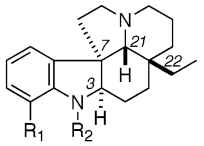



A total synthesis of (+)-aspidospermidine (**1**) is described. The key reactions used in the synthesis of this pentacyclic *Aspidosperma* alkaloid were a deracemizing imine alkylation/Robinson annulation sequence, a selective "redox ketalization", and an intramolecular Schmidt reaction. A Fischer indolization step carried out on a tricyclic ketone mirrored the sequence reported by Stork and Dolfini in their classic aspidospermine synthesis.

## Introduction

The *Aspidosperma* alkaloids have inspired considerable interest since the early days of complex organic synthetic chemistry research.[1] Over the years, a number of racemic[2,3] syntheses as well as enantioselective[4] approaches to (+)-aspidospermidine and (−)-aspidospermine, the prototypical members of the group, have been reported.

The first successful foray into this class was the total synthesis of (±)-aspidospermine **2** by Stork and Dolfini.[2]




One highlight of this synthesis was the use of a Fischer indole condensation to generate the core structure of the natural product (Scheme 1). This reaction proceeded through iminium ion **4**, so the configurations of C-7 and C-21 were controlled relative to the quaternary center C-22. The final stereocenter (C-3) was set through a stereoselective reduction of imine **5**. Thus, a stereoselective route to aspidospermine or aspidospermidine could arise, in principle, from any diastereomer of the Stork ketone **3**. Accordingly, an asymmetric synthesis of **3** presents a worthwhile challenge.[5] Herein we disclose a total synthesis of (+)-aspidospermidine (**1**) that uses the Stork approach in the context of modern enantioselective

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(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.

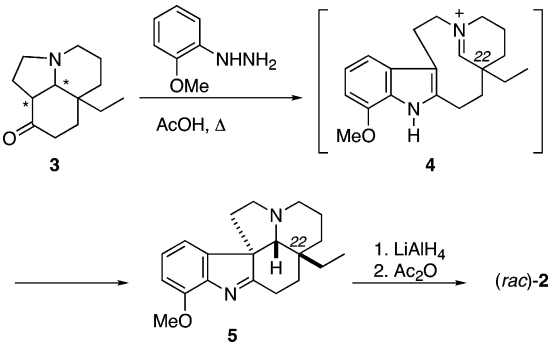
(2) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872−2973.

(3) (a) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965,** 2261−2268. (b) Barton, J. E. D.; Harley-Mason, J. *Chem. Commun.* **1965,** 298−299. (c) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966,** *88,* 3656−3657. (d) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967,** 915−916. (e) Inoue, I.; Ban, Y. *J. Chem. Soc.* **1970,** 602−610. (f) Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92,* 1727−1735. (g) Klioze, S. S.; Darmory, F. P. *J. Org. Chem.* **1975**, *40*, 1588−1592. (h) Dufour, M.; Gramain, J. C.; Husson, H. P.; Sinibaldi, M. E.; Troin, Y. *J. Org. Chem.* **1990**, *55,* 5483−5490. (i) Benchekroun-Mounir, N.; Dugat, D.; Gramain, J. C.; Husson, H. P. *J. Org. Chem.* **1993**, *58,* 6457−6465. (j) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, *59*, 7677−7682. (k) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995−1002. (l) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *Tetrahedron Lett.* **1999**, *40*, 161−164. (m) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599−3601. (n) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642−2645. (o) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2613−2618. (p) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, *3*, 213−215.

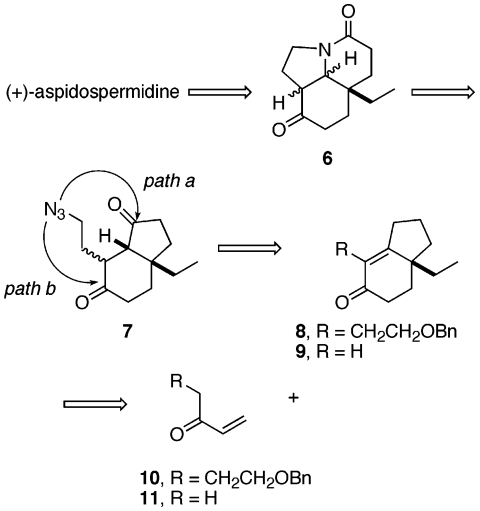
(4) (a) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517−521. (b) d'Angelo, J.; Revial, G.; Costa, P. R. R.; Castro, R. N.; Antunes, O. A. C. *Tetrahedron: Asymmetry* **1991**, *2,* 199−202. (c) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994,** *59,* 2292−2303. (d) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855−6861. (e) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002,** *124,* 4628−4641. (f) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002,** *124,* 13398−13399. (g) Tanino, H.; Fukuishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron Lett.* **2002,** *43,* 2385−2388. (h) Tanino, H.; Fukuishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004,** *60,* 3273−3282.

10.1021/jo051212n CCC: $30.25 
Published on Web 11/30/2005

**SCHEME 1**




**SCHEME 2**

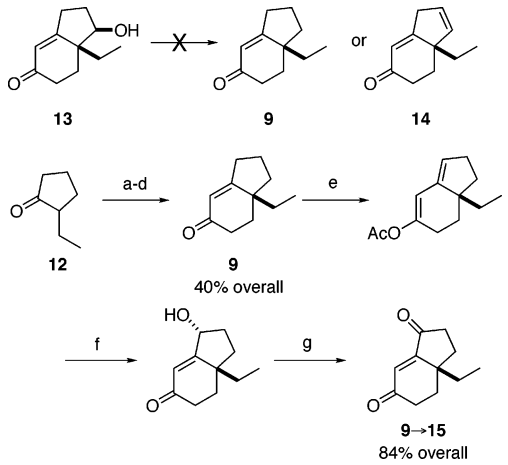



synthesis and also provided an opportunity to carefully examine the late-stage Fischer indole step.

Our plan for the construction of enantiomerically pure **6** involved an intramolecular Schmidt reaction[6] of **7** (Scheme 2), which could be derived from bicyclic enone **8**. To be successful, this step would require the selective Schmidt reaction of the azide with the cyclopentanone embedded in **7** (path a) to the exclusion of the six-membered cyclic ketone (path b). Although such selectivity had not been demonstrated prior to this work, model studies showed that compounds with four carbons separating the two reactive moieties underwent ring expansion chemistry much more easily than those with only three, which would support the selective formation of the desired product.[6] We envisioned an asymmetric synthesis of a precursor enone **8** or **9** from 2-ethylcyclopentanone **12** using the asymmetric variant of the Robinson annulation invented by d'Angelo's group,[7] thus establishing the critical quaternary stereocenter in the desired configuration.

