Total Synthesis of the Alkaloid (±)-Aspidophytine Based on Carbonyl Ylide Cycloaddition Chemistry

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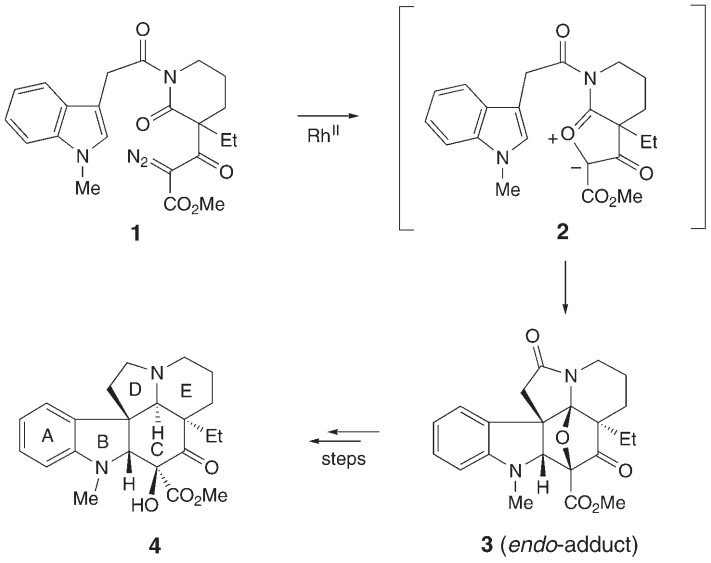
The Rh^{II}-catalyzed cycloaddition cascade of an indolyl-substituted α-diazo imide was used for the total synthesis of the complex pentacyclic alkaloid (±)-aspidophytine. Treatment of the resulting dipolar cycloadduct with $BF_3 \cdot OEt_2$ induces a domino fragmentation cascade. The reaction proceeds by an initial cleavage of the oxabicyclic ring and formation of a transient *N*-acyl iminium ion which reacts further with the adjacent *tert*-butyl ester and sets the required lactone ring present in aspidophytine. A three-step sequence was then used to remove both the ester and OH groups. Subsequent functional group manipulations allowed for the high-yielding conversion to (±)-aspidophytine.

Introduction. – Construction of azapolyheterocycles through dipolar cycloaddition chemistry has been a particularly fruitful area of investigation, and the synthesis of various types of alkaloids by this approach has been carried out by numerous investigators [1]. Several years ago, we began a synthetic program to provide general access to a variety of *Aspidosperma* alkaloids by making use of a rhodium(II)-catalyzed reaction of α-diazo imides [2]. The *Aspidosperma* alkaloids occupy a central place in natural-product chemistry because of their wide range of complex structural variations and diverse biological activity [3]. 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 of the stereogenic centers and most of the functional groups are located in this ring [4]. Individual members differ mainly in functionality and configuration. Our earlier approach toward deacetoxy-4-oxo-6,7-dihydrovindorosine (**4**) involved the initial generation of carbonyl ylide **2** from the Rh^{II}-catalyzed cyclization reaction of α-diazo imide **1** [5]. This was followed by an intramolecular 1,3-dipolar cycloaddition across the tethered indolyl π-bond [6]. The resulting pentacyclic adduct **3** was then converted into **4** in several additional steps (*Scheme 1*) [7]. Prompted by our initial work, we decided to initiate a synthetic project using this general approach for the construction of (±)-aspidophytine, a structurally more demanding aspidosperma target.

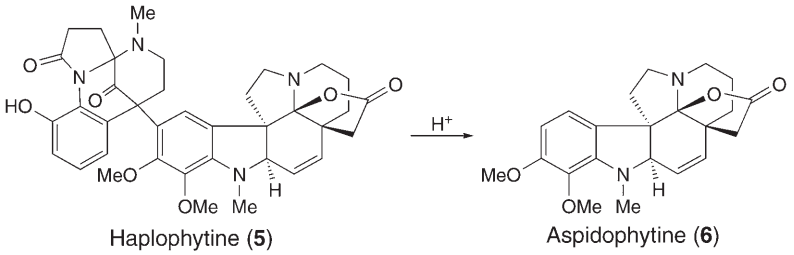
In 1973, *Cava* and *Yates* reported on the structural determination of haplophytine (**5**), a 'bisindole' alkaloid isolated from the leaves of *Haplophyton cimicidum* [8][9]. The structure of **5** was firmly established by an X-ray crystallographic analysis [10]. Acid cleavage of haplophytine (**5**) led to aspidophytine (**6**) [11] (*Scheme 2*), a lactonic *Aspidospermine* type of alkaloid which has been suggested to be not only a biosynthetic precursor of **5** but also a possible intermediate to be used in its synthesis [12][13]. Because of its intriguing structure, aspidophytine has attracted the attention of several

Scheme 1



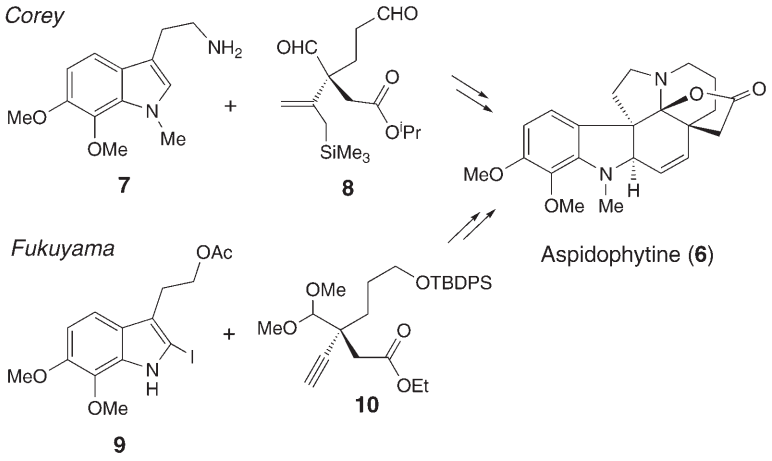
research groups. In 1999, *Corey* and co-workers reported a concise and creative protocol for the construction of (−)-aspidophytine which hinged on a novel cascade reaction between dialdehyde **8** and indole **7**, synthesized from vanillin acetate in ten steps (*Scheme 3*) [12]. Four years later, the *Fukuyama* and co-workers [13] accomplished the enantioselective synthesis of aspidophytine (**6**) using a radical cyclization of 2-alkenylphenyl isocyanide [14], followed by *Sonogashira* coupling [15] of indole **9** with alkyne **10**. An amine–aldehyde condensation cascade was then employed to furnish the aspidosperma skeleton. As was the case with *Corey*'s synthesis [12], the lactone ring was formed after construction of the pentacyclic skeleton to complete the total synthesis.

Scheme 2



More recently, *Marino* and *Cao* also successfully synthesized (−)-aspidophytine [16]. A key step in their synthesis involved the use of the *Marino* annulation reaction [17] of the chiral vinyl sulfoxide **11** with dichloroketene to set up the stereogenic quaternary C-center in **12**. Conversion of **12** to **13**, followed by a subsequent tandem

Scheme 3



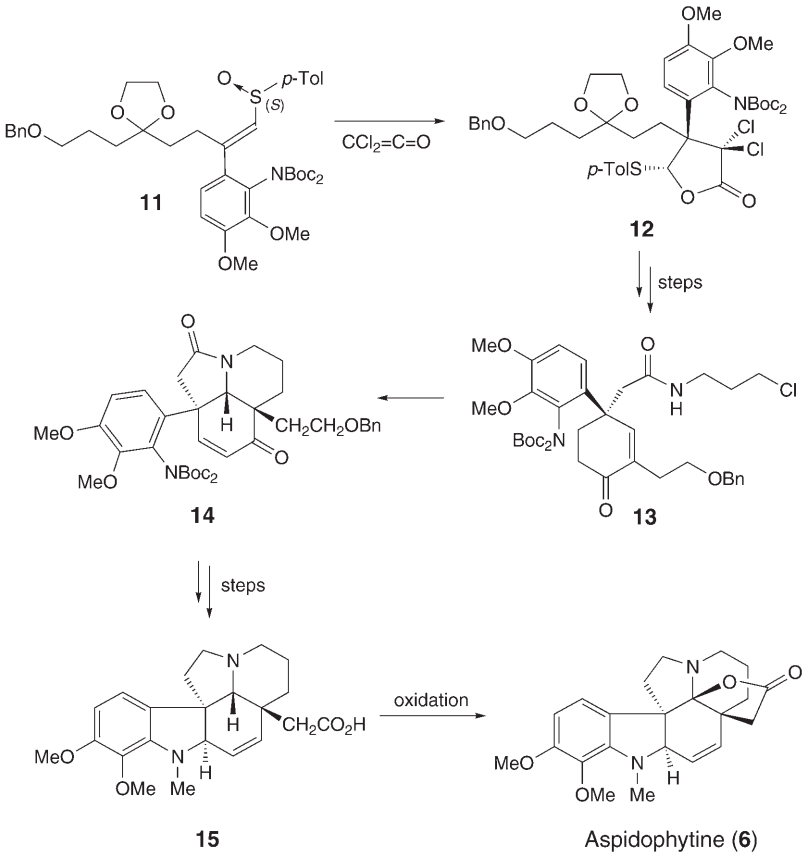
Michael addition–alkylation reaction, was utilized to form the polycyclic core skeleton (*i.e.*, **14**) [18]. Finally, application of *Corey*'s oxidative lactone ring formation reaction [12] using **15** afforded (−)-aspidophytine in 40% yield for the last two steps ($K_3Fe(CN)_6$, *t*-BuOH/H_2O then $NaHCO_3$; *Scheme 4*).

