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Xuechuan Hong, Emory University
Stefan France, Emory University
Albert Padwa, Emory University

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A Dipolar Cycloaddition Approach Toward the Kopsifoline Alkaloid Framework

Xuechuan Hong, Stefan France, and Albert Padwa*
Department of Chemistry, Emory University, Atlanta, GA 30322, USA

Abstract
Using a metal-catalyzed domino reaction as the key step, the heterocyclic skeleton of the kopsifoline alkaloid family was constructed by a 1,3-dipolar cycloaddition of a carbonyl ylide dipole derived from a Rh(II)-catalyzed reaction of a diazo ketoester across the indole $\pi$-bond. Ring opening of the resulting 1,3-dipolar cycloadduct followed by a reductive dehydroxylation step resulted in the formation of a critical silyl enol ether necessary for the final F-ring closure of the kopsifoline skeleton.

Keywords
diazoimide; synthesis; indole; cycloaddition; rhodium(II); kopsifoline; alkaloid

1. Introduction
In recent years, a widespread upsurge of activity in the stereoselective preparation of highly substituted nitrogen heterocycles, especially structurally complex alkaloids has occurred.1 In particular, the Aspidosperma alkaloid family has occupied a central place in natural product chemistry because of their diverse biological activity.2 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 six stereocenters and most of the functionalities are located in this ring.3 Individual members differ mainly in functionality and stereochemistry. Over the years, efficient and elegant routes to this molecular framework have been developed.4,5

*Corresponding Author: Tel.: 404-727-0283; Fax: 404-727-6629; e-mail: chemap@emory.edu.

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Our approach to the *Aspidosperma* skeleton was guided by a long-standing interest in developing new applications of the Rh(II) cyclization/cycloaddition cascade for the synthesis of complex natural products. The generation of onium 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. In earlier studies we described the formation of cyclic carbonyl ylide dipoles by a process involving cyclization of an electrophilic metallo carbenoid onto an adjacent carbonyl group. The general reaction investigated is illustrated in Scheme 1; variations in chain length (n = 0, 1, 2) and nature of the activating group (G) were explored. With limited exceptions, alkyl and aryl ketones were employed and dipole 5 was generated by the rhodium(II)-catalyzed decomposition of the diazoalkanedione in benzene at 80 °C.

More recently, we became interested in the formation of push-pull dipoles from the Rh(II)-catalyzed reaction of α-diazoimides and noted that a smooth intramolecular 1,3-dipolar cycloaddition occurred across both alkenyl and heteroaromatic π-bonds to provide novel pentacyclic compounds in good yield and in a stereocontrolled fashion. Our recent total synthesis of (±)-aspidophytine nicely demonstrates the utility of this cascade methodology for the construction of complex aspidosperma alkaloids. Thus, the Rh(II)-catalyzed reaction of diazoimido indole 7 produced cycloadduct 9 in 97% yield via the intermediacy of the carbonyl ylide dipole 8. The acid lability of cycloadduct 9 was exploited to provide the complete skeleton of aspidophytine in several additional steps (Scheme 2).

As an extension of our earlier work on (±)-aspidophytine (10) we became interested in using the Rh(II)-catalyzed cyclization/cycloaddition cascade for the synthesis of the hexacyclic framework of the kopsifoline alkaloids. The Malaysian members of the genus *Kopsia* have yielded a prodigious harvest of new natural products possessing novel carbon skeletons as well as useful bioactivities. In 2003, Kam and Choo reported the structures of several new hexacyclic monoterpenoid indoline alkaloids isolated from a Malayan *Kopsia* species known as *K. fruticosa*. The structures were secured by spectral analysis and are characterized by an unprecedented carbon skeleton, in which the C(18) carbon is linked to C(16). The kopsifolines are structurally intriguing compounds, related to and possibly derived from an aspidosperma-type alkaloid precursor 11. A possible biogenetic pathway to the kopsifolines from 11 could involve an intramolecular epoxide-ring opening followed by loss of H₂O as shown in Scheme 3. The interesting biological activity of these compounds combined with their fascinating and synthetically challenging structure, make them attractive targets for synthesis.

Our own work on the synthesis of the kopsifolines represents one component of a broad program focused on the synthesis of various aspidosperma alkaloids using [3+2]-cycloaddition chemistry. Our retrosynthetic analysis of 13 is shown in Scheme 4 and envisions the core skeleton to arise from a metal carbene-cyclization-cycloaddition cascade that our group has been studying for some time. Using this metal-catalyzed domino reaction as a key step, the heterocyclic skeleton of the kopsifolines could eventually be built by a 1,3-dipolar cycloaddition of a carbonyl ylide dipole derived from diazo ketoester 14 across the indole π-bond. Ring opening of the resulting cycloadduct 15 followed by a reductive dehydroxylation step would lead to the critical silyl enol ether necessary for the final F-ring closure. Although the very last step (i.e., 16 → 17) appears to be reasonable, no example of such a reaction had been previously reported in the literature. Accordingly, we decided to study the facility and stereoselectivity of this process with some model substrates prior to commencing the total synthesis of the kopsifolines. In this paper we detail the successful implementation of this strategy.
2. Results and Discussion

The 3-substituted diazoimides needed to test this approach were prepared according to the reaction sequence outlined in Scheme 5. Deprotonation of piperidone 18 with 1.1 equiv of n-butyllithium followed by reaction with 2-iodoethyl benzyl ether afforded lactam 19 in 70% yield. The ethyl ester portion of 19 was converted to the 3-oxopropanoate group using a modified Masamune procedure 23 which furnished either β-keto ester 20a or 20b in 82% or 84% yield, respectively. A related sequence of reactions was also used to prepare lactams 22 and 23. Thus, the anion derived from piperidone 18 was allowed to react with t-butyliodacetate together with a catalytic amount of tetrabutyl ammonium iodide which lead to the formation of lactam 21 in 80% yield. Treatment of the resulting t-buty1 ester 22 (derived from 21) with (MeO)3CH/MeOH in the presence of p-TsOH gave the corresponding methyl ester 23 in almost quantitative yield (Scheme 5). When these lactams were allowed to react with the acid chloride derived from 2-(N-phenylsulfonyl) or 2-((N-tosyl-1H-indol-3-yl)acetic acid, the expected imides were readily formed in high yield and were easily converted to the corresponding diazo substrates 24-26 using the Regitz diazotization procedure. 24

We first carried out a model study using cycloadduct 27 derived from the Rh(II)-catalyzed reaction of diazoimide 24 in order to test the viability of our design as well as the specific reactions to be used in a total synthesis effort. Heating a sample of diazoimide 24 with catalytic Rh2(OAc)4 in benzene at 80 °C afforded cycloadduct 27 in 94% yield as a single diastereomer (Scheme 6). The isolation of 27 is the consequence of endo cycloaddition with regard to the dipole, 14 and this is in full accord with the lowest energy transition state. The cycloaddition can also be considered doubly diastereoselective in that the indole moiety approaches the dipole exclusively from the side of the 2-(benzyloxy)ethyl group and away from the more sterically encumbered piperidone ring.

Having established a viable route to cycloadduct 27, efforts were next centered on the reductive opening of the oxido bridge. In 1991, Cossy and coworkers reported that a photoinduced electron transfer reaction from Et3N to 7-oxabicyclo[2.2.1]heptan-2-ones easily generated the corresponding 3-hydroxycyclohexanone derivatives (e.g. 29 to 30). 25 The reduction relies on the intermediacy of a ketyl radical anion 26 derived from the oxabicycloheptane under the photochemical conditions. With this result in mind, our initial attempts to carry out the reductive ring opening of 27 employed Cossy’s photoreductive approach. We found, however, that the irradiation of 27 in the presence of NEt3 (5 equiv) using CH3CN as the solvent only furnished the desulfonylated indoline 28 in 90% yield.

The ready photodesulfonylation of indoline 27 prompted us to carry out a broader study of this deprotection reaction since substituted N-sulfonyl-indoles are commonly employed in organic synthesis. The powerful electron-withdrawing property of the sulfonyl group coupled with its ortho-directing effect has been extensively utilized for selective metallation at the C2-position of the indole ring without having to use a large excess of metalling agent. 27 In addition, the product N-sulfonamides are often crystalline and stable to a variety of reaction conditions (e.g. alkaline hydrolysis and catalytic reduction). A corollary of the stability of the N-sulfonyl bond is the difficulty encountered in the removal of this type of protecting group. Harsh deprotection conditions are often required which limit the synthetic usefulness of these compounds. Thus, arylsulfonamides are cleaved by sodium in liquid ammonia, 28 sodium naphthalenide or anthracenide, 29 heating to reflux in strong acid 30 and reaction with highly nucleophilic 31 or reducing 32 reagents. These harsh conditions have led to the development of new methods for the deprotection of N-sulfonamides. This has included deprotection by using SmI2, 33 TiCl4/Zn, 34 Mg in methanol, 35 TBAF, 36 iodotrimethylsilane 37 or electrolysis. 38
While the desulfonylation of several alkyl N-sulfonyl amides has been achieved photochemically,\textsuperscript{39} the related reaction using indoles has not been reported in the literature. Since the serendipitous deprotection reaction that we encountered with indoline 27 proceeded in such high yield and under very mild conditions, we set out to further explore the generality and scope of the photodesulfonylation of a series of related indoles. The photolysis of indoles 31 was carried out in the presence of 5.0 equiv of Et\textsubscript{3}N and CH\textsubscript{3}CN in a quartz vessel using 254 nm lamps for 1 h under a nitrogen atmosphere (Scheme 7). Column chromatography of the crude residue followed by removal of the solvent gave the desired desulfonylated indoles 32 in 48-77\% yield based on recovered starting material (entries 1-5). Interestingly, we also observed the formation of both the \textit{ortho}- and \textit{para}-photo Fries like rearrangement products 33 and 34 in varying quantities (8-19\%) depending on the particular system. In most cases the \textit{para}-rearrangement product was the major isomer formed, suggesting leakage from a radical cage.

