An Isomünchnone-Based Method for the Synthesis of Highly Substituted 2(1*H*)-Pyridones

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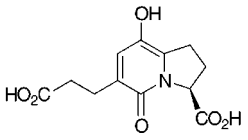
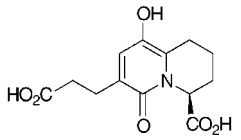
1-(Benzenesulfonyl-diazoacetyl)-pyrrolidin-2-one was prepared by a diazo transfer of 1-(benzenesulfonylacetyl)-pyrrolidin-2-one with *p*-acetamidobenzenesulfonyl azide and triethylamine. Treatment of the diazoimide with a catalytic quantity of rhodium(II) acetate resulted in the formation of an isomünchnone dipole, which underwent bimolecular trapping with various dipolarophiles in high yield. The initially formed cycloadducts were not isolable or observed, as they all readily underwent ring opening to give the 3-hydroxy-2(1*H*)-pyridone ring system. The 3-hydroxy-2(1*H*)-pyridones were readily converted to the corresponding triflates, which function as suitable substrates in various types of palladium-catalyzed cross-coupling reactions. Commercial tetrakis(triphenylphoshine)palladium was found to be a particularly effective catalyst for the cross-coupling with aryl, vinyl, and acetylenic partners. An application of the method to the synthesis of the indolizidine alkaloid (±)-ipalbidine was carried out in eight steps in 17% overall yield. The angiotensin-converting enzyme inhibitor (−)-A58365A was also synthesized by a process based on the [3 + 2]-cycloaddition reaction of a phenylsulfonyl substituted isomünchnone intermediate. The starting material for this process was prepared from L-pyroglutamic acid and involved using a diazo phenylsulfonyl substituted pyrrolidine imide. Treatment of the diazoimide with $Rh_2(OAc)_4$ in the presence of methyl vinyl ketone afforded a 3-hydroxy-2-pyridone derivative, which was subsequently converted to the ACE inhibitor in six additional steps.

Six-membered nitrogen heterocycles comprise the backbone of many biologically and structurally interesting alkaloids.[1,2] The 2(1*H*)-pyridone ring system is a valuable building block in natural product synthesis, as it can act as a common intermediate for the preparation of a wide variety of piperidine, pyridine, quinolizidine, and indolizidine alkaloids.[3,4] This substructure is also found in a large number of natural products such as camptothecin,[5] elastase,[6] and thrombin.[7] *N*-Alkyl substituted pyridones are known to exhibit both antibacterial and antifungal activity.[8] 4-Hydroxy-2(1*H*)-pyridones such as pyridoxatin[9] and huperzine A[10] have become increasingly important in the treatment of a variety of diseases. *N*-Substituted 2-pyridones have also been utilized as active ingredients in drugs for the therapy of fibrotic disease and have been evaluated as inhibitors of human leukocyte elastase.[11] The pyridone acids **1** and **2**, which



1; A58365A



2; A58365B

were obtained from the fermentation broth of the bacterium *Streptomyces chromofuscus* in the Eli Lilly laboratories, were found to be ACE inhibitors at nanomolar concentrations.[12] This property makes them of potential value as lead compounds for the design of drugs to lower blood pressure.

Numerous methods for the preparation of substituted 2-pyridones have been reported in the literature.[13] As far back as 1892, Decker investigated the oxidation of pyridinium salts to produce the corresponding 2-pyridones using ferricyanide under basic conditions.[14] This

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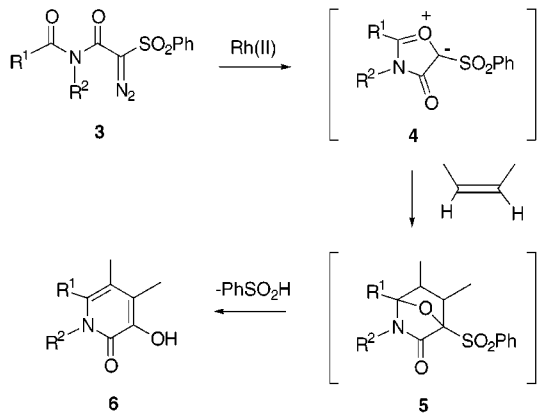
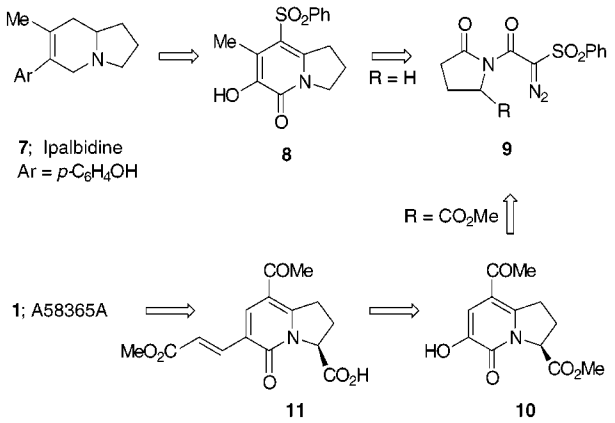
approach provides easy access to a variety of 2-pyridones as long as the starting pyridinium salts are available. Substituted 2-pyridones are generally prepared, however, from acyclic starting materials that often incorporate a Michael addition as the key synthetic step.[15] The 2-pyridone ring system has also been synthesized through a variety of cycloaddition[16,17] and cyclization procedures.[18] However, only a few methods of preparing 3-hydroxy-2(1*H*)-pyridones have been reported,[19] and they typically involve harsh conditions that preclude the presence of sensitive functional groups.[20] In this paper, we describe a new, general, and flexible entry to a variety of 3-hydroxy substituted 2-pyridones.[21] The cornerstone of our synthetic plan is the [3 + 2]-cycloaddition of a phenylsulfonyl substituted isomünchnone intermediate (i.e., **4**).[22,23] Once the cycloaddition reaction occurs, the resulting adduct **5** undergoes ready ring opening to give the desired pyridone **6** (Scheme 1).[24] The versatility of our strategy lies in the fact that, by appropriate selection of the diazo precursor **3** and dipolarophile, various groups can be introduced into the N-1 and C-4, C-5, C-6 positions. Moreover, substituents can be subsequently introduced at C-3 by conversion of the hydroxyl functionality to a triflate group,[25] followed by a palladium-catalyzed cross-coupling reaction.[26] To highlight the method, the above synthetic strategy was applied to the synthesis of several indolizidine alkaloids. Among other examples, this procedure was employed in an efficient synthesis of (±)-ipalbidine[27] (**7**) and the angiotensin converting enzyme inhibitor (−)-A58365A (**1**) (Scheme 2).[28]

Scheme 1



Scheme 2



Results and Discussion

The preparation of the requisite diazoimide **9** was accomplished by a diazo transfer reaction[29] of 1-[(benzenesulfonyl)acetyl]pyrrolidine-2-one with *p*-acetamidobenzenesulfonyl azide[30] and triethylamine. Formation of the isomünchnone ring was achieved by the reaction of **9** with $Rh_2(OAc)_4$ to give a rhodium carbenoid species that undergoes an intramolecular cyclization onto the neighboring carbonyl oxygen to form the mesoionic dipole **4**. Bimolecular trapping of the dipole with *N*-phenylmaleimide or phenyl vinyl sulfone proceeded in 87% and 63% yield, respectively (Scheme 3). The initially formed cycloadducts (i.e., **5**) were not isolable, as they readily underwent ring opening to give the 3-hydroxy-2(1*H*)-pyridones **12** and **14**. As a consequence of its hydrolytic reactivity, cycloadduct **12** was immediately reacted with triisopropylsilyl chloride to give silyl ether **13**. In a similar fashion, 3-hydroxy pyridone **14** was allowed to react with acetic anhydride, dimethyl sulfate, or *N*-phenyl trifluoromethanesulfonamide[31] to give the crystalline derivatives **15**−**17** in high yield.

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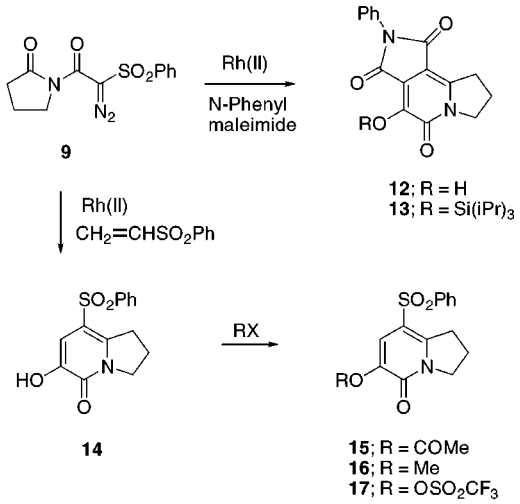
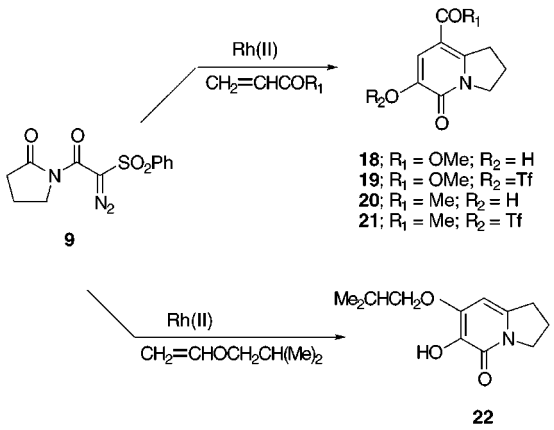
Scheme 3

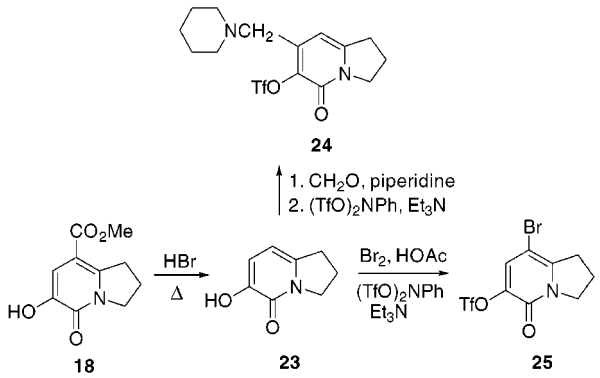


Scheme 4



Several types of dipolarophiles were examined to establish the scope and generality of the process. The tandem *cyclization−cycloaddition−ring opening* sequence using diazoimide **9** proceeded smoothly with methyl acrylate, methyl vinyl ketone, and isobutyl vinyl ether (Scheme 4). In all cases the initially formed isomünchnone dipole was trapped by the added dipolarophile, and good yields of the expected 3-hydroxy pyridones were obtained. Compounds **18** and **20** were readily converted to the corresponding triflates **19** and **21**. The Rh(II)-catalyzed reaction of **9** with isobutyl vinyl ether (vide infra) also proved to be a highly efficient process leading to 3-hydroxy pyridone **22**, which was isolated as a crystalline solid, mp 167−168 °C. The regiochemical crossover in product formation when an electron-rich dipolarophile is used is understandable on the basis of FMO theory.[32] The HOMO of the mesoionic dipole is the dominant MO when electron-deficient olefins are used, whereas the LUMO of the dipole is the controlling molecular orbital with electron-rich dipolarophiles.[33] The frontier orbital coefficients at the reacting centers of the isomünchnone dipole were calculated by using the QCPE AMPAC program with the AM1 Hamiltonian. The MO calculations indicate that the atomic coefficient at the amide carbonyl center (i.e., C_5) is larger (0.69) than that

Scheme 5



of the sulfonyl-substituted center (i.e., C_3 (0.30)) in the LUMO. It is well-known that the C_β-coefficient of the HOMO of enol ethers is larger than the C_α-coefficient,[34] and consequently pyridone **22** is predicted to be the major regioisomer formed.