In the course of our investigations dealing with the cycloaddition chemistry of push-pull dipoles and their application to the synthesis of indole alkaloids [19], we began studies geared toward a synthesis of aspidophytine and eventually haplophytine. The generation of carbonyl 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 [20][1]). Our plan for the synthesis of aspidophytine (**6**) is shown in retrosynthetic format in *Scheme 5* and is centered upon the construction of the key cycloadduct **17** by making use of α-diazo imide **16**. We describe herein full details of our total synthesis of (±)-aspidophytine which is based on a tandem cascade cyclization/cycloaddition sequence of a carbonyl ylide [22].

Results and Discussion. – As a preclude to the total synthesis of (±)-aspidophytine (**6**), we initially set out to prepare the core aspidosperma skeleton containing the lactone ring to test the viability of our approach as well as to probe specific reactions to be used in the total synthesis effort. With this in mind, we first investigated the Rh^{II}-catalyzed reaction of the prototypic system **23** which is devoid of the MeO groups in the 6,7-positions of the indole ring (see *Scheme 7*). Preparation of the precursor α-diazo lactam **22** commenced with commercially available δ-valerolactam **19**, which was deprotonated with excess base and allowed to react with *tert*-butyl bromoacetate to give lactam **20** in 80% yield. The ethyl ester portion of **19** was converted to the methyl

[1]) *Boger* and co-workers have recently described an alternate approach to carbonyl ylides based on a [4 + 2] cycloaddition of 1,3,4-oxadiazoles, followed by a thermal extrusion of N_2 and have elegantly exploited this chemistry for the construction of a variety of aspidosperma alkaloid targets (see [21]).

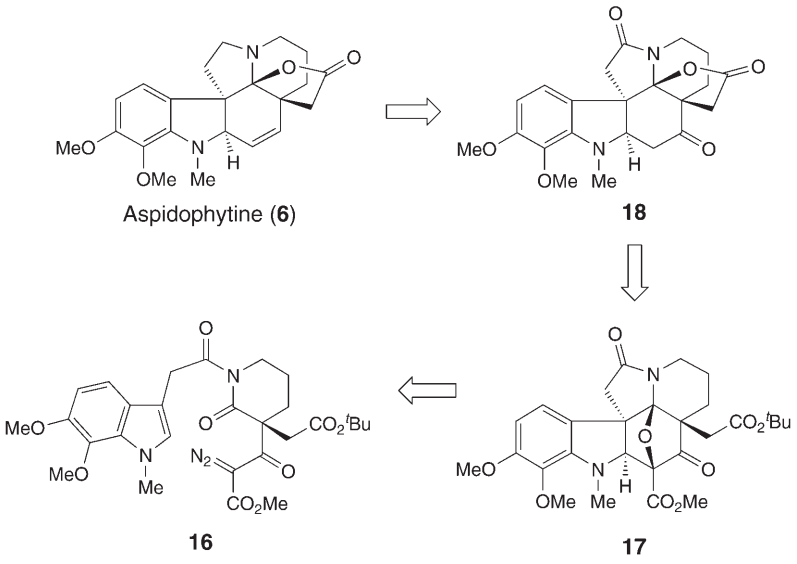
Scheme 4



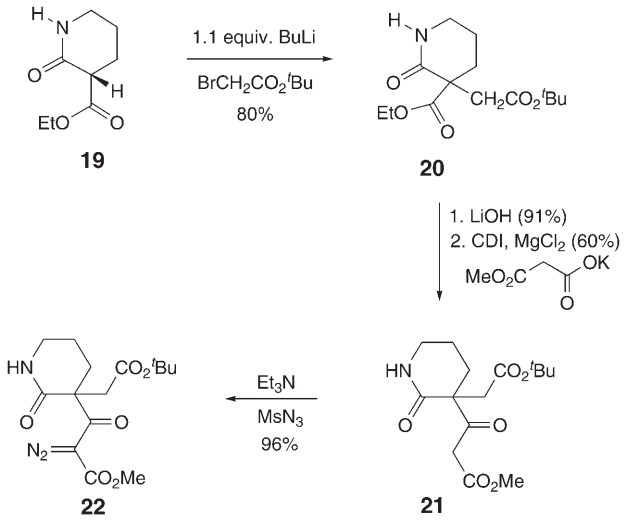
3-oxopropanoate group using a modified procedure of *Masamune* and co-workers [23] to furnish β-keto ester **21** in 54% overall yield. Finally, the requisite α-diazo lactam **22** was easily obtained from **21** using standard diazo transfer conditions [24] and was isolated in 96% yield (*Scheme 6*).

At this point, we joined diazolactam **22** with the acid chloride derived from the commercially available 1-methyl-1*H*-indole-3-acetic acid by stirring a benzene solution of the two reagents in the presence of 4-Å molecular sieves to give α-diazo imide **23**. Formation of the push-pull dipole **24** was achieved by reaction of **23** with $Rh_2(OAc)_4$ to give a Rh carbenoid that readily underwent cyclization onto the neighboring imido C=O group to form the carbonyl ylide dipole **24**. Subsequent intramolecular cycloaddition across the tethered indolyl group furnished cycloadduct **26** in 97% yield (*Scheme 7*). Most interestingly and in contrast to the previous experimental finding with α-diazo imide **1** (see *Scheme 1*) [7], the *exo*-cycloadduct **25** was the exclusive product (*vide infra*) isolated from the Rh^{II}-catalyzed reaction. We assume that the bulky *tert*-butyl ester functionality blocks the *endo*-approach thereby resulting in the

Scheme 5



Scheme 6

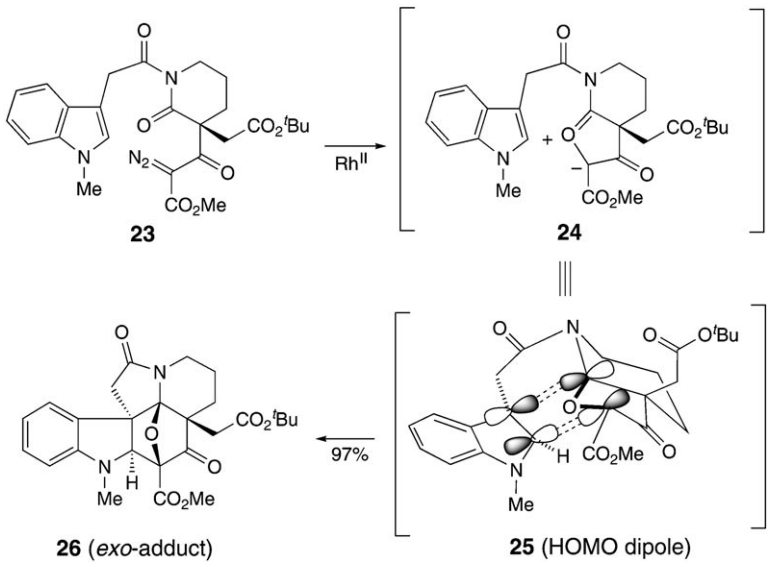


cycloaddition taking place from the less congested *exo*-face (see transition state pictorial **25**)[2]). The overall cycloaddition can also be considered doubly diastereose-

[2]) Our earlier studies dealing with the 1,3-dipolar cycloaddition reaction of carbonyl ylides showed that the reaction was a type-I dipole (HOMO) – dipolarophile (LUMO)-controlled process [7].

lective in that the indole moiety approaches the dipole exclusively from the opposite side of the $CH_2CO_2{}^tBu$ group and also from the less sterically encumbered piperidone ring.

Scheme 7

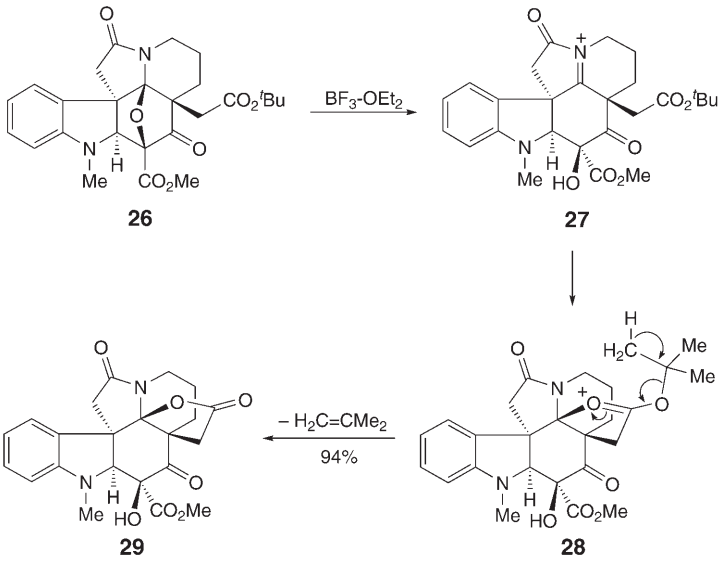


The acid lability of cycloadduct **26** was next investigated. We hoped that we could induce a domino fragmentation cascade which would involve *1*) cleavage of the oxabicyclic ring and formation of a transient *N*-acyl iminium ion **27**, and *2*) reaction of the cationic center of **27** with the adjacent C=O group of the *tert*-butyl ester to give oxonium ion **28**, which would then undergo loss of isobutene to furnish the pentacyclic skeleton of aspidophytine (**6**). Gratifyingly, the desired cyclization cascade proceeded smoothly upon treatment of **26** with a *Lewis* acid such as $BF_3 \cdot OEt_2$ affording **29** in 94% yield (*Scheme 8*). The structure of **29** was confirmed by a single-crystal X-ray analysis[3]) thereby establishing the certainty of the configurational assignment of **29** as well as the precursor *exo*-adduct **26**. The advantage of this fragmentation cascade approach over the other reported aspidophytine syntheses is that it avoids the oxidative lactonization step which requires the use of potassium ferricyanide. The critical tertiary amine oxidation reaction was previously used by *Corey* and others in order to set the lactone ring, but only proceeds in yields of 39% [13], 40% [16], and 81% [12], depending on the specific carboxylic acid precursor employed.