Herein, we describe the successful implementation of this strategy. The discussion is arranged along three

**SCHEME 3**[a]




[a] Reagents and conditions: (a) (*S*)-α-methylbenzylamine; (b) **11**, hydroquinone, 60 °C; (c) 10% aq AcOH; (d) NaOMe, MeOH, reflux; (e) isopropenyl acetate; (f) Oxone, acetone; (g) PCC, $CH_2Cl_2$.

major themes: (1) the development of a synthesis of dione **7**, (2) investigation of the key intramolecular Schmidt reaction, and (3) the conversion of enantiomerically pure Stork intermediate **6** into (+)-aspidospermidine.[8] Finally, a ketal-mediated rearrangement reaction, discovered during the course of this work, was the first time a bridged ring system was observed to result from an intramolecular Schmidt reaction.

## Results and Discussion

**Synthesis of Key Bicyclic Diketo Azide. Early Results.** Our first route to the bicyclic ring system revolved around the intermediacy of enone **9** (Scheme 3). The plan was to synthesize compound **13** from 2-ethyl-1,3-pentanedione using the well-documented Hajos–Parrish reaction,[9] followed by reduction of the saturated ketone carbonyl group. Once in hand, we planned to remove the extraneous alcohol in **13** using a deoxygenation or elimination reaction.[10] Although **13** was readily synthesized as planned, all attempts at converting **13** to **9** or **14** were unsuccessful. In contrast, the application of the d'Angelo annulation protocol to racemic 2-ethylcyclohexanone was successful and provided enone **9** in modest yield. The enone function provided a convenient handle for installing a carbonyl in the $\gamma$ position. Thus, enone **9** was allowed to reflux briefly with isopropenyl acetate and *p*-TsOH to effect its quantitative transformation to the corresponding dienol acetate depicted. Oxidation of this material with Oxone followed by PCC afforded enedione **15** in excellent overall yields for the three-step protocol.

The direct installation of an alkyl side chain by vinyl cuprate 1,4-addition to enedione **15** was unsuccessful, affording only reduction products. A variety of other reactions, including allylsilane additions to **15** or various reduction products of same, were unsuccessful, nonselec-

(5) (a) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989,** *54,* 4673–4676. (b) Fukuda, Y.-I.; Shindo, M.; Shishido, K. *Org. Lett.* **2003,** *5,* 749–751. (c) Gnecco, D.; Vazquez, E.; Galindo, A.; Teran, J. L.; Orea, L.; Bernes, S.; Enriquez, R. G. *ARKIVOC* (*Gainesville, FL, U.S.*) **2003,** part xi, 185–192.

(6) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.

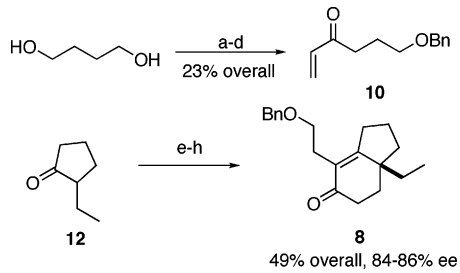
(7) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.

(8) Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625–1627.

(9) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974,** *39,* 1615–1621. (b) List, B. *Tetrahedron* **2002,** *58,* 5573–5590.

(10) Abel, U.; Koch, C.; Speitling, M.; Hansske Friedrich, G. *Curr. Opin. Chem. Biol.* **2002**, *6*, 453–458.

**SCHEME 4**[a]

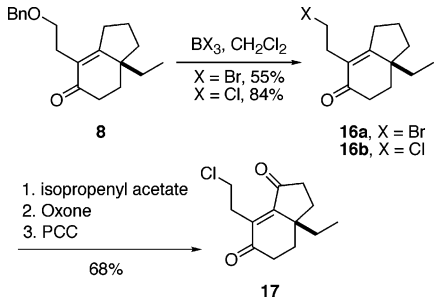



[a] Reagents and conditions: (a) NaH, BnBr, DMF; (b) PCC, $CH_2Cl_2$; (c) $CH_2{=}CH_2MgBr$, THF; (d) $CrO_3$, $H_2SO_4$, acetone; (e) (*S*)-α-methylbenzylamine; (f) **10**, hydroquinone, fused $ZnCl_2$, $Et_2O$, reflux; (g) 10% aq AcOH; (h) NaOMe, MeOH, reflux.

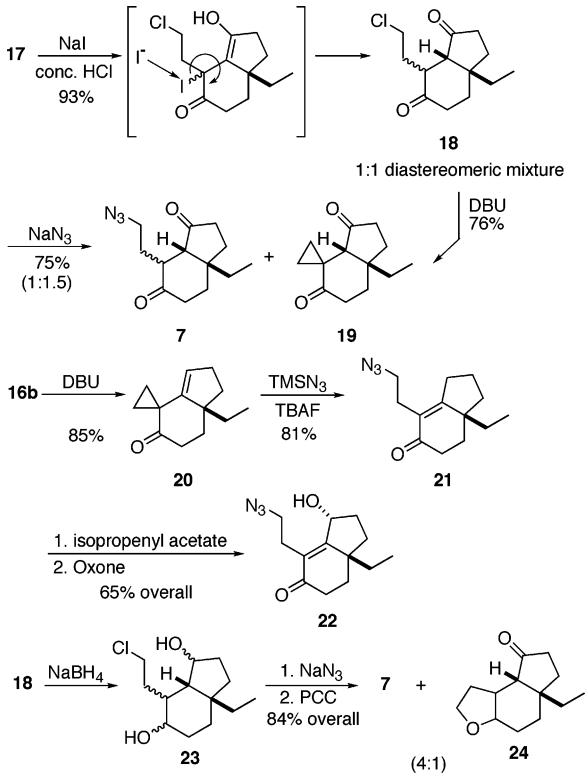
tive, or inefficient. Accordingly, we redirected our efforts to obtain enone **8**, already bearing the necessary side chain, in a more convergent fashion (Scheme 4). To this end, the α,*β*-unsaturated ketone **10** was synthesized from 1,4-butanediol. Turning again to the d'Angelo deracemization protocol, cyclopentanone **12** was condensed with (*S*)-α-methylbenzylamine, and the resulting enamine was condensed with vinyl ketone **10**. Alkene polymerization was moderated by the addition of a small amount of 1,4-hydroquinone. The multiday reaction was followed by acidic hydrolysis (10% aqueous $CH_3COOH$) and intramolecular aldol reaction under basic conditions (NaOMe, MeOH) to afford the bicyclic enone **8** in 49% overall yield and 66% ee (HPLC, Chiralcel AS, 20% 2-propanol/hexanes, 254 nm). The relatively low enantioselectivity was not surprising because the literature indicates that additional steric bulk in the enamine intermediate may result in poor face selectivity.[7] Ultimately, the selectivity was improved by applying Lewis acid activation[11] (fused $ZnCl_2$, refluxing ether, 3 d), followed by the usual cyclization methods, to generate 84−86% ee material in similar yield as before. This material was brought to enantiomeric purity at a later step.