Compound **18**, derived from the Rh(II)-catalyzed reaction of **9** with methyl acrylate, was easily decarboxylated by heating with 48% HBr at 135 °C for 12 h. This reaction resulted in the formation of the unsubstituted 3-hydroxy pyridone **23** in 91% yield (Scheme 5). At this juncture, we decided to examine the chemical behavior of **23** with various reagents because we were interested in introducing carbon-based substituents onto the pyridone ring for eventual indolizidine alkaloid synthesis. The presence of a 3-hydroxy substituent on the pyridone ring allows for an element of diversity, and this functionality can be used as a site for further modification. Our initial studies were designed to evaluate the reactivity of **23** with several electrophilic reagents. The Mannich reaction of **23** with the iminium ion derived from formaldehyde and piperidine gave the 4-substituted pyridone **24** (63%) after conversion to the corresponding triflate. In contrast, exposure of **23** to bromine in glacial acetic acid followed by triflation afforded the 5-bromo substituted triflate **25** in 71% overall yield.

The synthetic potential of vinyl triflates has been well established over the past decade,[25] and these compounds have been shown to be suitable substrates in various types of coupling reactions, including Stille couplings[26] and Heck reactions.[35] In contrast to the numerous examples of cross-coupling reactions with simple vinyl triflates, there were no examples of similar reactions with pyridone-derived triflates when we initiated work in this area.[36] To test the feasibility of the palladium-catalyzed cross-coupling reaction of this new class of triflates,[37] we subjected the easily available phenylsulfonyl and carbomethoxy substituted triflates **17** and **19** to various organometallic reagents in the presence of a Pd(0) catalyst (Scheme 6). Reaction of **17** with tributylphenyltin

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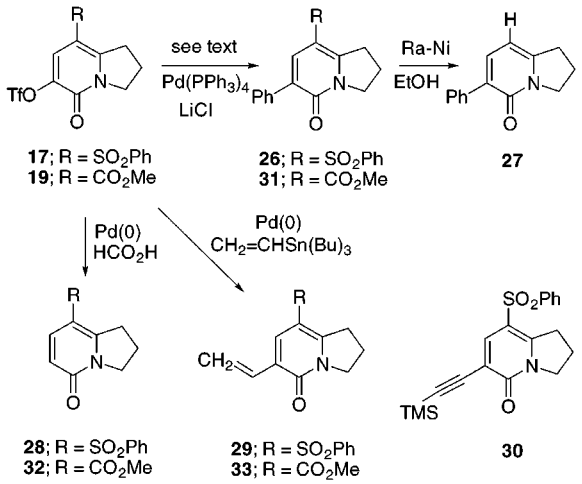
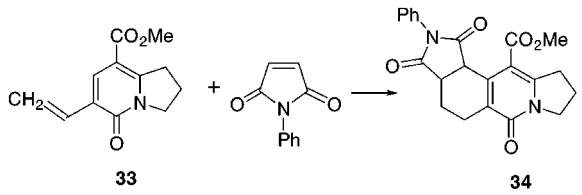
(36) Since this project was initiated in our laboratory, several examples of pyridones bearing a triflate group in the 3- or 4-position of the heteroaromatic ring have been reported to undergo palladium-catalyzed cross-coupling reactions. Fu, J. M.; Chen, Y.; Castelhano, A. L. *Synlett* **1998**, 1408. Collins, I.; Castro, J. L. *Tetrahedron Lett.* **1999**, *40*, 4069. Nadin, A.; Harrison, T. *Tetrahedron Lett.* **1999**, *40*, 4073.

(37) For a review on organometallic coupling reactions of enol triflates, see: Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.

Scheme 6

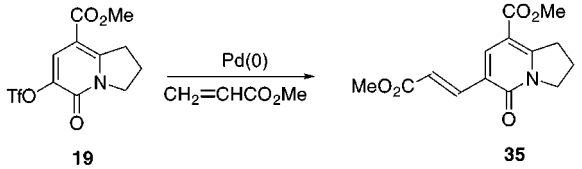


in the presence of lithium chloride (3 equiv) and tetrakis-(triphenylphosphine)palladium(0) (0.05 equiv) gave the phenyl-substituted pyridone **26** in 85% yield. Raney nickel reduction of **26** furnished the desulfonylated pyridone **27** in 97% yield. Conversion of the triflate group present in **17** or **19** into the unsubstituted 2-pyridone **28** or **32** was achieved via a palladium(0)-catalyzed formate reduction[38] in 92% yield. Stille coupling of **17** with vinyltributyltin afforded pyridone **29** in 78% yield. (Trimethylsilyl)acetylene also underwent palladium-catalyzed coupling with triflate **17** to provide acetylene **30** in 91% yield. Likewise, we successfully reduced and coupled the carbomethoxy substituted triflate **19** with phenyl and vinyltin reagents to give pyridones **31** and **33** in high yield. We found that the Diels−Alder reaction of **33** with *N*-phenylmaleimide at 110 °C afforded, after 4 h, cycloadduct **34** in 92% yield. Compound **34** is the result of



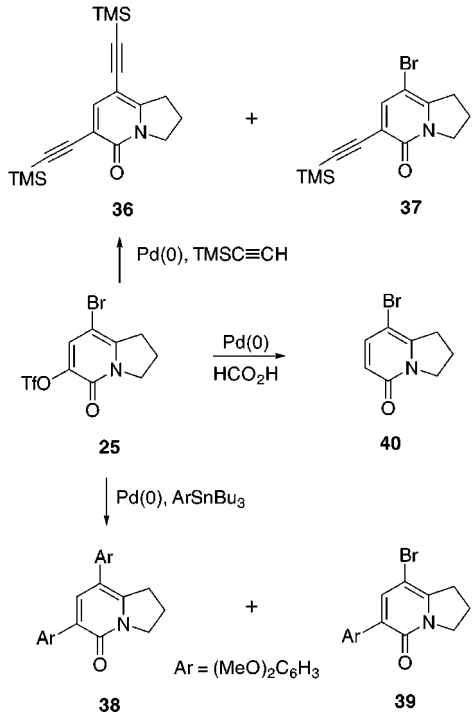
addition of the dienophile to the pyridone "*3,4-double bond/3-vinyl group*" diene system. The transient [4 + 2]-adduct undergoes tautomerization to **34** either during the course of the thermolysis or upon purification by silica gel chromatography.

Another example of the synthetic usefulness of the pyridone triflate intermediate involves a palladium(0) catalyzed Heck reaction of **19** with methyl acrylate to generate the propenoate ester **35** in 96% isolated yield.



The sequential cross-coupling of organometallic species with dihalides or bis(enoltriflates) in Stille-type chemistry

Scheme 7



offers versatile access to many functionalized targets.[39] As a continuation of our studies dealing with the chemistry of pyridone triflates, we questioned whether substrates such as the 5-bromo substituted pyridone triflate **25** could also undergo C−C bond formation in a sequential manner and thereby provide access to a variety of aryl and acetylenic pyridones. We discovered that when **25** was treated with an excess of the organometallic coupling partner in the presence of a Pd(0) catalyst, the bis-substituted pyridones **36** and **38** were formed in good yield. We expected that pyridone **25** might exhibit regioselectivity in its reactions with coupling partners and that the triflate portion of the molecule would be more reactive than the bromide toward cross-coupling. It was anticipated that **25** would react with 1 equiv of an organometallic agent to first give a 3-substituted 5-bromo pyridone (i.e., **37** or **39**) as the major product of the reaction. Indeed, a single bromo substituted pyridone (i.e., **37** or **39**) was produced when 1 equiv of the organometallic reagent was used or when the coupling reaction was carried out for shorter periods of time (Scheme 7). Further reaction of **37** (or **39**) with an additional equivalent of the organometallic species gave the 3,5-bispyridone **36** (or **38**) in high yield. Conversion of **25** into the 5-bromo substituted pyridone **40** could also be achieved via a palladium(0)-catalyzed formate reduction in 86% yield.

Application of the Method Toward the Synthesis of Indolizidine Alkaloids. Given the success in forming a variety of substituted 5,6-fused pyridones from the [3 + 2]-cycloaddition of phenylsulfonyl substituted isomünchnones, it seemed to us that this approach could well prove to be adaptable to the synthesis of a host of indolizidine alkaloids. The indolizidine skeleton comprises the backbone of a number of biologically and

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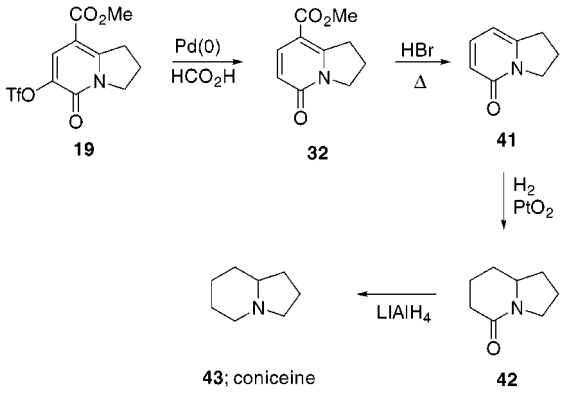
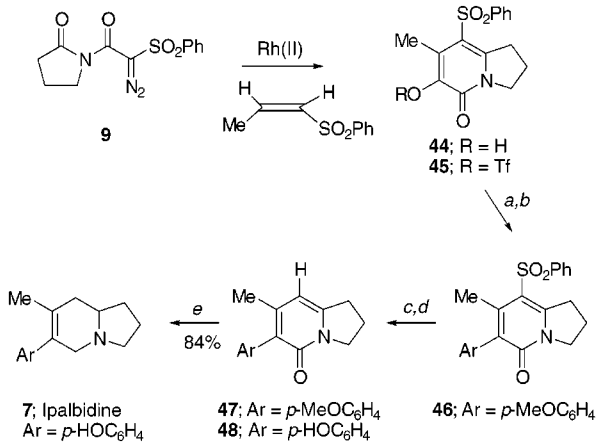
(39) For some examples of sequential cross-coupling, see: Moniatte, M.; Eckhardt, M.; Brickmann, K.; Bruckner, R.; Suffert, J. *Tetrahedron Lett.* **1994**, *35*, 1965. Chan, H. W.; Chan, P. C.; Liu, J. H.; Wong, H. M. C. *J. Chem. Soc., Chem. Commun.* **1997**, 1515.