(±)-Aspidophytine. – Having been encouraged by the preliminary Rh^{II}-catalyzed experiments with the model diazo imide system **23** as well as the *Lewis* acid-induced

[3]) The coordinates for structures **29** and **37** have been deposited with the *Cambridge Crystallographic Data Centre* with deposition Nos. CCDC-677109 and -677110, resp. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, B21EZ, UK.

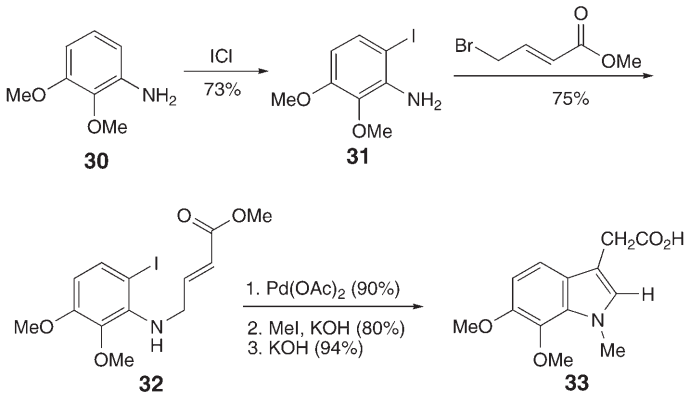
Scheme 8



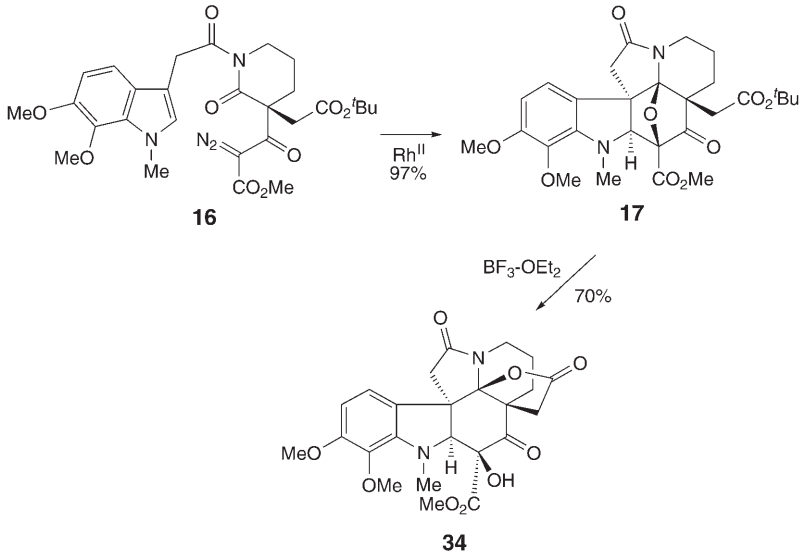
reorganization of the resulting cycloadduct **26**, we turned our attention to the preparation of α-diazo imide **16**, which we hoped to use for the eventual synthesis of ($\pm$)-aspidophytine. Construction of α-diazo imide **16** first entailed the synthesis of the dimethoxy-substituted 2-(1*H*-indol-3-yl)acetic acid **33**. The preparation of **33** was carried out in 36% overall yield starting from commercially available aniline **30** and is summarized in *Scheme 9*. 2,3-Dimethoxyaniline (**30**) was iodinated using ICl (73%), and the resulting iodoaniline **31** was subsequently alkylated with methyl bromocrotonate to give the secondary amine **32** in 75% yield based on recovered starting material. Intramolecular *Heck* cyclization (90%) of **32** afforded the expected indole ring [25] which was easily converted to **33** by *N*-methylation with MeI (80%), followed by a subsequent hydrolysis step (94%). Indole-acetic acid **33** was then coupled with diazo amide **22** *via* the acid chloride to furnish the required α-diazo imide **16** in 92% yield. We were pleased to find that the Rh^{II}-catalyzed reaction of **16** proceeded uneventfully and gave the expected *exo*-cycloadduct **17** in 97% yield. The high reactivity of oxabicyclic adduct **17** was then exploited in the next step of the synthesis. As was the case with the model system **26**, the reaction of **17** with $BF_3 \cdot OEt_2$ afforded the pentacyclic lactone **34** in 70% yield (*Scheme 10*). The relative configuration of **34** was assigned on the basis of its spectroscopic properties which were essentially identical to the related ring-opened product **29** whose structure had been confirmed by a single-crystal X-ray analysis.

With the rapid construction of the pentacyclic framework of aspidophytine in hand, the removal and installation of the other functional groups present on the C-ring of the target molecule was next investigated. Our first efforts focused on the removal of the OH group by a *Barton – McCombie* reaction [26]. Unfortunately, the reaction of **34** as its phenyl thiocarbonate derivative with Bu_3SnH led only to a complex mixture of

Scheme 9



Scheme 10

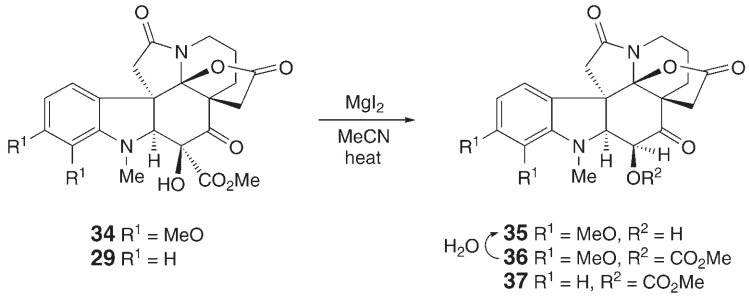


products. We opted instead to carry out a *Krapcho* demethoxycarbonylation reaction[4]) of **34**. Dealkoxycarbonylation of activated esters *via* nucleophilic dealkylation represents a one-step process for the removal of the alkyl ester entity, primarily when structurally hindered. This reaction usually involves heating of the substrate in a dipolar aprotic solvent in the presence of a nucleophile. Following *Krapcho*'s original development of this approach [28], which employed NaCl in DMSO, many other nucleophiles have also been found to be applicable [27], including thiolates, *tert*-

[4]) For a review of dealkoxycarbonylations, see [27].

butoxide, thiocyanates, amines, and acetate. Our initial attempts to convert hydroxy ester **34** into α-hydroxy ketone **35** made use of the one-pot *Krapcho* protocol. This involved heating **34** at reflux in DMSO in the presence of NaCl, which indeed furnished compound **35**, but only in 20% yield (*Scheme 11*). After numerous attempts at improving the yield of the demethoxycarbonylation reaction, the procedure that we eventually settled on for the aspidophytine synthesis involved heating **34** with MgI_2 in refluxing MeCN that contained a small amount of H_2O. Gratifyingly, these conditions resulted in the formation of alcohol **35** in 75% yield. Although a cursory analysis suggests that a *Krapcho* dealkoxycarbonylation reaction occurred, the isolation of small quantities of carbonate **36** from the mixture was somewhat surprising and led us to examine the MgI_2 reaction in more detail. By following the reaction over a period of time, we were able to demonstrate that carbonate **36** was actually the initial product formed and then underwent a further hydrolysis with H_2O to give alcohol **35**. Furthermore, the related carbonate **37** ($R_1 = H$) could also be obtained in 77% yield by treating **29** with either LiI or MgI_2 in acetonitrile. An X-ray crystal analysis of **37** showed that carbonate formation occurred stereospecifically and proceeded with complete retention of configuration[3]).

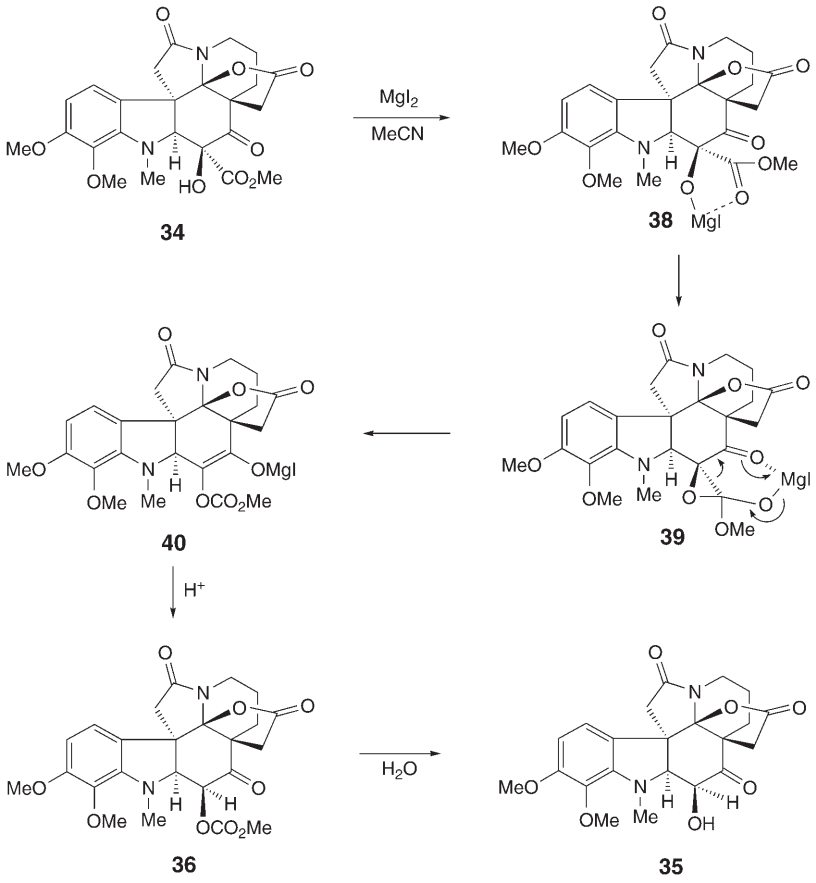
Scheme 11



A plausible mechanism for the formation of carbonate **36** (or **37**) involves coordination of MgI_2 with the more basic ester site followed by attack of the OH O-atom on the neighboring methoxycarbonyl group. Epoxide **39** is then formed as a transient species which readily isomerizes to the magnesium enolate **40**. This step is followed by ketonization to furnish the carbonate **36**, which undergoes further hydrolysis with some H^+ produced in the reaction with MgI_2 to provide the final product **35** (*Scheme 12*). Indeed, heating an authentic sample of the carbonate derived from **29** (*i.e.*, **37**) with MgI_2 in MeCN afforded the corresponding alcohol in high yield. The success of this reaction is probably due to activation of the ester by chelation of the Mg^{II} cation with both C=O groups. Analogous base-catalyzed rearrangements of α-hydroxy β-diketones to α-keto esters have been reported by *Davis et al.* [29] and others [30][31].