Encouraged by these positive results, we studied the effect of adding different additives in order to capture the initially produced sulfonyl radical and thereby enhance the yield of the desulfonylated indole. The use of \textit{t}-butyl mercaptan as a radical scavenger showed no improvement in the overall yield of the desulfonylated indole 32. However, in the presence of 1.0 equiv of \textit{n}-Bu\textsubscript{3}SnH, the photoreaction of 31d afforded indole 32d in 96\% yield (based on recovered starting material) with no signs of the rearranged aryl sulfones 33d and 34d. The more highly activated tin hydride (weaker Sn-H bond) allows for capture of the sulfonyl radical thereby suppressing attack at the \textit{ortho}- and \textit{para}-positions.

More than likely, the photodesulfonylation reaction can be attributed to a photoinduced electron transfer as outlined in Scheme 8. Amines are well known to undergo such a transfer with electronically excited carbonyl groups.\textsuperscript{40} The reaction is initiated by single electron transfer from NEt\textsubscript{3} to the electronically excited indole with formation of the radical cation of triethylamine (36) and the radical anion of the indole (35). Formation of 35 weakens the N-SO\textsubscript{2}Ph bond and facilitates bond cleavage.\textsuperscript{41} Proton transfer from the radical cation of NEt\textsubscript{3} (36) would lead to the observed desulfonylated indole 32. In competition with this process, the phenylsulfonyl radical can undergo addition to the aromatic framework of the indole anion 37 producing radical anion 38 as a transient species. A subsequent electron transfer from 38 to 36 would afford the rearranged indole 33 (and/or 34). In the presence of \textit{n}-Bu\textsubscript{3}SnH, the phenylsulfonyl radical undergoes bimolecular hydrogen atom transfer and is no longer available to add to the aromatic ring.\textsuperscript{42}

At this point of our studies we decided to examine the reduction of cycloadduct 39, derived from the Rh(II)-catalyzed reaction of diazoimide 25, using Et\textsubscript{3}SiH and BF\textsubscript{3}•OEt\textsubscript{2}. On the basis of our previous studies using related aza-oxabicyclic systems,\textsuperscript{43} we expected that this reaction would result in a reductive ring opening reaction. We found, however, that the rearranged nine-membered lactone 42 was obtained as the only identifiable product in 60\% yield. This unusual reorganization can be rationalized by the pathway proposed in Scheme 9. We assume that the first step involves a Lewis acid promoted debenzylation with Et\textsubscript{3}SiH and the transient alcohol 40 so produced undergoes ready cyclization onto the adjacent carbonyl group to generate a hemiketal intermediate. A subsequent ring opening of the oxabicyclic ring affords \textit{N}-acyliminium ion 41 which then undergoes cleavage of the C-C bond to dissipate the positive charge on the nitrogen atom thereby giving rise to the observed lactone 42.

We next investigated the key F-ring closure step that is the foundation of our kopsifoline strategy by making use of hemiketal 43. For these feasibility studies (Scheme 10), we converted 43 into keto-ester 45 which possesses a side chain mesylate group that could undergo intramolecular displacement with the carbamion derived from ketoester 45. Hemiketal 43 is easily available from cycloadduct 39 via lactam reduction followed by catalytic hydrogenation.
which causes reductive ring opening of the oxabicyclic ring, debenzylation and cyclization to
give 43 in 43% yield for the three-step sequence. Treatment of 43 with triethylamine/mesyl
chloride furnished 44 (85%) which was then reduced with SmI$_2$ to give 45 in 60% yield.
Unfortunately, all of our efforts to induce ring F-closure of 45 with various bases and under
different experimental conditions were unsuccessful.

This outcome suggested that the mesylate group was not sufficiently reactive enough to
undergo reaction with the anion resulting from deprotonation of the β-keto ester. Consequently,
we turned our attention to replacing the mesylate group with a more reactive aldehyde
functionality on the side chain. To access a suitable and useful substrate for the key aldol
reaction, we prepared cycloadduct 46 which bears a 2-methyl acetate group at the ring juncture
from the Rh(II)-catalyzed reaction of diazoimide 26. We then converted 46 into the ring-opened
hydroxy ester 47 (68%) using the same 3-step protocol that was used in Scheme 10. At this
point, the carbomethoxy and hydroxyl groups were sequentially removed using Cs$_2$CO$_3$
followed$^{15,44,45}$ by a samarium iodide reduction.$^{46}$ The remaining keto group was converted
into the corresponding TBS enol ether and this was followed by a two-step reduction/oxidation
of the ester functionality to give 48 in 59% yield for the five-step sequence (Scheme 11).
Gratifyingly, when 48 was treated with CsF in CH$_3$CN at reflux, it was cleanly converted to
the hexacyclic skeleton of the kopsifoline alkaloids (i.e., 49) in 78% yield.

Since all members of the kopsifoline family of alkaloids contain a carbomethoxy group at the
C(16)-position of the core skeleton, we decided to selectively remove the hydroxyl group from
hydroxy ester 47. To this end, the reduction of 47 was carried out with SmI$_2$ in HMPA and the
expected ketoester 50 was isolated in 93% yield (Scheme 12). This compound was easily
converted into the corresponding TBS silyl enol ether in 96% yield. Reaction of the enol ether
with LAH at 0 °C resulted in the selective reduction of the non-conjugated carbomethoxy group
affording 51 in 91% yield. The primary alcohol so formed was then subjected to oxidation
using TPAP (NMO) at 0 °C and the crude reaction mixture was subsequently treated with CsF
in refluxing CH$_3$CN to give the desired ring F-cyclized ester 52 in 34% yield for the two-step
sequence. Despite the additional manipulations associated with the processing of intermediate
47 and the somewhat lower yield, only five steps are required to prepare a complex racemic
hexacyclic structure that contains the complete skeleton of the kopsifoline alkaloids.

3. Conclusions

In summary, the new cyclization chemistry described herein gives rapid access to the
hexacyclic core skeleton of the kopsifoline alkaloids, and the products synthesized appear to
be suitable for further manipulation toward the natural products and their close analogues.
Further application of the metal carbene cyclization-cycloaddition cascade toward several
other monoterpenoid indoline alkaloids is currently being investigated.

4. Experimental

4.1 General

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70eV.
Unless otherwise noted, all reactions were performed in flame dried glassware under an
atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary
evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate-
hexane mixture as the eluent unless specified otherwise.

4.1.1 3-[3-{2-Benzyl oxyethyl}-2-oxo-piperidin-3-yl]-3-oxo-propionic Acid Methyl
Ester (20a)—To a stirred solution of 8.2 g (48 mmol) of 2-oxopiperidine-3-carboxylic acid
ethyl ester in 125 mL of THF at −78 °C was added 20 mL (48 mmol) of a 2.4 M n-butyllithium
solution in hexane. The resulting solution was allowed to warm to 0 °C for 10 min, re-cooled to −78 °C and 12.6 g (48 mmol) of 2-iodoethyl benzyl ether was added. The cooling bath was removed and the solution was heated at reflux for 3 days. The solution was allowed to cool to rt, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 10.2 g (70%) of 3-(2-benzyloxyethyl)-2-oxo-piperidine-3-carboxylic acid ethyl ester (19) as a colorless oil; IR (neat) 1729, 1669, 1194, 1119 and 1098 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.23 (t, 3H, J = 7.0 Hz), 1.78-1.90 (m, 2H), 1.95 (td, 1H, J = 13.2 and 4.0 Hz), 2.15-2.35 (m, 3H), 3.20-3.35 (m, 2H), 3.64 (td, 2H, J = 6.8 and 2.0 Hz), 4.10-4.23 (m, 2H), 4.46 (s, 2H), 6.03 (brs, 1H) and 7.20-7.73 (m, 5H); ¹³C-NMR (100 MHz, CDCl₃) δ 14.3, 19.8, 30.4, 35.2, 42.5, 53.0, 61.7, 67.3, 73.1, 127.7, 127.8, 128.5, 138.6, 171.0 and 172.8.

To a solution of 23.4 g (77 mmol) of the above ethyl ester in a 1:1 THF/H₂O mixture (300 mL) was added 8.6 g of potassium hydroxide (150 mmol) and the mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was taken up in water. The solution was washed with EtOAc and acidified to pH 2. The aqueous layer was extracted with chloroform and the combined organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure to give 19.2 g (91%) of the titled compound 20b as a colorless oil; IR (neat) 1729, 1669, 1194, 1119 and 1098 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.23-1.27 (m, 3H), 1.62-1.65 (m, 1H), 1.77-1.81 (m, 2H), 2.19 (dt, 1H, J = 14.4 and 6.0 Hz), 2.36-2.51 (m, 2H), 3.20-3.28 (m, 2H), 3.48-3.52 (m, 1H), 3.53-3.60 (m, 1H), 3.70 (d, 1H, J = 16.4 Hz), 3.96 (d, 1H, J = 16.4 Hz), 4.16 (q, 2H, J = 16.4 Hz), 4.45

To a solution of 9.0 g (33 mmol) of the above carboxylic acid in 150 mL of CH₂Cl₂ was added 6.3 g (39 mmol) of 1,1′-carbonyldiimidazole. The solution was allowed to stir at rt under N₂ overnight, concentrated under reduced pressure and taken up in water. The solution was washed with brine, filtered, and concentrated under reduced pressure to give 19.2 g (91%) of 3-[2-benzyloxyethyl]-2-oxo-piperidine-3-carboxylic acid as a white solid; mp 102-103 °C; IR (neat) 1700, 1653, 1492,1454, 1202 and 1100 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.38-1.62 (m, 3H), 3.58-3.67 (m, 2H), 4.48 (s, 2H), 6.28 (brs, 1H) and 7.20-7.38 (m, 5H) (the carboxylic acid proton was too broad to be detected); ¹³C-NMR (100 MHz, CDCl₃) δ 19.2, 27.8, 37.9, 42.9, 50.7, 66.4, 73.4, 127.9, 128.6, 138.2 and 175.5; Anal. Calcd for C₁₅H₁₉NO₄: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.87; H, 6.74; N, 4.96.