Scheme 8



Scheme 9[a]

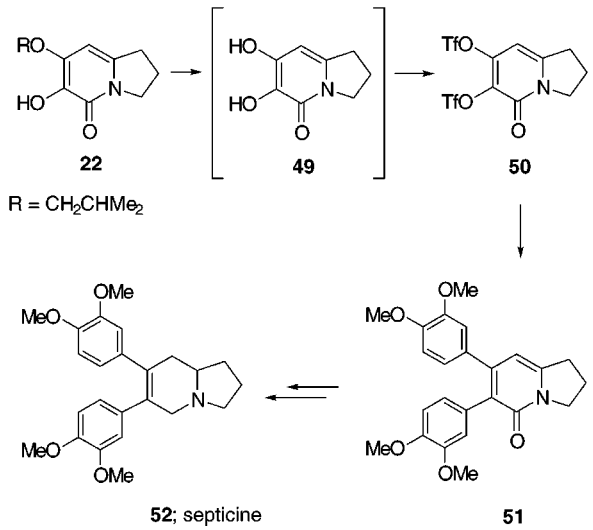


[a] Reagents: (a) $(TfO)_2NPh$, NEt_3; (b) $MeOC_6H_4SnBu_3$, $Pd(PPh_3)_4$, LiCl; (c) Ra-Ni, EtOH (65 °C); (d) 48% HBr, reflux; and (e) $LiAlH_4$, $AlCl_3$.

structurally interesting molecules isolated from diverse natural sources.[40] *δ*-Coniceine (**43**) was chosen as our initial target because its rather trivial structure[41] would allow us to easily test the basic principles of our method. The starting material for the synthesis of **43** was triflate **19**, which on Pd(0)-formate reduction gave pyridone **32** in 85% yield. After a sample of **32** was heated with 48% HBr at 135 °C, the decarboxylated pyridone **41** was formed in 96% yield. This compound was then catalytically hydrogenated to **42** (89%), which was further reduced with LAH to give *δ*-coniceine (**43**) (80%), comparable to authentic material (Scheme 8).[42]

The successful synthesis of *δ*-coniceine by the isomünchnone route prompted us to use a similar methodology for the preparation of (±)-ipalbidine (**7**).[43] A short synthesis of this alkaloid was carried out as depicted in Scheme 9. Reaction of α-diazoimide **9** with *cis*-1-(phenylsulfonyl)-1-propene and a catalytic quantity of Rh_2OAc_4 in benzene at 80 °C provided the expected 3-hydroxy-2(1*H*)-pyridone **44** in 51% isolated yield. Conversion of **44** to the corresponding vinyl triflate **45** (86%), followed by Stille coupling with tributyl(4-methoxyphenyl)tin,[44] gave the aryl substituted 2-pyridone **46** in 72% yield. Desulfonylation of **46** was effected using Raney nickel to give pyridone **47** in 90% yield. Heating a sample of **47** in 48% HBr afforded phenol **48** in 97% yield. Reduction of **48** with alane ($LiAlH_4$, $AlCl_3$) gave (±)-ipalbidine **7** in eight steps in 17% overall yield.

Scheme 10



The indolizidine alkaloid septicine (**52**) has been isolated from *Ficus septica*, a plant belonging to the Moraceae family, and is considered to be a biogenetic precursor to the phenanthroizidine alkaloid, tylophorine.[45,46] Our approach to this indolizidine alkaloid called for the preparation of bistriflate **50** followed by its sequential cross-coupling with the appropriate organometallic reagent. Pyridone **22**, prepared from the Rh(II)-catalyzed reaction of diazoimide **9** with isobutyl vinyl ether (see Scheme 4), was treated with BBr_3 to cleave the ether bond. The transient diol **49** was allowed to react with *N*-phenyl trifluoromethanesulfonamide in the presence of triethylamine to give the bistriflate **50** in 68% yield as a crystalline solid. The Pd(0)-catalyzed aryl zinc coupling of **50** provided the diaryl-substituted pyridone **51** in 64% yield (Scheme 10). The above sequence constitutes a formal synthesis of (±)-septicine (**52**), based on the successful reduction of **51** to **52** by Moore and coworkers.[47]

(40) Howard, A. S.; Michael, J. P. In *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, Chapter 3, pp 235−246.

(41) Pizzorno, M. T.; Albonico, S. M. *J. Org. Chem.* **1977**, *42*, 909. Stevens, R. V.; Luh, Y.; Sheu, J. T. *Tetrahedron Lett.* **1976**, 3799. Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387.

(42) Takahata, H.; Takamatsu, T.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 4812.

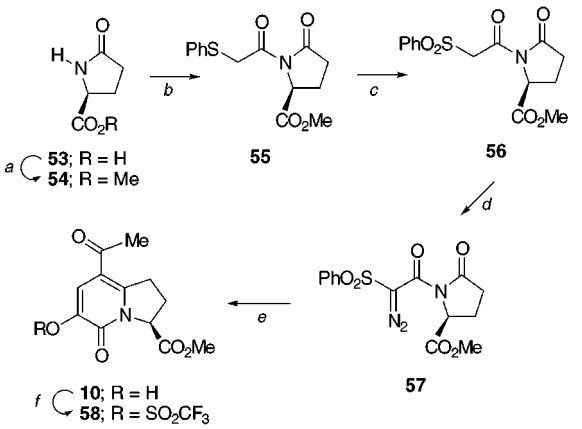
(43) For some alternate syntheses of (±)-ipalbidine, see: Danishefsky, S. J.; Vogel, C. *J. Org. Chem.* **1986**, *51*, 3915. Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 261. Cragg, J. E.; Hedges, S. H.; Herbert, R. B. *Tetrahedron Lett.* **1981**, *22*, 2127. Howard, A. S.; Gerrans, G. C.; Michnel, J. P. *J. Org. Chem.* **1980**, *45*, 1713. Hedges, S. H.; Herbert, R. B. *J. Chem. Res., Synop.* **1979**, *1*, 413. Stevens, R. V.; Luh, Y. *Tetrahedron Lett.* **1977**, 979. Govindachari, T. R.; Sidhaye, A. R.; Viswanathan, N. *Tetrahedron* **1970**, 26, 3829.

(44) Stille, J. K.; Echavarren, A. M.; Williams, R. M.; Hendrix, J. A. *Organic Synthesis*; Overman, L. E., Ed.; Wiley and Sons: New York, 1993; Vol. 71, p 97.

(45) Gellert, E. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley & Sons: New York, 1987; Vol. 5, p 55. Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1985; Vol. 25, Chapter 1, pp 3−355.

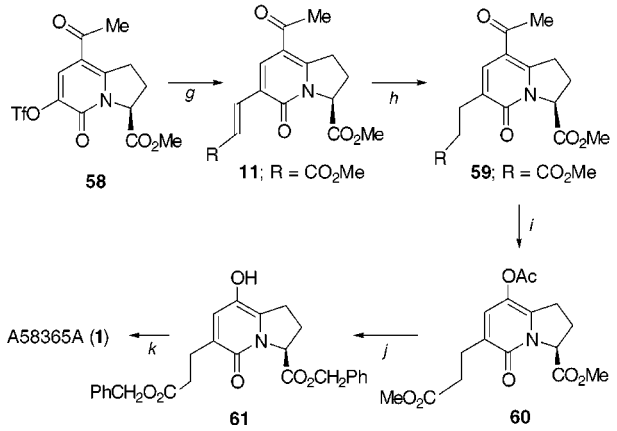
(46) Syntheses of (±)-septicine: Govindachari, T. R.; Viswanathan, N. *Tetrahedron* **1970**, *26*, 715. Iwashita, T.; Suzuki, M.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1980**, 383. Cragg, J. E.; Herbert, R. B.; Jackson, F. B.; Moody, C. J.; Nicolson, I. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2477. Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412. Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919. Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435. Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082.

Scheme 11[a]



[a] Reagents: (a) MeOH, Dowex; (b) $PhSCH_2COCl$ (**9**), benzene, 80 °C; (c) Oxone, MeOH, 25 °C; (d) *p*-$CH_3CONHC_6H_4SO_2N_3$, NEt_3; (e) $Rh_2(OAc)_4$, CH_2=$CHCOCH_3$, benzene, 80 °C; and (f) $(TfO)_2NPh$, NEt_3, 25 °C.

Scheme 12[a]



[a] Reagents: (g) CH_2=$CHCO_2Me$, $Pd(PPh_3)_2Cl_2$, NEt_3; (h) H_2, Pd/C, $CHCl_3$; (i) H_2O_2, CF_3CO_2H, 25 °C; (j) $PhCH_2OH$, toluene, Otera's catalyst, 120 °C; and (k) H_2, Pd/C, MeOH.

We also applied the above method to the synthesis of the ACE inhibitor (−)-A58365A (**1**). The four-step conversion of commercially available L-pyroglutamic acid **53** to the isomünchnone precursor **57** was carried out using conventional chemistry. Esterification of **53** with methanol in the presence of Dowex ion-exchange resin gave methyl ester **54** in 98% yield. Treatment of **54** with (phenylthio)acetyl chloride in benzene afforded 5-oxo-1-(2-phenylthioacetyl)-pyrrolidine-2-carboxylate (**55**) in 87% yield. Oxidation of **55** with Oxone furnished sulfone **56** (67%), which was converted to diazoimide **57** using established diazotization procedures[29] in 91% yield. Reaction of **57** with methyl vinyl ketone and a catalytic quantity of $Rh_2(OAc)_4$ in benzene at 80 °C provided the expected 3-hydroxy-2(1*H*)-pyridone **10** in 86% isolated yield (Scheme 11). The hydroxy-substituted pyridone **10** was easily converted to the corresponding triflate **58** (94%) by treatment with *N*-phenyl trifluoromethanesulfonamide and triethylamine.[31] A Heck reaction of **58** with methyl acrylate in the presence of $Pd(PPh_3)Cl_2$ at 25 °C in acetonitrile gave the prop-2-enoate derivative **11** in 86% yield (Scheme 12). Catalytic hydrogenation of **11** proceeded in quantitative yield to afford pyridone **59**. The next step involved the trifluoroperacetic acid induced Baeyer−Villiger oxidation of **59** to give acetate **60** in 96% yield. Compound **60** underwent transesterification and acetate cleavage to produce the dibenzyl ester **61** (98%, $[\alpha]^{25}_D$ −146 °, (CH_2Cl_2, *c* 0.39)) when subjected to heating with Otera's catalyst in the presence of benzyl alcohol/toluene.[48] Catalytic hydrogenation (Pd/C) of **61** in methanol has already been reported to give A58365A (**1**) in 96% yield.[28] Thus, the formal synthesis of **1** in 11 steps in 32.6% overall yield starting from L-pyroglutamic acid has been achieved. This synthesis further underscores the flexibility provided by the [3 + 2]-cycloaddition reaction of phenylsulfonyl isomünchnones.

In summary, we have shown that a range of highly substituted 2(1*H*)-pyridones can be rapidly and convergently assembled using the (i) [3 + 2]-cycloaddition of phenylsulfonyl-substituted isomünchnone intermediates and (ii) conversion of the resulting 3-hydroxy-2(1*H*)-pyridones into the corresponding triflates, which function as suitable substrates in various types of palladium-catalyzed cross-coupling reactions. This methodology allows the synthesis of highly substituted pyridones, which would be difficult to obtain through other methods. Further utilization of this sequence for the stereocontrolled synthesis of several indolizidine alkaloids is under current investigation.

Experimental Section

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 argon. 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. All solids were recrystallized from ethyl acetate/hexane for analytical data.

1-(Phenylsulfonylacetyl)pyrrolidin-2-one. To a solution containing 4.2 g (21 mmol) of phenylsulfonyl acetic acid in 20 mL of benzene was added 5.5 mL (63 mmol) of oxalyl chloride that contained 2 drops of DMF. The solution was allowed to stir for 2 h at 25 °C, and the excess oxalyl chloride was removed under reduced pressure. The crude acid chloride was taken up in 10 mL of benzene and was cannulated into a solution containing 1.3 mL (17 mmol) of 2-pyrrolidinone in 5 mL of benzene. The mixture was heated at reflux for 8 h, concentrated under reduced pressure, taken up in CH_2Cl_2, washed once with a saturated $NaHCO_3$ solution, and then with brine. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 4.3 g (91%) of 1-(phenylsulfonylacetyl)pyrrolidin-2-one as a white solid: mp 99−100 °C; IR (CH_2Cl_2) 1737, 1695, and 1332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (m, 2H), 2.58 (t, 2H, J = 7.5 Hz), 3.82 (t, 2H, J = 7.5 Hz), 4.25 (s, 2H), 7.20−7.31 (m, 3H), and 7.42−7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 32.6, 45.1, 60.1, 127.8, 128.6, 133.6, 138.8, 161.0, and 175.0. Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 54.04; H, 4.91; N, 5.23.