Having synthesized the required pentacyclic alcohol **35**, we then went ahead and manipulated the remaining functionality to arrive at (±)-aspidophytine. The two-step sequence that was used to remove the OH functionality involved acetylation with $AcCl/Et_3N$, and the resulting acetate was subsequently reduced with SmI_2 to give **18** in

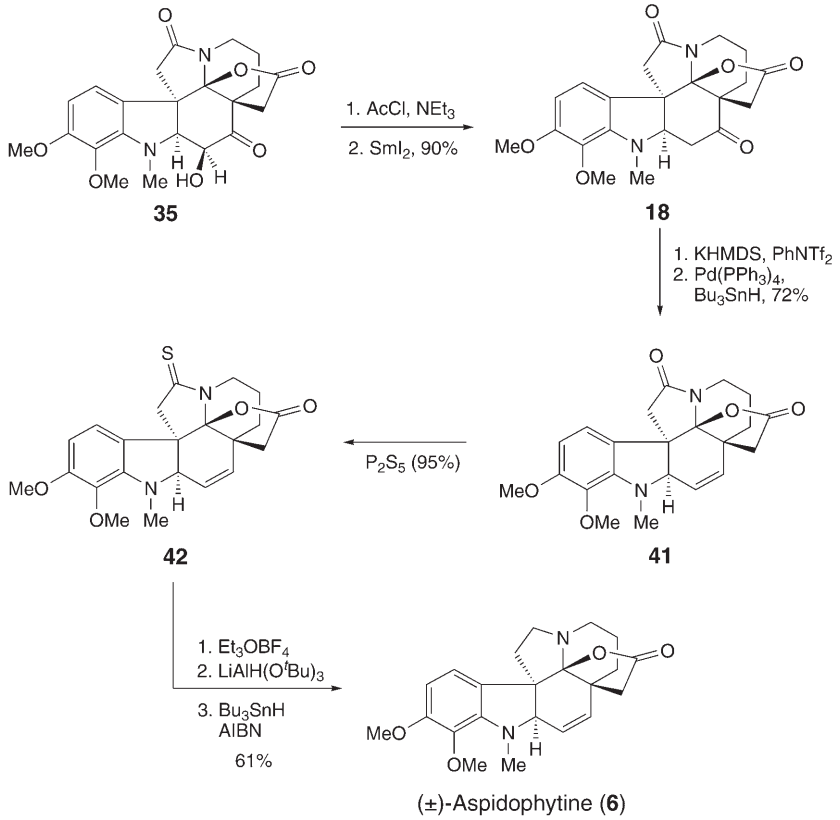
Scheme 12



90% yield (*Scheme 13*). The total synthesis was completed by converting the C=O group of **18** into the corresponding enol triflate which, upon treatment with $Pd(PPh_3)_4$ and Bu_3SnH according to experimental conditions of *Corey* and co-workers [12] gave **41** (72%). Treatment of **41** with P_2S_5 furnished thiolactam **42** in 95% yield [32]. Although not investigated in detail, our attempts to reduce **42** with *Raney*-Ni were not successful. Instead, *S*-ethylation of thiolactam **42** with *Meerwein*'s reagent, followed by $LiAlH(O^tBu)_3/Bu_3SnH$ reduction [33] provided (±)-aspidophytine (**6**) in 61% yield from **42**. Confirmation of the structure was achieved by comparison of the spectral data with those of an authentic sample of aspidophytine provided by Professor *Fukuyama*.

Conclusions. – We have developed a novel tandem dipole cascade sequence for the synthesis of the alkaloid (±)-aspidophytine. The key pentacyclic framework of the alkaloid was prepared by reaction of an indolyl substituted α-diazo imide with $Rh_2(OAc)_4$, which generates a rhodium carbenoid that readily cyclizes to furnish a

Scheme 13



carbonyl ylide dipole. The reactive carbonyl ylide then underwent a subsequent intramolecular dipolar cycloaddition across the indolyl π-bond. The resulting cycloadduct was used for the stereocontrolled installation of the other functionalities present in the C-ring of the target molecule. The remaining key features of the synthetic strategy include: *1*) a domino fragmentation cascade involving cleavage of the oxabicyclic ring and formation of a transient *N*-acyl iminium ion which reacts with the adjacent *tert*-butyl ester to set the required lactone ring; *2*) a *Lewis* acid-promoted α-hydroxy β-dicarbonyl to α-ketol ester rearrangement to effect demethoxycarbonylation and; *3*) a SmI_2-induced reduction of the remaining OH group. We plan to use this and related cascade methodology in approaches to other natural product targets, the results of which will be disclosed in due course.

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Experimental Part

*Ethyl 3-{[(*tert*-Butoxy)carbonyl]methyl}-2-oxopiperidine-3-carboxylate* (**20**). To a stirred soln. of 10.5 g (61 mmol) of ethyl 2-oxopiperidine-3-carboxylate in 120 ml of THF at −78° was added 28 ml (67 mmol) of a 2.4M BuLi soln. in hexane. The mixture was allowed to warm to 0° for 10 min and was recooled to −78°. Then, 11.2 g (67 mmol) of $BrCH_2CO_2{}^tBu$ were added, followed by 4.5 g (13 mmol) of Bu_4NI. The soln. was allowed to warm up to r.t. while stirring vigorously. After 15 h, the solvent was removed under reduced pressure, and to the residue was added H_2O. The aq. phase was extracted with AcOEt, and the combined org. extracts were washed with a sat. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. The residue was recrystallized with a mixture of AcOEt/hexane to give 13.9 g (80%) of **20**. White solid. M.p. 81–83°. IR (neat): 1733, 1674, 1366, 1246, 1155. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.22 (*t*, *J* = 7.2, 3 H); 1.38 (*s*, 9 H); 1.70–1.76 (*m*, 1 H); 1.86–1.96 (*m*, 1 H); 2.25 (*dt*, *J* = 13.6, 3.6, 1 H); 2.11–2.18 (*m*, 1 H); 2.71 (*d*, *J* = 16.8, 1 H); 3.01 (*d*, *J* = 16.8, 1 H); 3.29–3.35 (*m*, 2 H); 4.10–4.20 (*m*, 2 H); 6.87 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1; 19.8; 28.1; 30.3; 40.8; 42.2; 51.7; 61.7; 81.0; 170.1; 170.3; 172.0. Anal. calc. for $C_{14}H_{23}NO_5$: C 58.93, H 8.12, N 4.91; found: C 59.03, H 8.12, N 4.87.

*3-{[(*tert*-Butoxy)carbonyl]methyl}-2-oxopiperidine-3-carboxylic Acid.* A 5.4 g (19.1 mmol) sample of **20** and 2.4 g of LiOH (57 mmol) in THF (50 ml) and H_2O (50 ml) was stirred at r.t. for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in H_2O. The soln. was washed with AcOEt and acidified to pH 2. The aq. phase was extracted with $CHCl_3$, and the combined org. phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 4.5 g (91%) of the title compound as a white solid. M.p. 102–104°. IR (neat): 3282, 1727, 1700, 1628, 1366, 1257, 1155. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44 (*s*, 9 H); 1.78–2.10 (*m*, 3 H); 2.30–2.38 (*m*, 1 H); 2.68 (*d*, *J* = 16.4, 1 H); 3.12 (*d*, *J* = 16.4, 1 H); 3.32–3.46 (*m*, 2 H); 7.30 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.9; 28.2; 29.1; 41.8; 42.6; 51.4; 81.8; 170.0; 173.3; 173.9. Anal. calc. for $C_{12}H_{19}NO_5$: C 56.03, H 7.44, N 5.44; found: C 56.28, H 7.44, N 5.36.

*Methyl 3-(3-{[(*tert*-Butoxy)carbonyl]methyl}-2-oxopiperidin-3-yl)-3-oxopropanoate* (**21**). To a 2.1 g (8.3 mmol) sample of the above carboxylic acid in CH_2Cl_2 (50 ml) was added 1.62 g (10 mmol) of 1,1′-carbonyldiimidazole (CDI), and the soln. was allowed to stir at r.t. under Ar for 12 h. The mixture was concentrated under reduced pressure and redissolved in 50 ml of THF. In the meantime, 2.6 g (17 mmol) of potassium methyl malonate, 1.6 g (17 mmol) of powdered $MgCl_2$ and a catalytic amount of 4-(dimethylamino)pyridine (DMAP; 0.1 g, 0.8 mmol) were mixed in a soln. of 50 ml of THF and 25 ml of MeCN. After stirring for 2 h, the above lactam in THF was added dropwise to the malonate soln. together with 2.3 ml (17 mmol) of Et_3N. The soln. was allowed to stir at r.t. for 12 h, then 80 ml of 1N HCl was added. The org. layer was separated, and the aq. layer was extracted with Et_2O. The combined org. extracts were washed with a sat. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to flash silica-gel chromatography to give 1.3 g (61%) of **21**. Off-white solid. M.p. 102–104°. IR (neat): 1732, 1655, 1456, 1367, 1320, 1156. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.43 (*s*, 9 H); 1.75–1.90 (*m*, 3 H); 2.42–2.49 (*m*, 1 H); 2.69 (*d*, *J* = 16.4, 1 H); 2.94 (*d*, *J* = 16.4, 1 H); 3.28–3.43 (*m*, 2 H); 3.72 (*s*, 1 H); 3.77 (*d*, *J* = 16.6, 1 H); 3.94 (*d*, *J* = 16.6, 1 H); 6.01 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.2; 28.2; 28.4; 41.9; 42.8; 45.6; 52.5; 58.1; 82.0; 168.1; 169.5; 170.7; 200.8. Anal. calc. for $C_{15}H_{23}NO_6$: C 57.50, H 7.40, N 4.47; found: C 57.36, H 7.40, N 4.46.

