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A dipolar cycloaddition approach toward the kopsifoline alkaloid framework

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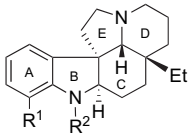
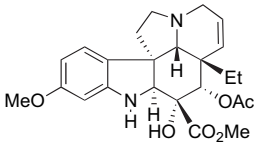
Abstract—Using a metal-catalyzed domino reaction as the key step, the heterocyclic skeleton of the kopsifoline alkaloid family was constructed by a 1,3-dipolar cycloaddition of a carbonyl ylide dipole derived from a Rh(II)-catalyzed reaction of a diazo ketoester across the indole π-bond. Ring opening 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.

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]

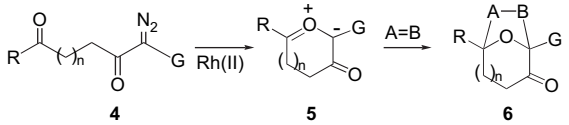


1; $R^1 = R^2 = H$ (Aspidospermidine)
2; $R^1 = OMe$; $R^2 = Ac$ (Aspidospermine)



3; Vindoline

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.[6] 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.[7] 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.[8] 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.[9] With limited exceptions,[10] 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.[11]



4 **5** **6**

Scheme 1.

More recently, we became interested in the formation of push–pull dipoles from the Rh(II)-catalyzed reaction of α-diazoimides[12] 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.[13,14] Our recent total synthesis of (±)-aspidophytine nicely demonstrates the utility of this cascade methodology for the construction of complex aspidosperma alkaloids.[15] 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).

Keywords: Diazoimide; Synthesis; Indole; Cycloaddition; Rhodium(II); Kopsifoline; Alkaloid.
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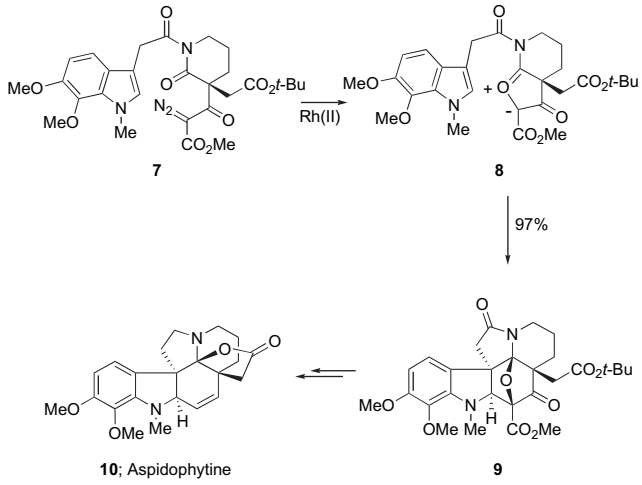
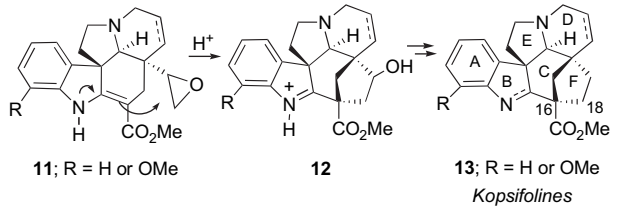


Scheme 2.

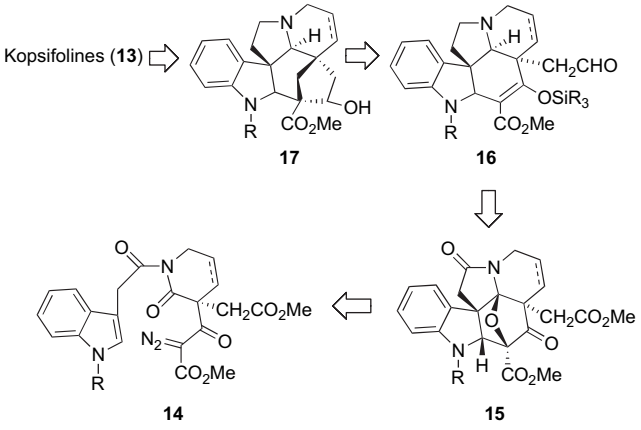
As an extension of our earlier work on (±)-aspidophytine (**10**) we became interested in using the Rh(II)-catalyzed cyclization/cycloaddition cascade for the synthesis of the hexacyclic framework of the kopsifoline alkaloids. The Malaysian members of the genus *Kopsia* have yielded a prodigious harvest of new natural products possessing novel carbon skeletons as well as useful bioactivities.[16] 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*.[17] The major components of the alkaloidal extracts were identified as the kopsifolines.[18] 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 H_2O as shown in Scheme 3.



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.[6] 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.[19,20] 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.[14,21] Ring opening of the resulting cycloadduct **15** followed by a reductive dehydroxylation step[15] would lead to the critical silyl enol ether **16** 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.[22]