4.1.2 3-[3-(2-Benzylxoyethyl)-2-oxo-piperidin-3-yl]-3-oxo-propionic Acid Ethyl Ester (20b)—Keto ester 20b was prepared in the same manner as described for 20a from the reaction of 9.0 g (33 mmol) of 3-[2-benzyloxyethyl]-2-oxo-piperidine-3-carboxylic acid and 11.1 g (65.0 mmol) of potassium ethyl malonate. Purification by flash silica gel chromatography gave 9.4 g (84%) of the titled compound 20b as a pale yellow oil; IR (neat) 2937, 2869, 1741, 1707, 1654, 1488, 1453, 1366, 1318, 1260, 1101 and 1028 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.26 (t, 3H, J = 7.6 Hz), 1.62-1.65 (m, 1H), 1.77-1.81 (m, 2H), 2.19 (dt, 1H, J = 14.4 and 6.0 Hz), 2.36-2.51 (m, 2H), 3.24-3.28 (m, 2H), 3.48-3.52 (m, 1H), 3.53-3.60 (m, 1H), 3.70 (d, 1H, J = 16.4 Hz), 3.96 (d, 1H, J = 16.4 Hz), 4.16 (q, 2H, J = 16.4 Hz), 4.45
4.1.3 Methyl 3-(3-(2-Methoxy-2-oxoethyl)-2-oxopiperidin-3-yl)-3-oxopropanoate (23)—A 8.8 g (28 mmol) sample of methyl 3-(3-(2-tert-butoxy-2-oxoethyl)-2-oxopiperidin-3-yl)-3-oxopropanoate (22) in MeOH (40 mL) and (MeO)₂CH (40 mL) was vigorously stirred for 10 min at 100 °C. To this mixture was added 5.3 g (28 mmol) of p-TsOH·H₂O in one portion and the mixture was allowed to stir for 4 h. The solution was cooled to rt and concentrated under reduced pressure. The colorless residue was subjected to flash chromatography on silica gel to give 0.82 g (99%) of the titled compound as a colorless oil; IR (neat) 3298, 3226, 2975, 2939, 2873, 2146, 1716, 1644, 1501, 1367, 1316, 1209 and 1106 cm⁻¹; ¹³C-NMR (100 MHz, CDCl₃) δ 14.1, 19.7, 27.8, 36.3, 42.4, 45.5, 58.5, 61.1, 66.1, 73.1, 127.6, 127.7, 128.4, 138.1, 167.1, 167.8, 171.6 and 201.3; HRMS Calcd for [(C₁₀H₂₅NO₃) + H]⁺: 348.1811. Found: 348.1821.

4.1.4 3-(2-Benzoyloxyethyl)-2-piperidin-3-yl)-2-diazo-3-oxo-propionic Acid Ethyl Ester—To 0.7 g (2.22 mmol) of ketoester 20b in 20 mL of CH₂CN was added 0.37 mL (2.7 mmol) of Et₃N. The solution was allowed to stir for 30 min at rt and then 0.54 g (4.4 mmol) of mesyl azide was added and the reaction was allowed to stir for 10 h at rt. The solution was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel to give 0.82 g (99%) of the titled compound as a colorless oil; IR (neat) 3349, 2953, 1732, 1710, 1655, 1489, 1436, 1354, 1319, 1271, 1223, 1194, 1174 and 1002 cm⁻¹; ¹³C-NMR (100 MHz, CDCl₃) δ 1.73-1.89 (m, 3H), 2.33-2.38 (m, 1H), 2.66 (d, 1H, J = 16.4 Hz), 3.01 (d, 1H, J = 16.4 Hz), 3.27-3.39 (m, 2H), 3.63 (s, 3H), 3.68 (s, 3H), 3.79 (dd, 1H, J = 19.6 and 16.8 Hz) and 7.02 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 20.1, 28.9, 40.3, 42.7, 45.9, 52.1, 52.5, 57.8, 167.9, 170.9, 171.1 and 201.0; HRMS Calcd for [(C₁₅H₁₇NO₅) + H]⁺: 272.1134. Found: 272.1129.

4.1.5 3-[1-{2-(1-Benzensulfonyl-1H-indol-3-yl)-acetyl}-3-(2-benzyloxy)ethyl]-2-diazo-3-oxo-propionic Acid Ethyl Ester (24) —In a 100 mL round bottomed flask was added 0.19 g (0.6 mmol) of (1-benzenesulfonyl-1H-indol-3-yl)acetyl chloride in 10 mL of CH₂Cl₂. After stirring for 5 min, 0.14 mL (1.6 mmol) of (COCl)₂ in 5 mL of DMF was added. The solution was allowed to stir for 3 h at rt and then concentrated under reduced pressure. The resulting solid was taken up in 2 mL of THF and was added dropwise to a solution of 0.2 g of the above diazo lactam (0.54 mmol) and 3 g of 4Å mesh molecular sieves in 10 mL of THF. The reaction mixture was allowed to stir at rt overnight, filtered through a pad of Celite and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.29 g (80%) of 24 as a pale yellow oil; IR (neat) 2975, 2929, 2847, 2130, 1726, 1675, 1470, 1388, 1326, 1152 and 1101 cm⁻¹; ¹³C-NMR (300 MHz, CDCl₃) δ 1.60 (t, 3H, J = 7.2 Hz), 1.48-1.53 (m, 1H), 1.71-1.83 (m, 2H), 2.00-2.23 (m, 3H), 3.29-3.36 (m, 1H), 3.45-3.58 (m, 2H), 3.72 (d, 1H, J = 17.4 Hz), 3.99-4.05 (m, 4H), 4.20 (s, 1H), 6.94-7.07 (m, 7H), 7.16-7.29 (m, 5H), 7.63-7.66 (m, 2H) and 7.74 (d, 1H, J = 8.4 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ 14.3, 19.3, 30.3, 34.9, 35.0, 44.2, 59.1, 61.7, 67.0, 72.9, 113.4, 116.5, 119., 123.0, 124.5, 124.7, 126.6, 127.4, 127.5, 128.1, 129.1, 130.8, 133.5, 134.8, 137.9, 138.2, 161.0, 173.3, 174.0 and 190.3; HRMS Calcd for [(C₃₅H₃₄N₄O₈S) + H]⁺: 671.2176. Found: 671.2182.

4.1.6 Methyl 3-(3-(2-Benzoyloxy)ethyl)-2-oxo-1-(2-(1-tosyl-1H-indol-3-yl)acetyl)piperidin-3-yl)-3-oxopropanoate—To 100 mL of CH₂Cl₂ in a 200 mL round bottomed
flask was added 6.0 g (18 mmol) of 2-(1-tosyl-1H-indol-3-yl) acetic acid. After stirring for 5 min, 5.3 mL (60 mmol) of (COCl)₂ was added dropwise. The solution was stirred for 5 h and then concentrated under reduced pressure. The resulting solid was taken up in 50 mL of CH₂Cl₂ and this solution was added dropwise to a solution of 5.0 g (15 mmol) of lactam 20a and 50 g of 4Å mesh molecular sieves in 250 mL of CH₂Cl₂. The reaction mixture was allowed to stir at rt for 12 h, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 8.1 g (84%) of the titled imide as a clear oil; IR (neat) 2954, 2872, 1752, 1683, 1593, 1466, 1360, 1290, 1160, 1115, 1086 and 976 cm⁻¹; 1H-NMR (400 MHz, CDCl₃) δ 1.61-1.72 (m, 1H), 1.83 (pent, 2H, J = 7.2 Hz), 2.21-2.32 (m, 2H), 2.30 (s, 3H), 2.46 (dt, 1H, J = 10.4 and 7.2 Hz), 3.42-3.50 (m, 1H), 3.53-3.74 (m, 4H), 3.64 (s, 3H), 3.84 (d, 1H, J = 21.2 Hz), 4.20 (s, 2H), 4.38 (s, 2H), 7.16-7.32 (m, 9H), 7.46 (d, 1H, J = 8.4 Hz), 7.55 (d, 1H, J = 8.4 Hz) and 7.96 (d, 1H, J = 8.4 Hz); 13C-NMR (100 MHz, CDCl₃) δ 20.0, 21.8, 27.6, 35.6, 36.7, 44.6, 44.9, 52.6, 61.9, 65.9, 73.5, 113.8, 116.0, 120.0, 123.4, 124.9, 125.4, 127.0, 127.8, 127.9, 130.1, 131.1, 135.1, 135.5, 137.8, 145.1, 168.0, 173.7, 174.0 and 200.1; HRMS Calcd for [(C₃₅H₃₆N₂O₈S) + H⁺]: 645.2271. Found: 645.2275.

4.1.7 Methyl 3-(3-(2-Benzoyloxy)ethyl)-2-oxo-1-(2-(1-tosyl-1H-indol-3-yl)acetyl) piperidin-3-yl)-2-diazo-3-oxopropanoate (25)—To a 2.4 g (3.7 mmol) sample of the above ketoester in 100 mL of CH₂CN was added 0.6 mL (4.5 mmol) of Et₃N. The solution was allowed to stir for 30 min at which time 0.47 g (3.9 mmol) of mesyl azide was added and the mixture was allowed to stir at rt for 5 h. The solution was subjected to reduced pressure and the residue was subjected to flash chromatography on silica gel to give 2.2 g (88%) of diazoidimide 25 as a pale yellow oil; IR (neat) 2982, 2864, 2167, 1707, 1687, 1446, 1368, 1303 and 1168 cm⁻¹; 1H-NMR (400 MHz, CDCl₃) δ 1.68-1.72 (m, 1H), 1.91-2.02 (m, 2H), 2.21-2.26 (m, 2H), 2.28 (s, 3H), 2.34 (dt, 1H, J = 14.4 and 6.0 Hz), 3.51 (dt, 1H, J = 10.0 and 6.0 Hz), 3.64-3.77 (m, 2H), 3.75 (s, 3H), 3.92 (d, 1H, J = 17.2 Hz), 4.21 (d, 1H, J = 17.2 Hz), 4.16-4.23 (m, 1H), 4.39 (s, 2H), 7.14-7.28 (m, 9H), 7.36 (d, 1H, J = 7.6 Hz), 7.43 (s, 1H), 7.72 (d, 2H, J = 8.0 Hz), 7.92 (d, 1H, J = 8.0 Hz); 13C-NMR (100 MHz, CDCl₃) δ 19.5, 21.7, 30.5, 35.1, 35.2, 43.0, 52.7, 59.4, 67.3, 73.2, 113.7, 117.6, 119.9, 123.3, 124.8, 125.1, 127.0, 127.7, 127.8, 128.5, 130.0, 131.2, 135.1, 135.5, 138.3, 145.0, 161.8, 173.7, 174.4 and 190.6; HRMS Calcd for [(C₃₅H₃₆N₄O₈S) + H⁺]: 671.2181. Found: 671.2181.