With an appropriately substituted [4.3.0]bicyclononenone in hand, it remained to install the azide nucleophile and an additional ketone function to arrive at the required Schmidt reaction substrate. It soon became apparent that precise choice and ordering of the steps was crucial. Initially, we envisioned utilizing a Mitsunobu reaction to transform the primary alcohol derived from **8** into the requisite azide. However, catalytic debenzylation of **8** performed under a variety of conditions also led to unwanted reduction of the enone function. Selective deprotection of the side chain could be achieved by brief exposure of the substrate to either boron tribromide or boron trichloride to directly yield the corresponding alkyl bromide **16a** or chloride **16b**, respectively (Scheme 5).[12] The unexpected halogenation of the terminal alcohol was considered a bonus as alkyl halides easily succumb to nucleophilic azide displacement. The chloride (prepared in higher yield and more stable than **16a**) was therefore transformed to the corresponding enedione **17** as in Scheme 5.

**SCHEME 5**




**SCHEME 6**



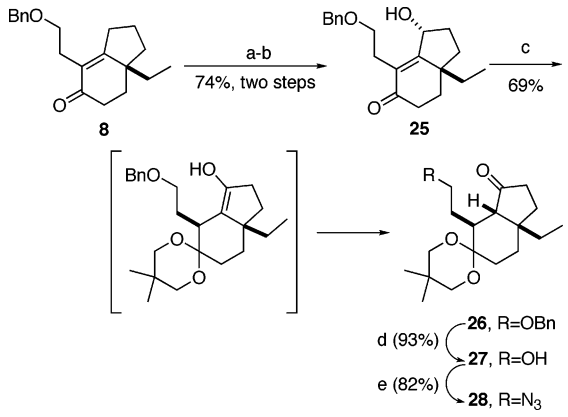

The chemoselective reduction of the double bond in enedione **17** was accomplished by treatment with concentrated HCl and sodium iodide to afford the bicyclic scaffold **18** as a 1:1 diastereomeric mixture (Scheme 6).[13] This reduction presumably involves initial 1,4-attack of iodide followed by a second displacement on the α-iodoketone to produce the reduced 1,4-dione. The stage was now set for azide displacement of the chloride; however, the reaction afforded mixtures of the expected product **7** and an undesired cyclopropane **19**. The ease of the intramolecular displacement process was confirmed by exposing **18** to base, which cleanly afforded **19** as the only product. This compound proved resistant to all nucleophilic ring opening attempts. In an effort to circumvent this problem, enone **16b** was subjected to base, cleanly affording cyclopropane **20** containing a nonconjugated double bond. In contrast to **19**, cyclopropane **20** proved amenable to ring opening, presumably because of the

(11) Williams, D.; Cortez, G. S. *Tetrahedron Lett.* **1998**, *39*, 2675−2678.

(12) (a) Amrollah-Madjdabadi, A.; Pham, T. N.; Ashby, E. C. *Synthesis* **1989**, 614−616. (b) Pelletier, J. D.; Poirier, D. *Tetrahedron Lett.* **1994,** *35,* 1051−1054.

(13) (a) Utaka, M.; Fujii, Y.; Takeda, A. *Chem. Lett.* **1986**, 1103−1104. (b) Vankar, Y. D.; Kumaravel, G.; Mukherjee, N.; Rao, C. T. *Synth. Commun.* **1987**, *17*, 181−187. (c) Gondos, G.; Orr, J. C. *Liebigs Ann. Chem.* **1990**, 213-215.

**SCHEME 7**[a]



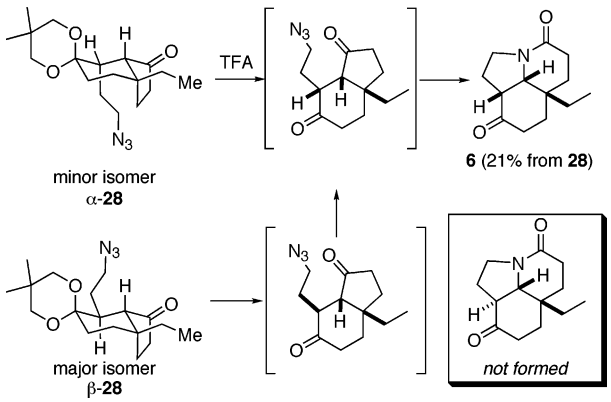

[a] Reagents and conditions: (a) isopropenyl acetate; (b) Oxone, acetone; (c) bis(trimethylsilyl)neopentyl glycol, TMSOTf, $CH_2Cl_2$, 0 °C → rt; (d) $H_2$, 10% Pd/C; (e) $HN_3$, $PPh_3$, DEAD, PhH, 0 °C → rt.

greater stability of the enolate anion formed upon nucleophilic attack.[14] The enone in **21** could be functionalized by $\gamma$-oxidation, but this route was abandoned because of the difficulty of selective double bond reduction in azide **22**.

Since enolization/intramolecular trapping was the major hurdle in the functionalization of **18**, we decided to reduce both carbonyls to alcohols, followed by an azidation/oxidation sequence. Thus, dione **18** was reduced with $NaBH_4$ to diol **23**, which was isolated as an inseparable mixture of products. This mixture was immediately subjected to azidation and oxidation to afford **7**. Unfortunately, the interference of another intramolecular process (displacement of the chloride by the proximal alcohol) gave the cyclic ether **24** as an unwanted byproduct (a 4:1 mixture of **7** and **24** was obtained). Compound **7** as obtained in these reactions was valuable as it allowed us to rehearse the critical Schmidt reaction and complete a first-generation synthesis of aspidospermidine (all such experiments are collected in the following section). However, all of the above routes were ultimately rejected for use in the final synthesis because of their inability to cleanly deliver the key intermediate **7**.

**Effective Synthesis of Key Bicyclic Diketo Azide 7.** Rethinking our plan, we decided to protect the bicyclic scaffold prior to side chain manipulation. Thus, $\gamma$-oxidation of **8** afforded alcohol **25**, which was treated with bis(TMS)neopentyl glycol and a catalytic amount of TMSOTf to afford ketal **26** directly (Scheme 7). This "redox ketalization" involves regioselective ketal and concomitant deconjugation, leading to an enol that undergoes tautomerization to ketone **26**. This step also rendered the carbon bearing the side chain nonepimerizable. $^1$H NMR analysis of **26** revealed a 12:1 mixture of diastereomers that contained other inseparable impurities. This material proved to be unstable and so was rapidly subjected to reductive debenzylation followed by a Mitsunobu reaction to afford azide **28**. Detailed examination of the NMR spectra, including NOESY and COSY experiments, indicated that the major component of this ca. 12:1 mixture had the stereostructure shown in Scheme 7. For details regarding this and other important structural assignments in this work, see Supporting Information.

