JOC Article

A Three-Component, One-Pot Synthesis of Indolizidines and Related Heterocycles via the [3+2] Cycloaddition of Nonstabilized Azomethine Ylides

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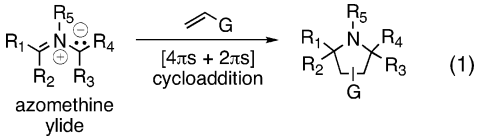
Nonstabilized azomethine ylides (i.e. those bearing only hydrogens or alkyl groups) can be generated from (2-azaallyl)stannanes and (2-azaallyl)silanes through an intramolecular *N*-alkylation/demetalation cascade. The resulting ylides undergo [3+2] cycloaddition with electron-poor or electron-rich dipolarophiles yielding indolizidines and related 1-aza[*m*.3.0]bicycloalkane systems in good yield. An in situ protocol allows for a one-pot, three-component synthesis of indolizidines. The (2-azaallyl)stannanes tolerate enolizable hydrogens in these cycloadditions, while (2-azaallyl)silanes do not. The mechanism of the cycloaddition cascade is clarified by a series of control experiments. The same (2-azaallyl)stannanes may be transmetalated by *n*-butyllithium to generate 2-azaallyllithiums, which also may undergo a [3+2] cycloaddition/*N*-alkylation cascade to form indolizidines.

Introduction

The 1,3-dipolar cycloaddition of azomethine ylides has emerged as a popular way of constructing heterocycles containing the pyrrolidine substructure, owing to its high synthetic efficiency and often high stereoselectivity (eq 1).[1] Azomethine ylides have traditionally been generated



(1)

bearing various stabilizing substituents such as aryl groups, esters, and cyano groups. However, the formation of azomethine ylides without such stabilizing groups has proven far more difficult. The ground-breaking efforts of Vedejs,[2] Padwa,[3] and Achiwa[4] allowed the formation of such *nonstabilized* azomethine ylides by the fluoride-assisted desilylation of (trimethylsilyl)methyl iminium salts. Variations on this theme, as well as a number of other methods for the generation of nonstabilized azomethine ylides, have been successfully applied to the synthesis of a variety of nitrogen-containing heterocycles.[1a]

Among the heterocycles targeted by such azomethine ylide cycloaddition methods are the pyrrolizidines[5] (1-aza[3.3.0]bicyclooctane) and indolizidines[6] (1-aza[4.3.0]-bicyclononane), which are present in a wide variety of natural products. Most commonly, these methods use azomethine ylides stabilized by ester or aryl groups.[7] However, azomethine ylides not substituted by such stabilizing groups are often most relevant to many synthetic targets in these families of natural products. For instance, Vedejs and co-workers[8] employed a nonstabilized azomethine ylide generated by desilylation of an iminium ion in their synthesis of (±)-retronecine. Starting from a chiral pool synthon, Pandey and co-workers[9] used their double-desilylation methodology to synthesize nonracemic (+)-retronecine via a nonstabilized azomethine ylide. Recently, Epperson and Gin[10] have

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(1) (a) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; pp 169−252. (b) Kanemasa, S.; Tsuge, O. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich CT, 1993; Vol. 3, pp 99−159. (c) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich CT, 1993; Vol. 3, pp 161−204. (d) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, pp 1069−1109. (e) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, pp 1111−1168. (f) Pearson, W. H. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, The Netherlands, 1988; Vol. 1, pp 323−358. (g) Vedejs, E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 33−51. (h) Lown, W. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, pp 653−733. (i) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2, pp 227−387.

(2) (a) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941−955. (b) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452−6454.

(3) Padwa, A.; Chen, Y.-Y. *Tetrahedron Lett.* **1983**, *24*, 3447−3450.

(4) (a) Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981−1008. (b) Achiwa, K.; Motoyama, T.; Sekiya, M. *Chem. Pharm. Bull.* **1983**, *31*, 3939−3945. (c) Achiwa, K.; Sekiya, M. *Chem. Lett.* **1981**, 1213−1216.

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(6) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719−741.

(7) Obst, U.; Betschmann, P.; Lerner, C.; Seiler, P.; Diederich, F.; Gramlich, V.; Weber, L.; Banner, D. W.; Schonholzer, P. *Helv. Chim. Acta* **2000**, *83*, 855−909. For a brief review see: Broggini, G.; Gaetano, Z. *Synthesis* **1999**, *6*, 905−917.

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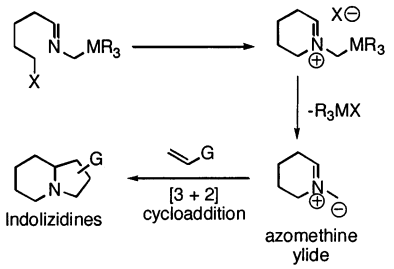
SCHEME 1. Overall Strategy To Obtain Indolizidines from (2-Azaallyl)stannanes

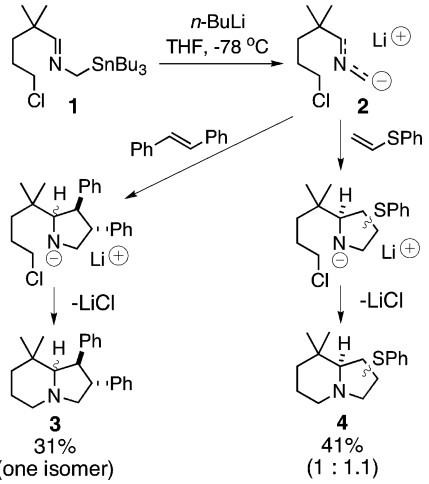


adapted a more-stabilized vinylogous version of iminium desilylation in their elegant approach toward asparagamine A. Several other groups have also reported the synthesis of pyrrolizidines and indolizidines using nonstabilized azomethine ylides with methods of varying generality.[11]

Although these methods of forming pyrrolizidines and indolizidines through azomethine ylide cycloadditions have proven useful, a number of significant limitations exist in this attractive approach. Most importantly, all of the methods reported thus far generate azomethine ylides from preexisting ring structures, which often limits the accessibility of azomethine ylide precursors and the convergency of this approach. Furthermore, azomethine ylide cycloadditions have not yet been applied to the formation of the 1-aza[5.3.0]bicyclodecane ring system, despite its prevalence in a growing number of natural products.[12] Hence, a general method for the rapid assembly of both rings of the 1-aza[*m*.3.0]bicycloalkane ring system addressing these limitations would be of great use in the synthesis of this biologically important class of structures.

We have previously reported that nonstabilized azomethine ylides can be generated from 2-(azaallyl)stannanes and 2-(azaallyl)silanes through a tandem intramolecular *N*-alkylation/demetalation cascade (Scheme 1).[13] The resulting azomethine ylides undergo [3+2] cycloaddition with certain alkenes and alkynes to yield indolizidines and other heterocycles. The 2-(azaallyl)stannanes and 2-(azaallyl)silanes can also be formed in situ from the condensation of aldehydes with aminomethylstannanes and aminomethylsilanes, leading to a highly convergent, multicomponent, one-pot synthesis of 1-aza-[*m*.3.0]bicycloalkanes. We now present a full account of our studies of the efficient construction of indolizidines and related heterocycles from 2-(azaallyl)stannanes and 2-(azaallyl)silanes via the generation of nonstabilized azomethine ylides. The geometry and cycloaddition chemistry of 1,3-substituted versions of the azomethine ylides described herein will be discussed in a subsequent report.

SCHEME 2. Initial Attempts To Obtain Indolizidines via 2-Azaallyllithium Cycloadditions[13]



Background and Initial Studies

The use of (2-azaallyl)stannanes as azomethine ylide precursors arose from our investigations into the generation and [3+2] cycloaddition of nonstabilized 2-azaallyllithiums (i.e. 2-azaallyl anions). We have previously demonstrated that (2-azaallyl)stannanes undergo tin−lithium exchange to form 2-azaallyllithiums, which can cycloadd to certain alkenes to form *N*-lithiopyrrolidines and thus *N*-substituted pyrrolidines upon treatment with an electrophile.[14] We reasoned that by employing a tethered electrophile, a tandem 2-azaallyllithium cycloaddition/*N*-alkylation sequence would generate indolizidine structures in one cascade (Scheme 2). Thus, treatment of (2-azaallyl)stannane **1** with *n*-BuLi at −78 °C in the presence of typical anionophile traps such as *E*-stilbene and phenyl vinyl sulfide yielded indolizidines **3** and **4** via 2-azaallyllithium **2**.[13]

The modest yield of these transformations prompted us to explore an alternative strategy wherein intramolecular *N*-alkylation of **1** was allowed to occur first in refluxing toluene followed by destannylation of the resultant iminium intermediate **5** to generate a nonstabilized azomethine ylide **6** (Scheme 3). Cycloaddition of **6** with *N*-phenylmaleimide yielded the indolizidine **7** in good yield as a 1:1 mixture of exo and endo diastereomers.[13]

Ample precedence existed for the initial intramolecular *N*-alkylation of an imine by a tethered alkyl halide.[15] The subsequent destannylation of iminium salts to form azomethine ylides had not been previously reported.

(10) Epperson, M. T.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1778−1780.

(11) For pyrrolizidines or indolizidines made from nonstabilized azomethine ylides (i.e. bearing only hydrogens or alkyl groups) see: (a) Castulik, J.; Marek, J.; Mazal, C. *Tetrahedron* **2001**, *57*, 8339−8347. (b) Grigg, R.; Savic, V.; Thornton-Pett, M. *Tetrahedron* **1997**, *53*, 10633−10642. (c) Novello, F.; Prato, M.; Da Ros, T.; De Amici, M.; Bianco, A.; Toniolo, C.; Maggini, M. *Chem. Commun.* **1996**, 903−904. (d) Pandey, G.; Lakshmaiah, G. *Tetrahedron Lett.* **1993**, *34*, 4861−4864. (e) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1988**, *53*, 653−659. (f) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1988**, *53*, 3808−3812. (g) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079−4089. (h) Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773−4774. (i) Terao, Y.; Imai, N.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167−3171. (j) Eschenmoser, A. *Chem. Soc. Rev.* **1976**, *5*, 377.

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(14) (a) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903−921. (b) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329−1345.

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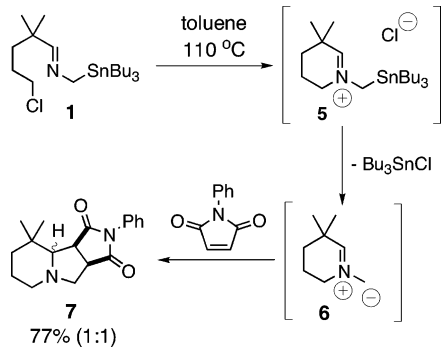
SCHEME 3. *N*-Alkylation/Destannylation Cascade to Indolizidines[13]

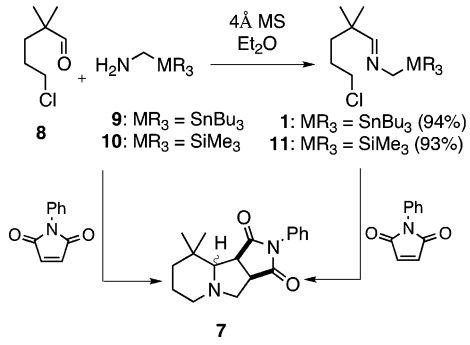


However, the desilylation of *N*-(trimethylsilyl)methyl iminium salts with reactive fluoride reagents has become the most general method for the generation of nonstabilized azomethine ylides.[1a,d−g,2−4] These *N*-(trimethylsilyl)-methyl iminium ions are generated through the intermolecular *N*-alkylation or *N*-acylation of imines, imidates, or thioimidates.[1a,d−g,2,4] A related method investigated by Padwa generates silyl-substituted iminium ions from the silver(I) fluoride-promoted decyanation of *N*-cyanomethyl-*N*-(trimethylsilyl)methylamines[3,16] or from Lewis acid-induced ionization of *N*-methoxymethyl-*N*-(trimethylsilyl)methylamines.[17] Similarly, the oxidative double-desilylation of bis-*N*-(trimethylsilyl)methylamines with silver(II) fluoride developed by Pandey also presumably proceeds through an *N*-(trimethylsilyl)methyl iminium intermediate.[18] Since our initial communication of this work, we have also described the generation and cycloaddition of nonstabilized *N*-unsubstituted azomethine ylides through an *N*-protonation/demetalation sequence of 2-(azaallyl)stannanes and 2-(azaallyl)silanes by treatment with HF-pyridine or pyridinium *p*-toluenesulfonate.[19]

The most relevant observation to the present study is the finding of Achiwa and co-workers that aryl-substituted (2-azaallyl)silanes can undergo intermolecular *N*-alkylation/desilylation with alkyl halides and tosylates to generate aryl-stabilized azomethine ylides.[20] However, nonstabilized (i.e. bearing only alkyl groups) or intramolecular variants have not been described, nor have examples been reported that bear enolizable hydrogens. Achiwa's method obviates the need for an external fluoride source for desilylation, although it appears that the reaction proceeds only in highly donating solvents such as HMPA, DMPU, or DMF.

Also of note are the studies of Hassner and Fischer,[21] who generated ester-stabilized azomethine ylides through an intramolecular *N*-alkylation/ring-opening sequence of 2-(4-bromobutyl)-5-ethoxy-1,3-oxazoles and formed 5,6,7,8-tetrahydroindolizines after trapping with dipolarophiles. Additionally, Bora and co-workers recently reported a three-component, one-pot synthesis of indolizines through pyridinium-derived stabilized azomethine ylides.[22] A novel three-component synthesis of pyrrolidines featuring ester-stabilized azomethine ylides derived from the ruthenium and copper-catalyzed reaction of α-diazoesters and *N*-benzylideneimines has recently been independently disclosed by Li and co-workers[23] and Galliford and co-workers.[24] The studies of Bora,[22] Li,[23] and Galliford[24] are illustrative of the growing impact of multicomponent reactions[25] (MCR) on the synthesis of heterocyclic structures.

TABLE 1. Exploration of Reaction Conditions



entry	sm	solvent (0.1 M)	temp (°C)	time (h)	yield[a] (%)
1	**1**	toluene	110	6	77
2	**11**	toluene	110	6	67
3	**8** + **9**	toluene	110	6	78
4	**8** + **10**	toluene	110	6	58
5	**8** + **9**	toluene	110	18	78
6	**8** + **9**	toluene (0.5 M)	110	6	84
7	**8** + **9**	toluene[b]	110	6	0
8	**8** + **9**	1,4-dioxane	100	2	74
9	**8** + **9**	THF	65	6	71
10	**8** + **9**	THF	25	14	62
11	**8** + **10**	THF	25	14	13
12	**8** + **9**	CH_2Cl_2	40	6	57
13	**8** + **9**	DMF	60	24	52
14	**8** + **9**	pyridine	115	6	75
15	**8** + **9**	pyridine	25	14	68
16	**8** + **9**	ethanol	78	14	0
17	**8** + **9**	none	110	6	0

[a] Isolated yields of 1:1 ratio of exo/endo diastereomers (separable). [b] With KF-Celite present during the reaction.

Results and Discussion

Before the [3+2] cycloaddition cascade in Scheme 1 could be realized, a convenient synthesis of the necessary (2-azaallyl)stannanes bearing a tethered leaving group had to be established. The preparation of various (2-azaallyl)stannanes had previously been developed in our

(16) (a) Padwa, A.; Fryxell, A.; Gasdaska, J. R.; Venkatramanan, M. K. *J. Org. Chem.* **1989**, *54*, 644−653. (b) Padwa, A.; Eisenbarth, P.; Venkatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1987**, *52*, 2427−2432. (c) Padwa, A.; Chen, Y.-Y.; Dent, W.; Nimmesgern, H. *J. Org. Chem.* **1985**, *50*, 4006−4014. (d) Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529−3535.

(17) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235−244.

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(21) Hassner, A.; Fischer, B. *J. Org. Chem.* **1992**, *57*, 3070−3075.

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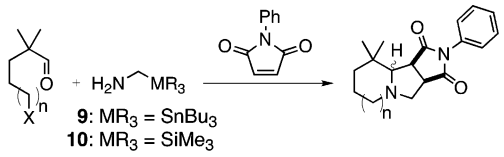
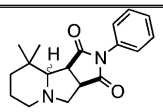
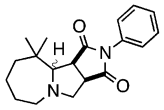
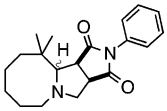
(24) Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487−3490.

(25) For reviews see: (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (c) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366−374.

TABLE 2. Comparison of Leaving Group and Ring Size for Nonenolizable Imines



entry	n	X	aldehyde	amine	solvent[a]	temp (° C)	time	compound[b] (yield)[c]
1	1	Cl	**8**	**9**	toluene	110	6 h	 **7** (78%)
2	1	OTs[d]	**12**	**9**	toluene	110	6 h	**7** (44%)
3	1	OTs[d]	**12**	**10**	toluene	110	6 h	**7** (44%)
4	1	I	**13**	**9**	toluene	110	6 h	**7** (28%)
5	2	Cl	**14**	**9**	CH_2Cl_2	25	36 h	 **15** (0%)
6	2	Cl	**14**	**9**	CH_2Cl_2[e]	25	36 h	**15** (0%)
7	2	Cl	**14**	**9**	toluene	110	6 h	**15** (0%)
8	2	Cl	**14**	**9**	toluene[e]	110	14 h	**15** (5%)[f]
9	2	Cl	**14**	**9**	pyridine[g]	115	6 h	**15** (19%)[f]
10	2	I	**16**	**9**	pyridine	115	6 h	**15** (34%)[f]
11	2	I	**16**	**9**	xylenes	136	14 h	**15** (88%)[f]
12	3	I	**17**	**9**	xylenes[h]	136	14 h	 **18** (17%)

[a] All reactions performed at 0.1 M. [b] 1:1 endo/exo ratio of diastereomers in all cases. [c] Isolated yields. [d] Ts = *p*-toluenesulfonate. [e] 5 mol % of Bu_4NI. [f] Diastereomers not separated. [g] 1.0 equiv of KI. [h] 0.05 M.

laboratories through the condensation of aldehydes and (tri-*n*-butylstannyl)methylamines using 4 Å molecular sieves in ether.[14a,26] We found that this method could be applied to the synthesis of (2-azaallyl)stannanes **1** by using 5-chloro-2,2-dimethylpentanal[27] **8** and (tri-*n*-butylstannyl)methylamine[26b,28] **9** (Table 1). The (2-azaallyl)-stannanes produced in this way were used immediately after preparation without further purification. For a comparison of tin and silicon in the cycloaddition cascade, we also formed (2-azaallyl)silane **11** from the condensation of **8** and commercially available (trimethylsilyl)-methylamine **10**. To simplify our initial studies into the cascade process, enolizable hydrogens on the imines were purposefully replaced by methyl groups to prevent possible enamine formation (vida infra).

When **1** was heated in toluene at reflux with *N*-phenylmaleimide a 77% yield of indolizidine cycloadduct **7** was isolated in a 1:1 ratio of exo and endo diastereomers (entry 1, Table 1). The cycloaddition with (2-azaallyl)silane **11** proceeded under identical conditions in 67% yield, demonstrating that *N*-(trimethylsilyl)-methyl iminium species can be desilylated by chloride at elevated temperatures in nonpolar solvents without the necessity of aryl stabilizing groups (entry 2). Although most previous work has employed anhydrous sources of fluoride anion to desilylate *N*-(trimethylsilyl)methyl iminium species, desilylation by chloride[4b,c,17] and water[29,30] has also been observed in several instances.

Conveniently, the aldehyde, amine, and dipolarophile could be mixed together in a 3-component, one-pot procedure (entries 3 and 4). The good yields obtained in these one-pot reactions showed that at least 1 equiv of water could be tolerated. Although the tolerance of some

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(27) Le Borgne, J.-F. *J. Organomet. Chem.* **1976**, *122*, 123−128.
(28) See the Supporting Information for an improved procedure for the preparation of **9**.