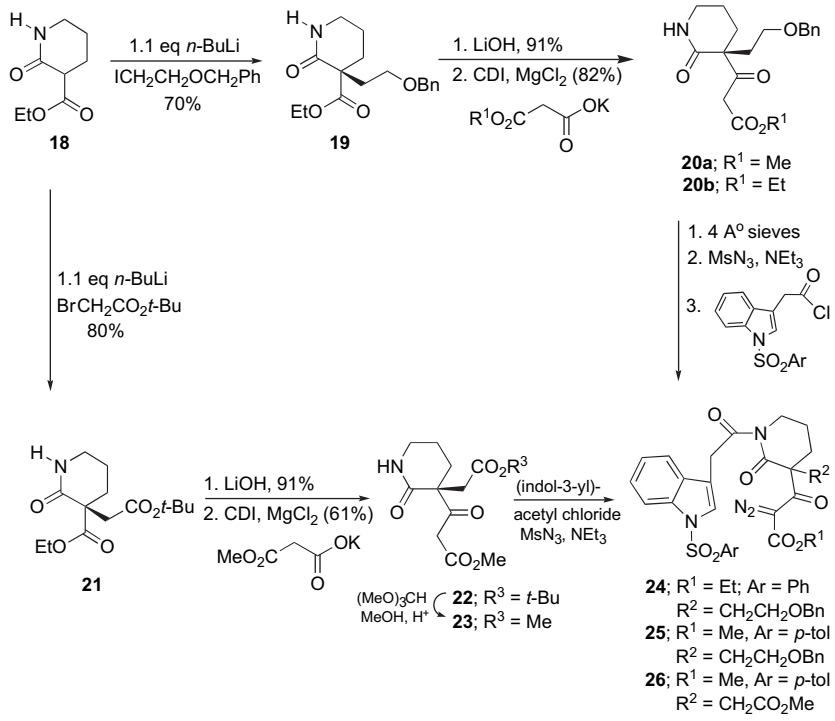


Scheme 4.

2. Results and discussion

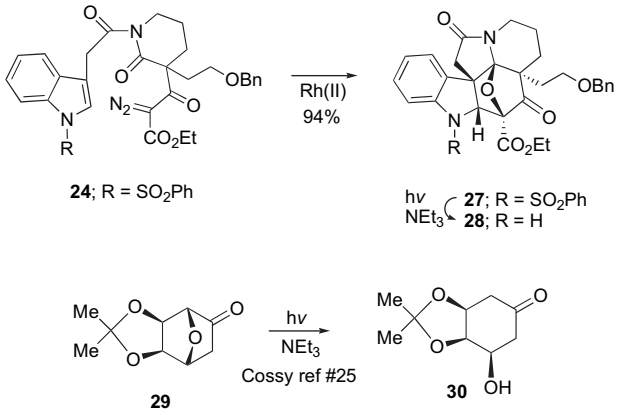
The 3-substituted diazoimides needed to test this approach were prepared according to the reaction sequence outlined in Scheme 5. Deprotonation of piperidone **18** with 1.1 equiv of *n*-butyllithium followed by reaction with 2-iodoethyl benzyl ether afforded lactam **19** in 70% yield. The ethyl ester 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 *tert*-butyl bromoacetate together with a catalytic amount of tetrabutyl ammonium iodide, which lead to the formation of lactam **21** in 80% yield. Treatment of the resulting *tert*-butyl 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-1*H*-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 $Rh_2(OAc)_4$ in benzene at 80 °C afforded cycloadduct **27** in 94% yield as a single diastereomer (Scheme 6). The isolation of **27** is the



Scheme 5.

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.



Scheme 6.

Having established a viable route to cycloadduct **27**, efforts were next centered on the reductive opening of the oxido bridge. In 1991, Cossy and co-workers reported that a photoinduced electron transfer reaction from Et_3N 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 NEt_3 (5 equiv) using CH_3CN as the solvent only furnished the desulfonylated indoline **28** in 90% yield.

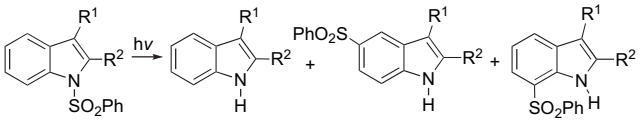
The ready photodesulfonylation of indoline **27** prompted us to carry out a broader study of this deprotection reaction since substituted *N*-sulfonyl-indoles are commonly employed in organic synthesis. The powerful electron-withdrawing property of the sulfonyl group coupled with its *ortho*-directing effect has been extensively utilized for selective metallation at the C_2-position of the indole ring without having to use a large excess of metallating 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 SmI_2,[33] $TiCl_4/Zn$,[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,[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_3N and CH_3CN 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 *ortho*- and *para*-photo Fries like rearrangement products **33** and **34** in varying quantities (8–19%) depending on the particular system. In most cases the *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 *tert*-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 *n*-Bu_3SnH, 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 *ortho*- and *para*-positions.

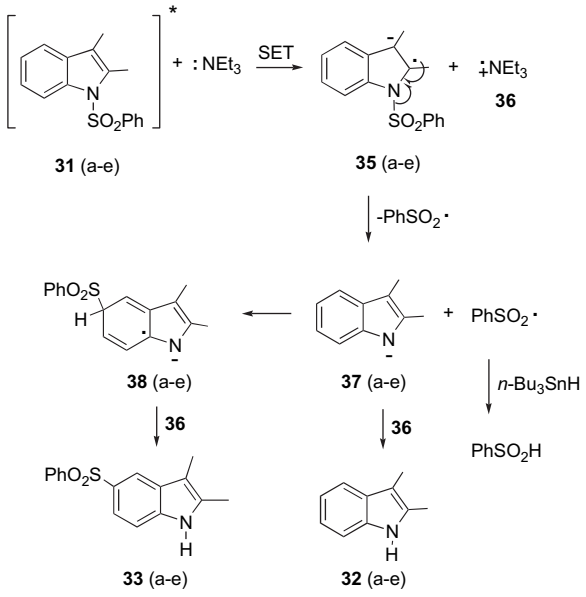
More than likely, the photodesulfonylation reaction can be attributed to a photoinduced electron transfer as outlined in Scheme 8. Amines are well known to undergo such a transfer with electronically excited carbonyl groups.[40] The reaction is initiated by single electron transfer from NEt_3 to the 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_2Ph bond and facilitates bond cleavage.[41] Proton transfer from the radical cation of NEt_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**



31 (a-e) **32** (a-e) **33** (a-e) **34** (a-e)

Entry	R^1	R^2	Product + Yield (%)		
31			**32**	**33**	**34**
a	H	H	48	11	8
b	Me	Me	55	11	11
c	CH_2CH_2OTBS	H	57	19	5
d	CO_2Me	H	77	4	4
e	COMe	CH_2OH	60	-	-

Scheme 7. Photodesulfonylation of indoles.