**SCHEME 8**




**Study of the Intramolecular Schmidt Reaction.** The scaffold was now appropriately functionalized for intramolecular Schmidt reaction with the unprotected carbonyl. Our initial attempts using TFA on **28** provided deketalized compound **6** as the single diastereomer shown, in 21% yield (Scheme 8; see Supporting Information for this structural elucidation). This isomer thus derives from the *minor* diastereomer of **28**, which is present in only a few percent in the starting material.

The poor yield in the Schmidt reaction is likely due to competitive pathways occurring in lieu of cyclization. It is possible that the azide in the major isomer $\beta$-**28** cannot reach the necessary carbonyl group and therefore azide decomposition occurs faster than deketalization or epimerization (note that cyclization of this isomer would afford a product containing a strained *trans*-[4.3.0]bicyclo ring system). Using TFA, only the isomer with the side chain in the axial position ($\alpha$-**28**) underwent cyclization to form the all-*cis* version of **6** (Scheme 8). The fact that the overall yield exceeds the amount of minor azido ketal $\alpha$-**28** present in the reaction mixture probably means that some deketalization can occur prior to Schmidt reaction but that this process is poorly competitive with azide decomposition. Deketalization may proceed prior to Schmidt reaction in $\alpha$-**28** as well, as shown in Scheme 8, but we have no evidence either in support of or against this.)

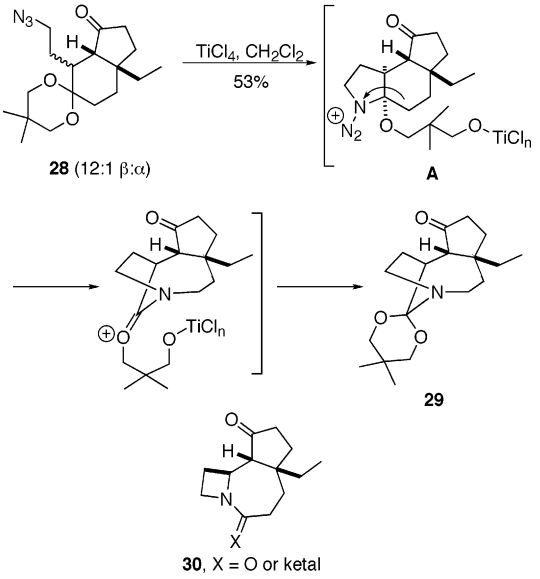
In contrast, treating the 12:1 mixture of **28** with $TiCl_4$ afforded **29** isolated in moderate yields (Scheme 9). This product apparently arose from Lewis acid activation of the ketal to afford oxenium ion, followed by attack of the azide and C → N migration. Under these conditions, none of the desired compound **6** was isolated.

This result was surprising in several ways. Although reactions of azides with ketals or enol ethers had been previously demonstrated,[15] we had expected that the ketal would in this case fulfill its designated role as a protecting group. The preferential reaction of the ketal over the carbonyl could be due to stereochemistry. Thus, carbonyl activation might occur but azide may not attack due to the trans relationship of the side chain to the ketone. Alternatively, $TiCl_4$ activation of the ketal could

(14) The ring opening of activated cyclopropanes is well established to proceed better when two activating groups are present. Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66−72.

(15) Mossman, C. J.; Aubé, J. *Tetrahedron* **1995**, *52*, 3403−3408.

**SCHEME 9**



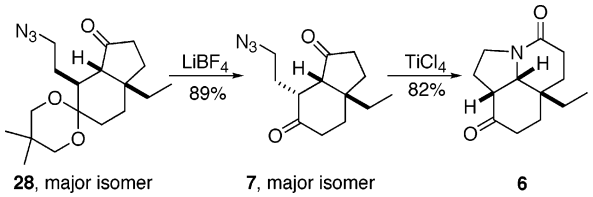

preferentially effect ketal opening over coordination to the C=O group. Unfortunately, the less stable $\gamma$-epimer was not easily prepared to address this question directly. However, we could confirm that $\beta$-**28** led to **29** by X-ray confirmation of the latter structure (Supporting Information).

Also noteworthy was the isolation of the bridged orthoaminal **29** in this reaction. Prior to this experiment, no bridged product had been isolated in an azido-Schmidt reaction carried out in our laboratory. In the present case, it is likely that ring system **30** containing a four-membered ring did not form due to strain. It is also possible that the azido-Schmidt reaction of the ketal better accommodates bridged product formation than the ketone version; in the latter case, the fused amide product enjoys resonance stabilization, whereas the bridged (or "twisted")[16] amide cannot. After this study, we discovered some specialized examples of bridged amides from azido ketones resulting from intramolecular Schmidt reactions of azides and ketones.[17] The factors that influence bridged versus fused product formation in intramolecular Schmidt reactions is the subject of current research in this laboratory.

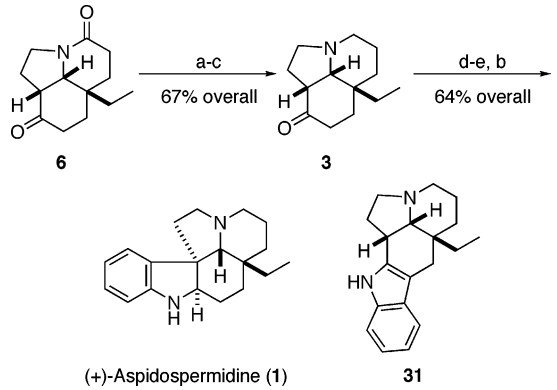
In light of this result, we returned to our original plan of selectively carrying out the ring expansion on diketone **7**, postulating that epimerization would precede Schmidt reaction in this substrate. Gratifyingly, deketalization was easily effected under mild conditions to afford the diketo azide **7**, predominantly as the desired isomer (1:10 $\beta$/$\alpha$, Scheme 10; see Supporting Information for structural assignment of **7**).

In contrast to the above examples, treatment of **7** with $TiCl_4$ gave tricyclic lactam **6** as a single diastereomer in 82% yield and 84% ee. The exclusive formation of this product confirmed our original hypothesis that a regioselective Schmidt reaction was possible in this system. The enantiomerically enriched lactam was then recrystallized from EtOAc/hexanes to enantiomeric purity (50% overall yield after recrystallization, ≥99% ee, Chiralcel OD, 10% EtOH/hexanes).

**SCHEME 10**




**SCHEME 11**[a]




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

**Conversion of the Stork Ketone to Aspidospermidine.** All that remained was the completion of the synthesis using the Fischer indole protocol. Most literature examples of this particular reaction have been reported to proceed in poor yield (or no yield was reported at all), a fact that lessens the impact of formal syntheses invoking the Stork[2] or related intermediates as well.[5] We therefore wished to directly address this issue.