4.1.8 Methyl 3-(3-(2-Methoxy-2-oxoethyl)-2-oxo-1-(2-(1-tosyl-1H-indol-3-yl) acetyl)-piperidin-3-yl)-3-oxopropanoate—To 100 mL of CH₂Cl₂ in a 200 mL round bottomed flask was added 6.9 g (21 mmol) of 2-(1-tosyl-1H-indol-3-yl) acetic acid. After stirring for 5 min, 7.0 mL (80 mmol) of (COCl)₂ was added dropwise together with 2 drops of DMF. The solution was stirred at rt for 4 h and was concentrated under reduced pressure. The resulting solid was taken up in 50 mL of CH₂Cl₂ and added dropwise to a solution of 5.4 g (20.0 mmol) of the above lactam 23 and 90 g of 4Å mesh molecular sieves in 300 mL of CH₂Cl₂. The reaction mixture was allowed to stir at rt for 12 h, filtered through a pad of Celite and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 10.6 g (91%) of the titled compound as a pale yellow oil: IR (neat) 2953, 1738, 1703, 1689, 1596, 1446, 1396, 1363 and 1171 cm⁻¹; 1H-NMR (400 MHz, CDCl₃) δ 1.72-1.91 (m, 2H), 1.95-2.02 (m, 1H), 2.29 (s, 3H), 2.38 (dt, 1H, J = 14.0 and 4.0 Hz), 2.72 (d, 1H, J = 16.8 Hz), 3.19 (d, 1H, J = 16.8 Hz), 3.95 (dt, 1H, J = 12.4 and 4.4 Hz), 4.30 (dd, 1H, J = 25.6 and 17.2 Hz), 7.18 (d, 2H, J = 8.0 Hz), 7.22 (d, 1H, J = 8.0 and 0.8 Hz), 7.30 (td, 1H, J = 8.0 and 1.2 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.61 (s, 1H), 7.76 (d, 2H, J = 8.4 Hz) and 7.97 (d, 1H, J = 8.0 Hz); 13C-NMR (100 MHz, CDCl₃) δ 19.7, 21.3, 28.8, 35.2, 40.1, 44.6, 52.1, 52.4, 60.8, 113.3, 115.7, 119.6, 123.0, 124.4, 125.0, 126.6, 129.7, 130.7, 134.7, 135.0, 144.7, 166.9, 170.5, 172.8, 173.6 and 199.4; HRMS Calcd for [(C₂₉H₂₉N₂O₈S) + H⁺]: 583.1750. Found: 583.1748.

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4.1.9 Methyl 2-Diazo-3-(3-(2-methoxy-2-oxoethyl)-2-oxo-1-(2-(tosyl)-1H-indol-3-yl)acetyl)-piperidin-3-yl)-3-oxopropanoate (26)—To a 8.7 g (15 mmol) sample of the above keto ester in 140 mL of CH$_2$CN at 0 °C was added 2.3 mL (16 mmol) of Et$_3$N. The solution was allowed to stir for 20 min and then 1.95 g (30 mmol) of mesyl azide was added and the reaction mixture was allowed to stir for 1.5 h. The solution was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel to give 8.1 g (89%) of the titled diazomide 26 as a pale yellow solid; mp 79-80 °C; IR (neat) 2954, 2143, 1688, 1649, 1437, 1356, 1329, 1294, 1195, 1170, 1127 and 1095 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.80-1.95 (m, 2H), 2.25 (s, 3H), 2.29 (dd, 1H, $J$ = 12.0 and 4.4 Hz), 2.48 (dt, 1H, $J$ = 13.2 and 3.6 Hz), 2.85 (d, 2H, $J$ = 4.0 Hz), 3.65 (s, 3H), 3.68-3.76 (m, 1H), 3.74 (s, 3H), 4.07 (dt, 1H, $J$ = 13.2 and 4.0 Hz), 4.20 (dd, 1H, $J$ = 19.6 and 17.6 Hz), 7.13 (d, 2H, $J$ = 8.0 Hz), 7.17 (t, 1H, $J$ = 8.0 Hz), 7.25 (td, 1H, $J$ = 8.0 and 1.2 Hz), 7.45 (d, 1H, $J$ = 7.6 Hz), 7.52 (s, 1H), 7.71 (d, 2H, $J$ = 8.4 Hz) and 7.92 (d, 1H, $J$ = 8.4 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 19.1, 21.3, 27.3, 35.0, 37.2, 44.2, 51.7, 52.3, 60.0, 113.3, 115.9, 119.5, 122.9, 124.4, 124.8, 126.6, 129.6, 130.7, 134.7, 137.5, 146.1, 161.3, 170.7, 172.6, 173.9 and 189.2; Anal. Calcd. for C$_29$H$_{38}$N$_2$O$_8$S: C, 57.23; H, 4.64; N, 9.21. Found: C, 57.35; H, 4.75; N, 9.17.

4.1.10 3a-[2-Benzoxoyethyl]-5,12b-epoxy-6-benzenesulfonyl-4,12-dioxo-2,3,3a,4,5,5a,6,11c,12b-decahydro-1H-6,12a-diaza-indeno[7,1-cd]fluorene-5-carboxylic Acid Ethyl Ester (27)—To a solution of 0.2 g (0.3 mmol) of diazomide 24 in 10 mL benzene under N$_2$ was added 5 mg of rhodium(II) acetate and the mixture was heated at reflux for 1 h. The mixture was allowed to cool to rt and was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 0.18 (94%) of cycloadduct 27 as a clear oil; IR (neat) 2991, 2919, 2873, 1787, 1726, 1434, 1372, 1296 and 1163 cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 0.11-0.20 (m, 1H), 1.12 (pent, 1H, $J$ = 7.2 Hz), 1.43 (t, 3H, $J$ = 7.2 Hz), 1.72-1.82 (m, 3H), 1.97-2.07 (m, 1H), 2.31 (d, 1H, $J$ = 17.1 Hz), 2.78 (d, 2H, $J$ = 17.1 Hz), 3.04-3.16 (m, 1H), 3.31-3.39 (m, 1H), 3.47-3.55 (m, 1H), 3.82-3.86 (m, 1H), 4.24 (s, 2H), 4.43 (q, 2H, $J$ = 7.2 Hz), 4.90 (s, 1H), 6.94 (d, 1H, $J$ = 7.5 Hz), 7.07 (t, 1H, $J$ = 7.5 Hz), 7.15 (d, 2H, $J$ = 6.3 Hz), 7.21-7.35 (m, 4H), 7.42 (t, 2H, $J$ = 7.5 Hz), 7.55 (d, 1H, $J$ = 7.5 Hz), 7.61 (d, 1H, $J$ = 8.4 Hz) and 7.67 (d, 1H, $J$ = 7.5 Hz); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 13.9, 17.7, 25.3, 27.1, 39.0, 44.1, 52.2, 57.8, 62.8, 65.8, 72.3, 75.4, 87.9, 103.9, 116.8, 124.5, 125.3, 127.2, 127.3, 127.4, 128.2, 129.1, 130.1, 130.4, 133.9, 135.7, 137.9, 142.4, 164.1, 175.6 and 203.3; HRMS Calcd for [(C$_8$H$_{38}$NS)$_2$O$_8$S] + H$^+$: 643.2114. Found: 643.2129.

4.1.11 3a-[2-Benzoxoyethyl]-5,12b-epoxy-6-H-4,12-dioxo-2,3,3a,4,5,5a,6,11c,12b-decahydro-1H-6,12a-diaza-indeno[7,1-cd]fluorene-5-carboxylic Acid Ethyl Ester (28)—A mixture of 0.02 g (0.017 mmol) of cycloadduct 27, Et$_3$N (12.5 μL, 0.085 mmol), and anhydrous CH$_3$CN (4 mL) was degassed with N$_2$ for 30 min. The mixture was irradiated (RPR-2537 A lamp in a RPR-100 reactor) in a quartz tube for 1 h under a nitrogen atmosphere. The solution was concentrated under reduced pressure and the residue was subjected to flash silica gel chromatography to give 0.008 g (90%) of the desulfonlated product 28 as a colorless oil; IR (neat) 3446, 2955, 2919, 2858, 1721, 1475, 1352, 1173 and 1065 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 0.70-0.78 (m, 1H), 1.18-1.26 (m, 1H), 1.36 (t, 3H, $J$ = 7.2 Hz), 1.70-1.92 (m, 3H), 1.88-2.24 (m, 1H), 3.15 (td, 1H, $J$ = 12.8 and 4.8 Hz), 3.34-3.39 (m, 1H), 3.50-3.56 (m, 1H), 3.86 (dd, 1H, $J$ = 12.8 and 4.0 Hz), 4.23 (dd, 2H, $J$ = 7.2 and 3.2 Hz), 4.31-4.43 (m, 3H), 4.73 (s, 1H), 6.58 (d, 1H, $J$ = 8.0 Hz), 6.73 (t, 1H, $J$ = 8.0 Hz), 6.97 (d, 1H, $J$ = 6.8 Hz), 7.10-7.17 (m, 3H) and 7.23-7.32 (m, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 14.3, 18.2, 26.2, 26.8, 35.2, 45.7, 51.0, 59.7, 62.8, 66.2, 72.6, 80.9, 92.6, 104.3, 108.1, 118.7, 123.8, 127.5, 127.6, 127.7, 128.5, 130.5, 138.4, 153.1, 166.0, 177.0 and 205.6.
4.1.12 Irradiation of N-Benzensulfonfyl-1H-Indole (31a)—The same irradiation procedure as described above was used starting from commercially available N-benzenesulfonfyl-1H-indole (31a) (0.26 g, 1.0 mmol). Purification by flash silica gel chromatography afforded 0.04 g (48%) of 1H-indole (31a).