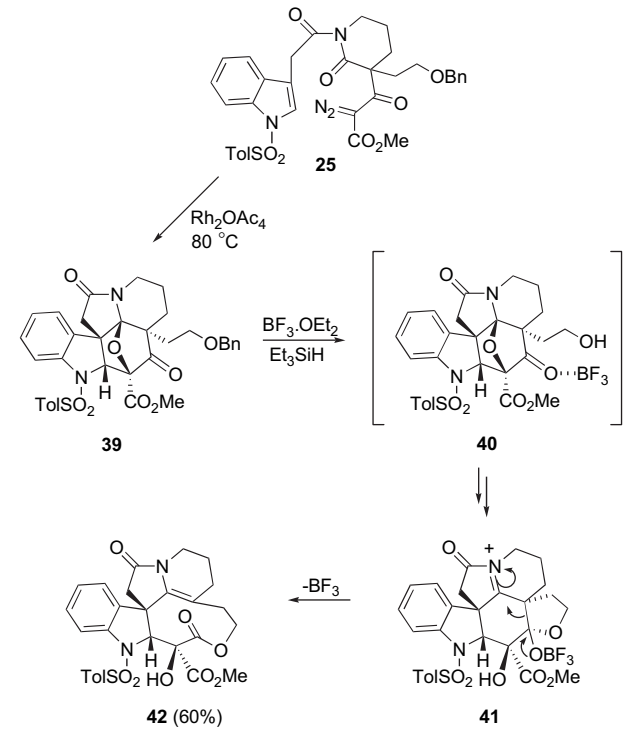


Scheme 8.

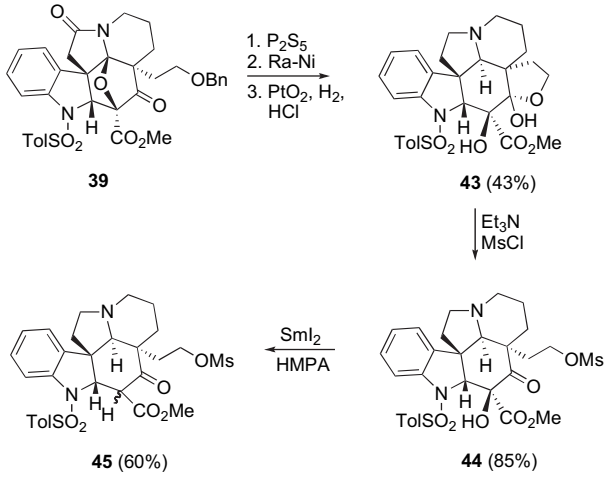
to **36** would afford the rearranged indole **33** (and/or **34**). In the presence of *n*-Bu_3SnH, the phenylsulfonyl radical undergoes bimolecular hydrogen atom transfer and is no longer available to add to the aromatic ring.[42]

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_3SiH and $BF_3 \cdot OEt_2$. On the basis of our previous studies using related aza-oxabicyclic systems,[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_3SiH 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 *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 carbanion 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.

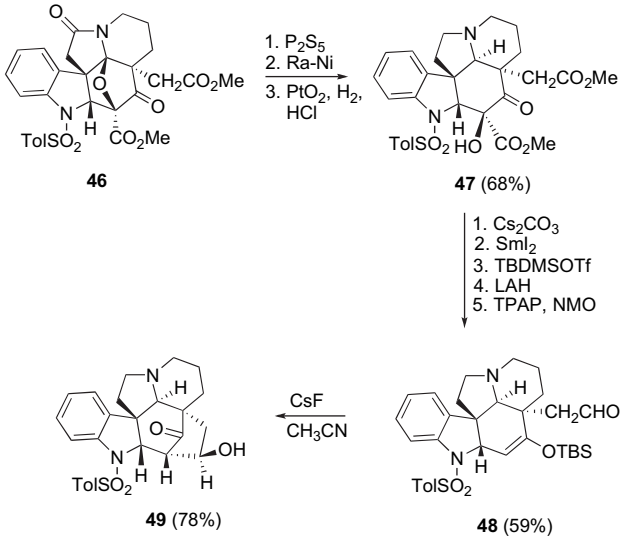


Scheme 9.



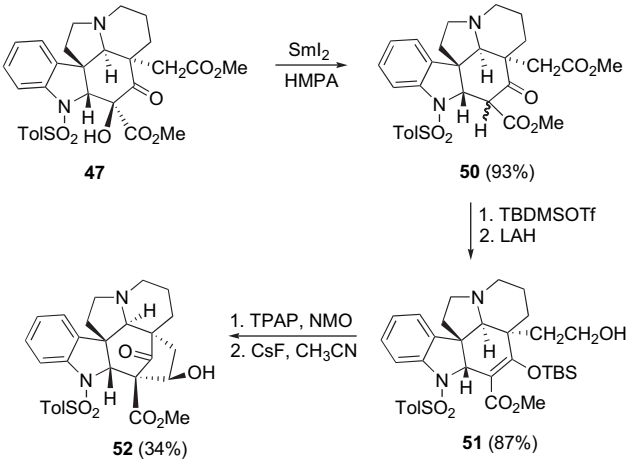
Scheme 10.

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 three-step protocol that was used in Scheme 10. At this point, the carbomethoxy and hydroxyl groups were sequentially removed using Cs_2CO_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_3CN at reflux, it was cleanly converted to the hexacyclic skeleton of the kopsifoline alkaloids (i.e., **49**) in 78% yield.



Scheme 11.

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_3CN 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



Scheme 12.

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 70 eV. 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-Benzyloxyethyl}-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, $CDCl_3$) 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 (br s, 1H), and 7.20–7.73 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 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/H_2O 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 $MgSO_4$, 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, $CDCl_3$) δ 1.79–1.92 (m, 2H), 2.03–2.10 (m, 1H), 2.23–2.34 (m, 3H), 3.27–3.36 (m, 2H), 3.59–367 (m, 2H), 4.48 (s, 2H), 6.28 (br s, 1H), and 7.20–7.38 (m, 5H) (the carboxylic acid proton was too broad to be detected); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.87; H, 6.74; N, 4.96.