1-(Phenylsulfonyldiazoacetyl)pyrrolidin-2-one (9). To a solution of 5.3 g (20 mmol) of the above imide in 20 mL of acetonitrile at 0 °C was added 6.7 mL (48 mmol) of triethylamine. The solution was allowed to stir at 0 °C for 20 min, after which time 5.7 g (24 mmol) of *p*-acetamidophenylsulfonyl azide[30] was added in one portion. The solution was allowed to warm to 25 °C and was stirred at room temperature for 14 h. The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2. The solution was filtered, and the mother liquor was concentrated to dryness under reduced

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pressure. The residue was subjected to flash silica gel chromatography to give 5.0 g (85%) of **9** as a yellow solid: mp 124−125 °C; IR (CH_2Cl_2) 2128, 1740, and 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (m, 2H), 2.54 (t, 2H, J = 7.5 Hz), 3.73 (t, 2H, J = 7.5 Hz), 7.51−7.62 (m, 3H), and 8.04−8.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 32.7, 46.2, 128.2, 129.0, 133.9, 141.5, 157.6, 174.2. Anal. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.78; N, 14.34. Found: C, 49.07; H, 3.61; N, 14.19.

2-Phenyl-4-triisopropylsilanyloxy-7,8-dihydro-6*H*-2,5*a*-diaza-*as*-indacene-1,3,5-trione (13). A solution containing 0.1 g (0.3 mmol) of diazoimide **9**, 0.09 g (0.5 mmol) of *N*-phenylmaleimide, and 2 mg of rhodium(II) acetate in 5 mL of benzene was heated at reflux for 12 h. The solvent was removed under reduced pressure, and the brown residue was dissolved in 5 mL of CH_2Cl_2. To this mixture was added 0.2 mL (0.7 mmol) of triisopropylsilyl chloride, the solution was cooled to 0 °C, and 0.1 mL (0.7 mmol) of triethylamine was added. The reaction mixture was stirred at 25 °C for 1 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.13 g (87%) of **13** as a clear oil: IR (neat) 1715, 1669, 1645, and 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, 18H, J = 7.5 Hz), 1.42−1.49 (m, 3H), 2.32−2.38 (m, 2H), 3.44 (t, 2H, J = 7.8 Hz), 4.18 (t, 2H, J = 7.5 Hz), and 7.35−7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.0, 21.8, 29.9, 49.1, 102.6, 118.4, 126.1, 127.9, 128.1, 129.0, 129.1, 131.8, 134.2, 142.9, 148.0, and 160.0; HRMS calcd for $C_{25}H_{32}N_2O_4$ 424.2362, found 424.2358.

5-Oxo-8-(phenylsulfonyl)-1,2,3-trihydroindolizin-6-yl Acetate (15). A solution of 0.9 g (3.1 mmol) of diazoimide **9**, 0.7 g (4.0 mmol) of phenyl vinyl sulfone, and 2 mg of rhodium(II) acetate in 30 mL of benzene was heated at reflux for 14 h. The mixture was cooled, and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.57 g (63%) of 8-phenylsulfonyl-6-hydroxy-2,3-dihydro-1*H*-indolizin-5-one (**14**) as a labile oil, which was immediately used in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 2.20−2.28 (m, 2H), 3.44 (t, 2H, J = 7.8 Hz), 4.15 (t, 2H, J = 7.5), 6.40 (s, 1H), 7.27 (s, 1H), 7.54−7.61 (m, 3H), 7.87 (s, 1H), and 7.90 (s, 1H).

To a solution of 0.1 g (0.3 mmol) of pyridone **14** and 0.1 mL (1.0 mmol) of acetic anhydride in 3 mL of CH_2Cl_2 at 0 °C was added 0.05 mL (0.4 mmol) of triethylamine. The mixture was stirred at room temperature for 2 h and concentrated under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give 0.11 g (96%) of **15** as a white crystalline solid: mp 166−167 °C; IR (CH_2Cl_2) 1773, 1666, and 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19−2.30 (m, 2H), 2.33 (s, 3H), 3.43 (t, 2H, J = 7.8 Hz), 4.15 (t, 2H, J = 7.8 Hz), 7.50−7.65 (m, 4H), 7.86 (s, 1H), and 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 21.0, 32.3, 49.7, 114.1, 127.0, 127.7, 129.5, 133.5, 138.9, 141.5, 152.0, 156.1, 168.1. Anal. Calcd for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20. Found: C, 57.59; H, 4.57; N, 4.13.

8-Phenylsulfonyl-6-methoxy-2,3-dihydro-1*H*-indolizin-5-one (16). To a solution of 0.4 g (1.4 mmol) of pyridone **14** in 3 mL of dimethyl sulfate at room temperature was added a 20% solution of KOH in methanol until the solution remained basic. The mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.3 g (73%) of **16** as a white crystalline solid: mp 167−168 °C; IR (CH_2Cl_2) 1652, 1405, 1250, and 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12−2.25 (m, 2H), 3.37 (t, 2H, J = 7.8 Hz), 3.87 (s, 3H), 4.14 (t, 2H, J = 7.5 Hz), 7.09 (s, 1H), 7.52−7.62 (m, 3H), 7.86 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 31.5, 49.2, 56.3, 110.4, 113.8, 126.6, 128.0, 133.1, 141.5, 145.4, 147.3, and 156.6. Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 59.07; H, 4.90; N, 4.51.

Trifluoromethanesulfonic Acid 8-Phenylsulfonyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl Ester (17). To a solution containing 0.1 g (0.3 mmol) of **14** in 2 mL of CH_2Cl_2 at 0 °C was added 0.05 mL of triethylamine. The mixture was allowed to stir for 20 min, after which time 0.1 g (0.3 mmol) of *N*-phenyl trifluoromethanesulfonamide was added in one portion. The reaction mixture was allowed to warm to room temperature, stirred for an additional 6 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.1 g (70%) of **17** as a white solid: mp 196−197 °C; IR (CH_2Cl_2) 1674, 1424, 1211, and 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25−2.37 (m, 2H), 3.47 (t, 2H, J = 7.9 Hz), 4.21 (t, 2H, J = 7.5 Hz), 7.56−7.69 (m, 3H), and 7.86−7.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 32.6, 50.2, 114.0, 118.5 [q, $^1J(^{13}C-^{19}F)$ = 320 Hz], 127.0, 129.5, 129.7, 133.9, 137.1, 140.9, 154.9, and 155.2. Anal. Calcd for $C_{15}H_{12}F_3NO_6S_2$: C, 42.55; H, 2.86; N, 3.31. Found: C, 42.60; H, 2.89; N, 3.27.

6-Hydroxy-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylic Acid Methyl Ester (18). A solution containing 1.0 g (3.4 mmol) of diazoimide **9**, 1.5 mL (17 mmol) of methyl acrylate, and 2 mg of rhodium(II) acetate in 35 mL of benzene was heated at reflux for 14 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.61 g (86%) of **18** as a white solid: mp 194−195 °C; IR (neat) 1713, 1640, 1609, and 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.22−2.30 (m, 2H), 3.48 (t, 2H, J = 7.8 Hz), 3.85 (s, 3H), 4.21 (t, 2H, J = 7.5 Hz), 6.40 (brs, 1H), and 7.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 32.7, 49.1, 51.8, 105.7, 115.0, 143.7, 146.9, and 165.3. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.40; H, 5.30; N, 6.70. Found: C, 57.51; H, 5.28; N, 6.74.

Methyl 5-Oxo-6-((trifluoromethyl)sulfonyloxy)-1,2,3-trihydroindolizine-8-carboxylate (19). To a solution containing 2.0 g (9.5 mmol) of pyridone **18** in 20 mL of CH_2Cl_2 at 0 °C was slowly added 2.6 mL (19 mmol) of triethylamine. The mixture was allowed to stir for 20 min at 0 °C, after which time 5.1 g (14 mmol) of *N*-phenyl trifluoromethanesulfonamide was added in one portion. The mixture was stirred at room temperature for 6 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 3.2 g (98%) of **19** as a white solid: mp 102−103 °C; IR (CH_2Cl_2) 1715, 1669, 1645, and 1353 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26−2.37 (m, 2H), 3.60 (t, 2H, J = 7.9 Hz), 3.88 (s, 3H), 4.26 (t, 2H, J = 7.6 Hz), and 7.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 33.7, 49.9, 52.1, 103.4, 118.6 [q, $^1J(^{13}C-^{19}F)$ = 320 Hz], 131.1, 136.6, 155.7, 157.5, and 163.8. Anal. Calcd for $C_{11}H_{10}F_3NO_6S$: C, 38.71; H, 2.96; N, 4.11. Found: C, 38.56; H, 2.97; N, 4.21.

8-Acetyl-6-hydroxy-2,3-dihydro-1*H*-indolizin-5-one (20). A solution containing 1.0 g (3.4 mmol) of diazoimide **9**, 1.0 mL (12 mmol) of methyl vinyl ketone, and 2 mg of rhodium(II) acetate in 30 mL of benzene was heated at reflux for 5 h. The solvent was removed under reduced pressure, and the crude residue was taken up in ethyl acetate and filtered to give 0.34 g (52%) of **20** as a clear oil: IR (neat) 1677, 1619, and 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (pent, 2H, J = 7.6 Hz), 2.48 (s, 3H), 3.48 (t, 2H, J = 7.6 Hz), 4.03 (brs, 1H), 4.19 (t, 2H, J = 7.6 Hz), and 7.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 28.0, 33.1, 48.9, 113.5, 116.1, 143.7, 147.0, 157.8, and 196.2. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.26; H, 5.83; N, 7.19.

Trifluoromethanesulfonic Acid 8-Acetyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl Ester (21). To a solution containing 0.26 g (1.4 mmol) of pyridone **20** and 0.7 g (2.0 mmol) of *N*-phenyl trifluoromethanesulfonamide in 10 mL of CH_2Cl_2 at 0 °C was slowly added 0.3 mL (2.0 mmol) of triethylamine. The mixture was stirred at room temperature for 16 h, the solvent was removed under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give 0.4 g (85%) of **21** as a white solid: mp 129−131 °C; IR (Nujol) 1695, 1661, and 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (tt, 2H, J = 8.0 and 7.6 Hz), 2.48 (s, 3H), 3.61 (t, 2H, J

= 8.0 Hz), 4.25 (t, 2H, J = 7.6 Hz), and 7.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 28.1, 34.5, 49.9, 111.4, 118.8 [q, $^1J(^{13}C-^{19}F)$ = 320 Hz], 131.2, 136.5, 155.6, 157.5, and 193.5. Anal. Calcd for $C_{11}H_{10}F_3NO_5S$: C, 40.62; H, 3.10; N, 4.31. Found: C, 40.65; H, 3.15; N, 4.24.

6-Hydroxy-7-(2-methylpropoxy)-2,3-dihydro-1*H*-indolizin-5-one (22). A solution containing 3.0 g (10.2 mmol) of diazoimide **9**, 4.2 g (41 mmol) of isobutyl vinyl ether, and 2 mg of rhodium(II) acetate in 60 mL of benzene was heated at reflux for 20 h. The solvent was removed under reduced pressure, and the crude residue was taken up in CH_2Cl_2 and filtered to give 0.8 g (34%) of **22**. The filtrate was concentrated and subjected to flash silica gel chromatography to give an additional 0.7 g (30%) of **22** as a white solid: mp 167−168 °C; IR (KBr) 1661, 1584, and 1551 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, 6H, J = 6.8 Hz), 2.05−2.15 (m, 1H), 2.17−2.24 (m, 2H), 3.02 (t, 2H, J = 7.6 Hz), 3.86 (d, 2H, J = 6.8 Hz), 4.15 (t, 2H, J = 7.6), 6.03 (s, 1H), and 6.19 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 22.3, 28.6, 31.2, 48.7, 76.2, 93.9, 130.6, 139.5, 149.0, and 157.8. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.37; H, 7.79; N, 6.12.