(29) (a) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523−2530. (b) Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda. K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2537−2545. (c) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *Heterocycles* **1985**, *23*, 2489−2492. (d) Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. *Chem. Lett.* **1984**, 801−804.
(30) Torii, S.; Okumoto, H.; Genba, A. *Chem. Lett.* **1996**, 747−748.

water in azomethine ylide cycloadditions is known[29,30] as in the case of the condensation of secondary α-amino acids and aldehydes,[11b,31] it is more rare for nonstabilized azomethine ylides.[32] Addition of activated 4 Å molecular sieves did not effect the outcome of the one-pot cycloaddition cascade.

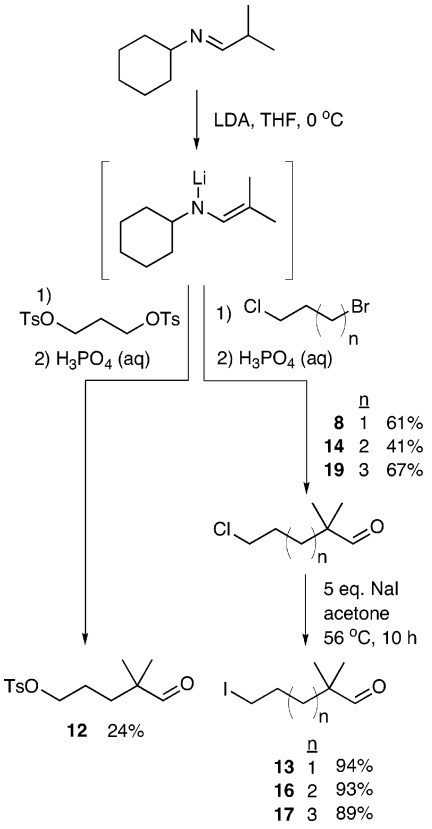
Increasing the reaction time or the concentration did not greatly affect the yield of the reaction (entries 5 and 6). Other solvents, such as 1,4-dioxane, THF, and pyridine, proved suitable for the reaction at elevated temperatures (entries 8, 9, and 14). In the case of (tri-*n*-butylstannyl)methylamine **9**, the solvents THF, pyridine, dimethylformamide, and methylene chloride gave good yields of cycloadduct at or near room temperature, although longer reaction times were necessary (entries 10, 12, 13, and 15). When (trimethylsilyl)methylamine **10** was used at ambient temperature (entry 11), a very low yield of cycloadduct **7** was obtained. This result may indicate desilylation is not as efficient as destannylation at ambient temperatures.

No cycloadduct was detected when the reaction was performed in ethanol or in the absence of solvent (entries 16 and 17). Although stannane byproducts made chromatographic purification of cycloadducts troublesome in certain cases, treatment of the crude reaction mixture with KF-Celite[33] or KF(aq)/ether often made purification easier. No cycloadduct was isolated when KF-Celite was present during the course of the reaction (entry 7).

The effects of varying leaving group and ring size were also studied by using the one-pot method with nonenolizable aldehydes (Table 2). The synthesis of the requisite aldehyde partners is outlined in Scheme 4. For the formation of indolizidine **7**, it was found that chloride was the most effective leaving group (entry 1), although the tosylate gave a moderate yield of cycloadduct **7** in the case of both tin and silicon (entries 2 and 3). Reactions with iodide as the leaving group gave poor yields in the formation of indolizidine **7** accompanied by rapid decomposition of the starting materials at room temperature (entry 4).

The homologous 1-aza[5.3.0]bicyclodecane (also known as pyrrolo[1,2-*a*]azepine) system is found in an increasing number of natural products, including those from the *Stemona*,[12a] *Cephalotaxus*,[12b] and *Dendrobates*[12c] genera. Initial efforts to form this system from 6-chloro-2,2-dimethylhexanal[27] **14**, (tri-*n*-butylstannyl)methylamine **9**, and *N*-phenylmaleimide were not successful (entries 5−7). This failure is despite several literature reports of the successful intramolecular alkylation of imines with primary chlorides to form seven-membered rings.[34] Heating **14** and **9** in toluene or pyridine with catalytic iodide sources gave the desired cycloadduct **15**, albeit in poor yield (entries 8 and 9). It was discovered that heating 6-iodo-2,2-dimethylhexanal **16** with **9** in refluxing pyridine gave cycloadduct **15** in 34% yield (entry 10). Examination of the crude ^{1}H NMR revealed unwanted elimination of the iodide as a competing process. Ultimately, an excellent yield of **15** was obtained when the reaction was performed in refluxing xylenes (entry 11). To the best of our knowledge, this constitutes the first synthesis of this ring system with an azomethine ylide cycloaddition.

SCHEME 4. Synthesis of Aldehydes Used in Table 2



The 1-aza[6.3.0]bicyclounadecane structure presents itself in a number of complex marine alkaloids.[35] By heating 7-iodo-2,2-dimethylheptanal **17** with (tri-*n*-butylstannyl)methylamine **9** and *N*-phenylmaleimide in refluxing xylenes, a modest yield of **18** was obtained (entry 12). The poor yield is probably due to a difficult intramolecular *N*-alkylation step. This ring system has not previously been made through azomethine ylide cycloaddition, although Coldham and co-workers[36] have recently proposed constructing the 1-aza[6.3.0]bicyclounadecane core of manzamine A through a stabilized azomethine ylide.

Our efforts next turned to the use of aldehydes with enolizable hydrogens in the cycloaddition cascade. In general, methods which generate azomethine ylides through the initial formation of *N*-(trimethylsilyl)methyl iminium salts followed by desilylation by an external fluoride source often tolerate the presence of enolizable hydrogens. Examples exist, however, where fluoride desilylation methods fail due to the presence of enolizable

(31) (a) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 47−49. (b) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49−51. (c) Tsuge, O.; Kanemasa, S.; Masayuki, O.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079−4089.

(32) In the generation of nonstabilized azomethine ylides by fluoride-induced desilylation of *N*-(trimethylsilyl)methyl iminium salts, the added fluoride source typically must be anhydrous. See refs 1d and 2.

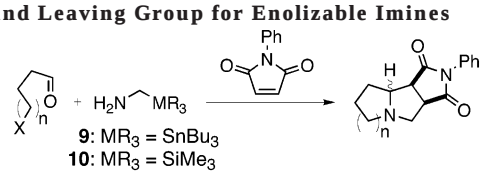
(33) Savall, B.; Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 3057−3060.

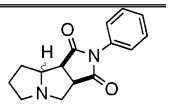
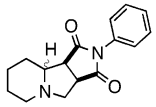
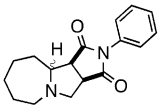
(34) (a) Jansen, A.; Pitter, S. *Monatsh. Chem.* **1999**, *130*, 783−794. (b) Clemens, M.; Meise, W.; Himmel, K.; Jansen, M. *Liebigs Ann. Org. Bioorg. Chem.* **1997**, *2*, 447−457. (c) Meise, W.; Arth, C.; Zlotos, D.; Jansen, M.; Feldmann, C. *Liebigs Ann. Org. Bioorg. Chem.* **1994**, 1135−1142. (d) Osbond, J. M. *J. Chem. Soc.* **1951**, 3464−3469.

(35) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201−6258.

(36) Coldham, I.; Crapnell, K. M.; Fernandez, J.-C.; Moseley, J. D.; Rabot, R. *J. Org. Chem.* **2002**, *67*, 6181−6187.

TABLE 3. Comparison of Ring Size and Leaving Group for Enolizable Imines



entry	aldehyde	n	X	amine	solvent[a]	temp (° C)	time	compound[b] (yield)[c]
1	**20**	1	Cl	**9**	toluene	110	6 h	 **21** (85%)
2	**20**	1	Cl	**10**	toluene	110	6 h	**21** (trace)
3	**22**	2	Br	**9**	toluene	110	6 h	 **23** (77%)
4	**24**	3	I	**9**	xylenes	136	14 h	 **25** (90%)
5	**24**	3	I	**10**	xylenes	136	14 h	**25** (0%)

[a] All reactions run at 0.1 M. [b] 1:1 ratio of exo/endo diastereomers in all cases (separated). [c] Isolated yields.

hydrogens.[37] When other species induce desilylation, such as chloride, bromide, iodide, water, and *p*-toluenesulfonate, enolizable hydrogens are typically not tolerated. Two interesting exceptions should be noted. Padwa and Dent have reported one example of azomethine ylide formation through zinc chloride mediated ionization/desilylation of *N*-methoxymethyl-*N*-(trimethylsilyl)-methylamine bearing enolizable hydrogens.[17] Also, Torii and co-workers have shown that azomethine ylides can be formed by simply heating trimethylsilylmethyl secondary amines and aldehydes in THF.[30] In Torii's work, three examples with enolizable hydrogens are noted. In general, however, the generation of azomethine ylides by desilylation of *N*-(trimethylsilyl)methyl iminium salts bearing enolizable hydrogens with nonfluoride nucleophiles has proved problematic.[38]

In this context, we were delighted to find that *N*-(tri-*n*-butylstannyl)methyl iminium salts bearing enolizable hydrogens readily form azomethine ylides without the need for an external fluoride source (Table 3). The pyrrolizidine cycloadduct **21** was made in excellent yield by condensation of 4-chlorobutanal[39] **20** with (tri-*n*-butylstannyl)methylamine **9** in refluxing toluene with *N*-phenylmaleimide as the dipolarophile (entry 1). When the same reaction was conducted with (trimethylsilyl)-methylamine **10**, only a trace of cycloadduct **21** was detected (entry 2). The reaction of 5-bromopentanal[40] **22**, **9**, and *N*-phenylmaleimide gave a good yield of indolizidine cycloadduct **23** (entry 3). This example demonstrates the viability of bromide as a leaving group in the cycloaddition cascade. Finally, the 1-aza[5.3.0]bicyclodecane cycloadduct **25** can be made in excellent yield by reaction of 6-iodohexanal **24**,[41] **9**, and *N*-phenylmaleimide in refluxing xylenes (entry 4). The analogous silane version yielded only decomposition (entry 5). Entries 2 and 5 underscore an important difference between the *N*-alkylation/destannylation and *N*-alkylation/desilylation cycloaddition cascades: *the tin version tolerates enolizable hydrogens but the silicon version does not*.

The azomethine ylide generated from the reaction of **1** or **11** also underwent cycloaddition with a variety of electron-poor dipolarophiles besides *N*-phenylmaleimide. Methyl acrylate, methyl maleate, and *trans*-methyl cinnimate all gave good yields of indolizidine cycloadducts **26**, **27**, and **30** (entries 1, 2, and 6, Table 4). Cycloadducts **30a**−**c** were taken on separately and reduced with $LiAlH_4$ to hydroxymethylderivatives **32a**−**c** to elucidate their stereostructure (Scheme 5). When **1** was heated in toluene with benzaldehyde or benzophenone good yields of bicyclic oxazolidines **28** and **29** were obtained (entries 3 and 4). A somewhat higher yield of **29** was observed when silane **11** was used in place of stannane **1** (entry 5).

(37) (a) Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *Tetrahedron Lett.* **1989**, 30, 4447−4448. (b) Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559−3568. (c) Livinghouse, T.; Smith, R. *J. Chem. Soc., Chem. Commun.* **1983**, 210−211.

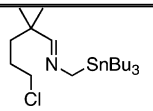
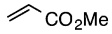
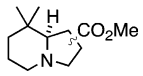
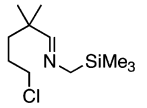
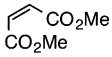
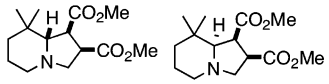
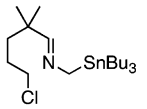
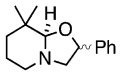
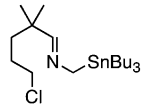
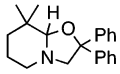
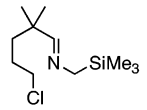
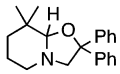
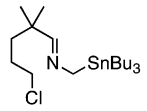
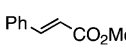
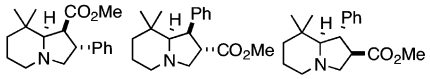
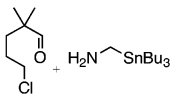
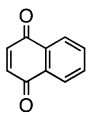
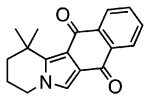
(38) Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554−1555 and refs 29a, 29c, and 37c. Many other reports of water or halide as desilylating agents for *N*-(trimethylsilyl)methyl iminiums conspicuously lack enolizable hydrogens. For example see refs 4b, 4c, 20a, 20b, 29b, and 29d.

(39) Hoffmann, H. M. R.; Henning, R. *Helv. Chim. Acta* **1983**, *66*, 828−841.

(40) Kulkarni, S. U.; Patil, V. D. *Heterocycles* **1982**, *18*, 163−167.

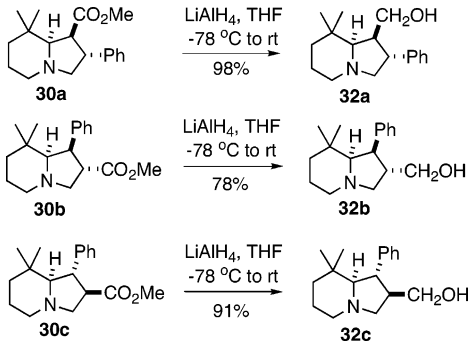
(41) Hon, Y.-S.; Chang, F.-J.; Lu, L.; Lin, W.-C. *Tetrahedron* **1998**, *54*, 5233−5246.

TABLE 4. Cycloadditions of Electron-Poor Alkene and Carbonyl Dipolarophiles[a]

entry	starting material	dipolarophile	products	yield[b] (ratio)
1	 **1**		 **26**	79% (1:1:1.8)
2	 **11**		 **27a** **27b**	74% (7.4:1)
3	 **1**	PhCHO	 **28**	63% (1.4:1)
4	 **1**		 **29**	65%
5	 **11**		 **29**	81%
6	 **1**		 **30a** **30b** **30c**	68% (10:1:5)
7	 **8** **9**		 **31**	7%

[a] Reaction conditions: toluene, 110 °C, 1−2 equiv of dipolarophile. [b] Isolated yields.

SCHEME 5. Hydroxymethyl Derivatives of 30a−c

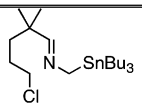
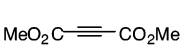
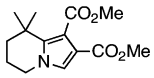
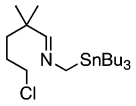
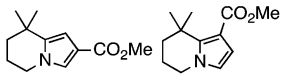
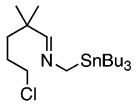
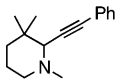
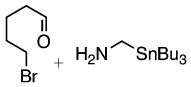
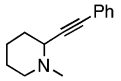
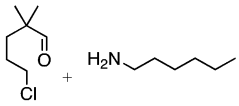
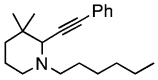


Cycloaddition with naphthoquinone under standard reaction conditions with the one-pot protocol, however, gave only a low yield of oxidized dione **31** (entry 7).

Electron-poor alkynes have been popular dipolarophiles in azomethine ylide cycloadditions,[1a,22−24] forming 2,5-dihydropyrroles or pyrroles after oxidation. Dimethyl acetylene dicarboxylate (DMAD) and methyl propiolate proved viable dipolarophiles, generating tetrahydroindolizines **33** and **34** after in situ DDQ oxidation (entries 1 and 2, Table 5). Diphenylacetylene and 2-(trimethylsilyl)phenylacetylene[42] gave no detectable cycloadduct under typical reaction conditions (refluxing toluene). Phenylacetylene (10 equiv) also yielded no cycloadduct, although curiously the piperidine **35** was isolated in moderate yield (entry 3). A similar reaction with aldehyde **22** using the one-pot method gave the analogous known piperidine **36**[43] as the only identifiable product (entry 4). The mechanism of these transformations is unclear, although no deuterium incorporation into piperidine **35** was seen by ^{1}H NMR or GCMS when 2-deuteriophenylacetylene was used or when the reaction was performed in toluene-d_8. When *n*-hexylamine was heated with aldehyde **8** and phenylacetylene, piperidine **37** was

(42) Kurita, J.; Ishii, M.; Yasuike, S.; Tsuchiya, T. *J. Chem. Soc., Chem. Commun.* **1993**, *17*, 1309−1310.

TABLE 5. Cycloadditions of Alkynes

entry	starting material[a]	dipolarophile	products	% yield[b] (ratio)
1	 **1**		 **33**	78%[c]
2	 **1**		 **34a** **34b**	51%[c] (1.4 : 1)
3	 **1**		 **35**	49%
4	 **22** **9**		 **36**	44%
5	 **8**		 **37**	61%

[a] Reaction conditions: refluxing toluene, 0.1−0.3 M. [b] Isolated yield. [c] After DDQ oxidation.

formed in 61% yield (entry 5). The formation of piperidine **37** shows that this transformation does not proceed through the azomethine ylide, but rather probably involves the addition of phenylacetylene or phenylacetylide to an iminium salt. In the case of entries 3 and 4, the final piperidines **35** and **36** are likely formed after protodestannylation of an intermediate (tri-*n*-butylstannyl)methylamine. The closest precedent to the formation of **37** may be the recent work of Jiang and Si,[44] who reported the addition of phenylacetylene to imines in toluene using chlorotrimethylsilane, zinc chloride, and triethylamine as promoters.

While the azomethine ylides generated from (2-azaallyl)stannanes and silanes cycloadd to typical electron-poor dipolarophiles such as maleimides and acrylates, a number of electron-rich dipolarophiles were observed to cycloadd as well, including phenyl vinyl sulfide, styrene, and triethyl vinyl silane (Table 6). This is an atypical result for azomethine ylide cycloadditions, although examples of electron-rich dipolarophiles undergoing inverse-electron demand cycloaddition with highly stabilized azomethine ylides exist.[45] Other electron-rich dipolarophiles such as ethyl vinyl ether (sealed tube), vinylene carbonate, and *N*-vinylpyrrolidinone failed to cycloadd in refluxing toluene. As is typical for most intermolecular azomethine ylide cycloadditions, unactivated dipolarophiles such as 1-hexene and norbornylene also failed to cycloadd. In contrast to styrene, no cycloaddition was detected with *E*-stilbene as dipolarophile in refluxing toluene.

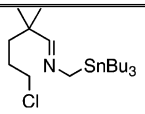
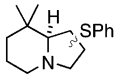
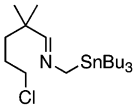
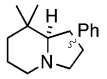
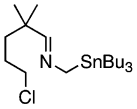
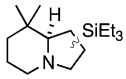
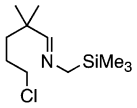
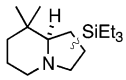
Several structural variations on the aldehyde partner were explored (Scheme 6 and Table 7). The use of ketimine **40** (not isolated) in place of the usual aldimine allowed access to the bridgehead-substituted indolizidine **41** in moderate yield (entry 1). The synthesis of such bridgehead-substituted indolizidines through azomethine ylide cycloaddition is not very common, but has recently been accomplished by Epperson and Gin.[10] A secondary bromide leaving group on imine **42** (not isolated), derived from aldehyde **43**, allows access to 5-substituted indolizidine **44**, although with a stereorandom outcome (entry 2). A one-pot version of this reaction with **43** and **9** provided **44** in comparible yield and stereoselectivity (entry 3). The successful formation of the 1-aza[5.3.0]-bicyclodecane cycloadduct **46** with chloroaldehyde **45** (entry 4) contrasts with the failure of 6-chloro-2,2-dimethylhexanal **14** to yield any cycloadduct **15** (recall Table 2, entry 7). This is likely due to the additional cyclic constraint of the benzo group, as well as the benzylic nature of the chloride leaving group.

Mechanism

What is the mechanism of this cycloaddition cascade? One can envision two likely reaction pathways: Path 1 (Scheme 7), in which the piperidine ring is formed first, followed by ylide generation and cycloaddition, or Path 2 (Scheme 7), which begins with ylide formation followed by cycloaddition, then finally closure of the piperidine

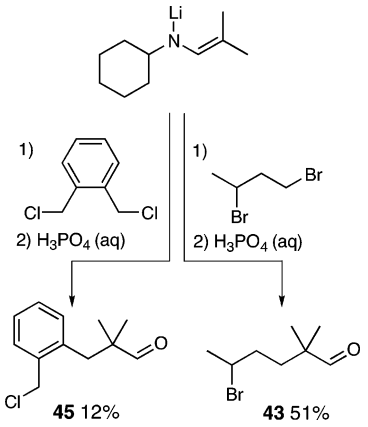
(43) Takahata, H.; Takahashi, K.; Wang, E. C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1211−1214.
(44) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767−6768.
(45) For a recent example see: Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592−11593.