*Methyl 3-(3-{[(*tert*-Butoxy)carbonyl]methyl}-2-oxopiperidin-3-yl)-2-diazo-3-oxopropanoate* (**22**). To a 4.8 g (15 mmol) sample of **21** in MeCN (125 ml) was added 1.9 g (18 mmol) of Et_3N, and the soln. was vigorously stirred for 30 min. To this mixture was added 3.5 g (31 mmol) of MsN_3, and the soln. was stirred at r.t. for 10 h. The soln. was concentrated under reduced pressure and recrystallized from Et_2O which contained a trace of CH_2Cl_2 to give 5.0 g (96%) of **22**. Pale yellow solid. M.p. 152–154°. IR (neat): 2124, 1725, 1669, 1480, 1437, 1321, 1153. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.47 (*s*, 9 H); 1.80–2.00 (*m*, 2 H); 2.29 (*dt*, *J* = 12.4, 4.0, 1 H); 2.68–2.74 (*m*, 1 H); 2.77 (*d*, *J* = 16.2, 1 H); 2.92 (*d*, *J* = 16.2, 1 H); 3.28–3.39 (*m*, 1 H); 3.64 (*dt*, *J* = 11.2, 4.8, 1 H); 4.22 (*s*, 3 H); 5.65 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.9; 25.7; 28.2; 38.4; 42.5; 52.4; 58.2; 80.8; 161.7; 170.4; 171.7; 189.9. Anal. calc. for $C_{15}H_{21}N_3O_6$: C 53.09, H 6.24, N 12.38; found: C 53.21, H 6.43, N 12.33.

*Methyl 3-(3-{[(*tert*-Butoxy)carbonyl]methyl}-1-[2-(1-methyl-1*H*-indol-3-yl)acetyl)-2-oxopiperidin-3-yl}-2-diazo-3-oxopropanoate* (**23**). A 0.6 g (3.2 mmol) sample of 1-methyl-1*H*-indole-3-acetic acid was dissolved in CH_2Cl_2 (20 ml), and 1.4 g (11.4 mmol) of oxalyl chloride was added dropwise. The soln. was stirred overnight and then concentrated under reduced pressure. The resulting solid was taken up in 20 ml of THF, which was immediately added to a vigorously stirred mixture containing 1.0 g (3.0 mmol) of **22**, 2 g of 4-Å molecular sieves and 0.036 g (0.29 mmol) of DMAP in 20 ml of THF. After stirring for 12 h, the mixture was filtered through a pad of *Celite* and concentrated under reduced pressure. The crude material was purified by flash silica-gel column chromatography (CC) to give 1.1 g (73%) of **23**. White solid. M.p. 79–81°. IR (neat): 2144, 1718, 1686, 1331, 1152. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.46 (*s*, 9 H); 1.61–1.70 (*m*, 1 H); 1.84 (*dt*, *J* = 14.0, 3.6, 1 H); 1.98 (*d*, *J* = 15.8, 1 H); 2.17 (*td*, *J* = 12.8, 4.4, 1 H); 2.31 (*d*, *J* = 15.8, 1 H); 2.62–2.70 (*m*, 1 H); 3.72 (*td*, *J* = 12.4, 4.0, 1 H); 3.78 (*s*, 6 H); 4.05–4.12 (*m*, 1 H); 4.11 (*d*, *J* = 16.4, 1 H); 4.47 (*d*, *J* = 16.4, 1 H); 6.96 (*s*, 1 H); 7.10 (*t*, *J* = 7.6, 1 H); 7.21 (*t*, *J* = 7.6, 1 H); 7.29 (*d*, *J* = 7.6, 1 H); 7.51 (*d*, *J* = 7.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5; 26.7; 28.3; 32.8; 36.2; 36.7; 44.7; 52.6; 60.5; 80.1; 107.6; 109.4; 118.9; 119.4; 121.8; 128.1; 128.9; 136.9; 161.6; 169.8; 173.0; 177.0; 189.9. Anal. calc. for $C_{26}H_{30}N_4O_7$: C 61.17, H 5.92, N 10.97; found: C 61.02, H 5.96, N 10.79.

*Methyl 3a-{[(*tert*-Butoxy)carbonyl]methyl}-5,12b-epoxy-6-methyl-4,12-dioxo-2,3,3a,4,5,5a,6,11,12,12b-decahydro-1*H*-6,12a-diazaindeno[7,1-*cd*]fluorene-5-carboxylate* (**26**). A 1.0 g (2.0 mmol) sample of **23** was stirred with $Rh(OAc)_2$ (10 mg) and 2.0 g of 4-Å molecular sieves in benzene (20 ml). The mixture was heated at reflux for 2 h, cooled to r.t. and was filtered through a pad of *Celite*. The solvent was removed under reduced pressure to give 0.9 g (97%) of **26**. Clear oil. IR (neat): 1779, 1732, 1609, 1343, 1155. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.37 (*s*, 9 H); 1.42 (*d*, *J* = 14.6, 1 H); 1.75 (*d*, *J* = 14.6, 1 H); 1.80–1.89 (*m*, 2 H); 2.01–2.13 (*m*, 1 H); 2.15–2.21 (*m*, 1 H); 2.82 (*d*, *J* = 17.2, 1 H); 3.01 (*s*, 3 H); 3.04 (*d*, *J* = 17.2, 1 H); 3.15–3.28 (*m*, 1 H); 3.84–3.92 (*m*, 1 H); 3.91 (*s*, 3 H); 4.50 (*s*, 1 H); 6.47 (*d*, *J* = 7.8, 1 H); 6.70 (*t*, *J* = 7.8, 1 H); 6.96 (*d*, *J* = 7.8, 1 H); 7.19 (*t*, *J* = 7.8, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.4; 26.9; 28.1; 33.7; 34.7; 39.2; 45.4; 50.3; 53.5; 59.7; 80.7; 81.2; 92.5; 104.0; 108.2; 118.6; 123.8; 126.8; 130.7; 152.9; 166.4; 169.0; 176.9; 202.3.

Lewis *Acid-Catalyzed Ring Opening of Cycloadduct* **26**. A 0.47-g (0.97 mmol) sample of **26** was dissolved in CH_2Cl_2 (60 ml) and cooled to 0° with an ice bath. A 0.7-g (5.1 mmol) sample of $BF_3 \cdot OEt_2$ in CH_2Cl_2 (15 ml) was added dropwise. The mixture was allowed to warm to r.t. overnight and then added to a sat. aq. soln. of $NaHCO_3$ (200 ml). The org. layer was separated, the aq. layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure. The product was recrystallized from Et_2O to give 0.39 g (94%) of **29**. White solid. M.p. 196–198°. IR (neat): 1797, 1743, 1725, 1489, 1264, 1190. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.61–1.72 (*m*, 3 H); 2.31 (*d*, *J* = 17.2, 1 H); 2.50–2.53 (*m*, 1 H); 2.52 (*d*, *J* = 17.2, 1 H); 2.95–2.99 (*m*, 1 H); 3.02 (*s*, 3 H); 3.08 (*d*, *J* = 17.6, 1 H); 3.21 (*dd*, *J* = 17.6, 1.0, 1 H); 3.79 (*s*, 3 H); 3.94–4.02 (*m*, 1 H); 4.28 (*s*, 1 H); 4.81 (*s*, 1 H); 6.61 (*d*, *J* = 7.8, 1 H); 6.93 (*td*, *J* = 7.8, 1.2, 1 H); 7.21 (*d*, *J* = 7.8, 1 H); 7.26 (*td*, *J* = 7.8, 1.2, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.5; 33.4; 36.6; 41.0; 42.1; 45.3; 51.8; 53.3; 53.7; 76.2; 83.0; 97.5; 110.5; 120.9; 127.3; 128.0; 131.0; 153.8; 166.4; 170.1; 173.7; 204.3. HR-MS: 427.15013 ($[(C_{22}H_{22}N_2O_7)+H]^+$; calc. 427.14998).

Preparation of Carbonate **37**. To a 0.04 g (0.09 mmol) of **29** in MeCN (10 ml) was added 0.04 g (0.28 mmol) of LiI, and the resulting soln. was heated at reflux for 17 h. The soln. was allowed to cool to r.t., concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2 (50 ml) and H_2O (50 ml). This soln. was added to a sat. aq. soln. of $NaHCO_3$ (100 ml), the org. layer was separated, the aq. layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure to give 0.025 g (77%) of carbonate **37**. White solid. M.p. 228–230°. IR (neat): 1796, 1759, 1743, 1721, 1394, 1277, 1191. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.28–1.40 (*m*, 1 H); 1.58–1.78 (*m*, 2 H); 2.29–2.40 (*m*, 3 H); 2.78 (*d*, *J* = 18.4, 1 H); 2.90 (*s*, 3 H); 3.46 (*d*, *J* = 18.4, 1 H); 3.85 (*d*, *J* = 2.6, 1 H); 3.90 (*s*, 3 H); 4.29–4.35 (*m*, 1 H); 5.62 (*d*, *J* = 2.6, 1 H); 6.56 (*d*, *J* = 7.4, 1 H); 6.90 (*t*, *J* = 7.4, 1 H); 7.24 (*t*, *J* = 7.4, 1 H); 7.22–7.29 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.2; 34.4; 36.8; 37.7; 40.3; 44.2; 53.2; 54.6; 55.9; 74.7; 80.8; 97.6; 109.3; 120.7; 125.9; 127.6; 131.2; 153.1; 154.9; 170.5; 172.4; 200.6.