As reported for related lactams,[5b,c] **6** did not prove amenable to a direct Fischer indole synthesis and so was reduced in a three-step process to the corresponding keto amine **3** by selective protection of the ketone carbonyl followed by a reduction/deprotection sequence (Scheme 11). Treatment of **3** with phenylhydrazine, acid, and finally LAH afforded (+)-aspidospermidine (**1**, 51% overall yield from **3**) accompanied by 13% of a side product **31**. This side product presumably arose via the Fischer indolization of the less-substituted enamine isomer. A similar product was mentioned in a paper addressing the synthesis of an oxygenated analogue of aspidospermine without ratios or yields.[18]

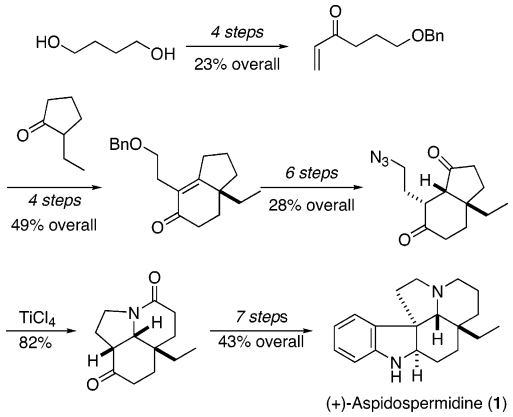
The structural analysis of this latter compound was nontrivial, and extensive NMR experiments were needed to deduce the structure (Supporting Information). Interestingly, it was necessary to rigorously rid (+)-aspidospermidine of **31** for analysis as even minor quantities of this "impurity" threw off the optical rotation of **1** substantially on account of large levorotatory rotation of (−)-**31** ($[\alpha]_D = -100$ (*c* 0.4, EtOH)) relative to that of (+)-**1**. Spectral data ($^1H$ and $^{13}C$ NMR, IR, MS), mp (118−119 °C), and specific rotation ($[\alpha]_D = 20.6$ (*c* 0.64, EtOH))

(16) Greenberg, A. In *Structure and Reactivity*; Liebman, J. F., Greenberg, A., Eds.; VCH: New York, 1988; pp 139−178.

(17) (a) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41,* 4316−4318. (b) Lei, Y.; Wrobleski, A. D.; Golden, J. E.; Powell, D. R.; Aubé, J. *J. Am. Chem. Soc.* **2005,** *127,* 4552−4553.

(18) Inoue, I.; Ban, Y. *J. Chem. Soc. C* **1970**, 602−610.

**SCHEME 12**




of purified **1** were fully consistent with reported values (mp 119.5−121 °C, $[\alpha]_D = 21$ (EtOH)).[19]

## Summary

In summary, a total synthesis of (+)-aspidospermidine was completed, with the ultimately crafted version summarized in Scheme 12. The most linear route comprised 22 steps and took place in 1.1% overall yield from butylene glycol. The most noteworthy elements of this synthesis include (1) a highly selective intramolecular Schmidt reaction on a nonsymmetrical diketone, (2) the establishment of the quaternary stereogenic center via a d'Angelo deracemization process (from which all of the rest of the target's stereocenters derive), (3) the conversion of an $\gamma$-hydroxy-$\alpha,\beta$-unsaturated ketone to a 1,4-diketone via an internal redox process, and (4) the first observation of a bridged orthoaminal from an intramolecular azide insertion process on a ketal.

## Experimental Section

**4-(2'-Benzyloxyethyl)-7a-ethyl-1,2,3,6,7,7a-hexahydroinden-5-one (8).** A solution of 2-ethylcyclopentanone[20] (5.36 g, 47.9 mmol), (*S*)-α-methylbenzylamine (6.38 g, 52.6 mmol) and *p*-TsOH (0.45 g, 2.4 mmol) in benzene (25 mL) was thoroughly degassed and was allowed to reflux for 17 h using a Dean−Stark trap. After the theoretical amount of $H_2O$ had been removed, the remaining benzene was distilled off at atmospheric pressure, and the crude imine residue was cooled to room temperature and suspended in $Et_2O$ (10 mL).

Fused $ZnCl_2$ (3.26 g, 24 mmol) was suspended in $Et_2O$ (15 mL) and was added to the imine, followed by 6-benzyloxy-1-hexen-3-one (11.7 g, 57.4 mmol) and hydroquinone (ca. 100 mg). The resulting solution was heated at reflux for 72 h, then cooled to room temperature and stirred for an additional 8 h. Aqueous acetic acid (25%, 60 mL) was added and the resulting biphasic solution was stirred vigorously for 3 h. The mixture was poured over 1 M HCl and extracted with $Et_2O$. The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was added to a solution of sodium methoxide (119.7 mmol) in methanol (70 mL) and allowed to reflux for 24 h. The reaction mixture was then cooled to room temperature, quenched with a few drops of acetic acid, and concentrated to yield a brown oil that was dissolved in $Et_2O$, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford a brown oil. Baseline impurities were removed by silica gel chromatography, eluting with 10% EtOAc in hexanes, and the crude product was distilled (200−220 °C, 1 Torr) to yield 7.00 g (49%) of the title compound **8** ($R_f = 0.20$, 20% $Et_2O$ in hexanes) as a light yellow oil. $[\alpha]_D = -33.3$ (*c* 3.63, $CH_2Cl_2$); IR (film) 1645 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.65 (t, $J = 7.5$ Hz, 3H), 1.27 (m, 1H), 1.44 (q, $J = 7.5$ Hz, 2H), 1.63 (td, $J = 13.8, 5.4$ Hz, 1H), 1.81 (m, 2H), 2.00 (dt, $J = 12.6, 4.2$ Hz, 1H), 2.18 (ddd, $J = 13.3, 5.3, 1.9$ Hz, 1H), 2.33 (ddd, $J = 18.2, 5.4, 1.9$ Hz, 1H), 2.45 (dd, $J = 14.2, 5.3$ Hz, 1H), 2.55 (m, 2H), 2.64 (t, $J = 7.7$ Hz, 2H), 3.49 (m, 2H), 4.50 (s, 2H), 7.32 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 9.6, 22.0, 26.0, 27.5, 30.4, 31.3, 33.9, 36.8, 46.7, 69.5, 73.1, 127.78, 127.83, 128.3, 128.7, 139.2, 175.5, 198.9; CIMS *m/z* (relative intensity) 299 ($MH^+$, 90), 207 (25), 191 (65), 91 (40). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.22; H, 9.00.