6-Hydroxy-1,2,3-trihydroindolizin-5-one (23). A solution containing 0.6 g (2.9 mmol) of pyridone **18** in 5 mL of a 48% HBr solution was heated at 135 °C for 12 h. The mixture was concentrated to dryness under reduced pressure, and the resulting residue was taken up in $CHCl_3$ and washed with water. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.4 g (91%) of **23** as a white solid: mp 168−169 °C; IR (CH_2Cl_2) 3400, 1643, and 1584 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19−2.28 (m, 2H), 3.03 (t, 2H, J = 7.5 Hz), 4.18 (t, 2H, J = 7.5 Hz), 6.08 (d, 1H, J = 7.5 Hz), and 6.83 (d, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 30.6, 48.6, 101.1, 115.6, 139.1, 144.6, and 157.3. Anal. Calcd for $C_8H_9NO_2$: C, 63.55; H, 6.00; N, 9.27. Found: C, 63.64; H, 5.94; N, 9.25.

7-(Piperidylmethyl)-6-((trifluromethyl)sulfonyloxy)-1,2,3-trihydroindolizin-5-one (24). To a solution containing 1 mL (13 mmol) of 37% formaldehyde in 2 mL of ethanol at 0 °C was added 1.6 mL (16 mmol) of piperidine. The solution was stirred at room temperature for 1.5 h and slowly added to a solution of 0.2 g (1.3 mmol) of pyridone **23** in 5 mL of ethanol. The mixture was allowed to stir at room temperature for 1 h, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed once with a saturated $NaHCO_3$ solution and again with brine. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford 0.3 g of a brown foam, which was taken up in 8 mL of CH_2Cl_2 and cooled to 0 °C. To this solution was added 0.25 mL (1.8 mmol) of triethylamine followed by 0.65 g (1.8 mmol) of *N*-phenyl trifluoromethanesulfonamide. The mixture was stirred at room temperature for 18 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.31 g (63%) of **24** as a white solid: mp 94−95 °C; IR (CH_2Cl_2) 1673, 1616, and 1417 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (brs, 2H) 1.59−1.66 (m, 4H) 2.13−2.19 (m, 2H), 2.49 (brs, 4H), 2.97 (t, 2H, J = 7.8 Hz), 3.48 (s, 2H), 4.15 (t, 2H, J = 7.2 Hz), and 5.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.9, 25.9, 31.6, 49.3, 54.7, 56.4, 100.3, 117.0, 118.6 [q, $^1J(^{13}C-^{19}F)$ = 320 Hz], 120.2, 135.7, 144.3, 149.0, and 155.5. Anal. Calcd for $C_{15}H_{19}F_3N_2O_4S$: C, 47.36; H, 5.04; N, 7.37; Found: C, 47.50; H, 5.11; N, 7.28.

8-Bromo-6-((trifluoromethyl)sulfonyloxy)-1,2,3-trihydroindolizin-5-one (25). To a solution containing 1.4 g (9.2 mmol) of pyridone **23** in 30 mL of glacial acetic acid was added 0.6 mL (11 mmol) of bromine. The solution was stirred at room temperature for 1 h, diluted with water, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was taken up in 30 mL of CH_2Cl_2 and cooled to 0 °C. To this solution was added 1.8 mL (13 mmol) of triethylamine. The mixture was allowed to stir for 20 min, after which time 4.6 g (13 mmol) of *N*-phenyl trifluoromethanesulfonamide was added in one portion. The mixture was allowed to warm to room temperature, stirred for an additional 6 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 2.4 g (71%) of **25** as a white solid: mp 104−105 °C; IR (CH_2Cl_2) 1656, 1455, and 1200 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30−2.36 (m, 2H), 3.16 (t, 2H, J = 7.6 Hz), 4.32 (t, 2H, J = 7.4 Hz), and 7.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 33.4, 51.2, 90.4, 118.6 [q, $^1J(^{13}C-^{19}F)$ = 319 Hz], 134.2, 137.8, 149.9, and 154.7. Anal. Calcd for $C_9H_7F_3NO_4S$: C, 29.92; H, 1.95; N, 3.88. Found: C, 30.02; H, 1.98; N, 3.83.

8-Phenylsulfonyl-6-phenyl-2,3-dihydro-1*H*-indolizin-5-one (26). To a solution containing 0.5 g (1.2 mmol) of triflate **17** in 10 mL of THF was added 0.5 mL (1.5 mmol) of tributylphenyltin. The solution was cannulated into a flask that contained 0.03 g of $Pd(PPh_3)_4$ and 0.15 g of LiCl (3.6 mmol) in 10 mL of THF. The mixture was heated at reflux for 17 h, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography. The major fraction isolated was taken up in 10 mL of CH_2Cl_2, poured into a saturated KF solution, and allowed to stir at room temperature for 5 h. The organic phase was separated, filtered through a pad of Celite, and concentrated under reduced pressure to give 0.34 g (86%) of **26** as a white solid: mp 195−196 °C; IR (CH_2Cl_2) 1648, 1548, and 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21−2.30 (m, 2H), 3.50 (t, 2H, J = 7.8 Hz), 4.19 (t, 2H, J = 7.5 Hz), 7.35−7.44 (m, 3H), 7.51−7.61 (m, 3H), 7.67−7.70 (m, 2H), 7.89 (s, 1H), 7.92 (s, 1H), and 7.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 32.7, 49.8, 115.7, 126.9, 128.2, 128.3, 128.4, 129.1, 129.4, 133.3, 135.1, 135.6, 141.9, 153.5, and 160.2. Anal. Calcd for $C_{20}H_{17}NO_3S$: C, 68.36; H, 4.88; N, 3.99. Found: C, 68.20; H, 4.87; N, 3.95.

6-Phenyl-1,2,3-trihydroindolizin-5-one (27). To a solution containing 0.2 g (0.6 mmol) of pyridone **26** in 6 mL of ethanol was added an excess of Raney nickel. The mixture was heated at reflux for 5 h, cooled to room temperature, filtered through a pad of Celite, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.12 g (97%) of **27** as a white solid: mp 133−134 °C; IR (CH_2Cl_2) 1642, 1584, and 1445 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18−2.32 (m, 2H), 3.13 (t, 2H, J = 7.5 Hz), 4.22 (t, 2H, J = 7.4 Hz), 6.21 (d, 1H, J = 7.2 Hz), 7.30 (d, 1H, J = 7.2 Hz), 7.36−7.41 (m, 2H), 7.49 (d, 1H, J = 6.9 Hz), and 7.69−7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 31.8, 49.1, 101.2, 127.2, 128.0, 128.1, 128.5, 136.9, 138.3, 149.6, and 160.7. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.38; H, 6.26; N, 6.54.

8-Phenylsulfonyl-2,3-dihydro-1*H*-indolizin-5-one (28). To a solution containing 0.15 g (0.3 mmol) of triflate **17** in 2 mL of DMF was added 0.1 mL (0.9 mmol) of triethylamine and 5 mg of $Pd(OAc)_2(PPh_3)_2$. To this mixture was added 24 μL (0.6 mmol) of 96% formic acid. The solution was stirred at 60 °C for 1 h, cooled to 0 °C, quenched with water, and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.08 g (92%) of **28** as a colorless solid: mp 174−175 °C; IR (CH_2Cl_2) 1660, 1320, and 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (m, 2H), 3.41 (t, 2H, J = 7.8 Hz), 4.07 (t, 2H, J = 7.5 Hz), 6.44 (d, 1H, J = 9.6 Hz), 7.52−7.63 (m, 3H), and 7.81−7.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 32.7, 49.3, 115.6, 117.6, 126.9, 129.4, 133.3, 138.2, 141.7, 155.0, and 161.2. Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 61.07; H, 4.78; N, 5.06.

8-Phenylsulfonyl-6-vinyl-2,3-dihydro-1*H*-indolizin-5-one (29). To a solution containing 0.2 g (0.4 mmol) of triflate

17 in 10 mL of THF was added 0.1 mL (0.5 mmol) of vinyltributyltin. The solution was cannulated into a flask containing 9 mg of $Pd(PPh_3)_4$ and 0.05 g of LiCl (1.2 mmol) in 10 mL of THF. The resulting mixture was heated at reflux for 17 h and cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography, and the major fraction isolated was taken up in 10 mL of CH_2Cl_2, poured into a saturated KF solution, and allowed to stir for 5 h. The organic phase was separated, filtered through a pad of Celite, and concentrated under reduced pressure to give 0.09 g (78%) of **29** as a white solid: mp 137−138 °C; IR (CH_2Cl_2) 1655, 1540, and 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.17−2.27 (m, 2H), 3.44 (t, 2H, J = 7.8 Hz), 4.15 (t, 2H, J = 7.5 Hz), 5.41 (dd, 1H, J = 11.2 and 1.0 Hz), 6.18 (dd, 1H, J = 17.7 and 1.0 Hz), 6.73 (dd, 1H, J = 11.7 and 11.3 Hz), 7.51−7.60 (m, 3H) and 7.86−7.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 32.5, 49.5, 115.5, 118.2, 126.0, 126.9, 129.4, 130.6, 133.3, 133.8, 141.8, 152.8, and 160.1. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.88; H, 5.09; N, 4.61.

8-Phenylsulfonyl-6-trimethylsilanylethynyl-2,3-dihydro-1*H*-indolizin-5-one (30). To a solution containing 0.08 g (0.03 mmol) of triphenyl phosphine in 6 mL of triethylamine was added 8 mg of CuI followed by 6 mg of $PdCl_2(PPh_3)_2$. To this solution was added 0.1 mL (0.8 mmol) of (trimethylsilyl)-acetylene in 6 mL of toluene followed by the addition of 0.2 g (0.4 mmol) of triflate **17** in one portion. The mixture was heated at 115 °C for 1 h, cooled to room temperature, poured into ice water, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.14 g (91%) of **30** as a light yellow oil: IR (neat) 1663, 1581, 1543, and 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 2.16−2.27 (m, 2H), 3.44 (t, 2H, J = 7.9 Hz), 4.13 (t, 2H, J = 7.5 Hz), 7.53−7.63 (m, 3H), 7.86−7.89 (m, 2H), and 8.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.19, 20.4, 32.9, 49.9, 98.4, 101.4, 113.5, 115.7, 127.0, 129.5, 133.5, 141.4, 154.6, and 160.1; HRMS calcd for $C_{19}H_{21}NO_3SSi$: 371.1012, found 371.1011.

Methyl-5-oxo-6-phenyl-1,2,3-trihydroindolizine-8-carboxylate (31). To a solution containing 0.6 g (1.7 mmol) of triflate **19** in 8 mL of THF was added 0.7 mL (2.3 mmol) of tributylphenyltin. The solution was cannulated into a flask containing 0.06 g of $Pd(PPh_3)_4$ and 0.2 g of LiCl (2.7 mmol) in 8 mL of THF. The mixture was heated at reflux for 17 h, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography. The major fraction isolated was taken up in 10 mL of CH_2Cl_2, poured into a saturated KF solution, and allowed to stir at room temperature for 5 h. The organic phase was separated, filtered through a pad of Celite, and concentrated under reduced pressure to give 0.39 g (81%) of **31** as a white crystalline solid: mp 121−122 °C; IR (CH_2Cl_2) 1715, and 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20−2.31 (m, 2H), 3.57 (t, 2H, J = 7.9 Hz), 3.86 (s, 3H), 4.23 (t, 2H, J = 7.4 Hz), 7.32−7.42 (m, 3H), 7.69−7.72 (m, 2H), and 8.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 33.8, 49.6, 51.7, 105.4, 127.6, 127.8, 128.1, 128.4, 135.8, 137.9, 156.2, 160.8, and 165.3. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.62; N, 5.20. Found: C, 71.12; H, 5.71; N, 5.09. Treatment of **31** with 48% HBr afforded **27** in 78% yield.