To a solution of 9.0 g (33 mmol) of the above carboxylic acid in 150 mL of CH_2Cl_2 was added 6.3 g (39 mmol) of 1,1′-carbonyldiimidazole. The solution was allowed to stir at rt under N_2 overnight, concentrated under reduced pressure, and taken up in 150 mL of THF. A 10.1 g (65 mmol) sample of potassium methyl malonate, 6.2 g (65 mmol) of powdered magnesium chloride, and a small amount (0.4 g, 3.2 mmol) of 4-(dimethylamino)pyridine was dissolved in 400 mL of THF and 200 mL of acetonitrile. After stirring for 2 h, the above lactam in THF was added dropwise to the malonate solution together with 9.0 mL (65 mmol) of triethylamine. The solution was allowed to stir at rt overnight and then 200 mL of a 1 N HCI solution was added. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 8.9 g (82%) of the titled compound **20a** as a colorless solid; mp 57–58 °C; IR (neat) 1749, 1706, 1437, 1319, and 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (pent, 1H, J=7.2 Hz), 1.66–1.75 (m, 2H), 2.08 (dt, 1H, J=14.4 and 6.0 Hz), 2.28–2.42 (m, 2H), 3.14–3.21 (m, 2H), 3.37–3.43 (m, 1H), 3.49–3.54 (m, 1H), 3.58 (s, 3H), 3.64 (d, 1H, J=16.6 Hz), 3.89 (d, 1H, J=16.6 Hz), 3.35 (s, 2H), and 7.21–7.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 27.4, 35.9, 41.9, 45.1, 51.7, 58.0, 65.7, 72.7, 127.2, 127.3, 128.0, 137.7, 167.9, 171.1, and 200.9. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.91; H, 7.06; N, 4.31.

4.1.2. 3-[3-{2-Benzyloxyethyl}-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, $CDCl_3$) 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 (s, 1H), 6.97 (s, 1H), and 7.20–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $[(C_{19}H_{25}NO_5)+H]^+$: 348.1811. Found: 348.1821.

4.1.3. Methyl 3-(3-(2-methoxy-2-oxoethyl)-2-oxo-piperidin-3-yl)-3-oxopropanoate (23). A 8.8 g (28 mmol) sample of methyl 3-(3-(2-*tert*-butoxy-2-oxoethyl)-2-oxo-piperidin-3-yl)-3-oxopropanoate (**22**) in MeOH (40 mL) and

$(MeO)_3CH$ (40 mL) was vigorously stirred for 10 min at 100 °C. To this mixture was added 5.3 g (28 mmol) of *p*-TsOH·H_2O 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 afford 7.5 g (99%) of the titled compound **23** as a colorless oil; IR (neat) 3349, 2953, 1732, 1710, 1655, 1489, 1436, 1354, 1319, 1271, 1223, 1194, 1174, and 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $[(C_{12}H_{17}NO_6)+H]^+$: 272.1134. Found: 272.1129.

4.1.4. 3-[3-(2-Benzyloxyethyl)-2-oxo-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 CH_3CN was added 0.37 mL (2.7 mmol) of Et_3N. 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) 3298, 3226, 2975, 2939, 2873, 2146, 1716, 1644, 1501, 1367, 1316, 1209, and 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3H, J=7.6 Hz), 1.62–1.74 (m, 2H), 1.92–2.04 (m, 1H), 2.18–2.35 (m, 3H), 3.20–3.23 (m, 1H), 3.39–3.68 (m, 3H), 4.16 (q, 2H, J=16.4 Hz), 4.42 (s, 1H), 5.81 (s, 1H), and 7.16–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 18.5, 29.0, 34.7, 42.2, 56.2, 61.1, 67.5, 72.8, 127.2, 127.5, 128.1, 138.5, 160.8, 172.2, and 191.0; HRMS calcd for $[(C_{19}H_{23}NO_5)+H]^+$: 374.1716. Found: 374.1723.

4.1.5. 3-[1-[2-(1-Benzenesulfonyl-1*H*-indol-3-yl)-acetyl]-3-(2-benzyloxyethyl)-2-oxo-piperidin-3-yl]-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-1*H*-indol-3-yl)acetyl chloride in 10 mL of CH_2Cl_2. After stirring for 5 min, 0.14 mL (1.6 mmol) of $(COCl)_2$ in 5 mL of DMF was added. The solution was stirred 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 4 Å 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}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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, 119.0, 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 $[(C_{35}H_{34}N_4O_8S)+H]^+$: 671.2176. Found: 671.2182.

4.1.6. Methyl 3-(3-(2-(benzyloxy)ethyl)-2-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)acetyl)piperidin-3-yl)-3-oxopropanoate. To 100 mL of CH_2Cl_2 in a 200 mL round bottomed flask was added 6.0 g (18 mmol) of 2-(1-tosyl-1*H*-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 CH_2Cl_2 and this solution was added dropwise to a solution of 5.0 g (15 mmol) of lactam **20a** and 50 g of 4 Å mesh molecular sieves in 250 mL of CH_2Cl_2. 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, 1446, 1360, 1290, 1160, 1115, 1086, and 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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 (s, 1H), 7.75 (d, 2H, J=8.4 Hz), and 7.96 (d, 1H, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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, 128.7, 130.1, 131.1, 135.1, 135.5, 137.8, 145.1, 168.0, 173.7, 174.0, and 200.1; HRMS calcd for $[(C_{35}H_{36}N_2O_8S)+H]^+$: 645.2271. Found: 645.2275.