**4-(2'-Benzyloxyethyl)-7a-ethyl-3-hydroxy-1,2,3,6,7,7a-hexahydroinden-5-one (25).** A solution of enone **8** (2.0 g, 6.7 mmol) and *p*-TsOH (0.25 g) in isopropenyl acetate (10 mL) was heated at reflux for 5 h. The reaction mixture was then cooled to room temperature and diluted with $Et_2O$. The organic layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The resulting solution was concentrated in vacuo to a light yellow oil. The residue was immediately dissolved in a mixture of acetone (40 mL), saturated aqueous $NaHCO_3$ (20 mL), and $H_2O$ (20 mL) and treated with 6 g of Oxone. After 3 h, the reaction mixture was poured into $H_2O$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography-(25% EtOAc/hexanes) to yield 1.85 g (88%) of **25** ($R_f = 0.35$, 30% EtOAc in hexanes) as a clear oil. $[\alpha]_D = -7.5$ (*c* 3.25, EtOH); IR ($CH_2Cl_2$) 3401, 1657 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.89 (t, $J = 7.4$ Hz, 3H), 1.25−1.40 (m, 2H), 1.67−1.72 (m, 2H), 1.80−1.88 (m, 2H), 1.90−2.00 (m, 1H), 2.15−2.20 (m, 1H), 2.30−2.35 (m, 1H), 2.39−2.47 (m, 2H), 2.78 (dt, $J = 2.2, 14.0$ Hz, 1H), 3.35 (ddd, $J = 2.2, 9.0, 11.5$ Hz, 1H), 3.58 (dt, $J = 4.0, 9.0$ Hz, 1H), 4.47 (d, $J = 5.6$ Hz, 1H), 4.51 (s, 1H), 4.78 (d, $J = 5.6$ Hz, 1H), 7.22−7.36 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 9.4, 27.3, 27.7, 30.6, 32.3, 33.2, 33.5, 46.0, 67.0, 70.9, 73.0, 127.8, 127.85, 128.3, 129.7, 137.0, 175.6, 199.3; CIMS *m/z* (relative intensity) 315 ($MH^+$, 100), 297 (45), 207 (52), 91 (49); HRMS calcd for $C_{20}H_{26}O_3$ 314.1882, found 314.1902.

**7-(2'-Benzyloxyethyl)-3a-ethyl-6-(5',5'-dimethyl[1,3]dioxan-2'-yl)octahydroinden-1-one (26).** TMSOTf (0.848 g, 3.82 mmol) was added dropwise to a 0 °C solution of allylic alcohol **25** (4.00 g, 12.7 mmol) and bis(trimethylsilyl)neopentyl glycol (4.74 g, 19.1 mmol) in $CH_2Cl_2$ (30 mL). This mixture was stirred for 10 h while it was allowed to warm to room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$ (20 mL), extracted with $CH_2Cl_2$, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (10% EtOAc/hexanes) to yield 3.50 g (69%) of **26** ($R_f = 0.7$, 25% EtOAc in hexanes) as a yellow oil. $[\alpha]_D = +30.6$ (*c* 3.6, $CH_2Cl_2$); IR ($CH_2Cl_2$) 1734 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.77 (s, 3H), 0.86 (t, $J = 7.4$ Hz, 3H), 1.05 (s, 3H), 1.43−1.95 (m, 11H), 2.12−2.20 (m, 1H), 2.29−2.36 (m, 1H), 2.99 (d, $J = 9.4$ Hz, 1H), 3.16 (dd, $J = 2.0, 11.7$ Hz, 1H), 3.26 (dd, $J = 2.0, 11.7$ Hz, 1H), 3.49−3.61 (m, 4H), 4.50 (d, $J = 3.0$ Hz, 2H), 7.24−7.36 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 8.17, 22.3, 23.0, 26.7, 28.0, 28.3, 29.5, 30.6, 31.3, 32.0, 34.6, 40.9, 53.2, 69.1, 69.5, 69.6, 70.5, 72.8, 96.5, 127.4, 127.5, 128.1, 128.2, 138.5, 219.0; FAB *m/z* (relative intensity) 401 ($MH^+$, 35), 307 (32), 207 (49), 154 (100); 136 (100); HRMS calcd for $C_{25}H_{36}O_4$ 400.2599, found 400.2614.

**7-(2'-Hydroxyethyl)-3a-ethyl-6-(5,5-dimethyl-[1,3]dioxan-2-yl)-octahydro-inden-1-one (27).** Benzyl ether **26** (3.10 g, 7.75 mmol) and 10% Pd/C (0.465 g, 15% w/w) were stirred in MeOH (75 mL) under a hydrogen atmosphere (balloon). After 12 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo, and the crude product residue was

(19) Camerman, A.; Camerman, N.; Kutney, J. P.; Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, 637−642.

(20) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702−4715.

purified by chromatography (30% EtOAc/hexanes) to yield 2.05 g (85%) of **27** ($R_f$ = 0.24) as a clear oil. $[\alpha]_D$ = +28.1 (*c* 1.4, $CH_2Cl_2$); IR (film) 3429, 1733 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 7.4 Hz, 3H), 0.94 (s, 3H), 0.97 (s, 3H), 1.40−1.49 (m, 3H), 1.55−1.70 (m, 5H), 1.75−1.85 (m, 1H), 1.89 (d, *J* = 6.2 Hz, 1H), 1.95−2.05 (m, 1H), 2.06−2.15 (m, 1H), 2.17−2.25 (m, 1H), 2.33−2.45 (m, 1H), 2.54 (m, 1H), 3.35−3.41 (m, 2H), 3.48−3.65 (m, 3H), 3.65−3.75 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 8.1, 22.7, 25.7, 27.1, 28.8, 29.7, 30.2, 32.3, 34.6, 35.8, 41.0, 57.3, 62.0, 69.6, 69.7, 98.5, 219.9; CIMS *m/z* (relative intensity) 310 ($M^+$, 3), 293 (9), 207 (100), 141 (65); 55 (16); HRMS calcd for $C_{18}H_{30}O_4$ 310.2144, found 310.2131.

**7-(2′-Azidoethyl)-3a-ethyl-6-(5′,5′-dimethyl[1,3]dioxan-2′-yl)-octahydroinden-1-one (28).** DEAD (2.58 g, 14.8 mmol) was added to a 0 °C solution of **27** (2.30 g, 7.42 mmol), $PPh_3$ (3.9 g, 14.8 mmol) and $HN_3$ (8.9 mL of a 2.5 M solution in benzene, 22.3 mmol) in benzene (40 mL) and stirred for 11 h while it was allowed to warm to room temperature. The reaction was quenched with $H_2O$ (100 mL) and extracted with $Et_2O$. The organic extracts were washed with saturated aqueous $NaHCO_3$, water, and brine (20 mL each), dried over $MgSO_4$, and concentrated in vacuo, and the resulting residue was purified by chromatography (5% EtOAc/hexanes), to yield 1.81 g (73%) of **28** ($R_f$ = 0.73, 30% EtOAc in hexanes) as a light yellow oil. $[\alpha]_D$ = +37.9 (*c* 5.54, $CH_2Cl_2$); IR ($CH_2Cl_2$) 2957, 2100, 1733 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.88 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 3H), 0.97 (s, 3H), 1.39−1.50 (m, 3H), 1.58−1.70 (m, 4H), 1.77−1.82 (m, 2H), 1.96−2.02 (m, 2H), 2.18−2.25 (m, 1H), 2.32−2.42 (m, 1H), 2.53−2.57 (m, 1H), 3.28−3.55 (m, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 8.1, 22.6, 22.7, 26.5, 26.8, 27.0 (2 peaks), 29.4, 29.6, 32.2, 34.2, 34.6, 50.8, 56.7, 69.6, 69.7, 98.5, 218.9; CIMS *m/z* (relative intensity) 336 ($MH^+$, 4), 293 (9), 308 (39), 279 (14), 222 (41); 141 (100); HRMS calcd for $C_{18}H_{29}N_3O_3$ 335.2209, found 335.2202.