4.1.13 Irradiation of N-Benzensulfonfyl-2,3-Dimethyl-1H-indole (31b)—The same irradiation procedure as described above was used starting from 0.07 g (0.17 mmol) of N-benzenesulfonfyl-2,3-dimethyl-1H-indole (31b). Purification by flash silica gel chromatography afforded 0.06 g (55%) of 2,3-dimethyl-1H-indole (31b).

4.1.14 N-Benzensulfonfyl-3-[2-(tert-Butyl-dimethylsilanyloxy)ethyl]-1H-Indole (31c)—The same irradiation procedure as described above was used starting from commercially available N-benzenesulfonfyl-3-[2-(tert-butyl-dimethylsilanyloxy)ethyl]-1H-indole (31c). Purification by flash silica gel chromatography yielded 0.03 g (57%) of the known 3-[2-(tert-butyl-dimethylsilanyloxy)ethyl]-1H-indole (31c).

4.1.15 Irradiation of N-Benzensulfonfyl-1H-indole-3-carboxylic Acid Methyl Ester (31d)—The same irradiation procedure as described above was used starting from 0.32 g (1.0 mmol) of N-benzenesulfonfyl-1H-indole-3-carboxylic acid methyl ester (31d). Purification by flash silica gel chromatography yielded afforded 0.13 g (77%) of 1H-indole-3-carboxylic acid methyl ester (31d).

Two additional fractions were obtained from the chromatography column and each was separately purified. One of the fractions contained a colorless oil whose structure was assigned as 5-benzenesulfonfyl-1H-indole-3-carboxylic acid methyl ester (31d); IR (neat) 3350, 2927, 1718, 1536, 1465, 1447, 1334, 1333 and 1152 cm⁻¹; ¹H-NMR (400 MHz, DMSO) δ 3.78 (s, 3H), 7.54-7.65 (m, 4H), 7.68 (d, 1H, J = 8.4 Hz), 7.92 (d, 2H, J = 8.4 Hz), 8.08 (s, 1H), 8.13 (d, 1H, J = 8.4 Hz), 8.35 (s, 1H); ¹³C-NMR (100 MHz, DMSO) δ 51.0, 106.9, 112.7, 119.8, 121.5, 127.1, 129.1, 132.6, 137.4, 142.6 and 166.4.

The second fraction was a clear oil and was identified as 7-benzenesulfonfyl-1H-indole-3-carboxylic acid methyl ester (31d); IR (neat) 3319, 2948, 1713, 1531, 1445, 1419, 1338, 1302 and 1155 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ 3.65 (s, 3H), 7.27 (t, 1H, J = 8.4 Hz), 7.48 (t, 2H, J = 7.8 Hz), 7.55-7.57 (m, 1H), 7.65 (d, 1H, J = 8.4 Hz), 7.72 (d, 1H, J = 2.4 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.89 (s, 1H), 7.90 (d, H, J = 8.4 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 51.7, 110.5, 117.5, 120.6, 122.1, 125.3, 126.7, 128.7, 131.0, 131.8, 132.6, 137.4, 142.6 and 166.4.

4.1.16 Irradiation of N-Benzensulfonfyl-(2-hydroxymethyl-1H-indol-3-yl)ethanone (31e)—The same irradiation procedure as described above was used starting from 0.33 g (1.0 mmol) of N-benzenesulfonfyl-(2-hydroxymethyl-1H-indol-3-yl)ethanone (31e). Purification by flash silica gel chromatography afforded 0.11 g (60%) of 1-(2-hydroxymethyl-1H-indol-3-yl)ethanone (31e) as a colorless oil; IR (neat) 3292, 3060, 2976, 2875, 1748, 1613, 1574, 1446, 1379, 1358, 1283, 1176 and 1078 cm⁻¹; ¹H-NMR (400 MHz, DMSO) δ 2.51 (s, 3H), 3.40 (s, 1H), 4.96 (s, 2H), 5.77 (s, 1H), 7.12-7.14 (m, 2H), 7.47-7.50 (m, 1H) and 7.92-7.94 (m, 1H); ¹³C-NMR (100 MHz, DMSO) δ 30.7, 58.1, 111.6, 112.3, 120.3, 121.5, 121.7, 126.7, 135.0, 149.0 and 193.0.

4.1.17 3a-(2-Benzoxoethyl)-5,12b-epoxy-6-tosyl-4,12-dioxo-2,3,3a,4,5,5a,6,11,12,12b-deca-hydro-1H-6,12a-diaza-indeno[7,1-cdf]fluorene-5-carboxylic Acid Methyl Ester (39)—To a solution of 2.0 g (3 mmol) of diazoimide 25 in 100 mL of benzene under N₂ was added 20 mg rhodium(II) acetate, and the mixture was heated at reflux for 1 h. The mixture was allowed to cool to rt and was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel
chromatography to give 1.5 g (90%) of the dipolar cycloaddition product 39 as a white solid, mp 169-170 °C; IR (neat) 3076, 3027, 2953, 2859, 1779, 1727, 1478, 1460, 1399, 1361, 1309 and 1171 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 0.18-0.24 (m, 1H), 1.13 (pent, 1H, J = 7.2 Hz), 1.70-2.06 (m, 5H), 2.35 (d, 1H, J = 17.2 Hz), 2.37 (s, 3H), 2.78 (d, 1H, J = 17.2 Hz), 3.04-3.17 (m, 1H), 3.35-3.42 (m, 1H), 3.43-3.59 (m, 2H), 3.82-3.90 (m, 1H), 3.99 (s, 3H), 4.24 (s, 2H), 4.87 (s, 1H), 6.95 (d, 1H, J = 7.5 Hz), 7.07 (t, 1H, J = 7.5 Hz), 7.17-7.33 (m, 7H), 7.55 (d, 2H, J = 8.1 Hz), and 7.63 (d, 1H, J = 8.1 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ 17.7, 21.4, 25.3, 27.1, 39.0, 44.1, 52.2, 53.2, 57.7, 65.7, 72.3, 75.6, 87.9, 104.0, 116.7, 124.4, 125.2, 127.2, 127.3, 128.1, 129.7, 130.1, 130.4, 132.6, 137.9, 142.4, 145.0, 164.6, 175.6 and 203.1; Anal. Calcd for C₃₃H₃₄N₂O₈S: C, 65.41; H, 5.33; N, 4.36. Found: C, 65.24; H, 5.50; N, 4.37.

4.1.18 Unusual Reductive Rearrangement of Cycloadduct 39 using Triethylsililylhydride and Boron Trifluoride Etherate—A solution containing 0.06 g (0.1 mmol) of cycloadduct 39 in CH₂Cl₂ (4 mL) was cooled to −78 °C and 160 μL (1 mmol) of Et₃SiH and 65 μL (0.5 mmol) of BF₃•Et₂O were added. The solution was allowed to warm to rt for 1 h and was then heated at reflux for 24 h. The reaction mixture was cooled to rt and washed with a saturated NaHCO₃ solution, brine and H₂O. The solution was extracted with CH₂Cl₂ and dried over MgSO₄. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to afford 0.03 g (60%) of 42 as a colorless solid, mp 250 °C; IR (neat) 3467, 2956, 2159, 1755, 1692, 1641, 1594, 1460, 1359, 1265, 1169 and 1135 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.36-1.42 (m, 2H), 1.63 (d, 1H, J = 15.2 Hz), 1.66-1.78 (m, 2H), 1.90 (dt, 1H, J = 11.2 and 3.2 Hz), 2.10-2.15 (m, 1H), 2.32 (s, 3H), 2.35 (d, 1H, J = 11.2 Hz), 2.35-3.30 (m, 1H), 3.56-3.58 (m, 1H), 7.00 (dd, 1H, J = 5.2 and 0.4 Hz), 7.12-7.14 (m, 3H), 7.30 (d, 2H, J = 5.2 Hz), 7.35 (td, 1H, J = 5.2 and 0.8 Hz) and 7.83 (d, 1H, J = 5.6 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 19.8, 21.5, 29.0, 32.6, 38.7, 51.1, 54.6, 55.6, 64.1, 72.9, 79.9, 115.1, 119.1, 124.3, 125.7, 128.0, 129.0, 129.6, 131.7, 134.8, 137.3, 143.4, 145.1, 169.1, 169.8 and 170.6; HRMS Calcd for [(C₂₈H₂₈N₂O₈S) + H⁺]: 553.1645. Found: 553.1636.

4.1.19 3a-{(2-Benzylxoyethyl)-5,12b-epoxy-6-tosyl-4-oxo-12-thioxo-2,3,3a,4,5,5a,6,11,12,12b-decahydro-1H-6,12a-diaza-indeno[7,1-cd]fluorene-5-carboxylic Acid Methyl Ester—To a solution containing 0.72 g (1.1 mmol) of the above cycloadduct 39 in 30 mL benzene under N₂ was added 0.2 g (0.45 mmol) of P₂S₅ and 255 μL (0.76 mmol) of (TMS)₂O at rt. The mixture was heated at reflux for 3 h, cooled to rt and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 0.67 g (90%) of the corresponding thioamide as a clear oil; IR (neat) 2953, 1776, 1746, 1597, 1477, 1390, 1367, 1320, 1170 and 1088 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.21 (dt, 1H, J = 14.8 and 5.6 Hz), 1.12 (pent, 1H, J = 8.0 Hz), 1.80-1.92 (m, 3H), 1.98-2.07 (m, 1H), 2.36 (s, 3H), 2.95 (d, 1H, J = 17.6 Hz), 3.14-3.22 (m, 1H), 3.23 (d, 1H, J = 17.6 Hz), 3.30-3.36 (m, 1H), 3.47-3.54 (m, 1H), 3.97 (s, 3H), 4.23 (s, 2H), 4.32 (dd, 1H, J = 13.6 and 4.4 Hz) 4.85 (s, 1H), 6.92 (dd, 1H, J = 7.6 and 0.8 Hz), 7.04 (td, 1H, J = 7.6 and 0.8 Hz), 7.15-7.34 (m, 8H), 7.53 (d, 2H, J = 8.4 Hz) and 7.60 (d, 1H, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 18.0, 21.5, 24.7, 27.2, 43.5, 52.8, 53.4, 56.1, 60.4, 65.7, 72.4, 74.7, 88.8, 107.1, 116.4, 124.7, 125.3, 127.3, 127.4, 127.5, 128.2, 129.7, 129.8, 130.7, 132.6, 137.9, 142.4, 145.1, 164.4, 202.5 and 207.0; HRMS Calcd for [(C₃₅H₃₄N₂O₇S₂) + H⁺]: 659.1886. Found: 659.1875.