4.1.7. Methyl 3-(3-(2-(benzyloxy)ethyl)-2-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)acetyl)piperidin-3-yl)-2-diazo-3-oxo-propanoate (25). To a 2.4 g (3.7 mmol) sample of the above ketoester in 100 mL of CH_3CN was added 0.6 mL (4.5 mmol) of Et_3N. 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 reaction mixture was allowed to stir at rt for 5 h. The solution was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel to give 2.2 g (88%) of diazoimide **25** as a pale yellow oil; IR (neat) 2982, 2864, 2167, 1707, 1687, 1446, 1368, 1303, and 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.7, 30.5, 35.1, 35.2, 43.0, 52.7, 59.4, 67.3, 73.2, 113.7, 116.6, 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 $[(C_{35}H_{34}N_4O_8S)+H]^+$: 671.2176. Found: 671.2181.

4.1.8. Methyl 3-(3-(2-methoxy-2-oxoethyl)-2-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)acetyl)piperidin-3-yl)-3-oxopropanoate. To 100 mL of CH_2Cl_2 in a 200 mL round bottomed flask was added 6.9 g (21 mmol) of 2-(1-tosyl-1*H*-indol-3-yl) acetic acid. After stirring for 5 min, 7.0 mL (80 mmol) of $(COCl)_2$ was added dropwise together with two 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 CH_2Cl_2 and added dropwise to a solution of 5.4 g (20.0 mmol) of the above lactam **23** and 90 g of 4 Å mesh molecular sieves in 300 mL of CH_2Cl_2. 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, $CDCl_3$) 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 (dt, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $[(C_{29}H_{30}N_2O_9S)+H]^+$: 583.1750. Found: 583.1748.

4.1.9. Methyl 2-diazo-3-(3-(2-methoxy-2-oxoethyl)-2-oxo-1-(2-(1-tosyl-1*H*-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_3CN at 0 °C was added 2.3 mL (16 mmol) of Et_3N. 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 diazoimide **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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 135.1, 144.6, 161.3, 170.7, 172.6, 173.9, and 189.2. Anal. Calcd for $C_{29}H_{28}N_4O_9S$: C, 57.23; H, 4.64; N, 9.21. Found: C, 57.35; H, 4.75; N, 9.17.

4.1.10. 3*a*-{2-Benzyloxyethyl}-5,12*b*-epoxy-6-benzenesulfonyl-4,12-dioxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]fluorene-5-carboxylic acid ethyl ester (27). To a solution of 0.2 g (0.3 mmol) of diazoimide **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 g (94%) of cycloadduct **27** as a clear oil; IR (neat) 2991, 2919, 2873, 1787, 1726, 1434, 1372, 1296, and 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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, 1H, 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, $CDCl_3$) δ 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 $[(C_{35}H_{34}N_2O_8S)+H]^+$: 643.2114. Found: 643.2129.

4.1.11. 3*a*-{2-Benzyloxyethyl}-5,12*b*-epoxy-6-H-4,12-dioxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-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_3N (12.5 μL, 0.085 mmol), and anhydrous CH_3CN (4 mL) was degassed with N_2 for 30 min. The mixture was irradiated (RPR-2537A 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 desulfonylated product **28** as a colorless oil; IR (neat) 3446, 2955, 2919, 2858, 1721, 1475, 1352, 1173, and 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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*-benzenesulfonyl-1*H*-indole (31a). The same irradiation procedure as described above was used starting from commercially available *N*-benzenesulfonyl-1*H*-indole (**31a**) (0.26 g, 1.0 mmol). Purification by flash silica gel chromatography afforded 0.04 g (48%) of 1*H*-indole **32a**.

4.1.13. Irradiation of *N*-benzenesulfonyl-2,3-dimethyl-1*H*-indole (31b). The same irradiation procedure as described above was used starting from 0.32 g (1.0 mmol) of *N*-benzenesulfonyl-2,3-dimethyl-1*H*-indole (**31b**).[47] Purification by flash silica gel chromatography afforded 0.06 g (55%) of 2,3-dimethyl-1*H*-indole **32b**.

4.1.14. *N*-Benzenesulfonyl-3-[2-(*tert*-butyl-dimethylsilanyloxy)ethyl]-1*H*-indole (31c). The same irradiation procedure as described above was used starting from 0.07 g (0.17 mmol) of *N*-benzenesulfonyl-3-[2-(*tert*-butyl-dimethylsilanyloxy)ethyl]-1*H*-indole (**31c**).[48] Purification by flash silica gel chromatography yielded 0.03 g (57%) of the known 3-[2-(*tert*-butyl-dimethylsilanyloxy)ethyl]-1*H*-indole **32c**.[49]

4.1.15. Irradiation of *N*-benzenesulfonyl-1*H*-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*-benzenesulfonyl-1*H*-indole-3-carboxylic acid methyl ester (**31d**).[47] Purification by flash silica gel chromatography yielded 0.13 g (77%) of 1*H*-indole-3-carboxylic acid methyl ester (**32d**).

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-benzenesulfonyl-1*H*-indole-3-carboxylic acid methyl ester (**33d**); 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); ^{13}C NMR (100 MHz, DMSO) δ 51.0, 106.9, 112.7, 119.8, 121.5, 127.1, 129.1, 129.7, 133.4, 134.5, 135.3, 136.6, 141.9, and 164.1.