Methyl-5-oxo-1,2,3-trihydroindolizine-8-carboxylate (32). To a solution containing 0.3 g (0.9 mmol) of triflate **19** in 2 mL of DMF were added 0.4 mL (2.6 mmol) of triethylamine and 13 mg of $Pd(OAc)_2(PPh_3)_2$ followed by 0.07 mL (1.7 mmol) of 96% formic acid. The solution was stirred at 60 °C for 1 h, cooled to 0 °C, quenched with water, and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.17 g (85%) of **32** as a white crystalline solid: mp 136−137 °C; IR (CH_2Cl_2) 1730 and 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.13−2.21 (m, 2H), 3.47 (t, 2H, J = 7.8 Hz), 3.87 (s, 3H), 4.09 (t, 2H, J = 7.8 Hz), 6.30 (d, 1H, J = 9.6 Hz), and 7.81 (d, 1H, J = 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 33.7, 49.0, 51.6, 105.4, 116.5, 140.0, 157.4, 161.9, and 165.0. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.28; H, 5.72; N, 7.32.

Methyl 5-Oxo-6-vinyl-1,2,3-trihydroindolizine-8-carboxylate (33). To a solution containing 1.0 g (3 mmol) of triflate **19** in 15 mL of THF was added 1.1 mL (4 mmol) of vinyltributyltin. The solution was cannulated into a flask containing 0.07 g of $Pd(PPh_3)_4$ and 0.37 g of LiCl (9 mmol) in 15 mL of THF. The reaction mixture was heated at reflux for 17 h and cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography, and the major fraction isolated was taken up in 10 mL of CH_2Cl_2, poured into a saturated KF solution, and allowed to stir for 5 h. The organic phase was separated, filtered through a pad of Celite, and concentrated under reduced pressure to give 0.47 g (73%) of **33** as a white solid: mp 94−95 °C; IR (CH_2Cl_2) 1706, 1654, 1549, and 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (tt, 2H, J = 7.8 and 7.5 Hz), 3.54 (t, 2H, J = 7.8 Hz), 3.86 (s, 3H), 4.20 (t, 2H, J = 7.5 Hz), 5.35 (dd, 1H, J = 11.4 and 1.2 Hz), 6.13 (dd, 1H, J = 17.6 and 1.2 Hz), 6.76 (dd, 1H, J = 17.6 and 11.4 Hz), and 7.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 33.7, 49.3, 51.8, 105.3, 116.8, 124.8, 131.1, 136.1, 155.6, 160.8, and 165.3. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.73; H, 5.98; N, 6.39. Found: C, 65.51; H, 5.95; N, 6.24.

Methyl 4,11-Diaza-3,5,10-trioxo-4-phenyltetracyclo-[7.7.0.0^{2,6}0^{11,15}]-hexadeca-1(9),15(16)-diene-16-carboxylate (34). To a stirred solution containing 0.2 g (0.9 mmol) of vinyl pyridone **33** in 20 mL of toluene was added 0.8 g (4.6 mmol) of *N*-phenylmaleimide. The solution was heated at reflux for 4 h, and the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.33 g (92%) of **34** as an yellow solid: mp 184−185 °C; IR (neat) 1710, 1648, 1385 and 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90−2.07 (m, 2H), 2.22−2.33 (m, 1H), 3.16−3.30 (m, 3H), 3.33−3.51 (m, 2H), 3.67−3.79 (m, 2H), 3.82−3.90 (m, 1H), 3.83 (s, 3H), 4.22 (dd, 1H, J = 5.7 and 9.0 Hz), 7.08−7.11 (m, 2H), and 7.33−7.44 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 26.6, 33.4, 37.3, 38.3, 43.1, 46.9, 51.7, 100.7, 126.6, 128.8, 129.2, 131.6 (2), 136.8, 152.7, 158.8, 167.0, 175.9, and 177.9. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.46; H, 5.31; N, 7.01.

Methyl 3-(8-(Methoxycarbonyl)-5-oxo-1,2,3-trihydroindolizin-6-yl)prop-2-enoate (35). To a solution containing 0.2 g (0.6 mmol) of triflate **19** in 2 mL of DMF were added 0.1 mL (1.0 mmol) of methyl acrylate, 7 mg of $Pd(PPh_3)Cl_2$, and 0.2 mL (1.6 mmol) of triethylamine. The solution was stirred at 80 °C for 2 h, cooled to 0 °C, quenched with water, and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.16 g (96%) of **35** as a white crystalline solid: mp 158−159 °C; IR (CH_2Cl_2) 1709, 1645, and 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.22−2.31 (m, 2H), 3.59 (t, 2H, J = 7.8 Hz), 3.79 (s, 3H), 3.87 (s, 3 H), 4.23 (t, 2H, J = 7.8 Hz), 7.11 (d, 1H, J = 15.9 Hz), 7.61 (d, 1H, J = 15.9 Hz), and 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 34.0, 49.6, 51.5, 51.9, 105.6, 120.2, 121.6, 139.5, 141.7, 158.0, 160.1, 164.7, and 168.0. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.63; H, 5.46; N, 5.05. Found: C, 60.49; H, 5.48; N, 4.99.

6,8-Bis(trimethylsilanylethynyl)-2,3-dihydro-1*H*-indolizin-5-one (36). To a solution of 0.02 g (0.08 mmol) of triphenyl phosphine in 6 mL of triethylamine was added 0.02 g of CuI followed by 15 mg of $PdCl_2(PPh_3)_2$. To this solution was added 0.3 mL (2.2 mmol) of (trimethylsilyl)acetylene in 6 mL of toluene followed by the addition of 0.2 g (0.6 mmol) of triflate **25** in one portion. The mixture was heated at 160 °C in a sealed tube for 72 h, cooled to room temperature, poured into ice water, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.11 g (61%) of **36** as a light yellow solid: mp 265−266 °C; IR (CH_2Cl_2) 1665, 1546, and 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (s,

9H), 0.21 (s, 9H), 2.18−2.24 (m, 2H), 3.20 (t, 2H, J = 8.0 Hz), 4.17 (t, 2H, J = 7.8 Hz), and 7.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.08, −0.10, 20.5, 32.4, 50.3, 97.2, 97.8, 99.3, 99.4, 99.5, 112.8, 145.7, 155.3, and 160.0. Anal. Calcd for $C_{18}H_{25}NOSi_2$: C, 66.03; H, 7.70; N, 4.28. Found: C, 66.04; H, 7.61; N, 4.22.

8-Bromo-6-trimethylsilanylethynyl-2,3-dihydro-1*H*-indolizin-5-one (37). To a solution containing 0.02 g (0.08 mmol) of triphenyl phosphine in 6 mL of triethylamine was added 0.2 g of CuI followed by 15 mg of $PdCl_2(PPh_3)_2$. To this mixture was added 0.1 mL (0.6 mmol) of (trimethylsilyl)-acetylene in 6 mL of toluene followed by the addition of 0.2 g (0.6 mmol) of triflate **25** in one portion. The reaction mixture was heated at 115 °C for 72 h, cool to room temperature, poured into ice water, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.09 g (53%) of **37** as a light yellow foam: IR (CH_2Cl_2) 1664, 1544, and 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9H), 2.11−2.28 (m, 2H), 3.13 (t, 2H, J = 7.9 Hz), 4.24 (t, 2H, J = 7.5 Hz), and 7.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.19, 20.4, 32.9, 49.9, 98.4, 99.3, 101.4, 113.5, 144.6, 154.6, and 160.1; HRMS calcd for $C_{13}H_{16}NOBrSi$: 309.0185, found 309.0181.

6,8-Bis(3,4-dimethoxyphenyl)-1,2,3-trihydroindolizine-5-one (38). To a solution of 0.3 mL (1.1 mmol) of bromoveratrole in 4 mL of THF at −78 °C was added 1.3 mL (2.2 mmol) of *tert*-butyllithium. The solution was stirred for 15 min at −78 °C, after which time 0.15 g (1.1 mmol) of zinc chloride was added, and the mixture was allowed to warm to room temperature over a period of 1 h. A 0.1 g (0.27 mmol) sample of triflate **25** and 13 mg of $Pd(PPh_3)_4$ were added, and the mixture was heated at reflux for 36 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.07 g (62%) of **38** as a clear oil: IR (CH_2Cl_2) 1630, 1502, and 1246 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 2.22−2.31 (m, 2H), 3.32 (t, 2H, J = 7.8 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.24 (t, 2H, J = 7.8 Hz), 6.85 (s, 1H), 6.93 (d, 1H, J = 8.4 Hz), 7.01 (s, 1H), 7.08 (s, 1H), 7.33 (m, 1H), 7.47 (s, 1H), 7.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 32.0, 49.3, 55.8, 55.9, 56.0 (2), 103.8, 110.8, 110.9, 112.9, 114.8, 121.5, 124.0, 126.1, 128.8, 132.7, 147.9, 148.3, 148.4 (2), 148.6, 150.2, and 161.8. Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.73; H, 6.19; N, 3.44. Found: C, 70.63; H, 6.08; N, 3.27.

6-(3,4-Dimethoxyphenyl)-8-bromo-1,2,3-trihydroindolizin-5-one (39). To a solution of 0.16 mL (0.06 mmol) of bromoveratrole in 4 mL of THF at −78 °C was added 0.7 mL (1.1 mmol) of *tert*-butyllithium. The solution was stirred for 15 min at −78 °C, after which time 0.15 g (1.1 mmol) of zinc chloride was added, and the mixture was allowed to warm to room temperature over a period of 1 h. A 0.1 g (0.27 mmol) sample of triflate **25** and 13 mg of $Pd(PPh_3)_4$ were added, and the reaction mixture was heated at reflux for 1 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.07 g (71%) of **39** as a white solid: mp 92−93 °C; IR (CH_2Cl_2) 1645, 1455, and 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20−2.31 (m, 2H), 3.14 (t, 2H, J = 7.8 Hz), 3.90 (s, 3H), 3.93 (s, 3H), 4.29 (t, 2H, J = 7.8 Hz), 6.82 (d, 1H, J = 8.4 Hz), 7.19−7.22 (m, 1H), 7.43 (d, 1H, J = 2.1 Hz), 7.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 33.1, 50.6, 55.9, 94.1, 110.8, 111.7, 120.8, 128.4, 129.6, 139.8, 147.3, 148.3, 148.8, 159.7. Anal. Calcd for $C_{16}H_{16}NO_3Br$: C, 55.01; H, 4.62; N, 4.01. Found: C, 55.12; H, 4.58; N, 3.94.

8-Bromo-1,2,3-trihydroindolizin-5-one (40). To a solution containing 0.1 g (0.3 mmol) of triflate **25** in 2 mL of DMF were added 0.1 mL (0.8 mmol) of triethylamine and 4 mg of $Pd(PPh_3)Cl_2$. To this solution was added 0.02 mL (0.6 mmol) of 96% formic acid. The mixture was stirred at 60 °C for 15 min, cooled to 0 °C, quenched with water, and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.05 g (86%) of **40** as a colorless solid: mp 154−155 °C; IR (CH_2Cl_2) 1645, 1455, and 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18−2.29 (m, 2H), 3.12 (t, 2H, J = 7.8 Hz), 4.23 (t, 2H, J = 7.5 Hz), 6.33 (d, 1H, J = 9.6 Hz), and 7.36 (d, 1H, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 33.3, 50.3, 94.0, 118,9, 142.9, 149.0, and 161.1. Anal. Calcd for C_8H_8NOBr: C, 45.07; H, 3.79; N, 6.57. Found: C, 45.12; H, 3.74; N, 6.47.