TABLE 6. Cycloadditions of Electron-Rich Alkenes[a]

entry	starting material	dipolarophile	products	% yield[b] (ratio)
1	 **1**		 **4**	61% (1:1:1)
2	 **1**		 **38**	31% (single isomer)
3	 **1**		 **39**	54% (single isomer)
4	 **11**		 **39**	67% (single isomer)

[a] Reaction conditions: refluxing toluene, 0.1−0.3 M. [b] Isolated yield.

SCHEME 6. Synthesis of Some Aldehyde Partners



ring to form an indolizidine. The initial ylide formation shown in Path 2 can be postulated by several possible mechanisms (A, B, and C). To clarify the cascade mechanism, we undertook a number of control experiments using (2-azaallyl)stannanes and silanes without a tethered electrophile.

In mechanism A, the ylide is generated via a 1,2-metal shift (Scheme 8). Komatsu and co-workers[46] have reported that 1,3-diaryl-substituted (2-azaallyl)silanes can undergo a 1,2-silyl shift at elevated temperatures (180 °C) to generate stabilized azomethine ylides. We found that both (2-azaallyl)stannane **47**[14b] and (2-azaallyl)silane **48** did not undergo such a process in refluxing toluene as evidenced by Scheme 8. In both cases, only starting material was observed at the end of the reaction.

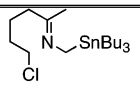
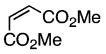
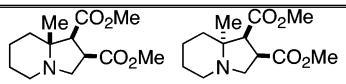
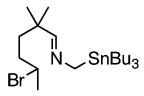
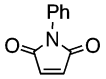
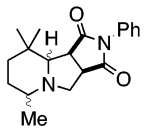
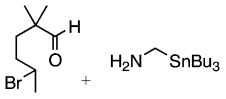
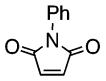
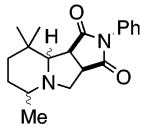
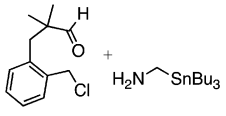
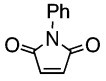
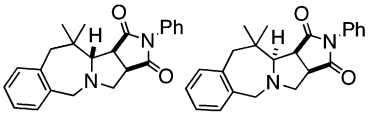
In mechanism B, a proton source may activate the (2-azaallyl)stannane or silane to generate the azomethine ylide (Scheme 9). Tsuge[29] has shown that water can initiate a protonation/desilylation sequence of aryl-stabilized (2-azaallyl)silanes. The work of Torii[30] has also suggested that water may be a viable desilylating agent under certain conditions. The possibility exists therefore that the water generated from the imine condensation in the one-pot protocol can initiate Path 2. Thus, (2-azaallyl)stannane **47** and (2-azaallyl)silane **48** were formed in situ and heated to reflux in the presence of *N*-phenylmaleimide. Only a trace of cycloadduct **49** was detected in the stannane case (<5% by ^{1}H NMR) and none at all in the case of the silyl version, showing that water cannot effectively initiate Path 2.

We have previously demonstrated that azomethine ylides can be formed from (2-azaallyl)stannanes and silanes by protonation/demetalation with HF·pyridine in THF or pyridinium *p*-toluenesulfonate in toluene.[19] Since both R_3MCl and H_2O are present together in the one-pot protocol, catalytic amounts of HCl may initiate azomethine ylide generation. This possibility was explored by forming the imine in situ, followed by addition of a substoichiometric amount of R_3MCl (20 mol %). A low yield (12%) of cycloadduct **49** was obtained in the stannane case, suggesting this may be a contributing, though probably minor, pathway. In the case of the silane, no cycloadduct was detected.

In mechanism C, chlorotri-*n*-butylstannane may act as the electrophile, forming an *N*-stannyl azomethine ylide and regenerating the chlorotri-*n*-butylstannane (Scheme 10). The feasibility of such a catalytic cycle has been demonstrated by Achiwa and co-workers in the case of the alkylation of aryl-substituted (2-azaallyl)silanes with alkyl halides and tosylates,[20] and in the generation of

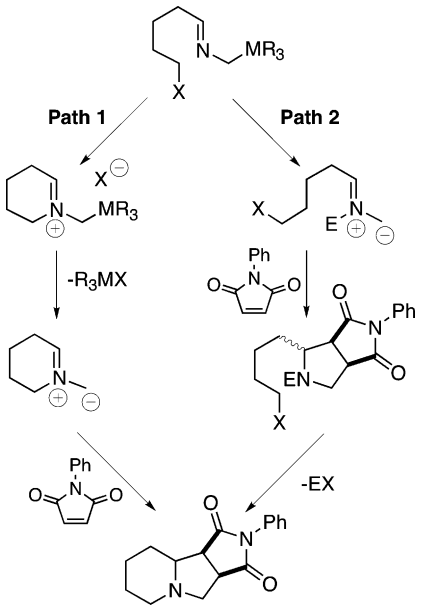
(46) (a) Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *Tetrahedron* **2003**, *59*, 197−205. (b) Komatsu, M.; Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S. *Org. Lett.* **2002**, *4*, 3505−3508. (c) Komatsu, M.; Ohno, M.; Tsuno, S.; Ohshiro, Y. *Chem. Lett.* **1990**, 575−576.

TABLE 7. Some Variations on the Carbonyl-Containing Partner[a]

entry	starting materials	dipolarophile	products	yield[b] (ratio)
1	 **40**		 **41a** **41b**	51% (1:1)
2	 **42**		 **44**	70%[c] (1:1.2:1.2:1.3)
3	 **43** **9**		 **44**	64%[c] (1:1:1:1)
4	 **45** **9**		 **46a** **46b**	77% (2:1)

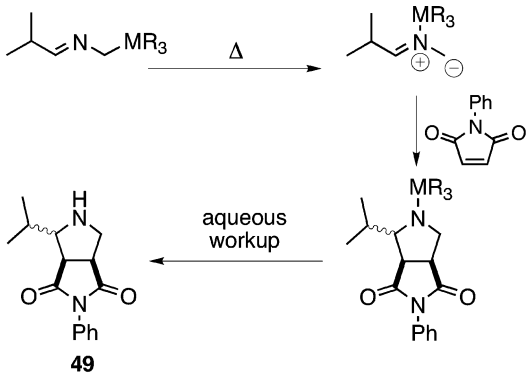
[a] Reaction conditions: toluene, 110 °C, 0.1−0.3 M, 1.2 equiv of dipolarophile. [b] Isolated yields. [c] Diastereomers not separated.

SCHEME 7. Two Possible Cascade Pathways



azomethine ylides with use of catalytic amounts of chlorotrimethylsilane and trimethylsilyltriflate from aryl- and amide-substituted (2-azaallyl)silanes.[47] However, these reactions proceeded only in polar aprotic solvents such as HMPA and not in nonpolar solvents such as benzene, which would be more relevent to our present studies. Komatsu and co-workers have recently investigated the generation of *N*-silylated azomethine ylides from the reaction of fluorosilanes with aryl-substituted

SCHEME 8. Mechanism A: 1,2-Metal Shift

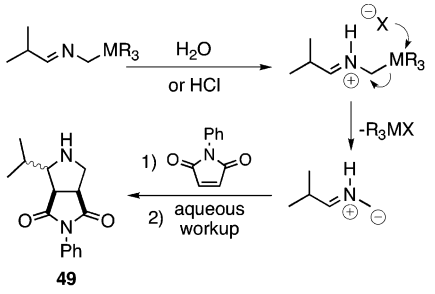


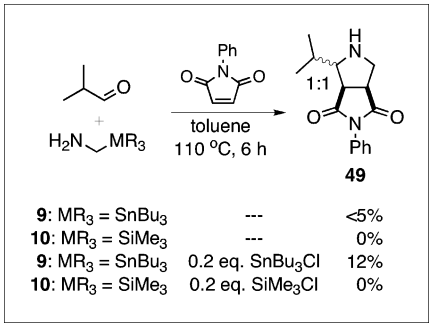
α-silylimines (i.e. (2-azaallyl)silanes) in benzene and THF, also apparently through a catalytic cycle.[48] To examine the possibility of such a pathway, we treated (2-azaallyl)stannane **47** with a substoichiometric amount of Bu_3SnCl (20 mol %) in refluxing toluene with *N*-phenylmaleimide present as the dipolarophile trap

(47) Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, *35*, 12646−12655.

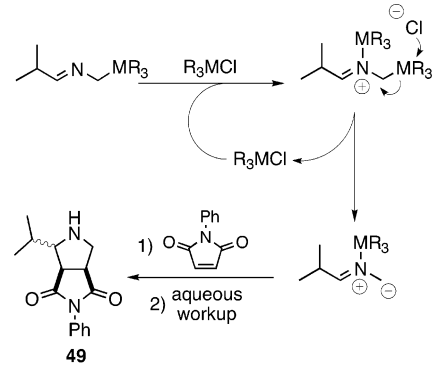
(48) Komatsu, M.; Okada, H.; Yokoi, S.; Minakata, S. *Tetrahedron Lett.* **2003**, *44*, 1603−1606. Also see ref 46a.

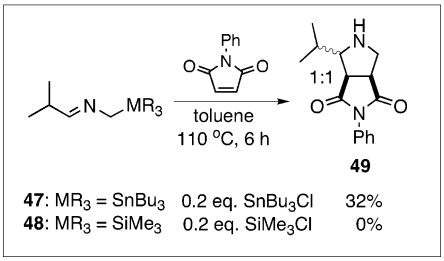
SCHEME 9. Mechanism B: Protonation−Demetalation





SCHEME 10. Mechanism C: R_3MCl Activation

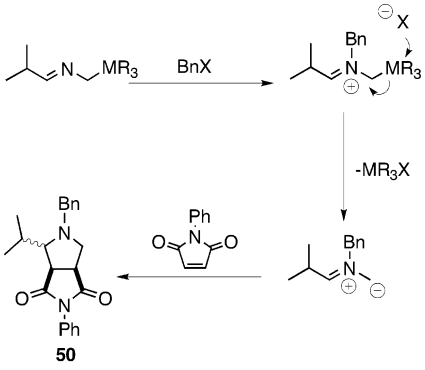


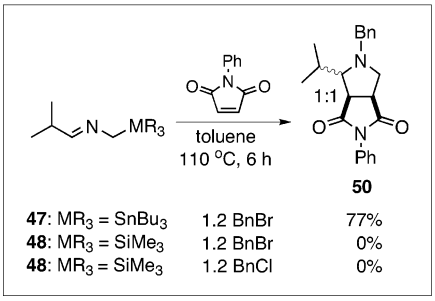


(Scheme 10). The cycloadduct **49** was isolated in 32% yield, indicating that the pathway is catalytic and may be operative in the cycloaddition cascade. In the case of (2-azaallyl)silane **48**, no cycloadduct was detected.

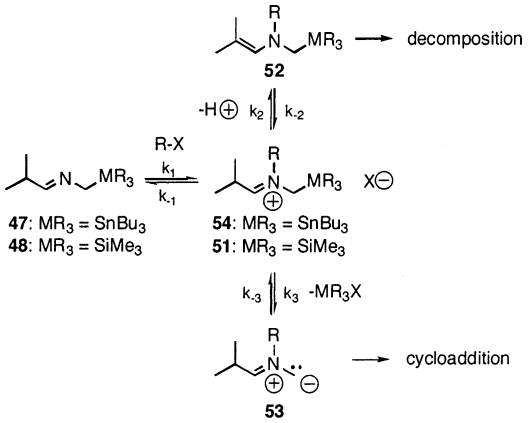
To check the viability of the proposed Path 1, (2-azaallyl)stannane **47** was treated with benzyl bromide in refluxing toluene in the presence of *N*-phenylmaleimide (Scheme 11). A good yield (77%) of the *N*-benzylated cycloadduct **50** was obtained, indicating Path 1 is most likely the predominant mechanism. The (2-azaallyl)silane **48** was similarly treated with benzyl bromide and benzyl chloride, but no cycloadduct was detected.[49] This result is in keeping with the complete failure of the cycloaddition cascade in the case of (2-azaallyl)silanes bearing

SCHEME 11. *N*-Alkylation/Demetalation Experiments





SCHEME 12. Enolizable Hydrogens in Azomethine Ylide Formation



enolizable hydrogens, and constitutes a key difference between the behavior of (2-azaallyl)stannanes and (2-azaallyl)silanes.

Why do (2-azaallyl)stannanes tolerate enolizable hydrogens in the cycloaddition cascade but (2-azaallyl)-silanes do not? Although we have not yet studied this aspect in great depth, we hypothesize that in the case of (2-azaallyl)silanes, deprotonation (k_2) of iminium **51** outpaces desilylation (k_3), leading to enamine **52** rather than azomethine ylide **53** (Scheme 12). For (2-azaallyl)-stannanes, the rate of destannylation (k_3) is greater than that of deprotonation (k_2), presumably because the Sn−C bond in **54** is much weaker than the Si−C bond in **51**. Although studies comparing the lability of carbon−metal

(49) Interestingly, Torii (ref 30) reports a successful azomethine ylide cycloaddition involving the condensation of isobutyraldehyde with *N*-(trimethylsilylmethyl)benzylamine in THF, which presumably proceeds through iminium **51** in Scheme 12. In Torii's case, water or hydroxide are the likely desilylating agents, as opposed to chloride or bromide in our case.

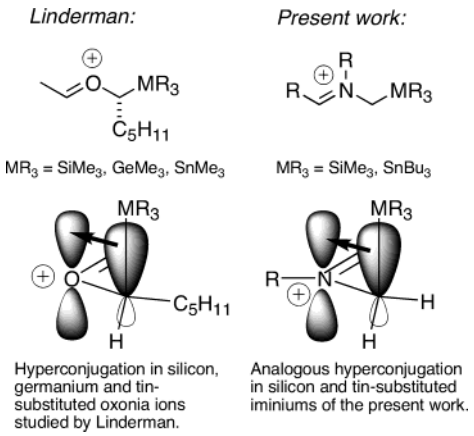
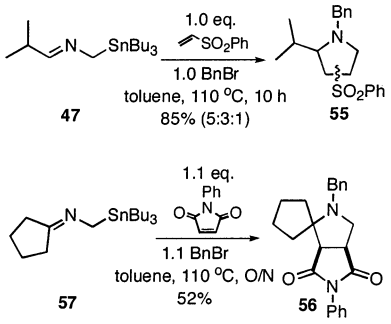


FIGURE 1. Hyperconjugation by carbon−metal bonds in oxonia and iminium cations.

bonds in metal-substituted iminiums have not been reported, observations regarding metal-substituted oxonia cations have been made by Linderman.[50] In these studies, a hyperconjugative interaction between an oxonia cation and a Sn−C, Ge−C, or Si−C bond, akin to the β-element effect, is inferred from product distribution studies of the diastereoselective addition of nucleophiles to oxonia cations (Figure 1). In our case, such a hyperconjugative interaction in **54** between the Sn−C bond and neighboring electron-deficient iminium π-system necessarily weakens the Sn−C bond, leading to facile destannylation. This is plausible because the β-element effect of tin has been found to be at least 10^4 times stronger than that of silicon and 10^3 times stronger than that of germanium.[51] On this basis, the reactivity profile of (2-azaallyl)germanes is more likely to mirror (2-azaallyl)-silanes than (2-azaallyl)stannanes, although this has not yet been experimentally investigated. Note, however, that both nonstabilized (2-azaallyl)stannanes and (2-azaallyl)-silanes bearing enolizable hydrogens can generate azomethine ylides when *N-protonated* with HF·pyridine or *p*-toluenesulfonic acid.[19] It is not clear whether this is because enamine formation is reversible in the presence of acid (i.e. $k_2 \sim k_{-2}$) or for some other reason. A finer examination of these mechanistic points will require additional experimentation.

As Scheme 11 demonstrated, the cycloaddition cascade can be extended to intermolecular *N*-alkylation of (2-azaallyl)stannanes to form *N*-benzylpyrrolidines. Two additional examples of *N*-benzylpyrrolidine formation are provided in Scheme 13. Treatment of the (2-azaallyl)-stannane **47** with benzyl bromide in refluxing toluene in the presence of phenyl vinyl sulfone gave pyrrolidine **55** in excellent yield as a mixture of three diastereomers (5:3:1). Phenyl vinyl sulfone has proven to be a synthetically useful dipolarophile[19b] since the phenylsulfonyl group can be reductively removed to give an unsubstituted pyrrolidine ring.[19b] Intermolecular *N*-alkylation of (2-azaallyl)stannane **57**[14b] with benzyl bromide in the presence of *N*-phenylmaleimide affords a moderate yield of spiropyrrolidine **56**, demonstrating that ketimines may be used in the intermolecular *N*-alkylation mode as well as aldimines.

SCHEME 13. *N*-Benzylpyrrolidines via Intermolecular *N*-Alkylation of (2-Azaallyl)stannanes



Conclusion

We have developed a concise synthesis of indolizidines and related 1-aza[*m*.3.0]bicycloalkanes from (2-azaallyl)-stannanes and (2-azaallyl)silanes through an intramolecular *N*-alkylation/demetalation/cycloaddition sequence featuring nonstabilized azomethine ylides. The (2-azaallyl)stannanes and (2-azaallyl)silanes can be made in situ, leading to a three-component, one-pot cycloaddition cascade. The method tolerates at least 1 equiv of water, and can utilize a range of electron-poor and electron-rich dipolarophiles. When (2-azaallyl)stannanes are used, enolizable hydrogens on the imine are tolerated. This convergent approach allows for the rapid assembly of the 1-aza[*m*.3.0]bicycloalkane ring system so prevalent among alkaloidal natural products. In an upcoming report we will extend these investigations to the conformations and cycloadditions of 1,3-disubstituted azomethine ylides.

Experimental Section

For general experimental procedures, see the Supporting Information.

5-Chloro-2,2-dimethylpentylidene[(tri-*n*-butyl)stannylmethyl]amine (1). (Tri-*n*-butylstannyl)methylamine **9**[26b,28] (450 mg, 1.41 mmol) was dissolved in ether (5 mL), then 4 Å molecular sieves (2 g) and 5-chloro-2,2-dimethylpentanal **8**[27] (210 mg, 1.41 mmol) were added at room temperature. After 3 h, the mixture was filtered through a pad of Celite and concentrated at 0 °C. The crude imine **1** was produced as a light yellow oil (560 mg, 94%) and used immediately in the cycloaddition reactions without further purification. IR (neat) 1645 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 [s, $4J(^{117/119}Sn-^1H) = 8.4$ Hz, 1 H], 3.54 (s, $2J(^{117/119}Sn-^1H) = 22.1$ Hz, 2 H), 3.50 (t, $J = 6.8$ Hz, 2 H), 1.78−1.66 (m, 3 H), 1.54−1.40 (m, 6 H), 1.40−1.24 (m, 7 H), 1.02 (s, 6 H), 0.98−0.80 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 46.7, 45.6, 38.5, 37.7, 29.0, 28.0, 27.8, 27.4, 25.1, 13.7, 9.1.

(1*R,2*R**,8a*R**)- or (1*R**,2*R**,8a*S**)-Octahydro-8,8-dimethyl-1,2-diphenylindolizine (3).** Imine **1** (300 mg, 0.67 mmol) and *trans*-stilbene (183 mg, 1.05 mmol) were dissolved in THF (2 mL) and cooled to −78 °C. The mixture was treated with *n*-butyllithium (0.80 mL of a 2.1 M solution in hexane, 1.68 mmol) over 5 min. After 1 h, the reaction was warmed to

(50) (a) Linderman, R. J.; Chen, K. *J. Org. Chem.* **1996**, *61*, 2441−2453. (b) Linderman, R. J.; Anklekar, T. V. *J. Org. Chem.* **1992**, *57*, 5078−5080. Also see: (c) Cossrow, J.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 147−150. (d) Rychnovsky, S. D.; Cossrow, J. *Org. Lett.* **2003**, *5*, 2367−2370.