The second fraction was a clear oil and was identified as 7-benzenesulfonyl-1*H*-indole-3-carboxylic acid methyl ester (**34d**); IR (neat) 3319, 2948, 1713, 1531, 1445, 1419, 1338, 1302, and 1155 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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*-benzenesulfonyl-(2-hydroxymethyl-1*H*-indol-3-yl)ethanone (31e). The same irradiation procedure as described above was used starting from 0.33 g (1.0 mmol) of *N*-benzenesulfonyl-(2-hydroxymethyl-1*H*-indol-3-yl)ethanone (**31e**).[50] Purification by flash silica gel chromatography afforded 0.11 g (60%) of 1-(2-hydroxymethyl-1*H*-indol-3-yl)ethanone (**32e**) 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); ^{13}C 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. 3*a*-{2-Benzyloxyethyl}-5,12*b*-epoxy-6-tosyl-4,12-dioxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]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 N_2 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, 1773, 1727, 1478, 1460, 1399, 1361, 1309, and 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{35}H_{34}N_2O_8S$: 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 triethylsilylhydride and boron trifluoride etherate. A solution containing 0.06 g (0.1 mmol) of cycloadduct **39** in CH_2Cl_2 (4 mL) was cooled to −78 °C and 160 μL (1 mmol) of Et_3SiH and 65 μL (0.5 mmol) of $BF_3 \cdot Et_2O$ 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 satd $NaHCO_3$ solution, brine, and H_2O. The solution was extracted with CH_2Cl_2 and dried over $MgSO_4$. 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, 1596, 1460, 1359, 1265, 1169, and 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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), 3.25–3.30 (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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.5, 29.0, 32.6, 38.7, 51.1, 54.6, 55.6, 64.1, 79.2, 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 $[(C_{28}H_{28}N_2O_8S)+H]^+$: 553.1645. Found: 553.1636.

4.1.19. 3*a*-{2-Benzyloxyethyl}-5,12*b*-epoxy-6-tosyl-4-oxo-12-thioxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-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 N_2 were added 0.2 g (0.45 mmol) of P_2S_5 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, 107.4, 116.6, 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 $[(C_{35}H_{34}N_2O_7S_2)+H]^+$: 659.1886. Found: 659.1875.

4.1.20. 3*a*-{2-Benzyloxyethyl}-5,12*b*-epoxy-6-tosyl-4-oxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester. An excess amount of Raney nickel in 100 mL round bottomed flask under N_2 was washed three times with H_2O, 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.9, 25.9, 27.8, 37.6, 46.7, 51.7, 52.0, 53.3, 62.6, 66.7, 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 $[(C_{35}H_{36}N_2O_7S)+H]^+$: 629.2321. Found: 629.2332.

4.1.21. Methyl 3*a*-(2-(benzyloxy)ethyl)-5-hydroxy-4-oxo-6-tosyl-2,3,3*a*,3a^1,4,5,5*a*,6,11,12-decahydro-1*H*-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 were added 8 mg of PtO_2 and one 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 satd $NaHCO_3$ solution, brine, and dried over $MgSO_4$. 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, $CDCl_3$) δ 1.06 (hex, 1H, J=7.2 Hz), 1.23–1.51 (m, 4H), 1.67 (ddd, 1H, J=14.4, 10.4, and 4.0 Hz), 1.99–2.05 (m, 1H), 2.31 (s, 3H), 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.8, 31.0, 33.9, 42.3, 49.1, 51.6, 52.2, 52.5, 52.6, 65.1, 72.5, 74.5, 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 $[(C_{35}H_{38}N_2O_7S)+H]^+$: 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 3*a*-{2-benzyloxyethyl}-5,12*b*-epoxy-6-tosyl-4-oxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester in 10 mL of MeOH and 2 mL THF were added 8 mg of PtO_2 and one 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 satd $NaHCO_3$ solution, brine, and dried over $MgSO_4$. 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $[(C_{28}H_{32}N_2O_7S)+H]^+$: 541.2008. Found: 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 CH_2Cl_2 at 0 °C was added 2.5 mL of Et_3N 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 satd NH_4Cl solution and washed with brine, H_2O, and dried over $MgSO_4$. 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 **44** as a colorless oil; IR (neat) 3047, 2962, 2921, 2855, 1760, 1711, 1593, 1466, 1352, 1254, and 1176 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[(C_{29}H_{34}N_2O_9S_2)+H]^+$: 619.1784. Found: 619.1774.

4.1.24. 3*a*-(2-Methoxy-2-oxoethyl)-5,12*b*-epoxy-6-tosyl-4,12-dioxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester (46). To a solution containing 8.4 g (13.8 mmol) of diazoimide **26** in 200 mL benzene under N_2 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{29}H_{28}N_2O_9S$: C, 59.99; H, 4.86; N, 4.82. Found: C, 60.20; H, 5.01; N, 4.73.

4.1.25. 3*a*-(2-Methoxy-2-oxoethyl)-5,12*b*-epoxy-6-tosyl-4-oxo-12-thioxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]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 N_2 were added 1.9 g (4.3 mmol) of P_2S_5 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}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, 125.1, 127.3, 129.0, 129.8, 130.9, 132.5, 142.4, 145.2, 164.1, 169.5, 199.8, and 206.2; HRMS calcd for $[(C_{29}H_{28}N_2O_8S_2)+H]^+$: 597.1365. Found: 597.1356.

4.1.26. 3*a*-(2-Methoxy-2-oxoethyl)-5,12*b*-epoxy-6-tosyl-4-oxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester. An excess amount of Raney nickel in a 250 mL round bottomed flask under N_2 was washed three times with H_2O, twice with dry MeOH, and finally three times with dry THF. A 6.3 g (10.6 mmol) sample of the above thiolactam in 100 mL THF was added dropwise. The solution was vigorously stirred for 14 h under 1 atm of H_2 gas. The reaction mixture 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 5.2 g (87%) 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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=12.4 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $[(C_{29}H_{30}N_2O_8S)+H]^+$: 567.1801. Found: 567.1794.