2,3-Dihydro-5(1H)-indolizinone (41). A solution of 0.15 g (0.8 mmol) of pyridone **32** in 6 mL of 48% HBr was heated at 135 °C for 12 h. The reaction mixture was taken to dryness under reduced pressure, and the resulting residue was taken up in CH_2Cl_2 and washed with water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.1 g (96%) of 2,3-dihydro-5(1*H*)-indolizinone (**41**) as a pale yellow oil:[49] IR (CH_2Cl_2) 1654, 1545, and 1149 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (m, 2H), 3.12 (t, 2H, J = 7.8 Hz), 4.17 (t, 2H, J = 7.5 Hz), 6.17 (d, 1H, J = 8.1 Hz), 6.43 (d, 1H, J = 8.5 Hz), and 7.30−7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 32.1, 48.8, 101.2, 117.9, 140.1, 150.5, and 163.1; HRMS calcd for C_8H_9NO 135.0684, found 135.0680.

5-Oxoindolizidine (42). To a solution of 0.08 g (0.6 mmol) of pyridone **41** in 7 mL of acetic acid was added a catalytic amount of PtO_2, and the reaction mixture was stirred under a hydrogen atmosphere of 90 psi for 2 h. After filtration of the catalyst, the solution was extracted with CH_2Cl_2 and washed with water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.07 g (89%) of 5-oxoindolizidine (**42**) as a pale yellow oil:[42] IR (CH_2Cl_2) 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09−2.45 (m, 10H), 3.20−3.70 (m, 3H, J = 7.8 Hz). Anal. Calcd for $C_8H_{13}NO$: C, 69.02; H, 9.42; N, 10.07. Found: C, 68.91; H, 9.38; N, 10.04.

***δ*-Coniceine (43).** A mixture of 0.05 g (0.36 mmol) of lactam **42** and 0.03 g (0.9 mmol) of lithium aluminum hydride in 5 mL of THF was heated at reflux for 15 h. After the mixture cooled to 0 °C, water, 15% sodium hydroxide, and water were successively added. The mixture was dried and filtered through Celite. The filtrate was evaporated to give **43** (98%) as a colorless oil (picrate mp 228−231 °C, lit.[50] mp 224−228 °C).

8-Phenylsulfonyl-6-hydroxy-7-methyl-2,3-dihydro-1*H*-indolizin-5-one (44). A solution containing 1.75 g (6 mmol) of diazoamide **9**, 1.6 g (9 mmol) of *cis*-phenylsulfonyl-1-propene, and 2 mg of rhodium(II) acetate in 60 mL of benzene was heated at reflux for 12 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.9 g (51%) of **44** as a white solid: mp 234−235 °C; IR (CH_2Cl_2) 3226, 1627, 1606, and 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.22−2.32 (m, 2H), 3.76 (t, 2H, J = 7.8 Hz), 4.22 (t, 2H, J = 7.5 Hz), 6.81 (brs, 1H), 7.52−7.60 (m, 3H), 7.80 (s, 1H), and 7.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 21.3, 33.5, 49.1, 116.1, 123.4, 126.5, 129.2, 133.1, 142.4, 142.5, 145.1, 148.6, and 156.5. Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 59.00; H, 4.95; N, 4.58. Found: C, 58.94; H, 4.95; N, 4.56.

Trifluoromethanesulfonic Acid 8-Phenylsulfonyl-7-methyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl Ester (45). To a solution containing 0.6 g (1.9 mmol) of pyridone **44** in 20 mL of CH_2Cl_2 at 0 °C was added 0.7 mL (5 mmol) of triethylamine. The solution was allowed to stir at 0 °C for 20 min, at which time 1.4 g (3.9 mmol) of *N*-phenyl trifluoromethanesulfonamide was added in one portion. The mixture was allowed to warm to room temperature, stirred for 14 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel

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chromatography to give 0.74 g (86%) of **45** as a white solid: mp 185−186 °C; IR (CH_2Cl_2) 1667, 1418, 1200, and 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20−2.39 (m, 5H), 3.83 (t, 2H, J = 7.8 Hz), 4.24 (t, 2H, J = 7.5 Hz), 7.56−7.65 (m, 3H), 7.81 (s, 1H), and 7.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.6, 34.6, 49.9, 114.2, 118.7 [q, $^1J(^{13}C-^{19}F)$ = 320 Hz], 126.5, 129.5, 133.7, 136.6, 141.0, 141.8, 154.6, and 155.3. Anal. Calcd for $C_{16}H_{14}F_3NO_6S_2$: C, 43.93; H, 3.23; N, 3.20. Found: C, 43.93; H, 3.24; N, 3.16.

8-Phenylsulfonyl-6-(4-methoxyphenyl)-7-methyl-2,3-dihydro-1*H*-indolizin-5-one (46). To a solution containing 0.4 g (0.9 mmol) of triflate **45** in 8 mL of *N*-methyl pyrrolidinone was added 0.47 g (1.2 mmol) of 4-methoxyphenyl tributyltin. The solution was cannulated into a flask containing 0.03 g of $Pd(PPh_3)_4$ and 0.11 g of LiCl (2.7 mmol) in 8 mL of *N*-methyl pyrrolidinone. The resulting mixture was heated at 150 °C for 2 h, cooled to room temperature, quenched with water, and extracted with ether. The combined organic extracts were poured into a saturated KF solution and allowed to stir for 5 h at room temperature. The organic phase was separated, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.26 g (72%) of **46** as a white crystalline solid: mp 182−183 °C; IR (CH_2Cl_2) 1644, 1526, and 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.23−2.30 (m, 2H), 3.81 (s, 3H), 3.87 (t, 2H, J = 7.8 Hz), 4.22 (t, 2H, J = 7.5 Hz), 6.90 (d, 2H, J = 8.7 Hz) 7.03 (d, 2H, J = 8.7 Hz), 7.50−7.62 (m, 3H), 7.83 (s, 1H), and 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 20.5, 34.7, 49.5, 55.1, 113.7, 115.2, 126.2, 126.3, 128.2, 128.4, 129.0, 129.1, 131.0, 131.7, 131.8, 131.9, 132.9, 142.7, 145.0, 154.5, 158.8, and 160.4. Anal. Calcd for $C_{23}H_{21}NO_4S$: C, 66.81; H, 5.35; N, 3.54. Found: C, 67.04; H, 5.58; N, 3.28.

6-(4-Methoxyphenyl)-7-methyl-2,3-dihydro-1*H*-indolizin-5-one (47). To a solution containing 0.2 g (0.50 mmol) of pyridone **46** in 6 mL of ethanol was added an excess of Raney nickel. The mixture was heated at reflux for 5 h, cooled to room temperature, filtered through a pad of Celite, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.12 g (90%) of **47** as a white solid: mp 126−127 °C; IR (CH_2Cl_2) 1646, 1586, and 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.11−2.26 (m, 2H), 3.06 (t, 2H, J = 7.8 Hz), 3.83 (s, 3H), 4.14 (t, 2H, J = 7.5 Hz), 6.07 (s, 1H), 6.93 (d, 2H, J = 8.7 Hz), and 7.18 (d, 2H, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 21.4, 31.5, 48.8, 55.2, 104.0, 113.5, 127.4, 128.5, 131.3, 147.3, 147.5, 158.4, and 161.4. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.72; N, 5.41. Found: C, 75.16; H, 6.79; N, 5.42.

6-(4-Hydroxyphenyl)-7-methyl-2,3-dihydro-1*H*-indolizin-5-one (48). A solution of 0.1 g (0.4 mmol) of **47** in 5 mL of 48% HBr was heated at 135 °C for 12 h. The reaction mixture was taken to dryness under reduced pressure. The resulting residue was taken up in CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.09 g (97%) of 6-(4-hydroxyphenyl)-7-methyl-2,3-dihydro-1*H*-indolizin-5-one (**48**) as a white solid: mp 231−233 °C (lit.[27] mp 232−234 °C); IR (CH_2Cl_2) 3400−2400, 1645,1560, and 1510 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.97 (s, 3H), 2.08 (quint, 2H, J = 7.5 Hz), 3.03 (t, 2H, J = 7.5 Hz), 3.96 (t, 2H, J = 7.5 Hz), 6.10 (s, 1H), 6.78 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), and 9.29 (s, 1H, exchangeable). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.98; H, 5.77; N, 6.17. Found: C, 73.85; H, 5.71; N, 6.03.

A 0.05 g (mmol) sample of **48** was subjected to alane reduction using the conditions described by Wick to give (±)-ipalbidine (**7**), mp 148−150 °C (lit[27] mp 149−150 °C).

6,7-Bis(trifluoromethyl)sulfonyloxy)-1,2,3-trihydroindolizin-5-one (50). To a stirred solution containing 0.4 g (1.7 mmol) of 6-hydroxy pyridone **22** in 20 mL of CH_2Cl_2 at −78 °C was slowly added 5.2 mL of BBr_3 (1.0 M solution in CH_2Cl_2). The resulting solution was allowed to warm to 25 °C, stirred overnight, and then cooled to −78 °C. The mixture was quenched with 5 mL of methanol, and the solvent was removed under reduced pressure. The resulting brown solid was used directly in the next step. To a solution containing the above diol and 2.5 g (6.9 mmol) of *N*-phenyl trifluoromethanesulfonamide in 20 mL of CH_2Cl_2 at 0 °C was added 1.0 mL (6.9 mmol) of triethylamine. The reaction mixture was allowed to warm to room temperature and stirred overnight, and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.5 g (68%) of **50** as a white solid: mp 115−116 °C; IR (neat) 1681, 1625, 1573, 1425 and 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (tt, 2H, J = 7.2 and 8.0 Hz), 3.22 (t, 2H, J = 8.0 Hz), 4.25 (t, 2H, J = 7.2 Hz), and 6.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 32.5, 50.2, 94.8, 118.6 (q), 128.4, 149.5, 152.1, and 155.9. Anal. Calcd for $C_{10}H_7F_6NO_7S_2$: C, 27.85; H, 1.64; N, 3.25. Found: C, 27.87; H, 1.67; N, 3.22.

6,7-Bis(3,4-dimethoxyphenyl)-1,2,3-trihydroindolizin-5-one (51). To a stirred solution containing 0.13 g (0.9 mmol) of 4-bromoveratrole in 3 mL of THF at −75 °C was added 1.3 mL of *tert*-butyllithium (1.6 M solution in pentane). The reaction mixture was stirred at −75 °C for 0.5 h, 1.9 mL of $ZnCl_2$ (0.8 M in THF) was added, and the mixture was allowed to warm to 25 °C while stirring for 0.5 h. To this mixture was added a solution of 0.1 g (0.2 mmol) of ditriflate **50** and 0.013 g (0.01 mmol) of $Pd(PPh_3)_4$ in 2 mL of THF. The reaction mixture was heated at reflux for 20 h, quenched with water, and extracted with EtOAc. The combined organic extracts were washed with a saturated brine solution, dried over $MgSO_4$, concentrated under reduced pressure, and subjected to flash silica gel chromatography. The major product eluted from the column (0.06 g, 64%) was identified as **51** and was obtained as a yellow solid: mp 193−195 °C; IR (neat) 1644, 1596, 1516, 1258, and 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (tt, 2H, J = 7.6 and 7.2 Hz), 3.15 (t, 2H, J = 7.6 Hz), 3.56 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.23 (t, 2H, J = 7.2 Hz), 6.27 (s, 1H), 6.54 (s, 1H), and 6.72−6.76 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 32.0, 49.3, 55.8, 55.9, 56.0 (2), 103.8, 110.8, 110.9, 112.9, 114.8, 121.5, 124.0, 126.1, 128.8, 132.7, 147.9, 148.3, 148.4 (2), 148.6, 150.2, and 161.8. Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.73; H, 6.19; N, 3.44. Found: C, 70.63; H, 6.08; N, 3.27.