4.1.20 3a-{(2-Benzylxoyethyl)-5,12b-epoxy-6-tosyl-4-oxo-2,3,3a,4,5,5a,6,11,12,12b-decahydro-1H-6,12a-diaza-indeno[7,1-cd]fluorene-5-carboxylic Acid Methyl Ester—An excess amount of Raney nickel in 100 mL round bottomed flask under N₂ was washed three times with H₂O₂ twice with dry MeOH and finally three times with dry THF. A 0.43 g (0.64 mmol) sample of the above thiolactam in 15 mL of THF was added dropwise to the Raney nickel suspension. The mixture was vigorously stirred for 14 h under 1
atm of hydrogen gas and then filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel to give 0.38 g (95%) of the titled compound as a clear oil; IR (neat) 2954, 1769, 1741, 1596, 1477, 1392, 1368, 1321 and 1173 cm−1; 1H-NMR (300 MHz, CDCl3) δ 0.21 (dt, 1H, J = 14.7 and 5.7 Hz), 1.14 (pent, 1H, J = 7.5 Hz), 1.56-1.99 (m, 5H), 2.08-2.16 (m, 1H), 2.34 (s, 3H), 2.81 (td, 1H, J = 11.1 and 3.6 Hz), 2.96 (dd, 1H, J = 9.6 and 3.6 Hz), 3.11-3.19 (m, 1H), 3.35-3.51 (m, 3H), 3.94 (s, 3H), 4.22 (s, 2H), 4.76 (s, 1H), 7.02-7.08 (m, 2H), 7.16-7.29 (m, 8H) and 7.55-7.61 (m, 3H); 13C-NMR (75 MHz, CDCl3) δ 20.2, 21.5, 21.8, 31.0, 33.9, 42.3, 49.1, 51.6, 52.2, 52.5, 65.1, 72.4, 77.9, 87.6, 116.3, 125.0, 125.6, 127.6, 127.8, 128.4, 129.8, 129.9, 133.3, 133.5, 138.6, 142.5, 144.8, 166.2 and 206.3; HRMS Calcd for [(C35H36N2O7S) + H]+: 629.2321. Found: 629.2332.

4.1.21 Methyl 3a-(2-(Benzyloxy)ethyl)-5-hydroxy-4-oxo-6-tosyl-2,3,3a, 3a1,4,5,5a,6,11,12-deca-hydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate—

To a 0.38 g sample (0.6 mmol) of the above compound in 10 mL MeOH and 2 mL THF was added 8 mg of PtO2 and 1 drop of concentrated HCl. The reaction mixture was subjected to hydrogenation at 1 atm of hydrogen gas for 1.5 h. The mixture was filtered through a pad of Celite, diluted with EtOAc, washed with a sat. NaHCO3 solution, brine, and dried over MgSO4. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to afford 0.26 g (68%) of the titled compound as a clear oil; IR (neat) 3047, 2926, 2859, 1755, 1712, 1596, 1485, 1361, 1264, 1170 and 1090 cm−1; 1H-NMR (400 MHz, CDCl3) δ 1.06 (hex, 1H, J = 7.2 Hz), 2.13-1.51 (m, 4H), 1.67 (dd, 1H, J = 14.4, 10.4 and 4.0 Hz), 1.99-2.05 (m, 1H), 2.28-2.40 (m, 2H), 2.50 (s, 1H), 3.03-3.21 (m, 4H), 3.77 (s, 3H), 4.21 (d, 1H, J = 12.0 Hz), 4.46 (s 1H), 6.99 (d, 1H, J = 7.6 Hz), 7.07 (t, 1H, J = 7.6 Hz), 7.11 (d, 2H, J = 8.4 Hz), 7.16 (d, 2H, J = 7.6 Hz), 7.23-7.31 (m, 4H), 7.48 (d, 2H, J = 8.4 Hz), 7.57 (s, 1H) and 7.67 (d, 1H, J = 8.4 Hz); 13C-NMR (100 MHz, CDCl3) δ 21.5, 21.8, 31.0, 33.9, 42.3, 49.1, 51.6, 52.2, 52.5, 65.1, 72.4, 77.9, 80.1, 117.8, 123.3, 125.5, 127.4, 127.5, 127.9, 128.2, 128.9, 129.3, 132.9, 136.8, 138.1, 141.9, 144.5, 168.3 and 203.7; HRMS Calcd for [(C35H34N2O7S) + H]+: 631.2478. Found: 631.2467.

4.1.22 Reductive Ring Opening of Oxabicyclic 39 to Give Hemiketal 43—To a 0.38 g (0.6 mmol) sample of 3a-[2-benzyloxyethyl]-5,12b-epoxy-6-tosyl-4-oxo-2,3,3a, 6,11,12-deca-hydro-1H-indolizino[7,1-cd]fluorene-5-carboxylic acid methyl ester in 10 mL of MeOH and 2 mL THF was added 8 mg of PtO2 and 1 drop of concentrated HCl. The reaction mixture was hydrogenated at 1 atm of hydrogen gas but now for 12 h. The mixture was filtered through a pad of Celite, diluted with EtOAc, washed with a sat. NaHCO3 solution, brine, and dried over MgSO4. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to give 0.17 g (51%) of the titled compound 43 as a colorless oil; IR (neat) 3047, 2962, 2928, 2850, 1739, 1597, 1358, 1264, 1170 and 1101 cm−1; 1H-NMR (400 MHz, CDCl3) δ 0.77-0.82 (m, 1H), 1.29-1.35 (m, 1H), 1.41-1.44 (m, 1H), 1.49 (dt, 1H, J = 9.2 and 2.8 Hz), 1.60-1.67 (m, 2H), 1.85-1.88 (m, 1H), 2.10-2.18 (m, 2H), 2.28-2.33 (m, 1H), 2.30 (s, 3H), 2.42-2.46 (m, 1H), 2.50 (s, 1H), 2.99-3.03 (m, 1H), 3.06-3.10 (m, 1H), 3.52 (q, 1H, J = 5.6 Hz), 3.92 (s, 3H), 4.24 (s, 1H), 6.97 (d, 1H, J = 7.6 Hz), 7.06 (t, 1H, J = 7.6 Hz), 7.08 (d, 2H, J = 8.4 Hz), 7.22-7.26 (m, 1H), 7.34 (d, 2H, J = 8.4 Hz) and 7.71 (d, 1H, J = 8.4 Hz); 13C-NMR (100 MHz, CDCl3) δ 21.7, 22.0, 32.2, 41.0, 42.6, 49.6, 50.3, 51.5, 53.2, 54.4, 63.5, 73.4, 76.3, 81.1, 105.1, 119.4, 122.6, 125.1, 128.1, 128.6, 129.5, 133.9, 136.8, 144.4, 144.5 and 170.2; HRMS Calcd for [(C28H32N2O5S) + H]+: 541.1999.

4.1.23 Preparation of Mesylate 44 from Hemiketal 43—To a 0.07 g sample of the above compound 15 (0.13 mmol) in 10 mL of CH2Cl2 at 0 °C was added 2.5 mL of Et3N followed by 50 μL of MsCl (0.65 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and then...
quenched with a saturated NH₄Cl solution and washed with brine, H₂O and dried over MgSO₄. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to afford 0.07 g (85%) of mesylate.

MgSO₄ NMR (400 MHz, CDCl₃) δ 1.03-1.07 (m, 1H), 1.24-1.27 (m, 2H), 1.56-1.67 (m, 4H), 2.04-2.08 (m, 1H), 2.16-2.36 (m, 1H), 2.34 (s, 3H), 2.40-2.42 (m, 1H), 2.55 (s, 1H), 2.86 (s, 3H), 3.07-3.09 (m, 1H), 3.14-3.16 (m, 1H), 3.83 (s, 3H), 3.84-3.87 (m, 1H), 3.96-3.99 (m, 1H), 4.47 (s, 1H), 7.04 (d, 1H, J = 7.2 Hz), 7.11-7.15 (m, 3H), 7.30 (td, 1H, J = 9.0 and 1.2 Hz), 7.50 (d, 2H, J = 8.4 Hz) and 7.68 (d, 1H, J = 8.4 Hz).

C-NMR (125 MHz, CDCl₃) δ 21.7, 21.7, 31.1, 33.6, 37.2, 42.0, 48.7, 51.3, 52.4, 52.5, 52.9, 65.6, 73.9, 77.8, 80.5, 117.7, 123.1, 125.8, 127.8, 129.2, 129.5, 133.0, 136.2, 141.8, 144.7, 168.3 and 203.8; HRMS Calcd for [(C₂₉H₃₄N₂O₅S₂) + H]+: 619.1784. Found: 619.1774.