4.1.27. Methyl 5-hydroxy-3*a*-(2-methoxy-2-oxoethyl)-4-oxo-6-tosyl-2,3,3*a*,3*a*^{1},4,5,5*a*,6,11,12-decahydro-1*H*-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 were added 10 mg of PtO_2 and one 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 satd $NaHCO_3$ solution, brine, and dried over $MgSO_4$. 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, 1596, 1480, 1435, 1358, 1254, 1169, 1114, 1097, and 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.35 (m, 1H), 1.51–1.71 (m, 2H), 1.87 (d, 1H, J=17.4 Hz), 2.07 (d, 1H, J=17.4 Hz), 2.09–2.14 (m, 2H), 2.29 (s, 3H), 2.37 (td, 1H, J=10.0 and 6.4 Hz), 3.03 (d, 1H, J=11.2 Hz), 3.14 (td, 1H, J=9.2 and 4.0 Hz), 3.24 (s, 1H), 3.36 (s, 3H), 3.82 (s, 3H), 4.45 (s, 1H), 6.96–7.04 (m, 2H), 7.10 (d, 2H, J=8.4 Hz), 7.22–7.26 (m, 1H), 7.44 (d, 2H, J=8.4 Hz), 7.65 (d, 1H, J=8.0 Hz), and 8.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.7, 30.2, 37.4, 42.1, 47.5, 51.2, 51.9, 52.1, 52.7, 69.5, 77.6, 79.9, 117.8, 123.7, 125.0, 127.8, 128.9, 129.3, 132.8, 135.6, 141.7, 144.5, 168.0, 169.8, and 202.9; HRMS calcd for $[(C_{29}H_{32}N_2O_8S)+H]^+$: 569.1958. Found: 569.1951.

4.1.28. Methyl 2-(5-(methoxycarbonyloxy)-4-oxo-6-tosyl-2,3,3*a*,3*a*^{1},4,5,5*a*,6,11,12-decahydro-1*H*-indolizino[8,1-*cd*]carbazol-3*a*-yl)acetate. To a 0.55 g (0.97 mmol) sample of compound **47** in 40 mL CH_3CN was added 1.95 g (6 mmol) of Cs_2CO_3 and the reaction mixture was heated at reflux for 1 h. The mixture was cooled to rt 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 0.41 g (75%) of the titled carbonate as a colorless solid; mp 97–98 °C; IR (neat) 2952, 1736, 1597, 1474, 1459, 1439, 1359, 1331, 1267, 1167, and 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (td, 1H, J=13.2 and 4.8 Hz), 1.15–1.29 (m, 2H), 1.40–1.44 (m, 1H), 1.73–1.83 (m, 1H), 1.98–2.10 (m, 1H), 2.14–2.20 (m, 2H), 2.18 (d, 1H, J=14.8 Hz), 2.34 (s, 3H), 2.48 (d, 1H, J=14.8 Hz), 2.88–2.91 (m, 2H), 2.93 (s, 1H), 3.49 (s, 3H), 3.74 (s, 3H), 4.47 (d, 1H, J=8.4 Hz), 5.24 (d, 1H, J=8.4 Hz), 7.10 (t, 1H, J=7.6 Hz), 7.19 (d, 3H, J=8.4 Hz), 7.28 (t, 1H, J=7.6 Hz), 7.63 (d, 1H, J=8.0 Hz), and 7.66 (d, 2H, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.4, 29.6, 38.0, 42.1, 48.8, 50.5, 51.7, 52.9, 54.3, 55.0, 70.7, 72.8, 78.3, 118.2, 122.7, 125.3, 126.8, 128.9, 129.5, 136.1, 136.6, 140.2, 144.0, 154.5, 169.3, and 200.1. Anal. Calcd for $C_{29}H_{32}N_2O_8S$: C, 61.25; H, 5.67; N, 4.93. Found: C, 61.36; H, 5.77; N, 4.79.

4.1.29. Methyl 2-(4-oxo-6-tosyl-2,3,3*a*,3*a*^{1},4,5,5*a*,6,11,12-decahydro-1*H*-indolizino[8,1-*cd*]carbazol-3*a*-yl)acetate. A solution containing 0.6 g (1.0 mmol) of the above carbonate in THF (5 mL) together with 0.5 mL of HMPA was degassed with argon at rt for 15 min. The mixture was allowed to react with a solution of samarium iodide in THF (0.1 M) at 0 °C until a blue color persisted for 10 s. The reaction mixture was then quenched with a satd $NaHCO_3$ solution, extracted with EtOAc, and dried over $MgSO_4$. Removal

of the solvent left a colorless residue, which was subjected to flash chromatography on silica gel to afford 0.37 g (72%) of the titled compound as a clear oil; IR (neat) 2939, 2795, 1738, 1718, 1475, 1459, 1355, 1168, and 1101 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 1.26–1.34 (m, 2H), 1.40–1.56 (m, 2H), 1.62 (td, 1H, J=13.8 and 3.6 Hz), 1.94–2.28 (m, 7H), 2.35 (s, 3H), 2.78 (s, 1H), 2.90–3.02 (m, 2H), 3.05 (dd, 1H, J=16.8 and 6.0 Hz), 3.11–3.14 (m, 1H), 3.35 (s, 3H), 4.26 (s, 1H), 7.10 (t, 1H, J=7.2 Hz), 7.21 (d, 1H, J=7.2 Hz), 7.27 (d, 1H, J=7.8 Hz), 7.30 (d, 2H, J= 8.4 Hz), 7.62 (d, 1H, J=7.8 Hz), and 7.79 (dd, 2H, J=6.6 and 1.8 Hz); ^{13}C NMR (150 MHz, CD_3CN) δ 21.9, 23.3, 31.6, 40.8, 41.8, 43.4, 49.7, 52.2, 53.0, 53.8, 71.2, 74.1, 117.1, 125.7, 126.3, 128.7, 130.1, 131.2, 135.2, 137.8, 141.8, 146.5, 171.2, and 209.5. Anal. Calcd for $C_{27}H_{30}N_2O_5S$: C, 65.57; H, 6.11; N, 5.66. Found: C, 65.11; H, 6.19; N, 5.46.