To a 0.43 g (1.0 mmol) of **37** in MeCN (20 ml) was added 0.42 g (1.5 mmol) of MgI_2 and the resulting soln. was heated at reflux for 6 h. The soln. was allowed to cool to r.t., concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2 (50 ml) and H_2O (50 ml). This soln. was added to a sat. aq. soln. of $NaHCO_3$ (100 ml), the org. layer was separated, the aq. layer was extracted with CH_2Cl_2,

dried ($MgSO_4$), and concentrated under reduced pressure to give 0.26 g (70%) of the demethoxycarbonylated alcohol as a white solid. M.p. 228–230°. IR (neat): 1794, 1719, 1489, 1397, 1264, 1191. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.30–1.43 (*m*, 1 H); 1.67 (*td*, *J* = 14.0, 3.6, 1 H); 1.77 (*dt*, *J* = 14.0, 2.8, 1 H); 2.31 (*d*, *J* = 17.2, 1 H); 2.39–2.44 (*m*, 1 H); 2.41 (*d*, *J* = 17.2, 1 H); 2.79 (*d*, *J* = 18.4, 1 H); 2.90–2.99 (*m*, 1 H); 2.94 (*s*, 3 H); 3.34 (*dd*, *J* = 18.4, 1.4, 1 H); 3.67 (*d*, *J* = 3.2, 1 H); 3.86 (*d*, *J* = 3.2, 1 H); 4.25–4.31 (*m*, 1 H); 4.87 (*t*, *J* = 3.2, 1 H); 6.55 (*d*, *J* = 7.8, 1 H); 6.90 (*td*, *J* = 7.8, 0.8, 1 H); 7.23 (*t*, *J* = 7.8, 1 H); 7.21–7.28 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.5; 34.1; 37.4; 38.7; 40.2; 44.6; 52.1; 53.6; 76.5; 77.3; 97.8; 109.6; 120.7; 126.4; 127.7; 131.0; 153.8; 170.4; 172.4; 207.8.

6-Iodo-2,3-dimethoxybenzenamine (**31**). A biphasic mixture of 220 ml of Et_2O, 30 ml of an aq. sat. Na_2CO_3 soln., and 5.0 g (33 mmol) of 2,3-dimethoxyaniline was stirred in the dark. To this mixture was added 8.8 g (54 mmol) of ICl in 36 ml of Et_2O. The mixture was stirred for 2 h, and the layers were separated. The org. layer was washed with a sat. Na_2SO_3 soln., and the combined org. layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to flash silica-gel chromatography (FC) to give 6.7 g (73%) of **31**. Yellow solid. M.p. 48–50°. IR (neat): 1601, 1481, 1458, 1291, 1109. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.83 (*s*, 3 H); 3.84 (*s*, 3 H); 4.25 (br. *s*, 2 H); 6.19 (*d*, *J* = 9.0, 1 H); 7.31 (*d*, *J* = 9.0, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 56.0; 60.1; 74.0; 104.4; 133.3; 135.4; 141.8; 153.2. Anal. calc. for $C_8H_{10}INO_2$: C 34.43, H 3.61, N 5.02; found: C 34.48, H 3.52, N 4.96.

Methyl 4-[(6-Iodo-2,3-dimethoxyphenyl)amino]but-2-enoate (**32**). To a stirred soln. of 4.5 g (16.1 mmol) of **31** in 60 ml of acetone/H_2O 85 : 15 was added 2.5 ml (21 mmol) of methyl bromocrotonate and 5 g (60 mmol) of $NaHCO_3$. The resulting mixture was heated at reflux for 3 h, and the dark mixture was allowed to cool, diluted with Et_2O, and filtered through a pad of *Celite*. The soln. was added to brine, and the org. layer was separated. The aq. layer was washed twice with 250 ml of Et_2O, and the combined org. extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to FC to give 1.7 g (38%) of starting material and 2.9 g (47%) of **32**. Clear oil. IR (neat): 1719, 1458, 1285, 1170. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.74 (*s*, 3 H); 3.77 (*s*, 3 H); 3.84 (*s*, 3 H); 3.91 (br. *s*, 1 H); 4.13 (*dd*, *J* = 5.3, 2.0, 1 H); 6.07 (*dt*, *J* = 15.6, 2.0, 1 H); 6.30 (*d*, *J* = 8.6, 1 H); 7.05 (*dt*, *J* = 15.6, 5.3, 1 H); 7.41 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 48.4; 51.8; 56.2; 60.4; 80.7; 107.0; 121.3; 134.0; 139.6; 142.4; 146.8; 154.3; 167.1.

2-(6,7-Dimethoxy-1-methyl-1H-indol-3-yl)acetic Acid (**33**). A 3.8-g (3.4 mmol) sample of **32** was dissolved in 60 ml of MeCN. To this soln. was added 0.12 g (0.5 mmol) of $Pd(OAc)_2$, 3 ml (21 mmol) of Et_3N, and 0.3 g (1.0 mmol) of tri-*o*-tolylphosphine. The mixture was heated at reflux for 3 h, and the solvent was removed under reduced pressure. The residue was partitioned between 200 ml of Et_2O and 50 ml of H_2O, and the layers were separated. The aq. layer was washed twice with 200 ml of Et_2O. The combined org. extracts were washed with a sat. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to FC to give 2.3 g (90%) of methyl 2-(6,7-dimethoxy-1*H*-indol-3-yl)acetate as an oil. IR (neat): 1735, 1508, 1463, 1260, 1127. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.72 (*s*, 3 H); 3.75 (*d*, *J* = 1.2, 2 H); 3.94 (*s*, 3 H); 4.00 (*s*, 3 H); 6.88 (*d*, *J* = 8.4, 1 H); 7.09 (*t*, *J* = 1.2, 1 H); 7.27 (*d*, *J* = 8.4, 1 H); 8.22 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 31.5; 52.2; 57.6; 61.0; 108.6; 108.9; 114.0; 122.9; 124.1; 130.9; 134.6; 147.4; 172.6.

To 4.9 g (20 mmol) of the above indole-acetate in anh. THF (150 ml) was added 2.6 g (39 mmol) of 85% KOH pellets, 6.1 ml (98 mmol) of MeI, 0.075 g (0.2 mmol) of Bu_4NI together with 6.0 g of 4-Å molecular sieves, and the mixture was stirred at r.t. for 2 h. The mixture was filtered over a pad of *Celite* with THF, and the solvent was removed under reduced pressure. The residue was subjected to FC to give 4.1 g (80%) of methyl 2-(6,7-dimethoxy-1-methyl-1*H*-indol-3-yl)acetate as an oil. IR (neat): 1735, 1508, 1463, 1260, 1127. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.71 (*s*, 5 H); 3.93 (*s*, 3 H); 3.95 (*s*, 3 H); 3.97 (*s*, 3 H); 6.85 (*d*, *J* = 8.8, 1 H); 6.87 (*s*, 1 H); 7.22 (*d*, *J* = 8.8, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 31.2; 35.5; 52.2; 57.7; 62.0; 106.8; 108.3; 114.1; 125.5; 129.0; 130.6; 136.1; 148.2; 172.7.

A 1.0-g (3.8 mmol) sample of the above methyl acetate and 0.5 g (7.6 mmol) of KOH pellets in 40 ml of THF/H_2O 1 : 1 was stirred for 2 h at r.t. The THF solvent was removed under reduced pressure, and 50 ml of H_2O was added. The resulting soln. was washed with 50 ml of $CHCl_3$, and the layers were separated, and the aq. layer was acidified to pH 2. The aq. phase was extracted twice with 100 ml of $CHCl_3$, and the combined org. phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 0.9 g (94%) of **33**. Clear oil. IR (neat): 1707, 1508, 1463, 1260, 1126. ^{1}H-NMR (400 MHz,

$CDCl_3$): 3.72 (*d*, *J* = 0.8, 2 H); 3.93 (*s*, 3 H); 3.94 (*s*, 3 H); 3.96 (*s*, 3 H); 6.85 (*d*, *J* = 8.6, 1 H); 6.87 (*s*, 1 H); 7.21 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 31.1; 35.5; 57.7; 62.0; 106.1; 108.5; 114.1; 125.4; 129.2; 130.6; 136.1; 148.3; 177.6.

*Methyl 3-(3-{[(*tert*-Butoxy)carbonyl]methyl}-1-[2-(6,7-dimethoxy-1-methyl-1*H*-indol-3-yl)acetyl]-2-oxopiperidin-3-yl)-2-diazo-3-oxopropanoate* (**16**). A 0.9-g (3.4 mmol) sample of **33** was dissolved in CH_2Cl_2 (40 ml), and 1.5 g (12 mmol) of oxalyl chloride was added dropwise. The soln. was stirred overnight, concentrated under reduced pressure, and the remaining solid was taken up in benzene and then immediately added to a vigorously stirred mixture containing 1.1 g (3.4 mmol) of **22** and 8 g of 4-Å molecular sieves in benzene (30 ml). After stirring for 8 h, the mixture was filtered through a pad of *Celite* and concentrated under reduced pressure. The crude material was purified by FC to give 1.8 g (92%) of **16**. Colorless oil: IR (neat): 2144, 1718, 1686, 1331, 1154. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.46 (*s*, 9 H); 1.65–1.77 (*m*, 1 H); 1.82–1.92 (*m*, 1 H); 2.14–2.30 (*m*, 1 H); 2.19 (*d*, *J* = 15.8, 1 H); 2.48 (*d*, *J* = 15.8, 1 H); 2.62–2.72 (*m*, 1 H); 3.72 (*dt*, *J* = 12.4, 4.4, 1 H); 3.78 (*s*, 3 H); 3.92 (*s*, 3 H); 3.93 (*s*, 3 H); 3.95 (*s*, 3 H); 4.03–4.10 (*m*, 1 H); 4.05 (*d*, *J* = 16.8, 1 H); 4.38 (*d*, *J* = 16.8, 1 H); 6.78 (*s*, 1 H); 6.80 (*d*, *J* = 8.8, 1 H); 7.14 (*d*, *J* = 8.8, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5; 26.8; 28.2; 35.4; 36.1; 37.2; 44.7; 52.6; 57.6; 60.6; 61.9; 81.1; 107.5; 108.3; 114.0; 125.9; 129.9; 130.4; 136.1; 148.1; 161.7; 169.9; 173.0; 176.9; 189.9.