(51) (a) Hagan, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961. (b) Lambert, J. B.; Wang, G.-T.; Teramura, D. H. *J. Org. Chem.* **1988**, *53*, 5422−5428. (c) Traylor, T. G.; Koermer, G. S. *J. Org. Chem.* **1981**, *46*, 3651−3657.

room temperature, diluted with water, and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×), dried ($MgSO_4$), and concentrated. The residue was chromatographed (20% ethyl acetate/hexanes) to provide 75 mg (31%) of the title compound as a yellow oil. $R_f = 0.30$ (20% ethyl acetate/hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.30−7.15 (m, 10 H), 3.72 (t, $J = 7.8$ Hz, 1 H), 3.55−3.45 (m, 1 H), 3.85−3.75 (m, 2 H), 2.28 (t, $J = 7.8$ Hz, 1 H), 2.21 (d, $J = 7.0$ Hz, 1 H), 1.90 (m, 1 H), 1.70 (m, 1 H), 1.50−1.40 (m, 1 H), 1.25−1.18 (m, 1 H), 1.15−1.10 (m, 1 H), 0.85 (s, 3 H), 0.24 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 130.6, 128.4, 127.4, 126.2, 126.1, 77.8, 64.6, 56.6, 55.9, 52.1, 43.3, 28.1, 22.0, 21.5; MS (EI, 70 eV) *m*/*z* (rel intensity) 305 (M^+, 1.0), 178 ($PhCCPh^+$, 22), 125 ([M − PhCH=CHPh]$^+$, 14); HRMS (CI, CH_4, and NH_3) calcd for $C_{22}H_{28}N$ ([M + H]$^+$) 306.2222, found 306.2209. The stereochemistry at C(8a) could not be determined, and it is assumed the two phenyl groups retain the trans geometry of the alkene.

Octahydro-8,8-dimethyl-1-(phenylthio)indolizine and Octahydro-8,8-dimethyl-2-(phenylthio)indolizine (4). A solution of the imine **1** (210 mg, 0.47 mmol) and phenyl vinyl sulfide (129 mg, 0.95 mmol) in THF (2 mL) was added to a solution of *n*-butyllithium (0.58 mL of a 2.1 M solution in hexane, 1.22 mmol) in THF (6.2 mL) over 10 min at −78 °C. After 1.5 h, the reaction was warmed to room temperature, diluted with water, and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×), dried ($MgSO_4$), and concentrated. The residue was chromatographed (20% ethyl acetate/hexanes) to afford 50 mg (41%) of the title compound as a yellow oil containing two inseparable isomers (1:1.1 by NMR integration). The regio- and stereochemistry could not be determined. $R_f = 0.25$ (20% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m), 7.20−7.10 (m), 3.75−3.65 (m), 3.50−3.40 (m), 3.10−3.00 (m), 3.00−2.90 (m), 2.30−2.10 (m), 2.10−1.95 (m), 1.95−1.85 (m), 1.80−1.60 (m), 1.50−1.35 (m), 1.25−1.10 (m), 1.05 (s), 1.00 (s), 0.90 (s), 0.82 (s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 129.2, 129.0, 128.9, 128.8, 125.9, 125.6, 77.5, 71.5, 62.2, 53.6, 53.5, 53.3, 44.0, 40.1, 40.0, 39.4, 33.9, 33.5, 29.5, 28.8, 22.3, 22.2, 19.8, 19.2; MS (EI, 70 eV) *m*/*z* (rel intensity) 261 (M^+, 26), 246 ([M − CH_3]$^+$, 4), 192 ([M − C_5H_9]$^+$, 38), 177 ([M − C_6H_{11}]$^+$, 34), 152 ([M − SPh]$^+$, 100), 125 ([M − CH_2CHSPh]$^+$, 21), 77 (Ph^+, 6); HRMS (EI, 70 eV) calcd for $C_{16}H_{23}NS$ (M^+) 261.1551, found 261.1551.

The title compound was also prepared by heating imine **1** (330 mg, 0.73 mmol) and phenyl vinyl sulfide (150 mg, 1.1 mmol) in toluene (3 mL) at reflux for 14 h. The reaction was concentrated and chromatographed (25% ethyl acetate/hexanes) to gave 117 mg (61%) of the title compound as a yellow oil that contained three inseparable isomers (1:1:1 by NMR integration). The regio- and stereochemistry could not be determined. Partial data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.10 (m, 5 H), 3.75−3.60 (m, 2 H × 0.33), 3.55−3.40 (m, 2 H × 0.33), 3.12−2.90 (m, 5 H × 0.33), 2.48 (t, $J = 9.5$ Hz, 1 H × 0.33), 2.30−2.12 (m, 3 H × 0.33), 2.12−1.60 (m, 15 H × 0.33), 1.58−1.40 (m, 6 H × 0.33), 1.20−1.10 (m, 2 H × 0.33), 1.05 (s, 3 H × 0.33), 1.00 (s, 3 H × 0.33), 0.96 (s, 3 H × 0.33), 0.92 (s, 3 H × 0.33), 0.85 (s, 6 H × 0.33); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.3, 129.0, 128.9, 128.8, 128.7, 126.0, 125.6, 77.5, 73.1, 71.5, 62.5, 62.2, 53.6, 53.5, 53.3, 44.0, 40.2, 40.1, 39.9, 39.4, 39.3, 33.8, 33.5, 33.3, 33.0, 32.3, 32.1, 29.5, 28.9, 28.8, 22.3, 22.1, 22.0, 19.8, 19.3, 19.2.

(3a*S,9a*R**,9b*R**)- (7a) and (3a*R**,9a*R**,9b*S**)-Octahydro-9,9-dimethyl-2-phenyl-1*H*-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (7b).** Imine **1** (100 mg, 0.22 mmol) and *N*-phenylmaleimide (40 mg, 0.23 mmol) were heated in toluene (1 mL) at reflux for 3 h. The reaction was concentrated and the residue chromatographed (30% to 40% ethyl acetate/hexanes, gradient) to afford 25 mg (38%) of **7a** as a clear oil, followed by 27 mg (40%) of **7b** as a yellow oil.

7a (endo): $R_f = 0.29$ (30% ethyl acetate/hexanes, stained with I_2); IR ($CHCl_3$) 1709 (s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.48−7.25 (m, 5 H), 3.59 (d, $J = 9.3$ Hz, 1 H), 3.35 (t, $J = 8.6$ Hz, 1 H, H-9b), 3.22 (dd, $J = 8.2$, 6.6 Hz, 1 H, H-3a), 3.16−3.13 (m, 1 H), 2.25 (dd, $J = 9.3$, 6.6 Hz, 1 H), 2.02 (d, $J = 8.8$ Hz, 1 H, H-9a), 1.86−1.79 (m, 1 H), 1.76−1.65 (m, 1 H), 1.46−1.39 (m, 2 H), 1.24 (s, 3 H), 1.10 (dt, 1 H), 1.00 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$, JMOD) δ 178.2 (−), 177.6 (−), 129.1 (+), 128.5 (+), 126.5 (+), 76.6 (+), 57.2 (−), 54.2 (−), 46.4 (+), 44.3 (+), 42.6 (−), 33.4 (−), 27.2 (+), 21.3 (−), 19.6 (+); MS (EI, 70 eV) *m*/*z* (rel intensity) 298 (M^+, 49), 283 ([M − CH_3]$^+$, 14), 269 ([M − C_2H_5]$^+$, 36), 229 ([M − C_5H_9]$^+$, 100), 214 (M − C_6H_{12}]$^+$, 14), 173 ([*N*-phenylmaleimide]$^+$, 16); HRMS (EI, 70 eV) calcd for $C_{18}H_{22}N_2O_2$ (M^+) 298.1681, found 298.1689.

7b (exo): $R_f = 0.21$ (30% ethyl acetate/hexanes, stained with I_2); IR ($CHCl_3$) 1713 (s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.50−7.24 (m, 5 H), 3.56 (dd, $J = 9.0$, 8.9 Hz, 1 H), 3.44 (q, $J = 8.9$ Hz, 1 H, H-3a), 3.23 (dd, $J = 8.9$, 8.4 Hz, 1 H, H-9b), 3.10−3.02 (m, 1 H), 2.30 (t, $J = 8.9$ Hz, 1 H), 2.01 (td, $J = 13.1$, 3.0 Hz, 1 H), 1.95 (d, $J = 8.1$ Hz, 1 H, H-9a), 1.76−1.62 (m, 1 H), 1.55−1.45 (m, 2 H), 1.22−1.14 (m, 1 H), 1.12 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$, JMOD) δ 176.7 (−), 176.5 (−), 129.1, 128.5 (+), 126.54 (+), 126.49 (+), 75.1 (+), 56.7 (−), 52.8 (−), 46.9 (+), 43.6 (+), 39.6 (−), 33.0 (+), 29.0 (−), 21.8 (+), 19.7 (−); MS (EI, 70 eV) *m*/*z* (rel intensity) 298 (M^+, 43), 283 ([M − CH_3]$^+$, 14), 229 ([M − C_5H_9]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_{18}H_{22}N_2O_2$ (M^+) 298.1681, found 298.1685. The stereochemical assignment of **7a** and **7b** was based on two-dimensional (2D) COSY and NOESY experiments. For **7a**, there were NOE cross-peaks between the resonances corresponding to H-9a and H-9b, H-9b and H-3a. For **7b**, there was an NOE cross-peak between the H-9b and H-3a resonance. However, no NOE cross-peak was observed between H-9a and H-9b.

5-Chloro-2,2-dimethylpentanal (8). According to a modification of the procedure described by Le Borgne,[27] diisopropylamine (3.97 g, 39.2 mmol) and anhydrous THF (40 mL) were cooled to 0 °C and treated with *n*-butyllithium (13.0 mL of a 2.5 M solution in hexanes, 32.5 mmol). After 30 min at 0 °C, *N*-cyclohexyl(2-methylpropylidene)amine[27] (5.00 g, 32.6 mmol) was added at 0 °C with an additional amount of THF (5 mL). After 30 min at 0 °C, 1-bromo-3-chloropropane (5.13 g, 32.6 mmol) was added dropwise over 1 min at 0 °C. After 10 min at 0 °C, the solution was quenched with saturated aqueous NH_4Cl and concentrated. Ether and water were added and the pH was adjusted to 5 with H_3PO_4. The biphasic mixture was stirred at room temperature for 4 h with H_3PO_4 being added as needed to readjust the pH to 5. The aqueous phase was extracted with ether (3×), washed with 2% H_3PO_4 (2×) and brine (1×), dried (Na_2SO_4), and concentrated at room temperature. The residue was chromatographed (pentane to 5% ether/pentane, gradient) to yield 2.97 g (61%) of aldehyde **8** as a clear, colorless oil. $R_f = 0.20$ (5% ether/pentane, stains black in phosphomolybdic acid); alternatively, aldehyde **8** could be purified by distillation (bp 70−76 °C/10 mmHg, lit.[27] bp 4 °C/15 mmHg); IR ($CHCl_3$) 1723 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1 H), 3.54 (t, $J = 6.8$ Hz, 2 H), 1.78−1.56 (m, 4 H), 0.19 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 45.1, 34.5, 27.8, 21.8; MS (CI, CH_4) *m*/*z* (rel intensity) 149 ([M + H]$^+$, 64), 133 ([M − CH_3]$^+$, 10), 113 ([M − Cl]$^+$, 100); HRMS (CI, CH_4) calcd for $C_7H_{14}{}^{35}ClO$ ([M + H]$^+$) 149.0733, found 149.0736.

5-Chloro-2,2-dimethylpentylidene(trimethylsilylmethyl)amine (11). 5-Chloro-2,2-dimethylpentanal **8**[27] (122 mg, 0.82 mmol) was added to a solution of (trimethylsilyl)methylamine **10** (85 mg, 0.82 mmol) in ether (3 mL), followed by 4 Å molecular sieves (1 g) and allowed to stir at room temperature. After 18 h, the mixture was filtered through a pad of Celite and concentrated at 0 °C to provide 178 mg (93%) of the title compound as a light yellow oil: IR (neat) 1654 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, $J = 1.4$ Hz, 1 H), 3.50 (t, $J = 6.7$ Hz, 2 H), 3.11 (d, $J = 1.4$ Hz, 2 H), 1.78−1.68 (m, 2 H), 1.52−1.46 (m, 2 H), 1.03 (s, 6 H), 0.005 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 53.3, 45.5, 38.6, 37.4, 27.9, 26.3, 25.0, −2.9.

Toluene-4-sulfonic Acid 4,4-Dimethyl-5-oxopentyl ester (12). Diisopropylamine (393 mg, 7.84 mmol) and anhydrous THF (10 mL) were cooled to 0 °C and treated with *n*-butyllithium (2.87 mL of a 2.5 M solution in hexanes, 7.18 mmol). After 30 min at 0 °C, *N*-cyclohexyl(2-methylpropylidene)amine[27] (1.00 g, 6.53 mmol) was added at 0 °C with an additional amount of THF (5 mL). After 30 min at 0 °C, this solution was added to a solution of 1,3-propanediol-1,3-di-*p*-toluenesulfonate (2.51 g, 6.53 mmol) in THF (10 mL) via cannula over 1 min at 0 °C. After 30 min at 0 °C, the solution was quenched with saturated aqueous NH_4Cl and concentrated. Ether and water were added and the pH was adjusted to 5 with H_3PO_4. The biphasic mixture was stirred at room temperature for 4 h with H_3PO_4 being added as needed to readjust the pH to 5. The aqueous phase was extracted with ether (3×), washed with 2% H_3PO_4 (2×) and brine (1×), dried (Na_2SO_4), and concentrated at room temperature. The residue was chromatographed (pentane to 5% ether/pentane, gradient) to yield 443 mg (24%) of aldehyde **12** as a clear, colorless oil. R_f = 0.25 (30% ether/pentane, stained black with phosphomolybdic acid); IR (CH_2Cl_2) 2701 (m), 1724 (s), 1356 (s), 1175 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 7.78 (d, J = 8.5 Hz, 2 H), 7.35 (d, J = 8.5 Hz, 2 H), 4.01 (t, J = 5.9 Hz, 2 H), 2.46 (s, 3 H), 1.60−1.52 (m, 2 H), 1.52−1.44 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.49, 144.83, 132.97, 129.86, 127.88, 70.51, 45.30, 32.62, 23.94, 21.64, 21.25; MS (EI, 70 eV) *m*/*z* (rel intensity) 285 (M^+, 1), 213 ($TsOCH_2CH_2CH_2^+$, 11), 173 ($CH_3C_6H_4SO_3H_2^+$, 79), 155 ($CH_3C_6H_4SO_2^+$, 27); HRMS (EI, 70 eV) calcd for $C_{14}H_{21}O_4S$ (M^+) 285.1161, found 285.1162.

5-Iodo-2,2-dimethylpentanal (13). Sodium iodide (2.00 g, 13.3 mmol) was added to a solution of chloroaldehyde **8**[27] (395 mg, 2.66 mmol) in anhydrous acetone (5.0 mL) and heated to reflux in the dark. After 12 h, the reaction was diluted with ether, washed with 5% Na_2SSO_3 (1×), water (1×), and brine (1×), dried (Na_2SO_4), and concentrated at room temperature. The residue was chromatographed (pentane to 5% ether/pentane gradient) to yield 366 mg (58%) iodoaldehyde **13** as a colorless oil. R_f = 0.23 (5% ether/pentane, stained black with phosphomolybdic acid); IR (CH_2Cl_2) 2700 (m), 1725 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1 H), 3.15 (t, J = 7.0 Hz, 2 H), 1.77−1.69 (m, 2 H), 1.59−1.53 (m, 2 H), 1.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.60, 45.38, 37.80, 28.36, 21.37; MS (EI, 70 eV) *m*/*z* (rel intensity) 241 (M^+, 1), 211 ([M − CHO]$^+$, 12), 169 ($ICH_2CH_2CH_2^+$, 22), 155 ($ICH_2CH_2^+$, 36), 127 (I^+, 4), 113 ([M − I]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_7H_{14}OI$ (M^+) 241.0089, found 241.0092.

(3a*S,3b*R**,9a*R**)- and (3a*S**,3b*S**,9a*R**)-4,4-Dimethyl-2-phenyloctahydro-2,8a-diazacyclopenta[*a*]azulene-1,3-dione (15).** Iodoaldehyde **16** (112 mg, 0.44 mmol) and (tri-*n*-butylstannyl)methylamine **9**[26b,28] (142 mg, 0.44 mmol) were dissolved in xylenes (4.4 mL) and allowed to stir at room temperature. After 10 min, *N*-phenylmaleimide (76 mg, 0.44 mmol) was added in one portion and the solution was heated to reflux for 14 h. The reaction was diluted in CH_2Cl_2, washed with 10% Na_2CO_3 (1×) and brine (1×), dried (Na_2SO_4), and concentrated. The residue was chromatographed (5% to 30% ethyl acetate/hexanes, gradient) to afford 121 mg (88%) **15** as a colorless oil as an inseparable 53:47 ratio of diastereomers. R_f = 0.18 (30% ethyl acetate/hexanes, stained with I_2); IR (CH_2Cl_2) 1712 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 2 H), 7.40−7.35 (m, 1 H), 7.30−7.25 (m, 2 H), 3.60 (t, J = 8.4 Hz, 1 H × 0.53), 3.47 (d, J = 9.5 Hz, 1 H × 0.53), 3.40 (q, J = 8.8 Hz, 1 H × 0.53), 3.34−3.28 (m, 1 H), 3.15 (t, J = 7.7 Hz, 1 H × 0.47), 2.99−2.92 (m, 1 H × 0.53), 2.92−2.86 (m, 1 H), 2.62 (t, J = 9.5 Hz, 1 H × 0.50), 2.58 (dd, J = 7.3, 9.5 Hz, 1 H × 0.50), 2.50−2.42 (m, 1 H), 2.34−2.25 (m, 1 H), 1.78−1.42 (m, 6 H + 1 H × 0.50), 1.32 (s, 3 H × 0.53), 1.04 (s, 6 H × 0.47), 0.94 (s, 3 H × 0.53); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.31, 178.13, 177.94, 176.56, 132.28, 131.84, 129.04, 128.44, 126.50, 126.32, 81.17, 74.70, 59.69, 58.83, 55.36, 52.13, 49.44, 47.74, 44.57, 43.72, 42.95, 42.61, 36.71, 35.69, 29.53, 29.05, 28.84, 24.64, 22.47, 22.14, 21.48, 18.39; MS (CI-NH_3) *m*/*z* (rel intensity) 313 ([M + H]$^+$, 100); HRMS (CI-NH_3) calcd for $C_{19}H_{24}N_2O_2Na$ ([M + H]$^+$) 313.1916, found 313.1920.

6-Iodo-2,2-dimethylhexanal (16). Sodium iodide (1.19 g, 7.96 mmol) was added to a solution of 6-chloro-2,2-dimethylhexanal **14**[27] (259 mg, 1.59 mmol) in anhydrous acetone (5 mL) and heated to reflux in the dark. After 10 h, the reaction was diluted with ether, washed with 5% Na_2SSO_3 (1×) and brine (1×), dried ($MgSO_4$), and concentrated at room temperature to yield 374 mg (93%) of iodoaldehyde **16** as a colorless oil that was sufficiently pure to be used without further purification. An analytical sample was purified by chromatography (pentane to 5% ether/pentane, gradient). R_f = 0.40 (5% ether/pentane, stained black in phosphomolybdic acid); IR (CH_2Cl_2) 2693 (m), 1724 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1 H), 3.19 (t, J = 7.0 Hz, 2 H), 1.82 (quint, J = 7.3 Hz, 2 H), 1.51−1.46 (m, 2 H), 1.38−1.29 (m, 2 H), 1.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 45.7, 35.8, 33.7, 25.2, 21.3, 6.4; MS (EI, 70 eV) *m*/*z* (rel intensity) 254 (M^+, 2), 225 ([M − CHO]$^+$, 20), 183 ($C_4H_8I^+$, 33), 169 ($C_3H_6I^+$, 30), 155 ($C_2H_4I^+$, 34), 127 (I^+, 66), 97 ($C_7H_{14}^+$, 54), 55 ($C_4H_7^+$, 100); HRMS (ESI) calcd for $C_8H_{16}OI$ ([M + H]$^+$) 255.0246, found 255.0251.