**6-Ethyl-12-(5′,5′-dimethyl[1,3]dioxan-2′-yl)-9-azatricyclo[7.2.1.0]dodecan-3-one (29).** $TiCl_4$ (0.07 g, 0.36 mmol) was added dropwise to a solution of **28** (0.040 g, 0.12 mmol) in $CH_2Cl_2$ (5 mL) maintained at 0 °C and stirred for 3 h while it warmed to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and *i*-PrOH (5 mL), poured into brine, and filtered through a pad of wet Celite. It was then extracted with $CH_2Cl_2$, the organic extracts were washed with saturated aqueous $NaHCO_3$, water and brine (10 mL each), dried over $MgSO_4$, and concentrated in vacuo, and the resulting residue was purified by chromatography, eluting with EtOAc and then 10% MeOH in EtOAc, to yield 0.020 g (52%) of **29** ($R_f$ = 0.75, 10% MeOH in EtOAc) as a light yellow solid: mp = 74−76 °C; IR ($CCl_4$) 2948, 1737 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.71 (s, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 1.10 (s, 3H), 1.25 (m, 1H), 1.36−1.43 (m, 3H), 1.52−1.60 (m, 1H), 1.79 (d, *J* = 3.6 Hz, 1H), 2.00−2.04 (m, 1H), 2.14−2.20 (m, 2H), 2.23−2.27 (m, 2H), 2.69 (m, 1H), 2.76 (m, 1H), 2.95−3.04 (m, 3H), 3.12 (dd, *J* = 10.6, 2.4 Hz, 1H), 3.22 (dd, *J* = 10.3, 2.4 Hz, 1H), 3.61 (d, *J* = 10.3 Hz, 1H), 3.81 (d, *J* = 10.6 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 8.6, 21.7, 22.8, 28.8, 29.3, 29.35, 33.0, 36.6, 38.8, 44.3, 44.8, 47.0, 49.0, 56.0, 68.0, 72.0, 112.0, 213.0; CIMS *m/z* (relative intensity) 308 ($MH^+$, 100), 307 ($M^+$, 14), 222 (51), 121 (45), 84 (20), 79 (15), 55 (31); HRMS calcd for $C_{18}H_{30}NO_3$ 308.2226, found 308.2202.

**7-(2′-Azidoethyl)-3a-ethylhexahydroindene-1,6-dione (7).** $LiBF_4$ (0.36 g, 3.88 mmol) was added to **28** (0.26 g, 0.77 mmol) in 20% $H_2O$ in $CH_3CN$ (20 mL total volume) and heated at 70 °C for 18 h. The reaction was then diluted with $H_2O$, extracted with $Et_2O$, dried ($MgSO_4$), concentrated in vacuo, and chromatographed to afford 0.17 g (89%) of **7** ($R_f$ = 0.44, 30% EtOAc in hexanes) as a colorless oil. IR ($CH_2Cl_2$) 3053, 1737, 1712 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (t, *J* = 7.4 Hz, 3H), 1.40 (sextet, *J* = 7.0 Hz, 1H), 1.54−1.60 (m, 2H), 1.81−2.10 (m, 8H), 2.36−2.45 (m, 4H), 2.58−2.62 (m, 1H), 3.26−3.31 (m, 1H), 3.39−3.44 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 8.0, 28.5, 29.3, 29.7, 31.1, 34.8, 35.8, 41.8, 43.6, 49.4, 60.1, 211.1, 217.9; CIMS *m/z* (relative intensity) 250 ($MH^+$, 2), 222 (44), 192 (12), 165 (17), 43 (100); HRMS calcd for $C_{13}H_{20}N_3O_2$ 250.1555, found 250.1547.

**(6a*S*)-Ethyloctahydropyrrolo[3,2,1-*ij*]quinoline-4,9-dione (6).** $TiCl_4$ (0.049 g, 0.256 mmol) was added dropwise to a 0 °C solution of diketo azide **7** (0.058 g, 0.233 mmol) in $CH_2Cl_2$ (3 mL) and stirred for 2 h, then allowed to warm to room temperature and stirred for an additional 15 min. The reaction was quenched with solid $NaHCO_3$/*i*-PrOH, poured into brine, and filtered through a pad of wet Celite. The filtrate was extracted with $CH_2Cl_2$, and the organic extracts washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The brown residue was purified by chromatography, eluting with EtOAc followed by 10% MeOH in EtOAc, to afford 0.042 g (82%) of **6** ($R_f$ = 0.24, EtOAc) as a light yellow crystalline solid. Mp = 139−140 °C; $[\alpha]_D$ = −89.1 (*c* 1.575, $CH_2Cl_2$); IR (film) 1705, 1630 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.00 (t, *J* = 7.5 Hz, 3H), 1.50 (m, 1H), 1.57−1.73 (m, 3H), 1.83 (m, 2H), 2.00 (m, 1H), 2.25−2.50 (m, 4H), 2.63 (m, 1H), 2.86 (t, *J* = 5.9 Hz, 1H), 3.42 (dd, *J* = 10.0, 4.7 Hz, 2H), 3.63 (d, *J* = 4.9 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 7.4, 22.1, 25.2, 27.9, 29.2, 29.7, 34.1, 36.3, 43.8, 49.4, 68.5, 168.2, 208.6; EIMS *m/z* (relative intensity) 222 ($MH^+$, 80), 49 (30); HRMS calcd for $C_{13}H_{20}NO_2$ 222.1504, found 222.1494.