4.1.30. 2-(4-(*tert*-Butyldimethylsilyloxy)-6-tosyl-2,3,3*a*,3*a*^{1},5*a*,6,11,12-octahydro-1*H*-indolizino[8,1-*cd*]carbazol-3*a*-yl)acetaldehyde (48). To a solution containing 0.12 g (0.2 mmol) of the above keto ester and 120 μL (0.5 mmol) of TBDMSOTf in 10 mL of CH_2Cl_2 was added dropwise 208 μL of (1.5 mmol) Et_3N. After 1 h of stirring at rt, the mixture was hydrolyzed with a satd $NaHCO_3$ solution. After extraction with CH_2Cl_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_2O, 15% NaOH, and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. To the resulting residue was added 5 mL of CH_3CN, 0.15 g of 4 Å molecular sieves, 0.04 g (0.35 mmol) 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}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.20 (s, 3H), 0.26 (s, 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) δ −4.8, −4.4, 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 $[(C_{32}H_{42}N_2O_4SSi)+H]^+$: 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_3CN was added 0.13 g (0.86 mmol) of Cs_2CO_3 and the reaction mixture was heated at 100 °C for 1 h. The mixture was then cooled to rt 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}; ^1H NMR ($CDCl_3$, 400 MHz) δ 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) δ 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 $[(C_{26}H_{28}N_2O_4S)+H]^+$: 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 s. The reaction mixture was quenched with a satd $NaHCO_3$ solution, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent under reduced pressure left a colorless residue, which was subjected to flash chromatography on silica gel to afford 0.08 g (93%) of compound **50** as a clear oil, which consisted of a 4.3:1 mixture of the keto and enol forms; IR (neat) 3068, 2954, 2921, 2855, 1728, 1450, 1258, 1237, 1176, and 1029 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 1.19–1.37 (m, 1H), 1.39–1.67 (m, 3H), 1.67–1.80 (m, 1H), 1.98–2.09 (m, 3H), 2.14 (d, 1H, J=16.8 Hz), 2.20–2.29 (m, 1H), 2.36 (s, 3H), 2.83–2.86 (m, 1H), 2.87 (s, 1H), 2.94 (hex, 1H, J=4.4 Hz), 3.34 (s, 3H), 3.76 (s, 3H), 4.33 (d 1H, J=4.0 Hz), 4.84 (d 1H, J=4.0 Hz), 7.04–7.06 (m, 2H), 7.22 (d, 2H, J=8.0 Hz), 7.25 (t, 1H, J=8.4 Hz), 7.64 (d, 2H, J=8.4 Hz), and 7.72 (d, 1H, J=8.4 Hz); ^{13}C NMR (100 MHz, CD_3CN) δ 22.3, 21.6, 29.7, 30.9, 38.5, 41.0, 48.4, 51.2, 51.4, 51.8, 52.4, 116.9, 124.1, 124.7, 127.9, 128.9, 129.6, 132.5, 135.4, 141.3, 144.6, 167.2, 170.0, and 205.0; HRMS calcd for $[(C_{29}H_{32}N_2O_7S)+H]^+$: 553.2008. Found: 553.2000.

4.1.33. Methyl 4-(*tert*-butyldimethylsilyloxy)-3*a*-(2-methoxy-2-oxoethyl)-6-tosyl-2,3,3*a*,3*a*^{1},5*a*,6,11,12-octahydro-1*H*-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 CH_2Cl_2 was added dropwise 121 μL (0.9 mmol) of Et_3N. After stirring overnight at rt, the mixture was hydrolyzed with a satd $NaHCO_3$ solution. After extraction with CH_2Cl_2, the organic layer was dried over $MgSO_4$ and filtered. Concentration of the solution under reduced pressure followed by flash chromatography on silica gel afforded 0.07 g (96%) of the titled enol ether as a colorless oil; IR (neat) 3402, 2948, 2931, 2857, 2787, 1727, 1596, 1477, 1436, 1358, 1260, 1169, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.26 (s, 3H), 0.31 (s, 3H), 0.94 (s, 9H), 1.30–1.38 (m, 1H), 1.43–1.59 (m, 3H), 1.70 (ddd, 1H, J=10.8, 8.8, and 2.0 Hz), 1.96–2.10 (m, 2H), 2.23 (t, 1H, J=4.8 Hz), 2.32 (s, 3H), 2.45 (d, 1H, J=16.4 Hz), 2.84 (s, 1H), 2.92–2.98 (m, 2H), 3.31 (s, 3H), 3.81 (s, 3H), 4.94 (s, 1H), 7.00 (td, 1H, J=7.6 and

1.2 Hz), 7.09 (dd, 1H, J=7.6 and 1.2 Hz), 7.15–7.20 (m, 3H), and 7.63–7.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −3.0, −2.4, 19.2, 21.5, 22.8, 26.2, 30.2, 38.7, 42.0, 43.2, 51.0, 51.6, 51.8, 51.9, 52.6, 70.5, 72.6, 109.2, 116.4, 124.2, 124.4, 127.7, 128.1, 129.4, 134.0, 137.4, 140.8, 143.9, 161.2, 167.1, and 170.7; HRMS calcd for $[(C_{35}H_{46}N_2O_7SSi)+H]^+$: 667.2873. Found: 667.2866.

4.1.34. Methyl 4-(*tert*-butyldimethylsilyloxy)-3*a*-(2-hydroxyethyl)-6-tosyl-2,3,3*a*,3*a*^{1},5*a*,6,11,12-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (51). To a solution of 0.069 g (0.1 mmol) of the above compound in 10 mL of THF was added 0.5 mL of a 1.0 M $LiAlH_4$ solution at −78 °C. The solution was allowed to warm to 0 °C and was stirred for 5 h. The mixture was quenched with H_2O, 15% NaOH, and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ 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, 1169, and 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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 (br s, 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); ^{13}C NMR ($CDCl_3$, 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 $[(C_{34}H_{46}N_2O_6SSi)+H]^+$: 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_3CN, 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_3CN. To the resulting mixture was added 0.14 g (0.94 mmol) of Cs_2CO_3 and the reaction mixture was heated at reflux at 80 °C for 1 h. The mixture was cooled to rt 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%) of 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) δ 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) δ 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 $[(C_{28}H_{30}N_2O_6S)+H]^+$: 523.1903. Found: 523.1899.

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