7-Iodo-2,2-dimethylheptanal (17). Sodium iodide (2.38 g, 15.8 mmol) was added to a solution of 7-chloro-2,2-dimethylheptanal **19** (700 mg, 3.96 mmol) in anhydrous acetone (10 mL) and heated to reflux in the dark. After 12 h, the reaction was diluted with ether, washed with 5% Na_2SSO_3 (1×), water (1×), and brine (1×), dried (Na_2SO_4), and concentrated at room temperature. The residue was chromatographed (pentane to 5% ether/pentane, gradient) to yield 704 mg (66%) of iodoaldehyde **17** as a colorless oil. Attempts at Kügelrohr distillation (100 °C, 1.0 mmHg) led to partial decomposition. R_f = 0.40 (5% ether/pentane, stained black in phosphomolybdic acid); IR (CH_2Cl_2) 2694 (m), 1725 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 3.18 (t, J = 7.0 Hz, 2 H), 1.82 (quint, J = 7.3 Hz, 2 H), 1.50−1.45 (m, 2 H), 1.39 (quint, J = 7.3 Hz, 2 H), 1.27−1.19 (m, 2 H), 1.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.21, 45.74, 36.96, 33.20, 31.00, 23.25, 21.29, 6.81; MS (EI, 70 eV) *m*/*z* (rel intensity) 239 ([M − CHO]$^+$, 11), 197 ($ICH_2CH_2CH_2CH_2CH_2^+$, 11), 183 ($ICH_2CH_2CH_2CH_2^+$, 16), 169 ($ICH_2CH_2CH_2^+$, 11), 155 ($ICH_2CH_2^+$, 16), 141 (ICH_2^+, 20), 49 (100); HRMS (ESI) calcd for $C_9H_{17}OINa$ ([M + Na]$^+$) 291.0222, found 291.0222.

(3a*S,3b*R**,10a*R**)- (18a) and (3a*S**,3b*S**,10a*R**)-4,4-Dimethyl-2-phenyldecahydro-2,9a-diazacycloocta[*a*]-pentalene-1,3-dione (18b).** Iodoaldehyde **17** (101 mg, 0.378 mmol) and (tri-*n*-butylstannyl)methylamine **9**[26b,28] (136 mg, 0.425 mmol) were dissolved in xylenes (7.6 mL) and allowed to stir at room temperature. After 10 min, *N*-phenylmaleimide (132 mg, 0.763 mmol) was added in one portion and the solution was heated to reflux for 14 h. The reaction was concentrated and the residue was chromatographed (5% to 30% ethyl acetate/hexanes, gradient) to afford 5.9 mg (6%) of **18a** and 12.5 mg (11%) of **18b** both as colorless oils.

18a (exo): R_f = 0.29 (30% ethyl acetate/hexanes, stained in I_2); IR (CH_2Cl_2) 1711 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45−7.50 (m, 2 H), 7.39 (tt, J = 7.6, 1.5 Hz, 1 H), 7.23−7.27 (m, 5 H), 3.63 (dd, J = 8.3, 12.3 Hz, 1 H), 3.43 (d, J = 2.7 Hz, 1 H, H-3b), 3.38 (dt, J = 2.4, 8.3 Hz, 1 H, H-3a), 3.30 (dd, J = 2.4, 6.8 Hz, 1 H), 3.28 (t, J = 2.7 Hz, 1 H), 2.71−2.81 (m, 2 H), 1.54−1.86 (m, 6 H), 1.35−1.48 (m, 2 H), 1.00 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 179.1, 132.1, 129.2, 128.5, 126.1, 72.3, 59.4, 57.9, 48.3, 48.0, 41.4, 38.1, 28.4, 27.9, 25.8, 23.7, 23.4; MS (EI, 70 eV) *m*/*z* (rel intensity) 326 (M^+, 43), 311 ([M − CH_3]$^+$, 6), 269 ([M − C_4H_8]$^+$, 31), 255 ([M − C_5H_{10}]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_{20}H_{26}N_2O_2$ (M^+) 326.1994, found 326.1991.

18b (endo): R_f = 0.19 (30% ethyl acetate/hexanes, stained in I_2); IR (CH_2Cl_2) 1709 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, J = 7.7 Hz, 2 H), 7.38 (tt, J = 1.5, 7.3 Hz, 1 H), 7.26−7.30 (m, 2 H), 3.33 (t, J = 8.3 Hz, 1 H, H-3a), 3.29 (d, J = 9.8 Hz, 1 H), 3.19 (t, J = 8.1 Hz, 1 H), 3.12 (dd, J = 15.4, 1.2 Hz, 1 H), 3.03 (dd, J = 8.3, 14.9 Hz, 1 H), 2.95 (d, J = 8.3

Hz, 1 H, H-3b), 2.89 (dd, J = 9.8, 7.3 Hz, 1 H), 1.58−1.77 (m, 6 H), 1.24−1.38 (m, 2 H), 1.32 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 178.3, 132.33, 129.10, 128.5, 126.6, 68.3, 55.7, 48.8, 47.6, 45.4, 43.7, 35.9, 30.1, 27.3, 22.8, 22.0, 20.0; MS (EI, 70 eV) m/z (rel intensity) 326 (M^+, 31), 311 ([M − CH_3]$^+$, 6), 269 ([M − C_4H_8]$^+$, 60), 255 ([M − C_5H_{10}]$^+$, 100); HRMS (ESI, 70 eV) $C_{20}H_{26}N_2O_2$ ([M + H]$^+$) 327.2073, found 327.2071. Stereochemical assignments were based on 2D COSY and 1D NOESY experiments, which showed a strong NOE between the H-3a and H-3b hydrogens (J_{3a-3b} = 8.3 Hz) in **18b**, but no similar NOE in **18a** (J_{3a-3b} = 2.4 Hz).

7-Chloro-2,2-dimethylheptanal (19). Diisopropylamine (3.97 g, 39.2 mmol) and anhydrous THF (40 mL) were cooled to 0 °C and treated with *n*-butyllithium (13.0 mL of a 2.5 M solution in hexanes, 32.5 mmol). After 30 min at 0 °C, *N*-cyclohexyl-(2-methylpropylidene)amine[27] (5.00 g, 32.6 mmol) was added at 0 °C with an additional amount of THF (5 mL). After 30 min at 0 °C, 1-bromo-5-chloropentane (5.52 g, 32.6 mmol) was added dropwise over 1 min at 0 °C. After 10 min at 0 °C, the solution was quenched with saturated aqueous NH_4Cl and concentrated. Ether and water were added and the pH was adjusted to 5 with H_3PO_4. The biphasic mixture was stirred at room temperature for 4 h with H_3PO_4 added as needed to readjust the pH to 5. The aqueous phase was extracted with ether (3×), washed with 2% H_3PO_4 (2×) and brine (1×), dried (Na_2SO_4), and concentrated at room temperature. The residue was chromatographed (pentane to 5% ether/pentane, gradient) to yield 3.86 g (67%) of chloroaldehyde **19** as a clear, colorless oil. R_f = 0.21 (5% ether/pentane, stained black with phosphomolybdic acid); IR (CH_2Cl_2) 2696 (m), 1725 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 3.53 (t, J = 6.6 Hz, 2 H), 1.81−1.73 (m, 2 H), 1.50−1.39 (m, 4 H), 1.27−1.19 (m, 2 H), 1.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 45.7, 44.8, 37.1, 32.4; MS (EI, 70 eV) m/z (rel intensity) 177 (M^+, 2), 147 ([M − CHO]$^+$, 34), 149 ([M − CHO + 2]$^+$, 14), 111 ([M − $ClCH_2CH_2$]$^+$, 54), 105 ($^{35}Cl(CH_2)_5^+$, 26), 107 ($^{37}Cl(CH_2)_5^+$, 10), 91 ($^{35}Cl(CH_2)_4^+$, 11), 93 ($^{37}Cl(CH_2)_4^+$, 4), 72 ([M − Cl-$(CH_2)_5$]$^+$, 67); HRMS (EI, 70 eV) calcd for $C_9H_{18}O^{35}Cl$ (M^+) 177.1046, found 177.1049.

(3a*S,3b*S**,8a*R**)- (21a) and (3a*S**,3b*R**,8a*R**)-2-Phenylhexahydropyrrolo[3,4-*a*]pyrrolizine-1,3-dione (21b).** 4-Chloropentanal **20**[39] (56.6 mg, 0.531 mmol) and (tri-*n*-butylstannyl)methylamine **9**[26b,28] (170 mg, 0.531 mmol) were dissolved in toluene (5.3 mL) and allowed to stir for 5 min. *N*-Phenylmaleimide (110 mg, 0.637 mmol) was added in one portion and the reaction was heated to reflux for 6 h. The reaction was concentrated and chromatographed (5% ethyl acetate/hexanes to ethyl acetate to 5% MeOH/ethyl acetate, gradient) to yield 51.0 mg (37.5%) of **21a** and 64.5 mg (47.4%) of **21b**.

21a (exo): R_f = 0.41 (50% ethyl acetate/hexanes, neutral alumina, stained with I_2); IR (CH_2Cl_2) 1775 (w), 1709 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.44 (m, 2 H), 7.38 (tt, J = 7.3, 1.1 Hz, 1 H), 7.34−7.30 (m, 2 H), 3.66 (td, J = 8.1, 2.2 Hz, 1 H), 3.51 (td, J = 8.4, 2.6 Hz, 1 H), 3.40 (dd, J = 10.6, 2.2 Hz, 1 H), 3.34 (dd, J = 8.4, 2.2 Hz, 1 H), 3.00−2.92 (m, 2 H), 2.83 (ddd, J = 12.8, 8.1, 4.8 Hz, 1 H), 2.19−2.10 (m, 1 H), 2.09−1.99 (m, 1 H), 1.85−1.74 (m, 1 H), 1.71−1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.00, 177.50, 131.88, 129.06, 128.54, 126.45, 69.19, 55.08, 52.00, 50.11, 45.94, 29.72, 23.61; MS (EI, 70 eV) m/z (rel intensity) 256 (M^+, 26), 228 ([M − C_2H_5]$^+$, 4), 119 ($PhNCO^+$, 5), 83 ([M − *N*-phenylmaleimide]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_{15}H_{16}N_2O_2$ (M^+) 256.1212, found 256.1213.

21b (endo): R_f = 0.29 (50% ethyl acetate/hexanes, neutral alumina, stained with I_2); IR (CH_2Cl_2) 1774 (w), 1706 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.43 (m, 2 H), 7.39 (tt, J = 7.4, 1.1 Hz, 1 H), 7.30−7.20 (m, 2 H), 3.76 (ddd, J = 4.0, 8.8, 7.7 Hz, 1 H), 3.58−3.52 (m, 1 H), 3.49 (dd, J = 8.4, 2.2 Hz, 1 H), 3.43−3.33 (m, 2 H), 3.07 (ddd, J = 4.7, 9.9, 8.4 Hz, 1 H), 2.52 (q, J = 8.4 Hz, 1 H), 2.28−2.18 (m, 1 H), 2.16−2.06 (m, 1 H), 1.98−1.78 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.73, 176.85, 131.93, 129.19, 128.59, 125.98, 68.63, 54.84, 53.00, 48.48, 48.34, 25.23, 24.91; MS (EI, 70 eV) m/z (rel intensity) 256 (M^+, 15), 228 ([M − C_2H_5]$^+$, 3), 119 ($PhNCO^+$, 6), 83 ([M − *N*-phenylmaleimide]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_{15}H_{16}N_2O_2$ (M^+) 256.1212, found 256.1217. The stereochemistry of **21a** and **21b** is based on correlation with close literature precident,[11g] as well as COSY and one-dimensional NOESY experiments.

(3a*S,9a*R**,9b*R**)- (23a) and (3a*R**,9a*R**,9b*S**)-Octahydro-2-phenyl-1*H*-pyrrolo[3,4-*a*]indolizidine-1,3(2*H*)-dione (23b).** 5-Bromopentanal **22**[40] (190 mg, 1.15 mmol) was added to a solution of (tri-*n*-butylstanyl)methylamine **9**[26b,28] (410 mg, 1.28 mmol) in toluene (2.5 mL), immediately followed by the addition of *N*-phenylmaleimide (220 mg, 1.27 mmol). The mixture was heated at reflux for 8 h. The reaction was concentrated and the residue was chromatographed (30% ethyl acetate/hexanes) to provide 130 mg (42%) of **23a** as a yellow oil. Further elution (ether) gave 136 mg (44%) of **23b** as a yellow oil.

23a (endo): R_f = 0.29 (30% ethyl acetate/hexanes, stained in I_2); IR ($CHCl_3$) 1708 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.15 (m, 5 H), 3.46 (d, J = 9.5 Hz, 1 H), 3.30−3.20 (dd, J = 5.3, 1.8 Hz, 2 H), 3.13−3.04 (m, 1 H), 2.45−2.35 (m, 1 H), 2.12−2.01 (m, 1 H), 2.01−1.91 (td, J = 11.4, 3.0 Hz, 1 H), 1.91−1.80 (m, 1 H), 1.70−1.57 (m, 1 H), 1.57−1.10 (m, 3 H), 0.98−0.85 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$, JMOD) δ 178.7 (−), 175.9 (−), 132.1 (−), 129.0 (+), 128.4 (+), 126.5 (+), 65.9 (+), 57.5 (−), 52.7 (−), 47.6 (+), 43.4 (+), 27.9 (−), 24.9 (−), 24.2 (−); MS (EI, 70 eV) m/z (rel intensity) 270 (M^+, 33), 269 ([M − H]$^+$, 21), 97 ([M − *N*-phenylmaleimide]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_{16}H_{18}N_2O_2$ (M^+) 270.1368, found 270.1371.

23b (exo): R_f = 0.35 (ether, stained in I_2); IR ($CHCl_3$) 1777 (m), 1712 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.20 (m, 5 H), 3.60−3.45 (m, 2 H), 3.15−2.98 (m, 2 H), 2.55−2.40 (m, 1 H), 2.30−2.05 (m, 3 H), 1.86 (m, 1 H), 1.70−1.15 (m, 4 H); ^{13}C NMR (90 MHz, $CDCl_3$, JMOD) δ 177.2 (−), 176.2 (−), 131.7 (−), 129.2 (+), 129.1 (+), 128.6 (+), 126.5 (+), 126.4 (+), 66.7(+), 55.4 (−), 51.7 (−), 50.9 (+), 43.5 (+), 29.4 (−), 23.9 (−), 23.8 (−); MS (EI, 70 eV) m/z (rel intensity) 270 (M^+, 56), 97 ([M − *N*-phenylmaleimide]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_{16}H_{18}N_2O_2$ (M^+) 270.1368, found 270.1360.

The stereochemistry was tentatively assigned based on the assumption that the geometry of the alkene was retained, and by analogy to **7a** and **7b**. NOESY experiments failed to confirm the stereochemical assignments for **23a** and **23b**.

(4a*S,4b*S**,9a*R**)- (25a) and (4a*S**,4b*R**,9a*R**)-2-phenyloctahydro-2,8a-diazacyclopenta[*a*]azulene-1,3-dione (25b).** 6-Iodohexanal **24**[41] (82.6 mg, 0.366 mmol) and (tri-*n*-butylstannyl)methylamine **9**[26b,28] (117 mg, 0.366 mmol) were dissolved in xylenes (3.7 mL) and allowed to stir for 5 min at room temperature. *N*-Phenylmaleimide (76 mg, 0.44 mmol) was added in one portion and the reaction was heated to reflux for 14 h. The reaction was concentrated and chromatographed (10% to 100% ethyl acetate/hexanes, gradient) to yield 47.0 mg (45%) of **25a** and 46.2 mg (45%) of **25b**, both as colorless oils.

25a (endo): R_f = 0.49 (ethyl acetate, stained with I_2); IR (CH_2Cl_2) 1773 (w), 1708 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.40 (m, 2 H), 7.34 (tt, J = 7.8, 1.1 Hz, 1 H), 7.27−7.22 (m, 2 H), 3.42 (d, J = 9.5 Hz, 1 H), 3.19−3.13 (m, 2 H), 2.94 (dt, J = 13.2, 4.0 Hz, 1 H), 2.59−2.54 (m, 1 H), 2.50 (td, J = 7.7, 2.6 Hz, 1 H), 2.18−2.08 (m, 2 H), 1.75−1.44 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.78, 176.37, 132.15, 129.03, 128.43, 126.49, 68.98, 58.84, 53.21, 48.69, 44.07, 29.21, 26.70, 26.62, 24.09; MS (EI, 70 eV) m/z (rel intensity) 284 (M^+, 6), 119 ($PhNCO^+$, 10), 57 (100); HRMS (EI, 70 eV) calcd for $C_{17}H_{20}N_2O_2$ (M^+) 284.1525, found 284.1528.

25b (exo): R_f = 0.19 (ethyl acetate, stained with I_2); IR (CH_2Cl_2) 1710 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.44 (m, 2 H), 7.38 (tt, J = 7.3, 1.2 Hz, 1 H), 7.30−7.27 (m, 2 H), 3.49 (td, J = 8.8, 6.1 Hz, 1 H), 3.42 (t, J = 9.0 Hz, 1 H), 3.07 (dd, J = 8.8, 6.1 Hz, 1 H), 2.90−2.83 (m, 2 H), 2.77 (dd, J = 9.8, 5.9 Hz, 1 H), 2.56 (ddd, J = 12.2, 9.8, 2.2 Hz, 1 H), 2.10−

2.03 (m, 1 H), 1.83−1.50 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.44, 177.09, 131.75, 129.07, 128.53, 126.43, 68.84, 57.26, 53.52, 52.83, 43.82, 33.22, 27.05, 26.22, 25.33; MS (EI, 70 eV) *m/z* (rel intensity) 284 (M^+, 100), 269 ([M − CH_3]$^+$, 10), 255 ([M − C_2H_5]$^+$, 58), 242 ([M − C_3H_7]$^+$, 94), 111 ([M − *N*-phenylmaleimide]$^+$, 78); HRMS (EI, 70 eV) calcd for $C_{17}H_{20}N_2O_2$ (M^+) 284.1525, found 284.1518.

Octahydro-8,8-dimethyl-1-indolizidinecarboxylic Acid Methyl Ester and Octahydro-8,8-dimethyl-2-indolizidinecarboxylic Acid Methyl Ester (26). Imine **1** (130 mg, 0.29 mmol) and methyl acrylate (47 mg, 0.54 mmol) were heated at reflux in toluene (0.5 mL) for 3 h. The reaction was concentrated and the residue chromatographed (40% ethyl acetate/hexanes) to give 48 mg (79%) of the title compound as a clear oil containing three inseparable isomers (1:1:1.8 by GC). Both the regio- and stereochemistry could not be determined. Data for the mixture: R_f = 0.23 (40% ethyl acetate/hexanes); IR ($CHCl_3$) 1738 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.692 (s, 3 H), 3.688 (s, 3 H), 3.678 (s, 3 H), 3.38−3.26 (m, 2 H), 3.10−2.90 (m, 4 H), 2.90−2.64 (m, 2 H), 2.30−2.16 (m, 3 H), 2.10−1.56 (m, 15 H), 1.56−1.35 (m, 6 H), 1.20−1.10 (m, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 3 H), 0.86 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 175.75, 175.72, 76.0, 72.9, 72.1, 58.3, 57.5, 54.4, 53.54, 53.47, 53.43, 51.8, 51.7, 51.6, 43.2, 39.6, 39.33, 39.26, 39.23, 39.1, 32.65, 32.24, 32.17, 29.0, 28.9, 28.8, 28.7, 28.3, 27.7, 22.2, 22.1, 22.0, 19.3, 19.1, 18.9; MS (EI, 70 eV) *m/z* (rel intensity) 211 (M^+, 30), 210 ([M − H]$^+$, 17), 196 ([M − CH_3]$^+$, 40), 180 ([M − OCH_3]$^+$, 26), 152 ([M − CO_2CH_3]$^+$, 34), 142 (100), 125 ([M − $CH_2CHCO_2CH_3$]$^+$, 19); HRMS (EI, 70 eV) calcd for $C_{12}H_{21}NO_2$ (M^+) 211.1572, found 211.1565.