*Methyl 3a-{[(*tert*-Butoxy)carbonyl]methyl}-5,12b-epoxy-2,3,3a,4,5,5a,6,11,12,12b-decahydro-7,8-dimethoxy-6-methyl-4,12-dioxo-1*H*-6,12a-diazaindeno[7,1-*cd*]fluorene-5-carboxylate* (**17**). A 1.2-g (2.2 mmol) sample of **16** was stirred with $Rh(OAc)_2$ (7.5 mg) and 8 g of 4-Å molecular sieves in benzene (100 ml), and the mixture was heated at reflux for 2 h. Then, the mixture was allowed to cool to r.t. and was filtered through a pad of *Celite*. The solvent was removed under reduced pressure to give 1.2 g (97%) of **17**. Colorless oil: IR (neat): 1778, 1733, 1613, 1474, 1342, 1262, 1156. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.13 (*d*, *J* = 14.6, 1 H); 1.27 (*s*, 9 H); 1.60 (*d*, *J* = 14.6, 1 H); 1.70–1.79 (*m*, 2 H); 1.91–2.01 (*m*, 1 H); 2.11–2.18 (*m*, 1 H); 2.70 (*d*, *J* = 17.2, 1 H); 2.95 (*d*, *J* = 17.2, 1 H); 3.04–3.12 (*m*, 1 H); 3.11 (*s*, 3 H); 3.60 (*s*, 3 H); 3.74 (*s*, 3 H); 3.80–3.86 (*m*, 1 H); 3.82 (*s*, 3 H); 4.27 (*s*, 1 H); 6.23 (*d*, *J* = 8.6, 1 H); 6.51 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.3; 26.6; 28.0; 28.2; 32.9; 38.2; 39.3; 45.3; 50.4; 53.5; 56.4; 59.0; 60.3; 81.2; 82.4; 92.1; 104.0; 104.1; 118.8; 122.0; 128.5; 135.5; 145.7; 155.3; 166.3; 169.1; 176.9; 202.4. HR-MS: 543.2339 ($[C_{28}H_{34}N_2O_9 + H]^+$; calc. 543.2337).

Lewis *Acid-Catalyzed Ring Opening of Cycloadduct* **17**. A 1.2 g (2.2 mmol) sample of **17** was dissolved in CH_2Cl_2 (100 ml) and cooled to 0°. To this mixture was added 1.5 g (12 mmol) of $BF_3 \cdot OEt_2$ in CH_2Cl_2 (10 ml). The mixture was allowed to warm to r.t. overnight. The soln. was then added to a sat. aq. soln. of $NaHCO_3$ (200 ml), the org. layer was separated, and the aq. layer was extracted three times with CH_2Cl_2. The soln. was dried ($MgSO_4$) and concentrated under reduced pressure. The product was recrystallized from Et_2O to give 0.72 g (70%) of **34**. White solid. M.p. 223–225°. IR (neat): 1798, 1727, 1608, 1493, 1262, 1064. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.54–1.70 (*m*, 3 H); 2.29 (*d*, *J* = 17.2, 1 H); 2.38 (*d*, *J* = 17.2, 1 H); 2.45–2.55 (*m*, 1 H); 2.85–2.95 (*m*, 1 H); 3.04 (*d*, *J* = 18.0, 1 H); 3.13 (*d*, *J* = 18.0, 1 H); 3.16 (*s*, 3 H); 3.67 (*s*, 3 H); 3.76 (*s*, 3 H); 3.81 (*s*, 3 H); 3.88–3.96 (*m*, 1 H); 4.26 (*s*, 1 H); 4.80 (*s*, 1 H); 6.50 (*d*, *J* = 8.4, 1 H); 6.86 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.5; 33.4; 36.6; 41.9; 43.3; 45.5; 51.6; 53.0; 53.7; 56.2; 60.1; 77.8; 82.9; 97.8; 105.5; 121.3; 123.3; 135.5; 146.7; 155.3; 166.6; 170.0; 173.7; 204.3. Anal. calc. for $C_{24}H_{26}N_2O_9$: C 59.25, H 5.39, N 5.76; found: C 59.19, H 5.51, N 5.56.

MgI_2 Demethoxycarbonylation of **34**. To 0.9 g (1.9 mmol) of **34** in MeCN (150 ml) was added 1.1 g (4 mmol) of MgI_2, and the soln. was heated at reflux for 4 h. The soln. was allowed to cool to r.t., concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2 (50 ml) and H_2O (50 ml). This soln. was added to a sat. aq. soln. of $NaHCO_3$ (200 ml). The org. layer was separated, and the aq. layer was extracted twice with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure to give 0.6 g (75%) of **35**. White solid. M.p. 210–212°. IR (neat): 1794, 1720, 1609, 1494, 1263, 1193. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.30–1.45 (*m*, 1 H); 1.58–1.81 (*m*, 2 H); 2.27 (*d*, *J* = 17.4, 1 H); 2.34 (*d*, *J* = 17.4, 1 H); 2.35–2.42 (*m*, 1 H); 2.80 (*d*, *J* = 18.0, 1 H); 2.93 (*dt*, *J* = 14.0, 6.7, 1 H); 3.14 (*s*, 3 H); 3.27 (*dd*, *J* = 18.0, 0.8, 1 H); 3.68 (*d*, *J* = 3.6, 1 H); 3.69 (*s*, 3 H); 3.83 (*s*, 3 H); 3.85 (*d*, *J* = 3.6, 1 H); 4.21–4.30 (*m*, 1 H); 4.84 (*t*, *J* = 3.6, 1 H); 6.48 (*d*, *J* = 8.6, 1 H); 6.89 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.4; 34.1; 37.3; 40.0; 41.4; 44.7; 51.7; 53.4; 56.2; 60.4; 78.0; 98.0; 105.1; 120.4; 122.9; 135.3; 146.5; 155.5; 170.4; 172.5; 207.8. Anal. calc. for $C_{22}H_{24}N_2O_7$: C 61.67, H 5.65, N 6.54; found: C 61.18, H 6.21, N 5.94.

Reduction of **35** *to* **18**. A 0.14-g (0.3 mmol) sample of **35** was dissolved in CH_2Cl_2 (20 ml), and the mixture was cooled to 0°. To this mixture was added 0.16 g (1.6 mmol) of Et_3N and 0.05 g (0.64 mmol) of AcCl. The soln. was stirred vigorously for 2 h and was then added to a sat. aq. soln. of $NaHCO_3$ (50 ml). The org. layer was separated, and the aq. layer was extracted twice with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure to give 0.14 g (95%) of the corresponding acetate as a white solid. M.p. 250–252°. IR (neat): 1797, 1721, 1495, 1264, 1227, 1191. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.55–1.80 (*m*, 3 H); 2.21–2.35 (*m*, 1 H); 2.25 (*d*, *J* = 17.2, 1 H); 2.27 (*s*, 3 H); 2.33 (*d*, *J* = 17.2, 1 H); 2.77 (*d*, *J* = 18.0, 1 H); 2.93 (*dt*, *J* = 12.4, 4.0, 1 H); 3.16 (*s*, 3 H); 3.29 (*dd*, *J* = 18.0, 1.4, 1 H); 3.69 (*s*, 3 H); 3.78 (*d*, *J* = 2.8, 1 H); 3.83 (*s*, 3 H); 4.25–4.32 (*m*, 1 H); 5.69 (*d*, *J* = 2.8, 1 H); 6.48 (*d*, *J* = 8.4, 1 H); 6.90 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.0; 20.7; 34.4; 37.7; 39.5; 40.1; 44.5; 52.9; 54.4; 56.2; 60.5; 76.2; 78.4; 98.1; 104.9; 119.9; 122.9; 135.1; 145.8; 155.6; 169.7; 170.6; 172.4; 200.6.