**6a-Ethyldecahydropyrrolo[3,2,1-*ij*]quinolin-9-one (3).** TMSOTf (0.06 g, 0.27 mmol) was added to a mixture of **6** (0.06 g, 0.27 mmol) and bis(trimethylsilyl)neopentyl glycol (0.402 g, 1.62 mmol) in $CH_2Cl_2$ (5 mL) maintained at 0 °C. The reaction was stirred for 6 h and warmed to room temperature. It was quenched with saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, dried ($MgSO_4$), and concentrated to a brown oil. $R_f$ = 0.5 (10% MeOH in EtOAc); IR ($CCl_4$) 2951, 1638 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.69 (s, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 1.17 (s, 3H), 1.20−1.25 (m, 3H), 1.50−1.56 (m, 2H), 1.72−1.79 (m, 3H), 2.23 (dd, *J* = 7.0, 5.4 Hz, 1H), 2.29−2.33 (m, 2H), 2.37−2.42 (m, 1H), 2.57 (dt, *J* = 10.5, 3.6 Hz, 1H), 3.22−3.31 (m, 4H), 3.48 (d, *J* = 11.4 Hz, 1H), 3.72 (d, *J* = 11.4 Hz, 1H), 3.80 (q, *J* = 11.2 Hz, 3H).

The crude ketal was added to $LiAlH_4$ (0.05 g, 1.35 mmol) in THF (5 mL) and heated at reflux for 10 h. The reaction was quenched with water, filtered through wet Celite, and extracted with $Et_2O$. The organic extracts were dried ($MgSO_4$) and concentrated to a brown oil. This oil was charged with $LiBF_4$ (0.126 g, 1.35 mmol) and dissolved in 10% $H_2O/CH_3CN$ and heated at 80 °C for 8 h. The reaction was then diluted with water, extracted with $Et_2O$, dried ($MgSO_4$), concentrated, and chromatographed to give 0.037 g (66% overall) of **3** as a colorless oil. $R_f$ = 0.51 (10% MeOH in EtOAc); IR (film) 1700 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.95 (t, *J* = 7.5 Hz, 3H), 1.12 (td, *J* = 13.4, 4.6 Hz, 1H), 1.34 (m, 1H), 1.51 (m, 2H), 1.59−1.87 (m, 4H), 1.93 (m, 3H), 2.22−2.47 (m, 4H), 2.68 (m, 1H), 3.30 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 7.6, 21.69, 21.72, 26.5, 30.5, 33.3, 35.1, 37.2, 48.6, 53.3, 53.6, 74.0, 211.9; CIMS *m/z* (relative intensity) 208 ($MH^+$, 100), 178 (30), 82 (50).

**(+)-Aspidospermidine 1 and Byproduct 31.** Amino ketone **3** (0.036 g, 0.174 mmol) and phenylhydrazine (0.02 g, 0.208 mmol) in 5 mL of PhH were allowed to reflux for 3.5 h. The reaction was then cooled to room temperature and concentrated in vacuo. The crude phenylhydrazone was allowed to reflux in 5 mL of AcOH for 4 h and then concentrated in vacuo to afford the crude indoline as a dark brown oil. This material was dissolved in THF (5 mL), treated with $LiAlH_4$ (0.066 g, 1.74 mmol), and allowed to reflux for 12 h. After cooling to 0 °C and quenching with $H_2O$/NaOH, the mixture was filtered through a plug of Celite and concentrated in vacuo. The resulting residue was purified by chromatography (EtOAc) to yield 0.025 g (51%) aspidospermidine (**1**) as a pale yellow oil that crystallized upon standing and **31** (0.0065 g, 13%) as a colorless oil. **Data for (+)-aspidospermidine (1):** $R_f$ = 0.29 (10% MeOH/EtOAc); mp = 117−119 °C (acetone) (lit.[19] 119−121 °C) $[\alpha]_D$ = +20.6 (*c* 0.65, EtOH) (lit.[2] +21 (*c* 7.4, EtOH)); IR (film) 3320, 1600 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.66 (t, *J* = 7.5 Hz, 3H), 0.88 (m, 1H), 1.07 (m, 1H), 1.13 (td, *J* =

13.5, 4.6 Hz, 1H), 1.36−1.57 (m, 4H), 1.66 (m, 2H), 1.76 (qt, $J$ = 12.8, 3.9 Hz, 1H), 1.97 (m, 2H), 2.24 (s, 1H), 2.22−2.37 (m, 2H), 3.08 (m, 1H), 3.14 (m, 1H), 3.53 (dd, $J$ = 11.0, 6.2 Hz, 1H), 6.66 (d, $J$ = 7.8 Hz, 1H), 6.75 (t, $J$ = 7.3 Hz, 1H), 7.04 (td, $J$ = 7.6, 0.9 Hz, 1H), 7.10 (d, $J$ = 7.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 7.2, 22.2, 23.4, 28.5, 30.4, 34.9, 36.0, 39.2, 53.5, 53.8, 54.3, 66.1, 71.7, 110.7, 119.4, 123.3, 127.5, 136.1, 149.8; CIMS *m/z* (relative intensity) 283 ($MH^+$, 60), 254 (25), 210 (25), 124 (100).

**Data for 5a-Ethyl-1,3,4,5,5a,6,11,11d-octahydro-2H,-11cH-2a,11-diazo-indeno[1,7-*ab*]fluorene** (**31**): $R_f$ = 0.1 (10% MeOH/EtOAc); $[\alpha]_D$ = −100 (*c* 0.4, EtOH); IR ($CH_2Cl_2$) 3459, 2934 $cm^{-1}$; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 0.86 (t, $J$ = 7.5 Hz, 3H), 1.23−1.38 (m, 3H), 1.45−1.55 (sextet, $J$ = 7.5 Hz, 1H), 1.68−1.77 (m, 2H), 1.89−2.05 (m, 3H), 2.16 (m, 1H), 2.24 (m, 1H), 2.36 (q, $J$ = 12.0 Hz, 1H), 2.51 (d, $J$ = 15.0 Hz, 1H), 2.79 (d, $J$ = 15.0 Hz, 1H), 3.12 (br t, $J$ = 9.0 Hz, 1H), 3.52 (m, 1H), 6.94 (td, $J$ = 7.0, 1.0 Hz, 1H), 7.04 (td, $J$ = 7.0, 1.0 Hz, 1H), 7.24 (d, $J$ = 7.8 Hz, 1H), 7.37 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (100 MHz, MeOH-$d_4$−$CDCl_3$) $\delta$ 5.6, 20.5, 22.1, 26.7, 29.2, 31.5, 32.7, 35.2, 52.2, 53.7, 71.5, 103.7, 104.3, 109.3, 116.2, 117.1, 119.3, 126.9, 136.4; EIMS *m/z* (relative intensity) 281 ($MH^+$, 100), 124 (70), 58 (14); HRMS calcd for $C_{19}H_{25}N_2$ 281.2018, found 281.2025.

**Acknowledgment.** We thank the National Institutes of Health (GM-49093) for the support of this work, David Vander Velde for NMR spectroscopy consultation, Doug Powell for X-ray crystallography, and Timothy Ribelin for help with compound characterization.

**Supporting Information Available:** Details of stereochemical assignments, additional experimental details, copies of $^1$H and $^{13}$C NMR spectra, and X-ray crystallographic details for compound **29** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO051212N