(1*S,2*R**,8a*R**)- (27a) and (1*R**,2*S**,8a*R**)-Octahydro-8,8-dimethyl-1,2-indolizinedicarboxylic Acid Dimethyl Ester (27b).** Imine **11** (490 mg, 1.09 mmol) and dimethyl maleate (160 mg, 1.11 mmol) were heated to reflux in toluene (2 mL) for 5 h. The reaction was concentrated and the residue chromatographed (20% to 40% ethyl acetate/hexanes, gradient) to provide 119 mg (41%) of **27a** and 92 mg (31%) of **27b**, both as yellow oils.

27a (exo): R_f = 0.23 (20% ethyl acetate/hexanes); IR ($CHCl_3$) 1736 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 3.64 (s, 3 H), 3.21−3.01 (m, 4 H, H-1, H-2, H-3, and H-5), 2.70−2.62 (m, 1 H), 2.17 (d, J = 8.4 Hz, 1 H, H-8a), 2.04 (dt, J = 10.0, 3.0 Hz, 1 H), 1.72−1.61 (m, 1 H), 1.50−1.40 (m, 2 H), 1.14 (dt, J = 11.1, 4.7 Hz, 1 H), 0.95 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 172.1, 76.4, 56.4, 53.1, 51.8, 46.5, 44.8, 39.5, 32.9, 28.1, 22.0, 19.3; MS (EI, 70 eV) *m/z* (rel int) 269 (M^+, 49), 254 ([M − CH_3]$^+$, 47), 238 ([M − OCH_3]$^+$, 35), 210 ([M − CO_2CH_3]$^+$, 42), 200 (100), 125 ([M − MeO_2-CCH=CHCO$_2$Me]$^+$, 31); HRMS (EI, 70 eV) calcd for $C_{14}H_{23}$-NO_4 (M^+) 269.1627, found 269.1640.

27b (endo): R_f = 0.19 (30% ethyl acetate/hexanes); IR ($CHCl_3$) 1733 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (dd, J = 9.8, 6.3 Hz, 1 H), 3.65 (s, 3 H), 3.64 (s, 3 H), 3.33 (dd, J = 8.0, 5.4 Hz, 1 H, H-1), 3.20−3.08 (m, 2 H, H-2 and H-5), 2.47 (dd, J = 11.1, 9.8 Hz, 1 H), 2.15 (d, J = 5.4 Hz, 1 H, H-8a), 1.94 (td, J = 11.5, 3.0 Hz, 1 H), 1.79−1.69 (m, 1 H), 1.44−1.32 (m, 1 H), 1.09−0.99 (m, 1 H), 1.02 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.1, 172.2, 76.5, 55.0, 51.9, 47.5, 44.0, 41.7, 33.0, 27.9, 21.9, 18.9; MS (EI, 70 eV) *m/z* (rel intensity) 269 (M^+, 34), 268 ([M − H]$^+$, 55), 254 ([M − CH_3]$^+$, 38), 238 ([M − OCH_3]$^+$, 35), 210 ([M − CO_2CH_3]$^+$, 48), 200 (100), 125 ([M − MeO_2CCH=$CHCO_2Me$]$^+$, 35); HRMS (CI, NH_3) calcd for $C_{14}H_{24}NO_4$ ([M + H]$^+$) 270.1705, found 270.1695.

The stereochemical assignment of **27a** and **27b** was made by 2D COSY and NOESY experiments. For **27a**, there was an NOE cross-peak between the H-1 and H-2 resonances and no cross-peak between H-8a and H-1. For **27b**, there were NOE cross-peaks between H-8a and H-1, and H-1 and H-2.

(2*S,8a*R**)- (28a) and (2*R**,8a*R**)-Hexahydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[3,2-*a*]pyridine (28b).** Imine **1** (100 mg, 0.22 mmol) and benzaldehyde (49 mg, 0.46 mmol) were heated in toluene (1.5 mL) at reflux for 1.5 h. The reaction was concentrated and the residue chromatographed (20% ethyl acetate/hexanes) to afford 32 mg (63%) of the title compounds as an inseparable mixture of two diastereomers (3:2), both as clear oils. Data for the mixture: R_f = 0.51 (30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.20 (m, 5 H), 5.05 (dd, J = 9.2, 6.2 Hz, 1 H × 0.60, H-2), 4.94 (dd, J = 8.8, 2.4 Hz, 1 H × 0.40, H-2), 3.70 (s, 1 H × 0.60, H-8a), 3.50 (dd, J = 9.7, 3.5 Hz, 1 H × 0.60), 3.36 (s, 1 H × 0.40, H-8a), 3.08 (dd, J = 8.7, 6.3 Hz, 1 H × 0.40), 3.02−2.88 (m, 1 H), 2.78 (t, J = 8.8 Hz, 1 H × 0.40), 2.48 (t, J = 9.5 Hz, 1 H × 0.60), 2.32 (td, J = 9.9, 3.3 Hz, 1 H × 0.60), 2.08 (td, J = 11.1, 3.1 Hz, 1 H × 0.40), 1.84−1.62 (m, 2 H × 0.60), 1.62−1.42 (m, 2 H), 1.30−1.18 (m, 2 H × 0.40), 1.17 (s, 3 H × 0.40), 1.07 (s, 3 H × 0.60), 1.06 (s, 3 H × 0.60), 1.03 (s, 3 H × 0.40); ^{13}C NMR (90 MHz, $CDCl_3$) δ 128.4, 128.2, 127.3, 126.5, 125.7, 101.4, 101.3, 76.6, 76.3, 62.2, 60.3, 50.8, 50.0, 37.1, 35.7, 34.0, 33.4, 27.3, 27.1, 21.9, 21.7, 20.9, 19.7; MS (EI, 70 eV) *m/z* (rel intensity) 231 (M^+, 16), 230 ([M − H]$^+$, 14), 216 ([M − CH_3]$^+$, 3), 125 ([M − PhCHO]$^+$, 100), 104 (PhCHO$^+$, 69), 91 (PhCH$_2^+$, 11); HRMS (EI, 70 eV) calcd for $C_{15}H_{21}NO$ (M^+) 231.1623, found 231.1615.

The regiochemistry was determined based on the splitting pattern of the bridgehead hydrogen H-8a. The stereochemistry of the major isomer could not be determined.

Hexahydro-8,8-dimethyl-2,2-diphenyl-5*H*-oxazolo[3,2-*a*]pyridine (29). Imine **1** (100 mg, 0.43 mmol) and benzophenone (75 mg, 0.43 mmol) were heated to reflux in toluene (2 mL) for 1.5 h. The reaction was concentrated and the residue chromatographed (10% ethyl acetate/hexanes) to afford 87 mg (66%) of the title compound as a colorless oil: R_f = 0.20 (10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.10 (m, 10 H), 3.89 (d, J = 9.1 Hz, 1 H), 3.53 (s, 1 H), 3.02 (d, J = 9.1 Hz, 1 H), 2.95−2.87 (m, 1 H), 2.12 (td, J = 10.6, 3.1 Hz, 1 H), 1.75−1.60 (m, 1 H), 1.54−1.40 (m, 1 H), 1.23−1.14 (m, 1 H), 1.10 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 128.2, 127.9, 126.7, 126.6, 126.3, 125.9, 100.7, 83.7, 67.2, 50.4, 36.5, 33.6, 27.1, 21.7, 20.4; MS (EI, 70 eV) *m/z* (rel intensity) 307 (M^+, 9), 180 (Ph$_2$CO$^+$, 51), 125 ([M − Ph$_2$CO]$^+$, 100), 77 (Ph$^+$, 22); HRMS (EI, 70 eV) calcd for $C_{21}H_{25}NO$ (M^+) 307.1936, found 307.1924.

(1*S,2*R**,8a*R**)-Octahydro-8,8-dimethyl-2-phenyl-1-indolizinecarboxylic Acid Methyl Ester (30a), (1*S**,2*R**,8a*R**)-Octahydro-8,8-dimethyl-1-phenyl-2-indolizinecarboxylic Acid Methyl Ester (30b), and (1*R**,2*S**,8a*R**)-Octahydro-8,8-dimethyl-1-phenyl-2-indolizinecarboxylic Acid Methyl Ester (30c).** Imine **1** (300 mg, 0.66 mmol) and *trans*-methyl cinnamate (161 mg, 1.0 mmol) were heated to reflux in toluene (4 mL) for 6 h. The reaction was concentrated and the residue chromatographed (15% to 25% ethyl acetate/hexanes, gradient) to afford 81 mg (42%) of **30a**, 8 mg (4%) of **30b**, and 40 mg (22%) of **30c**, all as light yellow oils.

30a: R_f = 0.36 (15% ethyl acetate/hexanes); IR ($CHCl_3$) 1729 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.15 (m, 5 H), 3.90−3.78 (m, 1 H, H-2), 3.69 (s, 3 H), 3.59 (t, J = 8.5 Hz, 1 H), 3.30−3.22 (m, 1 H), 3.08 (dd, J = 8.6, 5.4 Hz, 1 H, H-1), 2.19 (d, J = 8.6 Hz, 1 H, H-8a), 2.14 (t, J = 9.6 Hz, 1 H), 1.90−1.70 (m, 2 H), 1.50−1.35 (m, 2 H), 1.20−1.00 (m, 1 H), 1.08 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 143.3, 128.5, 128.3, 127.5, 126.7, 64.1, 55.0, 53.5, 51.8, 45.7, 42.7, 33.1, 29.1, 28.0, 21.6, 19.8; MS (CI, NH_3) *m/z* (rel intensity) 288 ([M + H]$^+$, 100), 287 (M^+, 4); HRMS (CI, NH_3) calcd for $C_{18}H_{26}$-NO_2 ([M + H]$^+$) 288.1963, found 288.1965. The stereochemical assignment was based on 2D NOESY experiments, which showed a cross-peak between H-1 and H-8a, but none between H-1 and H-2. Assignment of proton resonances was confirmed by COSY experiments on derivative **32a**.

30b: R_f = 0.26 (15% ethyl acetae/hexanes); IR ($CHCl_3$) 1728 (s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.50−7.05 (m, 5 H), 3.67 (s, 3 H), 3.65−3.55 (m, 2 H, H-1 and H-3), 3.25−3.18 (m, 1 H), 3.10 (td, J = 8.4, 3.0 Hz, 1 H, H-2), 2.32 (dd, J = 9.6, 7.9 Hz, 1 H), 2.06 (d, J = 6.6 Hz, 1 H, H-8a), 1.92−1.85 (m, 1 H),

1.68−1.58 (m, 1 H), 1.45−1.35 (m, 1 H), 1.28−1.12 (m, 1 H), 1.10−0.98 (m, 1 H), 0.90 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.7, 144.0, 130.1, 127.6, 126.5, 76.3, 58.6, 55.5, 52.0, 50.4, 50.1, 42.7, 33.4, 28.1, 21.9, 21.2; MS (EI, 70 eV) *m*/*z* (rel intensity) 287 (M^+, 48), 272 ($[M - CH_3]^+$, 31), 256 ($[M - OCH_3]^+$, 19), 228 ($[M - CO_2CH_3]$, 49), 218 (100), 125 ($[M - PhCH{=}CHCO_2Me]^+$, 96), 91 ($PhCH_2^+$, 24); HRMS (EI, 70 eV) calcd for $C_{18}H_{25}NO_2$ (M^+) 287.1885, found 287.1888. The stereochemical assignment was based on 2D NOESY experiments, which showed a cross-peak between H-1 and H-8a, but none between H-1 and H-2. Assignment of proton resonances was confirmed by COSY experiments on derivative **32b**.

30c: R_f = 0.15 (15% ethyl acetate/hexanes); IR (neat) 1728 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.15 (m, 5 H), 3.66 (s, 3 H), 3.28−3.20 (m, 1 H, H-2), 3.08−2.98 (m, 2 H), 2.74−2.66 (m, 2 H, H-1 and H-3), 2.19 (d, J = 9.5 Hz, 1 H, H-8a), 1.93 (td, J = 8.6, 3.0 Hz, 1 H), 1.80−1.66 (m, 1 H), 1.50−1.38 (m, 2 H), 1.14 (td, J = 13.3, 4.0 Hz, 1 H), 1.04 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 176.2 (−), 146.4 (−), 128.5 (+), 127.2 (+), 126.3 (+), 76.5 (+), 62.4 (−), 54.5 (+), 53.6 (−), 51.7 (+), 47.0 (+), 39.7 (−), 33.0 (−), 28.2 (+), 22.1 (−), 19.6 (+); MS (EI, 70 eV) *m*/*z* (rel intensity) 287 (M^+, 21), 272 ($[M - CH_3]^+$, 13), 256 ($[M - OCH_3]^+$, 12), 228 ($[M - CO_2CH_3]$, 23), 125 ($[M - PhCH{=}CHCO_2Me]^+$, 100), 91 ($PhCH_2^+$, 12); HRMS (EI, 70 eV) calcd for $C_{18}H_{25}NO_2$ (M^+) 287.1885, found 287.1886. The stereochemical assignment was based on 2D NOESY experiments, which showed no cross-peaks between H-1, H-2, and H-8a. Assignment of proton resonances was confirmed by COSY experiments on derivative **32c**.

1,1-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]pyrido[2,1-*a*]-isoindole-7,12-dione (31). Chloroaldehyde **8**[27] (54 mg, 0.36 mmol) and (tri-*n*-butylstannyl)methylamine **9**[26b,28] were extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×), dried (Na_2SO_4), and concentrated and the residue chromatographed (5% ethyl acetate/hexanes to ethyl acetate, gradient) to yield 7.2 mg (7%) of dione **31** as a white crystalline solid. R_f = 0.50 (30% ethyl acetate/hexanes); IR (CH_2Cl_2) 1657 (s), 1641 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J = 7.3, 1.8 Hz, 1 H), 8.20 (dd, J = 7.3, 1.8 Hz, 1 H), 7.69 (td, J = 7.0, 2.0 Hz, 1 H), 7.65 (td, J = 7.3, 1.5 Hz, 1 H), 7.28 (s, 1 H), 4.03 (t, J = 5.9 Hz, 2 H), 1.97−2.05 (m, 2 H), 1.79−1.82 (m, 2 H), 1.58 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 179.3, 146.0, 136.7, 134.7, 133.1, 132.4, 127.3, 126.29, 123.2, 122.9, 117.0, 53.4, 47.6, 37.8, 33.3, 26.7, 19.9; MS (EI, 70 eV) *m*/*z* (rel intensity) 279 (M^+, 47), 264 ($[M - CH_3]^+$, 100); HRMS (EI, 70 eV) calcd for $C_{18}H_{17}NO_2$ (M^+) 279.12593, found 279.1264.

(1*S,2*R**,8a*R**)-1-Hydroxymethyl-8,8-dimethyl-2-phenylindolizidine (32a).** Ester **30a** (66 mg, 0.23 mmol) was dissolved in THF (1 mL) and cooled to −78 °C. Lithium aluminum hydride (17 mg, 0.46 mmol) was added in one portion and the reaction was allowed to warm to room temperature. The reaction was quenched by addition of water (50 μL), 20% NaOH (50 μL), and water (150 μL) in sequence. The mixture was diluted with ether, filtered through a pad of Celite, and concentrated and the residue chromatographed (50% ethyl acetate/hexanes) to yield 58 mg (98%) of the title compound as a colorless oil: R_f = 0.12 (40% ethyl acetate/hexanes); IR ($CHCl_3$) 3316 (br) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36−7.10 (m, 5 H), 3.90−3.75 (m, 2 H), 3.55 (t, J = 9.0 Hz, 1 H, H-3), 3.30 (td, J = 8.8, 3.7 Hz, 1 H, H-2), 3.24−3.15 (m, 1 H, H-5), 2.50 (br s, 1 H, −OH), 2.42−2.34 (m, 1 H, H-1), 2.12 (d, J = 8.9 Hz, 1 H, H-8a), 2.08 (d, J = 9.4 Hz, 1 H, H-3), 1.85−1.70 (m, 2 H, H-5 and H-6), 1.50−1.35 (m, 2 H, H-6 and H-7), 1.25−1.10 (m, 1 H, H-7), 1.15 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 145.7, 128.5, 127.6, 126.2, 75.6, 65.2, 64.9, 55.7, 51.4, 46.4, 43.0, 33.3, 28.4, 21.8, 21.6; MS (CI, NH_3) *m*/*z* (rel intensity) 260 ($[M + H]^+$, 80), 259 (M^+, 25), 242 ($[M - OH]^+$, 9), 228 ($[M - CH_2OH]^+$, 21), 125 ($[M - PhCH{=}CHCH_2OH]^+$, 100), 91 ($PhCH_2^+$, 13); HRMS (CI, NH_3) calcd for $C_{17}H_{26}NO$ ($[M + H]^+$) 260.2014, found 260.2005.

(1*S,2*R**,8a*R**)-2-Hydroxymethyl-8,8-dimethyl-1-phenylindolizidine (32b). 32b** was prepared from the ester **30b** (10 mg, 0.035 mmol) and lithium aluminum hydride (3 mg, 0.08 mmol) according to the procedure for the formation of **32a**. Chromatography (40% ethyl acetate/hexanes) afforded 7 mg (78%) of the title compound as a yellow oil. R_f = 0.12 (30% ethyl acetate/hexanes); IR ($CHCl_3$) 3615 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.10 (m, 5 H), 3.61 (dABq, J = 7.0 Hz, Du = 20.6 Hz, J_{AB} = 10.7 Hz, 2 H), 3.59−3.51 (m, 1 H, H-3), 3.27−3.20 (m, 1 H, H-5), 3.07 (dd, J = 6.6, 2.6 Hz, 1 H, H-1), 2.50−2.38 (m, 1 H, H-2), 1.95−1.75 (m, 3 H, H-8a, H-3 and H-5), 1.75−1.45 (m, 2 H), 1.45−1.30 (m, 1 H), 1.20−1.10 (m, 1 H), 1.03 (dt, J = 13.2, 4.0 Hz, 1 H), 0.88 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 130.5, 129.9, 128.1, 127.3, 126.1, 66.4, 59.4, 56.0, 50.1, 48.6, 42.9, 33.3, 29.7, 28.2, 21.9, 21.2; MS (EI, 70 eV) *m*/*z* (rel intensity) 259 (M^+, 22), 228 ($[M - CH_2OH]^+$, 19), 125 ($[M - PhCH{=}CHCH_2OH]^+$, 100), 91 ($PhCH_2^+$, 11); HRMS (EI, 70 eV) calcd for $C_{17}H_{25}NO$ (M^+) 259.1936, found 259.1932.

(1*R,2*S**,8a*R**)-2-Hydroxymethyl-8,8-dimethyl-1-phenylindolizidine (32c). 32c** was prepared from the ester **30c** (48 mg, 0.17 mmol) and lithium aluminum hydride (13 mg, 0.34 mmol) according to the procedure for the formation of **32a**. Chromatography (25% ethyl acetate/hexanes) produced 40 mg (91%) of the title compound as a colorless oil: R_f = 0.38 (40% ethyl acetate/hexanes); IR ($CHCl_3$) 3316 (m) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40−7.10 (m, 5 H), 3.75−3.60 (m, 2 H), 3.26 (br s, 1 H), 3.15−3.08 (m, 1 H, H-5), 3.07 (d, J = 9.2 Hz, 1 H, H-3), 2.98 (dd, J = 9.3, 4.3 Hz, 1 H, H-1), 2.62 (dd, J = 8.9, 7.7 Hz, 1 H, H-3), 2.12−2.05 (m, 1 H, H-2), 2.05 (d, J = 9.3 Hz, 1 H, H-8a), 2.00−1.90 (m, 1 H, H-5), 1.80−1.60 (m, 2 H, H-6ax and H-6eq), 1.52−1.42 (m, 1 H, H-7), 1.40−1.30 (m, 1 H, H-7), 1.08 (s, 3 H), 0.48 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.5, 128.5, 128.1, 126.1, 80.5, 67.2, 59.2, 53.9, 49.4, 48.2, 40.3, 33.7, 29.2, 22.1, 19.8; MS (EI, 70 eV) *m*/*z* (rel intensity) 259 (M^+, 6), 228 ($[M - CH_2OH]^+$, 85), 125 ($[M - PhCH{=}CHCH_2OH]^+$, 91), 91 ($PhCH_2^+$, 37); HRMS (EI, 70 eV) calcd for $C_{17}H_{25}NO$ (M^+) 259.1936, found 259.1933.