4.1.24 3a-(2-Methoxy-2-oxoethyl)-5,12b-epoxy-6-tosyl-4,12-dioxo-2,3,3a,4,5,5a,6,11,12,12b-decahydro-1H-6,12a-diaza-indeno[7,1-c](fluorene-5-carboxylic Acid Methyl Ester (46)—To a solution containing 8.4 g (13.8 mmol) of diazooxime 26 in 200 mL benzene under N₂ was added 50 mg rhodium(II) acetate and the mixture was heated at reflux for 1 h. The mixture was allowed to cool to rt and was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel to give 7.8 g (98%) of cycloadduct 46 as a colorless solid, mp 220-221 °C; IR (neat) 2952, 1781, 1728, 1731, 1597, 1401, 1364, 1188 and 1171 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.04 (d, 1H, J = 15.2 Hz), 1.60 (d, 1H, J = 15.2 Hz), 1.64-1.79 (m, 2H), 2.02-2.10 (m, 2H), 2.32 (s, 3H), 2.80 (d, 1H, J = 17.6 Hz), 2.76 (d, 1H, J = 17.6 Hz), 3.11 (td, 1H, J = 12.4 and 4.0 Hz), 3.49 (s, 3H), 3.78-3.82 (m, 1H), 3.92 (s, 3H), 4.85 (s, 1H), 6.93 (dd, 1H, J = 7.6 and 0.4 Hz), 7.03 (td, 1H, J = 8.0 and 0.8 Hz), 7.18 (d, 2H, J = 8.0 Hz), 7.33 (td, 1H, J = 7.8 and 1.2 Hz), 7.50 (d, 2H, J = 8.0 Hz) and 7.58 (d, 1H, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 17.9, 21.5, 26.3, 32.5, 38.9, 44.1, 51.7, 51.8, 53.3, 57.8, 75.6, 87.8, 103.6, 116.9, 124.4, 125.2, 127.3, 129.5, 129.8, 130.8, 132.6, 142.4, 145.1, 164.3, 169.6, 175.2 and 200.3; Anal. Calcd for C₂₉H₂₈N₂O₅S: C, 59.99; H, 4.86; N, 4.82. Found: C, 60.20; H, 5.01; N, 4.73.

4.1.25 3a-(2-Methoxy-2-oxoethyl)-5,12b-epoxy-6-tosyl-4-oxo-12-thioxo-2,3,3a,4,5,5a,6,11,12,12b-decahydro-1H-6,12a-diaza-indeno[7,1-c](fluorene-5-carboxylic Acid Methyl Ester—To a solution containing 6.3 g (11 mmol) of the above cycloadduct 46 in 200 mL benzene under N₂ was added 1.9 g (4.3 mmol) of P₂S₅ and 2.5 mL (18 mmol) of (TMS)₂O at rt. The mixture was heated at reflux for 6 h, cooled to rt and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel to give 6.4 g (90%) of the titled thiolactam as a white solid, mp 221-222 °C; IR (neat) 3052, 2953, 2970, 2929, 1785, 1744, 1372, 1270 and 1172 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.30 (d, 1H, J = 16.0 Hz), 1.63 (d, 1H, J = 16.0 Hz), 1.81-1.97 (m, 2H), 2.06-2.19 (m, 2H), 2.39 (s, 3H), 2.99 (d, 1H, J = 18.0 Hz), 3.26 (d, 1H, J = 18.0 Hz), 3.34 (td, 1H, J = 13.2 and 5.2 Hz), 3.54 (s, 3H), 4.00 (s, 3H), 4.29 (dq, 1H, J = 14.0 and 2.8 Hz), 4.89 (s, 1H), 6.95 (dd, 1H, J = 7.2 and 0.8 Hz), 7.05 (t, 1H, J = 7.2 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.37 (td, 1H, J = 8.0 and 1.6 Hz), 7.55 (d, 2H, J = 8.0 Hz) and 7.64 (d, 1H, J = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 18.3, 21.5, 26.1, 33.1, 43.3, 51.8, 52.2, 53.4, 55.9, 60.5, 74.7, 88.4, 107.0, 116.6, 124.7, 125.1127.3, 129.0, 129.8, 130.9, 132.5, 142.4, 145.2, 164.1, 169.5, 199.8 and 206.2; HRMS Calcd for [(C₂₉H₂₈N₂O₅S₂) + H]+: 597.1365. Found: 597.1356.

4.1.26 3a-(2-Methoxy-2-oxoethyl)-5,12b-epoxy-6-tosyl-4-oxo-2,3,3a,4,5,5a,6,11,12,12b-decahydro-1H-6,12a-diaza-indeno[7,1-c](fluorene-5-carboxylic Acid Methyl Ester—An excess amount of Raney nickel in a 250 mL round bottomed flask
4.1.27 Methyl 5-Hydroxy-3a,4,5,5a,6,11,12-decahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate (47) — To a 0.6 g (1.0 mmol) sample of above compound in 10 mL MeOH and 2 mL THF was added 10 mg of PtO2 and 1 drop of concentrated HCl. The reaction mixture was hydrogenated at 1 atm of hydrogen gas for 12 h. The mixture was filtered through a pad of Celite, diluted with EtOAc, washed with a sat. NaHCO3 solution, brine and dried over MgSO4. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to give 0.54 g (95%) of 47 as a white solid, mp 187-188 °C; IR (neat) 3517, 2950, 2823, 1760, 1739, 1598, 1547, 1477, 1436, 1358, 1254, 1169, 1114, 1097 and 1039 cm−1; 1H-NMR (400 MHz, CDCl3) ð 0.81 (d, 1H, J = 14.4 Hz), 1.60-1.69 (m, 2H), 1.73 (d, 1H, J = 14.4 Hz), 1.87-2.00 (m, 2H), 2.06-2.13 (m, 2H), 2.32 (s, 3H), 2.80 (td, 1H, J = 14.4 and 4.0 Hz), 2.92 (dd, 1H, J = 10.4 and 3.2 Hz), 3.08-3.15 (m, 1H), 3.40 (hex, 1H, J = 4.0 Hz), 3.49 (s, 3H), 3.90 (s, 3H), 4.73 (s, 1H), 7.01 (d, 2H, J = 4.4 Hz), 7.17 (d, 2H, J = 7.6 Hz), 7.23-7.28 (m, 1H) and 7.54-7.57 (m, 3H); 13C-NMR (100 MHz, CDCl3) δ 19.6, 21.4, 25.8, 32.1, 37.0, 46.2, 51.1, 51.5, 51.6, 53.0, 62.3, 87.4, 110.8, 116.3, 124.7, 125.0, 127.4, 129.6, 129.8, 132.3, 133.2, 142.3, 144.5, 165.6, 170.7 and 203.1; HRMS Calcd for [(C29H30N2O8S) + H]+: 567.1801. Found: 567.1794.

4.1.28 Methyl 2-(5-(Methoxycarbonyloxy)-4-oxo-6-tosyl-2,3,3a,3a4,4,5,5a,6,11,12-decahydro-1H-indolizino[8,1-cd]carbazole-5-acetate: A solution of containing (0.6 g, 1.0 mmol) of the above carbonate in 40 mL CH2CN was added 1.95 g (6 mmol) of Cs2CO3 and the reaction mixture was heated at reflux for 1 h. The mixture was cooled to room temperature and filtered through a pad of Celite. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to give 0.55 g (97%) of compound 48 in 40 mL CH2CN which was added 1.95 g (6 mmol) of Cs2CO3 and the reaction mixture was heated at reflux for 1 h. The mixture was cooled to room temperature and filtered through a pad of Celite. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to give 0.55 g (97%) of the titled compound as a white solid, mp 200-202 °C; IR (neat) 2951, 2859, 1774, 1738, 1598, 1477, 1436, 1293, 1267, 1170 and 1036 cm−1; 1H-NMR (400 MHz, CDCl3) ð 0.81 (d, 1H, J = 14.4 Hz), 1.60-1.69 (m, 2H), 1.73 (d, 1H, J = 14.4 Hz), 1.87-2.00 (m, 3H), 2.06-2.13 (m, 1H), 2.32 (s, 3H), 2.80 (td, 1H, J = 14.4 and 4.0 Hz), 2.92 (dd, 1H, J = 10.4 and 3.2 Hz), 3.08-3.15 (m, 1H), 3.40 (hex, 1H, J = 4.0 Hz), 3.49 (s, 3H), 3.90 (s, 3H), 4.73 (s, 1H), 7.01 (d, 2H, J = 4.4 Hz), 7.17 (d, 2H, J = 7.6 Hz), 7.23-7.28 (m, 1H) and 7.54-7.57 (m, 3H); 13C-NMR (100 MHz, CDCl3) δ 19.6, 21.4, 25.8, 32.1, 37.0, 46.2, 51.1, 51.5, 51.6, 53.0, 62.3, 87.4, 110.8, 116.3, 124.7, 125.0, 127.4, 129.6, 129.8, 132.3, 133.2, 142.3, 144.5, 165.6, 170.7 and 203.1; HRMS Calcd for [(C29H30N2O8S) + H]+: 569.1588. Found: 569.1595.
To a solution containing 0.12 g (0.2 mmol) of the above keto ester and 120 mL (0.5 mmol) of TBDDMSOTf in 10 mL of CH$_2$Cl$_2$ was added dropwise 208 mL of (1.5 mmol) Et$_3$N. After 1 h of stirring at rt, the mixture was hydrolyzed with a saturated NaHCO$_3$ solution. After extraction with CH$_2$Cl$_2$, the organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in 10 mL of THF and a 1.2 mL of a 1.0 M LiAlH$_4$ solution was added at 0 °C. After stirring for 4 h, the mixture was quenched with H$_2$O, 15% NaOH and extracted with EtOAc. The combined organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The resulting residue was added 5 mL of CH$_3$CN, 0.15 g of 4 Å molecular sieves, 0.04 g of NMO and 0.025 g (0.07 mmol) of TPAP at 0 °C. The mixture was allowed to warm to rt for 4 h and was filtered through a pad of Celite. After removing the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.092 g (68%) of aldehyde 48 as a colorless oil; IR (neat) 2930, 2856, 1718, 1664, 1598, 1475, 1461, 1356, 1261 and 1168 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 0.20 (3H, 3H), 0.26 (3H, 3H), 0.87 (s, 9H), 0.91-1.00 (m, 1H), 1.11-1.18 (m, 1H), 1.34-1.41 (m, 1H), 1.45-1.50 (m, 2H), 1.81 (dd, 1H, $J$ = 15.2 and 3.6 Hz), 1.96-2.00 (m, 1H), 2.06 (dd, 1H, $J$ = 15.2 and 2.0 Hz), 2.14-2.22 (m, 2H), 2.34 (s, 3H), 2.54 (s, 1H), 2.96-3.00 (m, 2H), 4.50 (d, 1H, $J$ = 4.4 Hz), 5.03 (d, 1H, $J$ = 4.0 Hz), 6.97-7.00 (m, 2H), 7.16-7.25 (m, 3H), 7.57 (d, 2H, $J$ = 8.0 Hz), 7.67 (d, 1H, $J$ = 8.0 Hz) and 9.43-9.45 (m, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ -48.3, -44.8, 18.0, 21.5, 22.6, 25.6, 30.9, 41.2, 41.9, 51.4, 51.5, 52.4, 54.2, 70.4, 72.0, 101.8, 116.7, 123.5, 124.6, 127.0, 128.6, 129.5, 134.9, 136.7, 140.8, 143.9, 153.6 and 201.4; HRMS Calcd for [(C$_{32}$H$_{42}$N$_2$O$_4$S)$_2$]+: M+ 579.2713. Found: 579.2707.