A 0.18-g (0.4 mmol) sample of the above acetate was taken up in THF (35 ml) and cooled to 0°. The soln. was stirred vigorously, while 13.5 ml (1.4 mmol) of a 0.1M soln. of SmI_2 was added dropwise while maintaining a light blue color. When the addition was finished, the mixture was diluted with AcOEt (20 ml), and then 20 ml of a 0.1M soln. of HCl was added to the mixture and the soln. was stirred for 10 min. The soln. was allowed to stir for an additional 15 min, the aq. layer was separated, and then extracted with AcOEt. The org. layer was washed successively with $Na_2S_2O_3$ (30 ml) and $NaHCO_3$ (30 ml). The combined org. layers were dried ($MgSO_4$), and concentrated under reduced pressure to give 0.15 g (95%) of **18** as a white solid. M.p. 210–212°. IR (neat): 1791, 1716, 1652, 1471, 1266, 1186. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20–1.44 (*m*, 2 H); 1.70–1.78 (*m*, 1 H); 2.27 (*d*, *J* = 17.4, 1 H); 2.36 (*d*, *J* = 17.4, 1 H); 2.41–2.46 (*m*, 1 H); 2.66 (*d*, *J* = 18.2, 1 H); 2.80 (*dd*, *J* = 15.1, 2.4, 1 H); 2.90–2.96 (*m*, 1 H); 2.99 (*s*, 3 H); 3.04 (*dd*, *J* = 15.3, 3.9, 1 H); 3.28 (*dd*, *J* = 18.3, 1.5, 1 H); 3.62 (*dd*, *J* = 4.0, 2.4, 1 H); 3.71 (*s*, 3 H); 3.84 (*s*, 3 H); 4.24–4.30 (*m*, 1 H); 6.46 (*d*, *J* = 8.4, 1 H); 6.92 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.8; 33.8; 35.5; 37.5; 40.6; 41.0; 44.9; 51.6; 52.2; 56.1; 60.9; 74.0; 99.0; 104.5; 120.9; 123.3; 134.7; 145.0; 155.4; 171.1; 172.8; 206.6. HR-MS: 413.1707 ($[C_{22}H_{24}N_2O_6 + H]^+$; calc. 413.1707).

Preparation of Olefinic Intermediate **41**. To 0.025 g (0.06 mmol) of **18** dissolved in THF (4 ml) at −78° was added 0.25 ml (0.072 mmol) of a 0.5M soln. of potassium bis(trimethylsilyl)amide (KHMDS) in toluene. The soln. turned a deep yellow color. The mixture was stirred at −78° for 1 h, and then 0.25 ml (0.072 mmol) of a 0.29M soln. of *N*-phenyltriflimide in THF was added. The mixture was stirred at −78° for 30 min, and the reaction was quenched with water. The resulting soln. was added to a sat. aq. soln. of $NaHCO_3$ (10 ml) and CH_2Cl_2 (20 ml). The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to prep. aluminum thick layer chromatography to give 0.017 g (68%) of recovered starting material and 0.01 g (30%) of the enol triflate of **18**. Clear oil. IR (neat): 1780, 1732, 1609, 1471, 1418, 1138. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44–1.80 (*m*, 3 H); 2.30–2.38 (*m*, 1 H); 2.54 (*d*, *J* = 16.8, 1 H); 2.59 (*d*, *J* = 16.8, 1 H); 2.76 (*s*, 2 H); 3.27 (*dt*, *J* = 13.0, 3.4, 1 H); 3.16 (*s*, 3 H); 3.76 (*s*, 3 H); 3.83 (*s*, 3 H); 3.85 (*d*, *J* = 2.8, 1 H); 4.05–4.10 (*m*, 1 H); 6.10 (*d*, *J* = 2.8, 1 H); 6.29 (*d*, *J* = 8.6, 1 H); 7.01 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5; 29.6; 35.7; 37.6; 44.0; 44.1; 45.1; 52.8; 56.1; 61.4; 70.7; 100.7; 103.7; 117.3; 120.6; 123.8; 129.9; 134.7; 143.3; 146.8; 155.1; 171.5; 173.1. HR-MS: 545.1199 ($[C_{23}H_{23}N_2O_8F_3S + H]^+$; calc. 545.1200).

A 10-mg (0.018 mmol) sample of the above enol triflate was dissolved in THF (5 ml), and to this soln. was added 0.004 g (0.003 mmol) of $Pd(PPh_3)_4$, followed by 0.043 g (0.15 mmol) of Bu_3SnH. The mixture was stirred at r.t. for 1 h and was then concentrated under reduced pressure. The resulting residue was taken up in 10 ml of MeCN and washed with 100 ml of hexane. The layers were separated, and the MeCN layer was concentrated under reduced pressure. The residue was subjected to prep. aluminum thick layer chromatography to give 0.006 g of **41**. Colorless oil. IR (neat): 1797, 1777, 1719, 1609, 1465, 1070. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20–1.75 (*m*, 3 H); 1.80–1.90 (*m*, 1 H); 2.38 (*d*, *J* = 16.8, 1 H); 2.43 (*d*, *J* = 16.8, 1 H); 2.69 (*d*, *J* = 17.4, 1 H); 2.76 (*d*, *J* = 17.4, 1 H); 2.88 (*dt*, *J* = 13.2, 3.4, 1 H); 3.16 (*s*, 3 H); 3.67 (*dd*, *J* = 2.8, 1.6, 1 H); 3.76 (*s*, 3 H); 3.80 (*s*, 3 H); 4.00–4.07 (*m*, 1 H); 5.59 (*dd*, *J* = 10.4, 1.6, 1 H); 6.00 (*d*, *J* = 10.4, 2.8, 1 H); 6.24 (*d*, *J* = 8.6, 1 H); 7.01 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.9; 34.7; 35.6; 37.4; 41.4; 44.8; 52.3; 56.0; 61.3; 72.4; 100.5; 102.8; 120.7; 122.0; 126.6; 129.9; 134.1; 143.7; 154.7; 173.3; 173.8. HR-MS: 397.1760 ($[C_{22}H_{24}N_2O_5 + H]^+$; calc. 397.1758).

Thiolactam Derivative **42** *of Aspidophytine.* A 0.004-g (0.01 mmol) sample of **41** was dissolved in 10 ml of benzene, and then 0.002 g (0.006 mmol) of P_2S_5 and 0.002 g (0.016 mmol) of hexamethyldisiloxane was added. The resulting mixture was heated at reflux under Ar for 2 h. The soln. was allowed to cool to r.t., and the solvent was removed under reduced pressure. The residue was taken up in AcOEt (containing 5% Et_3N) and filtered through a pad of *Florisil* to give 0.004 g of **42**. Colorless oil. IR (neat): 1799, 1771, 1652, 1457, 1070. ^{1}H-NMR (600 MHz, $CDCl_3$): 1.50–1.60 (*m*, 1 H); 1.73–1.90 (*m*, 3 H); 2.45 (*s*, 2 H); 3.01–3.07 (*m*, 1 H); 3.13 (*dd*, *J* = 18.0, 1.8, 1 H); 3.16 (*s*, 3 H); 3.32 (*d*, *J* = 18.0, 1 H); 3.67 (*dd*, *J* = 2.4, 0.8, 1 H); 3.77 (*s*, 3 H); 3.81 (*s*, 3 H); 4.75–4.80 (*m*, 1 H); 5.60 (*dd*, *J* = 10.2, 0.8, 1 H); 6.02 (*dd*, *J* = 10.2, 2.4, 1 H); 6.24 (*d*, *J* = 8.7, 1 H); 6.98 (*d*, *J* = 8.7, 1 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 19.8; 29.9; 34.0; 35.6; 41.9; 42.5; 46.3; 56.0; 56.4; 61.3; 71.2; 102.0; 102.9; 120.6; 121.2; 127.3; 128.8; 129.3; 131.8; 134.2; 143.8; 154.8; 172.7; 204.8. HR-MS: 413.1533 ($[C_{22}H_{24}N_2O_4S + H]^+$; calc. 413.1529).

(±)-Aspidophytine (**6**). A 0.003-g (0.0073 mmol) sample of **42** in anh. CH_2Cl_2 (1 ml) was cooled to 0°, and then 0.02 ml (0.02 mmol) of a 1.0M soln. of Et_3OBF_4 in CH_2Cl_2 was added, and the mixture was stirred for 12 h. The soln. was cooled to −78° and 0.027 ml (0.027 mmol) of a 1.0M soln. of $LiAlH(O^tBu)_3$ in THF was added to the mixture. The soln. was stirred for 1 h at −78° and was allowed to slowly warm to r.t. The soln. was added to a sat. aq. soln. of $NaHCO_3$ (10 ml), and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was taken up in 10 ml of benzene, and 0.002 g (0.015 mmol) of AIBN and 0.1 ml (0.37 mmol) of Bu_3SnH was added. The mixture was heated at reflux for 10 h, cooled to r.t., and the solvent was removed under reduced pressure. The residue was dissolved in 10 ml of MeCN and washed with 100 ml of hexane. The layers were separated, and the MeCN layer was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and was then added to a sat. aq. soln. of $NaHCO_3$. The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to prep. thick layer chromatography to give 0.0017 g of *(±)-aspidophytine* (**6**). White solid. IR (neat): 1733, 1609, 1494, 1463, 1457, 1265, 1071. ^{1}H-NMR (600 MHz, $CDCl_3$): 1.50–1.74 (*m*, 4 H); 2.08 (*ddd*, *J* = 12.8, 10.5, 6.9, 1 H); 2.24 (*d*, *J* = 16.5, 1 H); 2.30 (*ddd*, *J* = 12.8, 8.4, 3.3, 1 H); 2.37 (*d*, *J* = 16.5, 1 H); 2.75 (br. *d*, *J* = 11.4, 1 H); 2.92 (*td*, *J* = 10.8, 4.2, 1 H); 3.01 (*td*, *J* = 9.6, 3.0, 1 H); 3.16 (*s*, 3 H); 3.19 (*q*, *J* = 8.4, 1 H); 3.76 (*s*, 1 H); 3.79 (*s*, 3 H); 5.52 (*dd*, *J* = 10.0, 1.2, 1 H); 6.02 (*dd*, *J* = 10.0, 2.4, 1 H); 6.20 (*d*, *J* = 8.4, 1 H); 6.97 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 21.7; 34.7; 35.4; 35.5; 41.6; 43.6; 47.5; 48.0; 55.9; 57.3; 61.4; 72.0; 102.2; 120.4; 125.7; 125.8; 130.7; 133.9; 143.8; 154.1; 176.0. HR-MS: 383.19608 ($[C_{22}H_{26}N_2O_4 + H]^+$; calc. 383.19653). This compound was identical in all respects (NMR, IR, HR-MS, and TLC) to a sample of aspidophytine kindly provided by Prof. *Fukuyama.*

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