5,6,7,8-Tetrahydro-8,8-dimethyl-1,2-indolizinedicarboxylic Acid Dimethyl Ester (33). Dimethylacetylene dicarboxylate (53 mg, 0.37 mmol) was added to a solution of imine **1** (160 mg, 0.36 mmol) in toluene (1.5 mL) and heated at reflux for 48 h. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (38 mg, 0.17 mmol) was then added and the reaction was heated at reflux for an additional 24 h. The reaction was concentrated and the residue was chromatographed (30% ethyl acetate/hexanes) to afford 73 mg (78%) of the title compound as a yellow oil: R_f = 0.23 (30% ethyl acetate/hexanes); IR (neat) 1713 (s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.02 (s, 1 H), 3.89 (t, J = 6.2 Hz, 3 H), 3.86 (s, 3 H), 3.75 (s, 3 H), 2.02−1.94 (m, 2 H), 1.70−1.64 (m, 2 H), 1.36 (s, 6 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.0, 164.2, 138.6, 123.8, 114.0, 112.7, 52.0, 51.2, 46.4, 37.4, 32.5, 29.1, 27.8, 19.7; MS (EI, 70 eV) *m*/*z* (rel intensity) 265 (M^+, 24), 250 ($[M - CH_3]^+$, 11), 234 ($[M - OCH_3]^+$, 23), 218 (100); HRMS (EI, 70 eV) calcd for $C_{14}H_{19}NO_4$ (M^+) 265.1314, found 265.1305.

5,6,7,8-Tetrahydro-8,8-dimethyl-1-indolizinecarboxylic Acid Methyl Ester (34a) and 5,6,7,8-Tetrahydro-8,8-dimethyl-2-indolizinecarboxylic Acid Methyl Ester (34b). Methyl propiolate (72 mg, 0.85 mmol) and imine **1** (192 mg, 0.43 mmol) were heated to reflux in toluene (2.5 mL) for 10 h. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (290 mg, 1.28 mmol) was then added and the mixture was kept at reflux for an additional 1 h. The reaction was concentrated and the residue chromatographed (5% ethyl acetate/hexanes) to afford 37 mg (21%) of **34a** and 53 mg (30%) of **34b**, both as orange oils. The regiochemistry was assigned according to similar literature precedents.

34a: R_f = 0.45 (10% ethyl acetate/hexanes); IR ($CHCl_3$) 1701 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, J = 2.9 Hz, 1 H), 6.38 (d, J = 2.9 Hz, 1 H), 3.90 (t, J = 5.9 Hz, 2 H), 3.77 (s, 3 H), 1.96−1.90 (m, 2 H), 1.74−1.68 (m, 2 H), 1.50 (s, 6 H);

^{13}C NMR (90 MHz, $CDCl_3$, JMOD) δ 118.6 (+), 111.6 (+), 50.7 (+), 46.8 (−), 38.9 (−), 32.9 (−), 29.7 (−), 27.6 (+), 20.1 (−); MS (EI, 70 eV) *m/z* (rel intensity) 207 (M^+, 39), 192 ([M − CH_3]$^+$, 72), 176 ([M − OCH_3]$^+$, 13), 160 (100); HRMS (EI, 70 eV) calcd for $C_{12}H_{17}NO_2$ (M^+) 207.1259, found 207.1269.

34b: R_f = 0.27 (10% ethyl acetate/hexanes); IR (neat) 1697 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 1.9 Hz, 1 H), 6.32 (d, J = 1.9 Hz, 1 H), 3.90 (t, J = 6.1 Hz, 2 H), 3.78 (s, 3 H), 2.02−1.95 (m, 2 H), 1.69−1.64 (m, 2 H), 1.28 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 140.1, 123.6, 114.8, 104.0, 50.8, 45.9, 36.1, 31.6, 21.2, 20.2; MS (EI, 70 eV) *m/z* (rel intensity) 207 (M^+, 21), 192 ([M − CH_3]$^+$, 100); HRMS (EI, 70 eV) calcd for $C_{12}H_{17}NO_2$ (M^+) 207.1259, found 207.1261.

1-Methyl-3,3-dimethyl-2-phenylethynylpiperidine (35). Imine **1** (178 mg, 0.76 mmol) and phenylacetylene (755 mg, 7.60 mmol) were dissolved in toluene (7.6 mL) and heated to reflux overnight. The reaction was concentrated and chromatographed (15% ethyl acetate/hexanes) to afford 85 mg (49%) of the title compound as a colorless oil. R_f = 0.25 (10% ethyl acetate/hexanes, stained with I_2); IR ($CHCl_3$) 2200 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.40 (m, 2 H), 7.35−7.25 (m, 3 H), 3.05 (br s, 1 H), 2.62 (m, 1 H), 2.38 (s, 3 H), 2.30 (m, 1 H), 1.70−1.45 (m, 3 H), 1.25−1.15 (m, 1 H), 1.12 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, JMOD) δ 131.6 (+), 128.1 (+), 127.6 (+), 123.8 (−), 87.2 (−), 86.8 (−), 65.9 (+), 52.2 (−), 44.9 (+), 34.7 (−), 34.4 (−), 26.9 (+), 26.7 (+), 22.1 (−); MS (EI, 70 eV) *m/z* (rel intensity) 227 (M^+, 46), 212 ([M − CH_3]$^+$, 33), 115 (100), 91 ($PhCH_2^+$, 13), 77 (Ph^+, 18); HRMS (EI, 70 eV) calcd for $C_{16}H_{21}N$ (M^+) 227.1674, found 227.1666.

1-Methyl-2-phenylethynylpiperidine (36). By an alternate procedure for this known compound,[43] phenylacetylene (1.03 g, 10.0 mmol) was added to a solution of (tri-*n*-butylstannyl)methylamine **9**[26b,28] (330 mg, 1.03 mmol) and 5-bromopentanal[40] (170 mg, 1.03 mmol) in toluene (6 mL) and heated at reflux overnight. The reaction was concentrated and the residue chromatographed (80% ether/hexane) to yield 90 mg (44%) piperidine **36** as a yellow oil: R_f = 0.35 (80% ether/hexanes, stained with I_2); IR ($CHCl_3$) 2253 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.40 (m, 2 H), 7.34−7.26 (m, 3 H), 3.55 (br s, 1 H), 2.70−2.60 (m, 1 H), 2.42 (s, 3 H), 2.40−2.32 (m, 1 H), 1.98−1.42 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6, 128.1, 127.7, 123.5, 87.7, 86.0, 54.9, 52.1, 44.5, 32.0, 25.9, 21.0; MS (EI, 70 eV) *m/z* (rel intensity) 199 (M^+, 48), 198 ([M − H]$^+$, 69), 170 ([M − C_2H_5]$^+$, 100), 157 ([M − C_3H_6]$^+$, 29), 142 ([M − C_4H_7]$^+$, 43), 115 ($PhCCCH_2^+$, 44); HRMS (EI, 70 eV) calcd for $C_{14}H_{16}N$ ([M − H]$^+$) 198.1283, found 198.1276.

The ^{1}H NMR resonances do not match the literature data exactly.[43] The authors do not specify the field strength (60 or 270 MHz) of their spectrometer.

lit.[43] ^{1}H (60 or 270 MHz)	**36** ^{1}H (300 MHz)
7.20−7.10 (m, 5 H)	7.48−7.30 (m, 2 H), 7.34−7.26 (m, 3 H)
3.54 (t, J = 4 Hz, 1 H)	3.55 (br s, 1 H)
2.90−2.10 (m, 2 H)	2.70−2.58 (m, 1 H)
2.24 (s, 3 H)	2.42 (s, 3 H)
2.10−1.13 (m, 6 H)	2.40−2.32 (m, 1 H), 1.98−1.42 (m, 6 H)

1-Hexyl-3,3-dimethyl-2-phenylethynylpiperidine (37). Aldehyde **8**[27] (44.4 mg, 0.30 mmol), *n*-hexylamine (30.3 mg, 0.30 mmol, and phenylacetylene (306 mg, 3.0 mmol) were dissolved in toluene (3.0 mL) and heated to reflux for 6 h. The reaction was diluted with 10% Na_2CO_3 and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×), dried (Na_2SO_4), and concentrated. The residue was chromatographed (5% to 20% ethyl acetate/hexanes gradient) to yield 54.2 mg (61%) of piperidine **37** as a colorless oil. R_f = 0.60 (20% ethyl acetate/hexanes, stained with I_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.42 (m, 2 H), 7.33−7.27 (m, 3 H), 3.32 (s, 1 H), 2.55−2.42 (m, 4 H), 1.78−1.65 (m, 1 H), 1.58 (td, J = 12.8, 4.0 Hz, 1 H), 1.52−1.40 (m, 3 H), 1.37−1.26 (m, 7 H), 1.22 (dt, J = 12.5, 3.3 Hz, 1 H), 1.15 (s, 3 H), 1.10 (s, 3 H), 0.90 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.65, 128.17, 127.59, 123.84, 87.29, 86.48, 62.25, 55.83, 48.76, 34.06, 33.95 (br), 31.80, 27.11, 27.02, 25.66, 22.67, 22.11, 14.09; MS (EI, 70 eV) *m/z* (rel intensity) 297 (M^+, 19), 282 ([M − CH_3]$^+$, 9), 268 ([M − C_2H_5]$^+$, 5), 254 ([M − C_3H_7]$^+$, 27), 240 ([M − C_4H_9]$^+$, 18), 226 ([M − C_6H_{11}]$^+$, 100), 212 ([M − C_6H_{13}]$^+$, 38); HRMS (EI, 70 eV) calcd for $C_{21}H_{31}N$ (M^+) 297.24565, found 297.2450.

Octahydro-8,8-Dimethyl-1-phenylindolizine or Octahydro-8,8-dimethyl-2-phenylindolizine (38). Imine **1** (160 mg, 0.35 mmol) and styrene (75 mg, 0.72 mmol) were heated to reflux in toluene (1.0 mL) for 14 h. The reaction was concentrated and the residue chromatographed (25% ethyl acetate/hexanes) to afford 25 mg (31%) of the title compound as a colorless oil. The regio- and stereochemistry could not be determined. R_f = 0.37 (30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5 H), 3.39 (dd, J = 8.3, 7.9 Hz, 1 H), 3.34−3.20 (m, 1 H), 3.15−3.05 (m, 1 H), 2.16 (dd, J = 9.3, 9.2 Hz, 1 H), 2.08 (dd, J = 12.0, 10.9 Hz, 1 H), 2.01−1.88 (m, 2 H), 1.85−1.70 (m, 2 H), 1.54−1.42 (m, 2 H), 1.14 (td, J = 13.1, 4.5 Hz, 1 H), 0.97 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$, JMOD) δ 145.5 (−), 128.3 (+), 127.5 (+), 126.0 (+), 73.8 (+), 64.5 (−), 53.8 (−), 41.0 (+), 39.6 (−), 34.0 (−), 32.5 (−), 28.9 (+), 22.4 (−), 19.0 (+); MS (EI, 70 eV) *m/z* (rel intensity) 229 (M^+, 100), 228 ([M − H]$^+$, 51), 214 ([M − CH_3]$^+$, 15), 125 ([M − $PhCHCH_2$]$^+$, 65), 91 ($PhCH_2^+$, 18), 77 (Ph^+, 8); HRMS (EI, 70 eV) calcd for $C_{16}H_{23}N$ (M^+) 229.1830, found 229.1829.

Octahydro-8,8-dimethyl-1-(triethylsilyl)indolizine or octahydro-8,8-dimethyl-2-(triethylsilyl)indolizine (39). Vinyl triethylsilane (120 mg, 0.85 mmol) was added to a solution of imine **1** (188 mg, 0.42 mmol) in toluene (3.0 mL) and heated at reflux for 6 h. The reaction was concentrated and the residue chromatographed (25% ethyl acetate/hexanes) to give 61 mg (54%) of the title compound as a yellow oil, whose regio- and stereochemistry could not be determined: R_f = 0.38 (30% ethyl acetate/hexanes, stained with I_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12−3.01 (m, 2 H), 1.92−1.20 (m, 10 H), 1.10−1.05 (m, 1 H), 0.95 (t, J = 7.5 Hz, 9 H), 0.90 (s, 3 H), 0.84 (s, 3 H), 0.55 (q, J = 7.5 Hz, 6 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 73.8, 58.1, 54.1, 39.7, 32.5, 28.9, 26.7, 22.4, 19.0, 18.2, 7.7, 2.7; MS (CI, NH_3) *m/z* (rel intensity) 268 ([M + H]$^+$, 100), 267 (M^+, 8), 238 ([M − CH_2CH_3]$^+$, 2), 152 ([M − $SiEt_3$]$^+$, 7); HRMS (CI, NH_3) calcd for $C_{16}H_{34}NSi$ ([M + H]$^+$) 268.2461, found 268.2470. The regio- and stereochemistry could not be determined.

(1*S,2*R**,8a*R**)- (41a) and (1*R**,2*S**,8a*R**)-Octahydro-8a-methyl-1,2-indolizinedicarboxylic Acid Dimethyl Ester (41b).** 6-Chlorohexan-2-one (150 mg, 1.11 mmol) and (tri-*n*-butylstannylmethyl)amine **9**[26b,28] (355 mg, 1.11 mmol) were mixed neat at room temperature, immediately followed by the addition of toluene (3 mL) and 4 Å molecular sieves (0.5 g) to form ketimine **40** in situ. After being stirred for 6 h, the reaction mixture was filtered through a cotton pipet plug. Dimethyl maleate (400 mg, 2.78 mmol) was added to the filtrate and the mixture was heated at reflux for 5 h. The reaction mixture was concentrated and the residue chromatographed (80% ether/petroleum ether to ether, gradient) to give 70 mg (25%) of **41a** and 73 mg (26%) of **41b**.

41a: R_f = 0.45 (ether); IR ($CHCl_3$) 1729 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 3.69 (s, 3 H), 3.58 (ddd, J = 10.3, 7.7, 5.1 Hz, 1 H), 3.42 (t, J = 10.3 Hz, 1 H), 3.16 (d, J = 7.7 Hz, 1 H), 3.07 (dd, J = 9.5, 5.1 Hz, 1 H), 2.94−2.74 (m, 2 H), 1.70−1.46 (m, 3 H), 1.44−1.34 (m, 1 H), 1.32 (s, 3 H), 1.28−1.20 (m, 1 H), 1.14−1.06 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.5, 172.5, 61.8, 58.0, 52.2, 51.9, 50.8, 43.8, 42.1, 26.9, 20.9, 20.3, 18.9; MS (EI, 70 eV) *m/z* (rel intensity) 255 (M^+, 22), 240 ([M − CH_3]$^+$, 100), 224 ([M − OCH_3]$^+$, 55), 196 ([M − CO_2CH_3]$^+$, 62), 137 ([M − 2 × CO_2CH_3]$^+$, 17); HRMS (EI, 70 eV) calcd for $C_{13}H_{21}NO_4$ (M^+) 255.1471, found 255.1460.

41b: R_f = 0.20 (ether); IR ($CHCl_3$) 1731 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 3.69 (s, 3 H), 3.50 (ddd, J = 10.3, 8.8, 4.0 Hz, 1 H), 3.14 (dd, J = 10.2, 4.0 Hz, 1 H), 3.08 (d, J = 8.8 Hz, 1 H), 2.94 (t, J = 10.3 Hz, 1 H), 2.68−2.60 (m, 1 H), 2.52−2.42 (m, 1 H), 1.90−1.80 (m, 1 H), 1.64−1.40 (m, 5 H), 0.82 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.7, 172.5, 62.1, 57.0, 52.3, 52.2, 51.8, 45.6, 42.6, 36.3, 24.6, 19.9, 11.3; MS (EI, 70 eV) m/z (rel intensity) 255 (M^+, 27), 240 ([M − CH_3]$^+$, 100), 224 ([M − OCH_3]$^+$, 53), 196 ([M − CO_2CH_3]$^+$, 62); HRMS (EI, 70 eV) calcd for $C_{13}H_{21}NO_4$ (M^+) 255.1471, found 255.1463. The stereochemical assignments are arbitrary since NOESY experiments failed to elucidate the stereostructure of **41a** and **41b**. However, it is assumed the geometry of the alkene was retained, as in the case of compounds **27a** and **27b**.

5-Bromo-2,2-dimethylhexanal (43). Diisopropylamine (7.61 g, 75.24 mmol) and anhydrous THF (40 mL) were cooled to 0 °C and treated with *n*-butyllithium (27.6 mL of a 2.5 M solution in hexanes, 69.0 mmol). After 30 min at 0 °C, *N*-cyclohexyl-(2-methylpropylidene)amine[27] (9.61 g, 62.7 mmol) was added at 0 °C, using an additional amount of THF (5 mL). After 30 min at 0 °C, 1,3-dibromobutane (13.54 g, 62.7 mmol) was added and allowed to stir for an additional 30 min at 0 °C. The solution was quenched with saturated aqueous NH_4Cl and concentrated. Ether and water were added and the pH was adjusted to 5 with H_3PO_4. The biphasic mixture was stirred at room temperature for 4 h with H_3PO_4 being added as needed to readjust the pH to 5. The aqueous phase was extracted with ether (3×), washed with 2% H_3PO_4 (2×) and brine (1×), dried (Na_2SO_4), and concentrated at room temperature. Kügelrohr distillation (bp 110−113 °C, 1 mmHg) afforded 6.59 g (51%) of aldehyde **43** as a colorless oil. IR (neat) 1726 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 4.16−4.00 (m, 1 H), 1.80−1.60 (m, 6 H), 1.60−1.45 (m, 1 H), 1.10 (s, 6 H); ^{13}C NMR (400 MHz, $CDCl_3$, APT) δ 205.6 (−), 51.4 (−), 45.3 (+), 35.7 (+), 34.9 (+), 26.3 (−), 21.5 (−), 21.1 (−); MS (CI, NH_3) m/z (rel intensity) 226 ([M + NH_4 + 2]$^+$, 99), 224 ([M + NH_4]$^+$, 99), 179 ([M + 2]$^+$, 19), 177 (M^+, 19), 127 (100), 97 ([M − Br]$^+$, 84); HRMS (CI, NH_3) calcd for $C_8H_{19}NO^{79}Br$ ([M + NH_4]$^+$) 224.0650, found 224.0662.

Octahydro-6,9,9-trimethyl-2-phenyl-1*H*-pyrrolo[3,4-*a*]-indolizine-1,3(2*H*)-dione (44). 5-Bromo-2,2-dimethylhexanal **43** (269 mg, 1.30 mmol) was added to a solution of (tri-*n*-butylstannyl)methylamine **9**[26b,28] (416 mg, 1.30 mmol) in toluene (4.3 mL) at room temperature, followed by *N*-phenylmaleimide (338 mg, 1.95 mmol) in one portion. The mixture was heated at reflux for 10 h. Analysis by GC-MS showed four isomeric products (**a**:**b**:**c**:**d** = 1:1.2:1.2:1.3) in the reaction mixture. After concentration, the residue was chromatographed (20% to 30% ethyl acetate/hexanes) to afford 72 mg (18%) of a mixture of **44a** and **44d**, 54 mg (18%) of a mixture of **44b** and **44c**, and 134 mg (33%) of a mixture of all isomers, all as yellow oils. The regio- and stereochemistry of the diastereomers could not be determined.

44a and **44d**: R_f = 0.56 (40% ethyl acetate/hexanes, stained with I_2); IR ($CHCl_3$) 1778 (m), 1706 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50−7.20 (m, 5 H), 3.76−3.65 (m, 1 H), 3.40−3.30 (m, 1 H), 3.22−3.14 (m, 1 H), 2.25−2.00 (m, 2 H), 1.95−1.85 (m, 1 H), 1.55−1.25 (m, 4 H), 1.50−1.15 (m, 3 H), 1.15−1.05 (m, 3 H), 1.05−0.90 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.3, 177.6, 132.3, 129.1, 128.5, 128.4, 126.5, 126.4, 76.8, 75.2, 60.1, 58.7, 54.9, 54.1, 46.9, 46.4, 44.1, 43.4, 42.9, 40.0, 33.2, 32.9, 30.8, 30.3, 29.0, 27.1, 21.2, 20.9, 19.7, 19.6; MS (EI, 70 eV) m/z (rel intensity) 312 (M^+, 19), 297 ([M − CH_3]$^+$, 100), 243 ([M − C_5H_9]$^+$, 81), 173 (*N*-phenylmaleimide, 35); HRMS (EI, 70 eV) calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1838, found 312.1833.