Methyl 5-Oxo-1-(2-phenylthioacetyl)pyrrolidine-2-carboxylate (55). To a stirred solution containing 10.0 g (77 mmol) of L-pyroglutamic acid (**53**) in 200 mL of methanol was added 0.8 g of Dowex 50WX2−200 ion-exchange resin. The suspension was heated at reflux for 3 h and cooled to room temperature, and the ion-exchange resin was filtered. The filtrate was concentrated under reduced pressure to give L-methyl pyroglutamate (**54**) as a light yellow oil, which was used directly in the next step. An 11 g sample of **54** was dissolved in 50 mL of benzene, and this solution was added slowly to a stirred solution of phenylthioacetyl chloride in 100 mL of benzene. The mixture was heated at reflux for 24 h, concentrated under reduced pressure, taken up in Et_2O, and washed once with a saturated $NaHCO_3$ solution and then with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 19.7 g (87%) of **55** as an orange oil: IR (neat) 1745, 1688, and 1581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08−2.15 (m, 1H), 2.30−2.42 (m, 1H), 2.55−2.64 (m, 1H), 2.70−2.81 (m, 1H), 3.73 (s, 3H), 4.18 (d, 1H, J = 15.4 Hz), 4.36 (d, 1H, J = 15.4 Hz), 4.76 (dd, 1H, J = 9.6 and 2.8 Hz), 7.19−7.23 (m, 1H), 7.26−7.31 (m, 2H), and 7.40−7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 31.7, 38.9, 52.7, 57.9, 126.8, 128.9, 130.2, 135.1, 169.2, 171.1, and 174.2. Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.06; H, 5.17; N, 4.68.

Methyl 5-Oxo-1-(2-(phenylsulfonyl)acetyl)pyrrolidine-2-carboxylate (56). To a stirred solution containing 19.0 g (65 mmol) of **55** in 300 mL of methanol and 150 mL of water at 0 °C was slowly added 200 g of OXONE. The suspension was stirred at ambient temperature for 7 h and filtered, and the combined organic layers were concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, washed with

water, dried over $MgSO_4$, and concentrated under reduced pressure to give a colorless oil. Trituration with Et_2O gave 14.0 g (66%) of **56** as a white solid: mp 99−101 °C; IR (KBr) 1748, 1706, 1459 and 1341 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09−2.15 (m, 1H), 2.29−2.40 (m, 1H), 2.53−2.60 (m, 1H), 2.65−2.73 (m, 1H), 3.75 (s, 3H), 4.62 (d, 1H, J = 14.0 Hz), 4.75 (dd, 1H, J = 9.6 and 2.4 Hz), 5.30 (d, 1H, J = 14.0 Hz), 7.56−7.60 (m, 2H), 7.66−7.70 (m, 1H), and 7.96−7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 31.7, 53.0, 58.1, 60.7, 128.7, 129.3, 134.3, 139.4, 161.7, 170.8, and 174.4. Anal. Calcd for $C_{14}H_{15}NO_6S$: C, 51.69; H, 4.65; N, 4.31. Found: C, 51.73; H, 4.66; N, 4.32.

Methyl 5-Oxo-1-(2-(phenylsulfonyl)diazoacetyl)pyrrolidine-2-carboxylate (57). To a stirred solution containing 4.0 g (12 mmol) of imide **56** in 75 mL of acetonitrile at 0 °C was added 4.1 mL (30 mmol) of triethylamine. The solution was allowed to stir at 0 °C for 20 min, and then 3.6 g (15 mmol) of *p*-acetamidobenzenesulfonyl azide was added in one portion. The solution was allowed to warm to 25 °C and was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the resulting residue was taken up in CH_2Cl_2. The solution was filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3.9 g (91%) of **57** as a yellow solid: mp 108−109 °C; IR (Nujol) 2136, 1740, 1683, and 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04−2.11 (m, 1H), 2.33−2.43 (m, 1H), 2.51−2.59 (m, 1H), 2.65−2.74 (m, 1H), 3.71 (s, 3H), 4.70 (dd, 1H, J = 8.8 and 4.4 Hz), 7.53−7.57 (m, 2H), 7.62−7.67 (m, 1H), and 8.04−8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 31.4, 52.9, 58.5, 128.2, 129.2, 134.1, 141.6, 157.7, 170.7, and 173.4. Anal. Calcd for $C_{14}H_{13}N_3O_6S$: C, 47.86; H, 3.73; N, 11.96. Found: C, 47.96; H, 3.79; N, 11.91.

Methyl 8-Acetyl-6-hydroxy-5-oxo-1,2,3-trihydroindolizine-3-carboxylate (10). To a solution of 3.9 g (11 mmol) of diazoimide **57** in 70 mL of benzene w343 added 2.5 g (37 mmol) of methyl vinyl ketone and 2 mg of rhodium(II) acetate, and the reaction mixture was heated at reflux for 20 h. The mixture was allowed to cool to 25 °C, and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 2.4 g (86%) of **10** as a beige solid: mp 124−126 °C; IR (Nujol) 1748, 1740, 1684, 1628 and 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35−2.42 (m, 1H), 2.47 (s, 3H), 2.50−2.61 (m, 1H), 3.37−3.46 (m, 1H), 3.59−3.67 (m, 1H), 3.81 (s, 3H), 5.18 (dd, 1H, J = 9.6 and 3.2 Hz), 6.79 (s, 1H), and 7.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 28.4, 32.2, 53.2, 61.5, 113.6, 115.5, 143.9, 146.7, 157.6, 170.1, and 195.6. Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.35; H, 5.20; N, 5.50.

Methyl 8-Acetyl-5-oxo-6-((trifluoromethyl)sulfonyloxy)-1,2,3-trihydroindolizine-3-carboxylate (58). To a solution containing 1.7 g (6.7 mmol) of the above 3-hydroxy-2(1*H*)-pyridone **10** and 3.6 g (10.0 mmol) of *N*-phenyl trifluoromethanesulfonamide in 50 mL of CH_2Cl_2 at 0 °C was added 1.4 mL (10 mmol) of triethylamine. The reaction mixture was allowed to warm to room temperature while stirring overnight. The solvent was removed under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give 2.4 g (94%) of **58** as a white solid: mp 83−84 °C; IR (neat) 1752, 1686, 1667 and 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37−2.44 (m, 1H), 2.49 (s, 3H), 2.58−2.69 (m, 1H), 3.46−3.55 (m, 1H), 3.69−3.77 (m, 1H), 3.79 (s, 3H), 5.22 (dd, 1H, J = 10.0 and 3.2 Hz), and 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 28.0, 33.1, 53.1, 62.1, 111.5, 118.6 (q), 131.8, 136.5, 155.1, 157.3, 169.3, and 193.3. Anal. Calcd for $C_{13}H_{12}F_3NO_7S$: C, 40.74; H, 3.16; N, 3.65. Found: C, 40.80; H, 3.20; N, 3.69.

Methyl 3-(8-Acetyl-3-(methoxycarbonyl)-5-oxo-1,2,3-trihydroindolizin-6-yl)prop-2-enoate (11). To a solution containing 0.015 g (0.2 mmol) of $Pd(PPh_3)_2Cl_2$ in 5 mL of CH_3CN at 25 °C was added a solution of 0.2 g (0.5 mmol) of triflate **58**, 0.08 g (0.9 mmol) of methyl acrylate, and 0.2 mL (1.4 mmol) of triethylamine in 2 mL of CH_3CN. The reaction mixture was heated at reflux for 3 h, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.14 g (86%) of **11** as a pale yellow solid: mp 189−191 °C; IR (neat) 1748, 1704, 1682, 1653, 1588 and 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33−2.40 (m, 1H), 2.47−2.62 (m, 1H), 2.52 (s, 3H), 3.50−3.60 (m, 1H), 3.71−3.81 (m, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 5.21 (dd, 1H, J = 10.0 and 3.2 Hz), 7.15 (d, 1H, J = 16.0 Hz), 7.57 (d, 1H, J = 16.0 Hz) and 8.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 28.9, 34.5, 52.8, 54.2, 62.9, 114.8, 122.1, 122.9, 140.2, 143.5, 158.9, 160.4, 169.1, 171.1, and 195.5. Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.30; H, 5.42; N, 4.32.

Methyl 3-(8-Acetyl-3-(methoxycarbonyl)-5-oxo-1,2,3-trihydroindolizin-6-yl)propanoate (59). To a solution containing 0.35 g (1.1 mmol) of **11** in 20 mL of $CHCl_3$ was added 0.07 g of 10% Pd/C. The mixture was hydrogenated at 50 psi for 5 h, filtered through a bed of Celite, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.35 g (100%) of **59** as a white solid: mp 115−116 °C; IR (Nujol) 1733, 1681, 1644, 1603, and 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25−2.36 (m, 1H), 2.46−2.58 (m, 1H), 2.47 (s, 3H), 2.68 (t, 2H, J = 7.2 Hz), 2.81−2.91 (m, 2H), 3.41−3.58 (m, 1H), 3.60−3.71 (m, 1H), 3.66 (s, 3H), 3.80 (s, 3H), 5.12 (dd, 1H, J = 10.0 and 3.6 Hz), and 7.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 26.2, 28.2, 32.5, 33.2, 51.8, 53.1, 61.7, 113.4, 128.0, 138.5, 155.4, 161.1, 170.5, 173.6, and 195.2. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.72; H, 5.94; N, 4.30.

Methyl 3-(8-Acetyloxy-3-(methoxycarbonyl)-5-oxo-1,2,3-trihydro-indoliz-in-6-yl) propanoate (60). To a stirred solution containing 1.9 g (9.0 mmol) of trifluoroacetic acid in 8 mL of CH_2Cl_2 at 0 °C was added 0.3 g of 30% H_2O_2. The reaction mixture was stirred at 0 °C for 0.5 h, and the solution was slowly added to a stirred solution containing 0.2 g (0.6 mmol) of **59** in 10 mL of CH_2Cl_2 at 0 °C. The mixture was allowed to warm to 25 °C and was stirred for an additional 4.5 h at room temperature. The mixture was slowly added to 10 mL of a saturated $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and subjected to flash silica gel chromatography to give 0.2 g (96%) of **60** as a light yellow oil: IR (neat) 1747, 1671, 1601, 1571, and 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.28−2.34 (m, 1H), 2.47−2.58 (m, 1H), 2.63−2.67 (m, 2H), 2.74−2.90 (m, 2H), 2.92−3.00 (m, 1H), 3.02−3.11 (m, 1H), 3.65 (s, 3H), 3.80 (s, 3H), 5.10 (dd, 1H, J = 9.2 and 3.6 Hz), and 7.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 26.2, 26.6, 28.1, 32.4, 51.7, 53.0, 62.2, 128.4, 129.7, 135.0, 139.4, 160.1, 169.0, 170.5, and 173.6. Anal. Calcd for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 56.80; H, 5.72; N, 4.08.

Phenylmethyl 3-(8-Hydroxy-5-oxo-3-(benzyloxycarbonyl)-1,2,3-trihydroindolizin-6-yl)propanoate (61). To a stirred solution containing 0.15 g (0.4 mmol) of **60** in 5 mL of toluene was added 1.0 g (9.1 mmol) of benzyl alcohol and 0.05 g (0.1 mmol) of Otera's[48] catalyst. The reaction mixture was heated at reflux for 15 h, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.2 g (98%) of **61**: $[\alpha]^{25}_D$ −146 (*c* 0.39, CH_2Cl_2); IR (neat) 1740, 1675, 1546, 1409, 1285, and 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19−2.24 (m, 1H), 2.36−2.47 (m, 1H), 2.62−2.66 (m, 2H), 2.72−2.87 (m, 2H), 2.99−3.08 (m, 2H), 5.06 (s, 2H), 5.12 (m, 1H), 5.12 (d, 1H, J = 12.4 Hz), 5.22 (d, 1H, J = 12.4 Hz), 6.53 (brs, 1H), 7.10 (s, 1H), and 7.28−7.34 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.8, 27.4, 32.9, 62.3, 66.4, 67.6, 128.3 (2), 128.4, 128.6, 128.7, 128.8, 128.9, 132.5, 133.9, 134.8, 135.4, 136.2, 159.1, 170.2, and 173.2.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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