4.1.31 Cesium Fluoride Induced Intramolecular Aldol Reaction of Silyl Enol Ether 48:

To a solution of 0.05 g (0.086 mmol) of the above aldehyde in 10 mL of CH$_3$CN was added 0.13 g (0.86 mmol) of Cs$_2$CO$_3$ and the reaction mixture was heated at 100 °C for 1 h. The mixture was then cooled to room temperature and filtered through a pad of Celite. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to afford 0.03 g (78%) of the aldol product 49 as a colorless solid; mp 249-250 °C; IR (neat) 3500, 2927, 2787, 1749, 1596, 1553, 1456, 1355, 1168, 1093 and 1043 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 0.89 (dd, 1H, $J$ = 13.2 and 7.6 Hz), 0.94-1.04 (m, 1H), 1.15 (td, 1H, $J$ = 13.6 and 4.8 Hz), 1.34 (d, 1H, $J$ = 14.4 Hz), 1.48-1.54 (m, 1H), 1.67 (d, 2H, $J$ = 26 Hz), 1.88-2.04 (m, 4H), 2.21-2.31 (m, 1H), 2.34 (s, 3H), 2.51 (s, 1H), 2.73 (d, 1H, $J$ = 5.6 Hz), 2.82 (t, 1H, $J$ = 8.8 Hz), 3.07 (dd, 1H, $J$ = 11.2 and 2.8 Hz), 4.00 (d, 1H, $J$ = 8.0 Hz), 4.38 (d, 1H, $J$ = 5.6 Hz), 7.13-7.16 (m, 2H), 7.18 (d, 2H, $J$ = 8.4 Hz), 7.30-7.34 (m, 1H), 7.58 (d, 2H, $J$ = 8.0 Hz) and 7.77 (d, 1H, $J$ = 8.0 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 21.5, 21.6, 28.4, 40.7, 44.2, 47.7.
51.4, 53.2, 54.2, 61.9, 64.3, 75.8, 81.1, 115.9, 122.6, 125.3, 126.9, 128.8, 129.7, 134.9, 138.5, 141.0, 144.4 and 213.1; HRMS Calcd for \([\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_7\text{S}]^+\): 465.1848. Found: 465.1843.

### 4.1.32 Samarium Iodide Reduction of Hydroxy Ester 47:
A solution containing 0.11 g (0.18 mmol) of the above compound 47 in THF (1 mL) together with 0.2 mL of HMPA was degassed with argon at rt for 15 min. A solution of samarium iodide in THF (0.1 M) at 0 °C was added to this mixture until a blue color persisted for 10 sec. The reaction mixture was quenched with a saturated NaHCO₃ solution, extracted with EtOAc and dried over MgSO₄. Removal of the solvent under reduced pressure left a colorless residue which was subjected to flash chromatography on silica gel to give 0.06 g (91%) of the reduced alcohol.

### 4.1.33 Methyl 4-(tert-Butyldimethylsiloxy)-3a-(2-methoxy-2-oxoethyl)-6-tosyl-2,3,3a, -3b,4,5,6,11,12-octahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate:
To a solution of 0.06 g (0.11 mmol) keto ester 50 and 100 μL (0.4 mmol) of TBDMSOTf in 5 mL of CH₂Cl₂ was added dropwise 121 μL (0.9 mmol) of Et₃N. After stirring overnight at rt, the mixture was hydrolyzed with a saturated NaHCO₃ solution. After extraction with CH₂Cl₂, the organic layer was dried over MgSO₄ and filtered. Concentration of the solution under reduced pressure followed by flash chromatography on silica gel afforded 0.08 g (93%) of compound 51 as a colorless oil.

### 4.1.34 Methyl 4-(tert-Butyldimethylsiloxy)-3a-(2-hydroxyethyl)-6-tosyl-2,3,3a, -3b,4,5,6,11,12-octahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate (51):
To a solution of 0.069 g (0.1 mmol) of the above compound of 10 mL of THF was added 0.5 mL of a 1.0 M LiAlH₄ solution at −78 °C. The solution was allowed to warm to 0 °C and was stirred for 5 h. The mixture was quenched with H₂O, 15% NaOH and extracted with EtOAc. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 0.06 g (91%) of the reduced alcohol 51 as a colorless solid, mp 190-192 °C; IR (neat) 3402, 2948, 2931, 2857, 2787, 1727, 1596, 1477, 1436, 1358, 1260 and 1030 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 0.30 (s, 3H), 0.33 (s, 3H), 0.95 (s, 9H), 1.07 (td, 1H, J = 13.6 and 8.0 Hz), 1.42-1.69 (m, 5H), 1.70-1.90 (m, 3H), 2.17 (s, 1H), 2.12-2.23 (m, 2H), 2.34 (s, 3H), 2.96-3.00 (m, 3H), 3.24 (brs, 1H), 3.81 (s, 3H), 5.01 (s, 1H), 7.03-7.10 (m, 2H), 7.18-7.25 (m, 3H) and 7.65-7.68 (m, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ −2.7, −2.2, 19.3, 21.5, 22.9, 26.4, 31.0, 39.2, 42.3, 44.3, 51.5, 52.0, 52.4, 53.3, 58.4, 71.0, 76.4, 107.9.
116.1, 123.7, 124.5, 127.7, 128.4, 129.4, 134.0, 138.2, 141.3, 143.9, 164.6 and 167.2; HRMS Calcd for [(C$_{34}$H$_{46}$N$_2$O$_6$SSi) + H]$^+$: 639.2924. Found: 639.2919.

4.1.35 Oxidation and Cesium Fluoride Induced Aldol Reaction of Primary Alcohol 51:
A solution containing 0.06 g (0.094 mmol) of the above primary alcohol 51 in 5 mL of CH$_3$CN, containing 200 mg of 4 Å molecular sieves, 17 mg (0.14 mmol) of NMO and 10 mg (0.028 mmol) of TPAP at 0 °C was allowed to stir at rt for 12 h. The solution was filtered through a pad of Celite, the solvent was removed under reduced pressure and the residue was taken up in 5 mL of CH$_3$CN. To the resulting mixture was added 0.14 g (0.94 mmol) of Cs$_2$CO$_3$ and the reaction mixture was heated at reflux at 80 °C for 1 h. The mixture was cooled to room temperature and filtered through a pad of Celite. Removal of the solvent left a colorless residue which was subjected to flash chromatography on silica gel to afford 0.017 g (34%) the aldol product 52 as a colorless oil; IR (neat) 3497, 2931, 2850, 2785, 1758, 1714, 1596, 1445, 1362, 1271, 1171 and 1092 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 0.76 (dd, 1H, $J$ = 13.6 and 7.6 Hz), 0.96-1.04 (m, 1H), 1.15 (td, 1H, $J$ = 13.6 and 5.2 Hz), 1.33 (d, 1H, $J$ = 14.8 Hz), 1.49-1.53 (m, 1H), 1.79 (dd, 1H, $J$ = 14.8 and 8.0 Hz), 1.84-2.04 (m, 3H), 2.33 (s, 3H), 2.25-2.42 (m, 1H), 2.48 (s, 1H), 2.83 (t, 1H, $J$ = 8.4 Hz), 3.08 (dd, 1H, $J$ = 10.8 and 3.6 Hz), 4.03 (s, 3H), 4.30-4.32 (m, 2H), 4.83 (m, 1H), 7.13 (d, 3H, $J$ = 8.0 Hz), 7.20 (d, 1H, $J$ = 7.6 Hz), 7.34 (d, 1H, $J$ = 8.0 Hz), 7.41 (d, 2H, $J$ = 8.0 Hz) and 7.79 (d, 1H, $J$ = 8.0 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 21.5, 21.6, 29.2, 38.5, 43.7, 46.3, 51.7, 53.0, 53.4, 54.5, 65.9, 68.5, 78.5, 81.4, 118.1, 122.6, 126.3, 127.4, 128.9, 129.6, 134.2, 139.8, 141.0, 144.7, 169.4 and 206.2; HRMS Calcd for [(C$_{28}$H$_{30}$N$_2$O$_6$S) + H]$^+$: 523.1903. Found: 523.1899.

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References


19. For some leading references, see: Padwa A. Helv Chim Acta 2005;88:1357.


21. Boger and coworkers have recently described [3+2]-cycloaddition chemistry across the indole π-bond and have elegantly exploited this chemistry for the construction of a variety of aspidosperma alkaloid targets, see: Choi Y, Ishikawa H, Velcicky J, Elliott GI, Miller MM, Boger DL. Org Lett 2005;7:4539. [PubMed: 16178578] and references therein


42. In the case of indoles 31a-31c, which are devoid of an electron withdrawing substituent at the 2-position of the ring, no significant effect on the yield of the desulfonylated indole 32 was noticed when n-Bu$_3$SnH was added to the reaction mixture. We assume that with these systems the initially formed indolyl anion (i.e. 37a-37c) is simply more reactive and therefore undergoes reaction with the phenylsulfonyl radical at a faster rate than bimolecular hydrogen transfer with n-Bu$_3$SnH.
Scheme 1.
Scheme 2.

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Scheme 3.
Scheme 4.
Scheme 5.
Scheme 6.
Scheme 7.
Photodesulfonylation of Indoles

<table>
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Scheme 8.
Scheme 9.
Scheme 10.
Scheme 11.
Scheme 12.