44b and **44c**: R_f = 0.41 (40% ethyl acetate/hexanes, stained with I_2); IR ($CHCl_3$) 1777 (m), 1708 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50−7.20 (m, 5 H), 3.45−3.10 (m, 4 H), 2.80−2.60 (m, 2 H), 2.00−1.60 (m, 1 H), 1.55−1.25 (m, 3 H), 1.25−0.80 (m, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.4, 177.8, 177.2, 177.1, 132.3, 131.9, 129.0, 128.8, 128.4, 127.4, 126.7, 126.5, 126.3, 126.1, 125.1, 67.8, 66.0, 52.7, 51.4, 50.2, 50.0, 46.6, 46.3, 44.5, 43.3, 37.0, 34.1, 33.6, 32.9, 29.0, 27.3, 27.0, 26.9, 20.2, 20.0, 9.2; MS (EI, 70 eV) m/z (rel intensity) 312 (M^+, 17), 297 ([M − CH_3]$^+$, 100), 243 ([M − C_5H_9]$^+$, 70); HRMS (EI, 70 eV) calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1838, found 312.1838.

3-(2-Chloromethylphenyl)-2,2-dimethylpropionaldehyde (45). Diisopropylamine (793 mg, 7.84 mmol) and anhydrous THF (12 mL) were cooled to 0 °C and treated with *n*-butyllithium (2.87 mL of a 2.5 M solution in hexanes, 7.18 mmol). After 30 min at 0 °C, *N*-cyclohexyl-(2-methylpropylidene)amine[27] (1.00 g, 6.53 mmol) was added at 0 °C, using an additional amount of THF (3 mL). After 30 min at 0 °C, 1,2-bis(chloromethyl)benzene (1.14 g, 6.53 mmol) was added dropwise over 1 min at 0 °C. After 10 min at 0 °C, the solution was quenched with saturated aqueous NH_4Cl and concentrated. Ether and water were added and the pH was adjusted to 5 with H_3PO_4. The biphasic mixture was stirred at room temperature for 4 h with H_3PO_4 added as needed to readjust the pH to 5. The aqueous phase was extracted with ether (3×), washed with 2% H_3PO_4 (2×) and brine (1×), dried (Na_2SO_4), and concentrated at room temperature. The residue was chromatographed (pentane to 5% ether/pentane, gradient) to yield 171 mg (12%) of aldehyde **45** as a clear, colorless oil. R_f = 0.26 (5% ether/pentane, stained black with phosphomolybdic acid); IR (CH_2Cl_2) 1722 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H), 7.35−7.39 (m, 1 H), 7.21−7.28 (m, 2 H), 7.07−7.11 (m, 1 H), 4.63 (s, 2 H), 2.98 (s, 2 H), 1.11 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 136.3, 135.8, 131.5, 130.8, 128.7, 127.3, 47.3, 44.4, 38.2, 21.8; MS (EI, 70 eV) m/z (rel intensity) 139 ($H_2C(C_6H_4)CH_2{}^{35}Cl^+$, 100), 141 ($H_2C(C_6H_4)CH_2{}^{37}Cl^+$, 41); HRMS (CI, NH_4) calcd for $C_{12}H_{19}NO^{35}Cl$ ([M + NH_4]$^+$) 228.1155, found 228.1150.

(3a*S,3b*R**,11a*R**)- (46a) and (3a*S**,3b*S**,11a*R**)-4,4-Dimethyl-2-phenyl-3b,4,5,10,11,11a-hexahydro-3a*H*-2,-10a-diazabenzo[*f*]cyclopenta[*a*]azulene-1,3-dione (46b).** Chloroaldehyde **45** (79.6 mg, 0.378 mmol) and (tri-*n*-butylstannyl)methylamine **9**[26b,28] (121 mg, 0.378 mmol) were dissolved in toluene (3.8 mL) and allowed to stir at room temperature. After 5 min, *N*-phenylmaleimide (78.5 mg, 0.454 mmol) was added in one portion and the solution was heated to reflux for 2 h. The reaction was allowed to cool to room temperature, diluted with 5% Na_2CO_3, and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×), dried (Na_2SO_4), and concentrated. The residue was chromatographed (5% to 30% ethyl acetate/hexanes, gradient) to afford 66.0 mg (49%) of **46a** as a colorless oil and 38.4 mg (28%) of **46b** as a colorless crystalline solid.

46a (exo): R_f = 0.15 (20% ethyl acetate/hexanes, stained with I_2); IR (CH_2Cl_2) 1713 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, J = 7.7 Hz, 2 H), 7.39 (t, J = 7.0 Hz, 1 H), 7.30 (d, J = 7.3 Hz, 2 H), 7.09−7.21 (m, 4 H), 4.01 (d, J = 14.7 Hz, 1 H), 3.74 (d, J = 14.3, 1 H), 3.43 (t, J = 8.4 Hz, 1 H), 3.34 (dt, J = 6.2 Hz, 1 H), 3.27 (dd, J = 4.4, 8.8 Hz, 1 H, H-3a), 3.12 (s, 1 H, H-3b), 3.10 (d, J = 9.9 Hz, 1 H), 2.89 (dd, J = 5.9, 9.2 Hz, 1 H), 2.51 (d, J = 14.3 Hz, 1 H), 1.21 (s, 3 H), 0.68 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.68, 177.28, 139.6, 137.7, 132.0, 130.5, 129.1, 128.51, 128.48, 127.3, 126.43, 126.37, 78.1, 56.53, 56.31, 48.95, 48.68, 44.2, 36.1, 30.5, 21.1; MS (EI, 70 eV) m/z (rel intensity) 360 (M^+, 41), 345 ([M − CH_3]$^+$, 39), 215 ([M − $H_2C(C_6H_4)CH_2C(CH_3)_2$]$^+$, 94), 145 ($H_2C(C_6H_4)CH_2C(CH_3)_2{}^+$, 59), 131 ($H_2C(C_6H_4)CH_2C(CH_3)^+$, 88), 91 ($PhCH_2{}^+$,100); HRMS (ESI) calcd for $C_{23}H_{25}N_2O_2$ ([M + H]$^+$) 361.1916, found 361.1912.

46b (endo): R_f = 0.08 (20% ethyl acetate/hexanes, stained with I_2); mp 206−207 °C; IR (CH_2Cl_2) 1709 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.41 (m, 3 H), 7.10−7.19 (m, 5 H), 7.02−7.05 (m, 1 H), 3.82 (d, J = 13.6 Hz, 1 H), 3.72 (d, J = 9.5 Hz, 1 H), 3.48 (t, J = 8.4 Hz, 1 H, H-3a), 3.38 (d, J = 13.6 Hz, 1 H), 3.22 (dd, J = 7.0, 8.4 Hz, 1 H), 2.95 (d, J = 14.3 Hz, 1 H), 2.65 (dd, J = 7.0, 9.5 Hz, 1 H), 2.56 (d, J = 8.4, 1 H, H-3b), 2.42 (d, J = 14.3 Hz, 1 H), 1.47 (s, 3 H), 0.64 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.78, 177.71, 139.9, 136.7, 132.1, 130.1, 129.08, 128.99, 128.6, 127.3, 126.51, 126.45, 83.3, 60.2, 59.1,

51.3, 48.4, 43.6, 35.6, 28.5, 19.5; MS (EI, 70 eV) *m/z* (rel intensity) 360 (2, M^+), 215 ([M − $H_2C(C_6H_4)CH_2C(CH_3)_2]^+$, 100); HRMS (ESI) calcd for $C_{23}H_{25}N_2O_2$ (M + H^+) 361.1916, found 361.1917. Stereochemistry was assigned on the basis of 2D COSY and 1D NOESY experiments. No NOE was seen between the H-3a and H-3b hydrogens (J_{3a-3b} = 0 Hz) in **46a**, but a strong NOE was observed between the H-3a and H-3b hydrogens (J_{3a-3b} = 8.4 Hz) in **46b**.

2-Methylpropylidene(trimethylsilyl)methylamine (48). Isobutyraldehyde (181 mg, 2.51 mmol) and (trimethylsilyl)-methylamine **10** (259 mg, 2.51 mmol) were dissolved in ether (7 mL) at room temperature. After 10 min, 4 Å molecular sieves (1 g) were added. After 18 h, the reaction mixture was filtered through Celite and concentrated at room temperature. The residue was purified by Kügelrohr distillation (35 mmHg, 65 °C) to give 285 mg of **48** (72%) as a colorless oil. IR (CH_2Cl_2) 1660 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (td, J = 5.5, 1.1 Hz, 1 H), 3.10 (s, 2 H), 2.46−2.34 (m, 1 H), 1.05 (s, 3 H), 1.03 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.06, 53.38, 34.08, 19.68, −2.82; MS (EI, 70 eV) *m/z* (rel intensity) 156 ($[M - H]^+$, 30), 142 ($[M - CH_3]^+$, 19), 87 ($(CH_3)_3SiCH_2^+$, 32), 73 ($(CH_3)_3Si^+$, 100); HRMS (EI, 70 eV) calcd for $C_8H_{18}NSi$ ($[M - H]^+$) 156.12085, found 156.1208.

(3a*R,4*S**,6a*S**)- (49a) and (3a*R**,4*R**,6a*S**)-4-Isopropyl-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3-dione (49b).** Chloro(tri-*n*-butyl)stannane (14 mg, 0.043 mmol) was added to a solution of imine **47**[14b] (80 mg, 0.21 mmol) and *N*-phenylmaleimide (44 mg, 0.257 mmol) in toluene (2.1 mL) at room temperature. The reaction was heated to reflux for 6 h, then diluted with 10% Na_2CO_3. The reaction was extracted with CH_2Cl_2 (4×) and the combined organic layers were washed with brine (1×), dried, and concentrated. The residue was chromatographed (20% to 100% ethyl acetate/hexanes, gradient) to yield 17.5 mg (32%) of a 1:1 mixture of **49a** and **49b** as a colorless oil.

49a (exo): R_f = 0.24 (ethyl acetate, stained in I_2); IR (CH_2Cl_2) 3340 (w), 1773 (m), 1712 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.42 (m, 2 H), 7.41−7.36 (m, 1 H), 7.31−7.25 (m, 2 H), 3.46−3.31 (m, 3 H), 3.23 (app. t, J = 7.3 Hz, 2 H), 1.90 (br s, 1 H), 1.80−1.70 (m, 1 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 177.7, 131.9, 129.1, 128.5, 126.3, 69.6, 49.6, 49.3, 46.8, 31.3, 19.9, 19.2; MS (CI-NH_3) *m/z* (rel intensity) 259 ($[M + H]^+$, 100), 215 ($[M - CH(CH_3)_2]^+$, 56); HRMS (CI-NH_3) calcd for $C_{15}H_{19}N_2O_2$ ($[M + H]^+$) 259.1447, found 259.1441.

49b (endo): R_f = 0.17 (ethyl acetate, stained in I_2); IR (neat) 3349 (m), 1771 (s), 1722 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2 H), 7.41−7.35 (m, 1 H), 7.31−7.25 (m, 2 H), 3.62 (d, J = 10.6 Hz, 1 H), 3.36 (m, 2 H), 3.08 (dd, J = 6.8, 10.6 Hz, 1 H), 2.83 (dd, J = 6.0, 9.7 Hz, 1 H), 1.98−1.86 (m, 1 H), 1.76 (br s, 1 H), 1.22 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 175.7, 132.0, 129.0, 128.5, 126.5, 70.8, 50.0, 46.6, 46.3, 29.6, 21.1, 20.8; MS (CI-NH_3) *m/z* (rel intensity) 259 ($[M + H]^+$, 100), ($[M - CH(CH_3)_2]^+$, 71); HRMS (CI-NH_3) calcd for $C_{15}H_{19}N_2O_2$ (M + H^+) 259.1447, found 259.1435. Stereochemistry was assigned by NOESY experiments and similarity to compounds **50a** and **50b**.

(3a*R,4*R**,6a*S**)- (50b) and (3a*S**,4*R**,6a*R**)-5-Benzyl-4-isopropyl-2-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-dione (50a).** Benzyl bromide (110 mg, 0.64 mmol) was added to a solution of imine **47**[14b] (220 mg, 0.59 mmol) and *N*-phenylmaleimide (112 mg, 0.65 mmol) in toluene (1.2 mL) at room temperature and heated to reflux overnight. The reaction was concentrated and chromatographed (20% ethyl acetate/hexanes) to afford 43 mg (21%) of **50a** and 75 mg (36%) of **50b**, both as colorless oils.

50a (exo): R_f = 0.35 (20% ethyl acetate/hexanes, stained in I_2); IR ($CHCl_3$) 1713 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50−7.20 (m, 10 H), 3.98 (d, J = 13.1 Hz, 1 H), 3.40−3.28 (m, 4 H, $-NCH_2Ph$, H-3a, H-6), 2.94, (t, J = 4.6 Hz, 1 H, H-4), 2.64−2.56 (m, 1 H), 2.16−2.06 (m, 1 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 177.8, 177.3, 138.5, 129.1, 128.5, 128.4, 127.2, 126.3, 72.1, 57.8, 55.6, 46.7, 44.6, 28.7, 20.0, 16.9; MS (CI, NH_3) *m/z* (rel int) 349 ($[M + H]^+$, 100), 212 (75), 108 (19); HRMS (CI, NH_3) calcd for $C_{22}H_{25}N_2O_2$ ($[M + H]^+$) 349.1916, found 349.1905.

50b (endo): R_f = 0.23 (20% ethyl acetate/hexanes, stained in I_2); IR ($CHCl_3$) 1712 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50−7.20 (m, 10 H), 4.12 (d, J = 13.1 Hz, 1 H), 3.43 (d, J = 9.8 Hz, 1 H), 3.33 (t, J = 8.3 Hz, 1 H, H-3a), 3.20 (dd, J = 8.0, 7.0 Hz, 1 H), 2.98 (d, J = 13.1 Hz, 1 H), 2.66 (dd, J = 8.3, 4.0 Hz, 1 H, H-4a), 2.50−2.40 (m, 1 H), 2.26 (dd, J = 9.8, 7.0 Hz, 1 H), 1.29 (d, J = 7.0 Hz, 3 H), 1.07 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.1, 177.5, 138.2, 132.3, 129.2, 128.5, 128.2, 127.2, 126.4, 72.8, 56.8, 55.5, 46.3, 43.8, 26.6, 17.9, 17.0; MS (CI, NH_3) *m/z* (rel intensity) 349 ($[M + H]^+$, 100), 305 ($[M - CH(CH_3)_2]^+$, 10), 257 ($[M - PhCH_2]^+$, 13), 215 ([M − $PhCH_2$ − $CH(CH_3)_2]^+$, 6); HRMS (CI, NH_3) calcd for $C_{22}H_{25}N_2O_2$ ($[M + H]^+$) 349.1916, found 349.1900. The stereochemistry at C(4) was determined by examination of the coupling constant between H-4 and H-3a (**50a**, J_{3a-4} = 4.6 Hz; **50b**, J_{3a-4} = 8.3 Hz) with the aid of molecular models.

1-Benzyl-3-benzenesulfonyl-2-isopropylpyrrolidine and 1-Benzyl-4-benzenesulfonyl-2-isopropylpyrrolidine (55). Benzyl bromide (244 mg, 1.43 mmol) was added to a solution of imine **47**[14b] (535 mg, 1.43 mmol) in toluene (7.5 mL), followed by the addition of phenyl vinyl sulfone (241 mg, 1.43 mmol). The mixture was heated at reflux for 10 h. After being cooled to room temperature, the reaction was treated with concentrated NH_4OH and stirred for 15 min.[52] The reaction mixture was extracted with ether (3×), then the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (15% to 20% ethyl acetate/hexanes, gradient) to afford 416 mg (85%) of the title compound as a colorless oil. The product mixture contained three inseparable isomers (5:3:1 by ^1H NMR integration): R_f = 0.28 (20% ethyl acetate/hexanes, stained in I_2); IR ($CHCl_3$) 1305 (s), 1148 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.90 (m, 2 H × 0.56), 7.88−7.84 (m, 2 H × 0.33), 7.82−7.76 (m, 2 H × 0.11), 7.70−7.50 (m, 3 H), 7.40−7.10 (m, 5 H), 4.01 (d, J = 13.2 Hz, 1 H × 0.33), 4.00 (d, J = 13.5 Hz, 1 H × 0.56), 3.91 (d, J = 13.2 Hz, 1 H × 0.11), 3.64−3.45 (m, 1 H), 3.36−3.30 (m, 1 H × 0.56), 3.23 (t, J = 4.0 Hz, 1 H × 0.56), 3.12 (d, J = 13.2 Hz, 1 H × 0.33), 3.02 (dd, J = 9.7, 7.5 Hz, 1 H × 0.33), 2.88−2.80 (m, 1 H × 0.56), 3.70−3.50 (m, 1 H × 1.66), 2.44−2.32 (m, 1 H × 0.11), 2.28−2.14 (m, 1 H × 0.89), 2.10−1.72 (m, 2 H), 0.94−0.83 (m, 3 H × 1.56), 0.80 (d, J = 7.1 Hz, 3 H × 0.33), 0.66 (d, J = 6.9 Hz, 3 H × 0.11); ^{13}C NMR (90 MHz, $CDCl_3$) δ 140.2, 138.8, 138.5, 137.8, 133.6, 133.5, 129.3, 129.2, 129.1, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.0, 126.8, 68.8, 68.6, 68.1, 67.9, 65.9, 61.1, 60.8, 59.6, 57.5, 56.9, 54.3, 53.9, 52.5, 31.4, 27.6, 27.2, 27.1, 26.5, 25.7, 19.9, 19.0, 17.3, 14.5, 14.1. Anal. Calcd for $C_{20}H_{25}NO_2S$: C, 69.94; H, 7.34; N, 4.08. Found: C, 69.60; H, 7.30; N, 4.02.

(6′a*R,3′a*S**)-Dihydro-5′-phenyl-2′-(phenylmethyl)-spiro[cyclopentane-1,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrol]-4′,6′(3′*H*,5′*H*)-dione (56).** Cyclopentylidene[(tri-*n*-butyl)stannylmethyl]amine **57**[14b] (200 mg, 0.52 mmol) and *N*-phenylmaleimide (99 mg, 0.57 mmol) were dissolved in toluene (1.1 mL) and treated with benzyl bromide (97 mg, 0.57 mmol) at room temperature. The reaction was heated to reflux overnight. The reaction was concentrated and the residue chromatographed (25% ethyl acetate/hexanes) to afford 97 mg (52%) of the title compound as a colorless oil. R_f = 0.24 (30% ethyl acetate/hexanes, stained in I_2); IR ($CHCl_3$) 1777 (m), 1708 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.20 (m, 10 H), 3.93 (d, J = 13.7 Hz, 1 H), 3.32−3.24 (m, 3 H), 3.07 (d, J = 8.0 Hz, 1 H), 2.71 (dd, J = 9.9, 7.9 Hz, 1 H), 2.35−2.25 (m, 1 H), 1.9−1.4 (m, 7 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.5, 176.5, 139.4, 129.1, 128.5, 128.4, 127.7, 127.0, 126.5, 75.5, 53.9, 53.5,

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51.1, 43.1, 30.5, 29.7, 26.8, 23.8; MS (EI, 70 eV) *m*/*z* (rel intensity) 360 (M^+, 5), 269 ([M − $PhCH_2$]$^+$, 30), 91 ($PhCH_2^+$, 100); HRMS (EI, 70 eV) calcd for $C_{23}H_{24}N_2O_2$ (M^+) 360.1838, found 360.1847.

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Supporting Information Available: General experimental methods, ^{1}H NMR or ^{13}C NMR spectra of stable new compounds without elemental analysis, and an improved synthesis of (tri-*n*-butylstannyl)methylamine. This material is available free of charge via the Internet at http://pubs.acs.org.

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