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Tuning the Acceptors in Catalyzed Cyclizations Initiated by Allenes. Silylstannylation/Cyclization of Allene-Aldehydes for Synthesis of Polyalkylated Indolizidines Including 223A Congeners

Ramaiah Kumareswaran, Judith Gallucci,† and T. V. RajanBabu*

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210

rajanbabu.1@osu.edu

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Starting from succinamide and 1,2-heptadiene-4-ol, a racemic allene-aldehyde substrate, **20**, suitable for $R_3SiSnR'_3$-mediated cyclization was synthesized in six steps and in 21% yield. Stereoselective cyclization (relative cis configuration at the new stereogenic centers of the homoallyl alcohol generated) proceeded smoothly, giving a mixture of indolizidinols bearing five contiguous stereocenters in a combined yield of 80%. Relative configurations of each of the products were unequivocally established by a combination of 2D NMR experiments and single-crystal X-ray analysis. The major indolizidinol obtained in 32% yield was elaborated into indolizidine 5,8-epi-indolizidine 223A via a five-step reaction sequence in 32% overall yield. The second major component (24%) of the key cyclization yielded, in four steps, indolizidine 6,8-epi-223 in 14% yield. Even though revision of the initially postulated structure foiled our original synthetic plans for the natural product, indolizidine 223A, the new stereoselective cyclization strategy and several selective transformations of the indolizidine derivatives reported here may find further applications for the synthesis of highly alkylated indolizidine and other related alkaloids.

Introduction

Highly alkylated indolizidine alkaloids are found in trace quantities in a variety of terrestrial and marine sources such as bacteria, fungi, higher plants, invertebrates, and vertebrates.[1] Some of these compounds exhibit important biological effects such as noncompetitive blockage of nicotinic receptor channels. Many of these and related alkaloids serve as a defense against predation and are used by hunters in the rain forests of Central and South America as blow-gun dart poisons. In 1997, a new subclass of trisubstituted indolizidines was identified in a family of frogs called Dendrobatidae found in Panama.[2] The structure of indolizidine 223A bearing 5,6,8-substitutents was initially proposed to be **2** (Figure 1) on the basis of GC−MS, GC−FTIR, and ^{1}H NMR data.[2] Subsequently, the C_6 configuration in **2** was found to be incorrect, and the structure has been revised to **1** by a total synthesis involving a series of Michael additions in 26 steps.[3] Recently, yet another diasteroselective synthesis of **1**, which uses the addition of lithium (R)-*N*-benzyl-α-methylbenzylamide to α,*β*-unsaturated esters as the key step, has been reported.[4] The unnatural alkaloid **2** has also been synthesized from α-methylfurylamine using the aza-Achmatowicz rearrangement to form a key dihydro-2*H*-pyridone intermediate, which was subsequently elaborated using organometallic conjugate additions.[5]

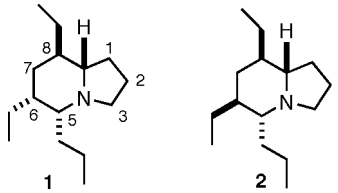

FIGURE 1. Indolizidine 223A and indolizidine 6-epi-223A.

Results and Discussion

The major challenge in the synthesis of highly alkylated indolizidines such as indolizidine 223A involves the assembly of the piperidine core with the correct stereochemistry. When we started this work, our plan (Figure 2) was to exploit the stereoselective silylstannylation-cyclization[6a]

† Any questions related to X-ray crystallography should be addressed to ⟨jgallucc@chemistry.Ohio-State.edu⟩.

(1) Recent general reviews on pyrrolizidines, indolizidines, and quinolizidine alkaloids: (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. Alkaloids from amphibian skins. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: Oxford, 1998; Vol. 13, pp 1−161. (b) Colegate, S. M.; Dorling, P. R. In *Handbook of Plant and Fungal Toxicants*; D'Mello, J. P. F., Ed.; CRC Press: Boca Raton, 1997; Chapter 1, pp 1−18. (c) Nash, R. J.; Watson, A. A.; Asano, N. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 11, pp 345−375. (d) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162. (e) Michael, J. P. Indolizidine and Quinolizidine Alkaloids. *Nat. Prod. Rep.* **1997**, *14*, 630; **1998**, *15*, 571; **1999**, *16*, 675.; **2000**, *17*, 579.

(2) Garraffo, H. M.; Jain, P.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **1997**, *60*, 2.

(3) (a) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715.

(4) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400.

(5) Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371.

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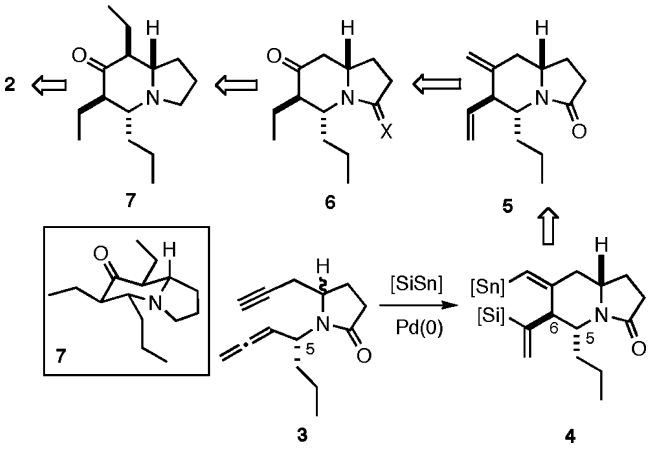
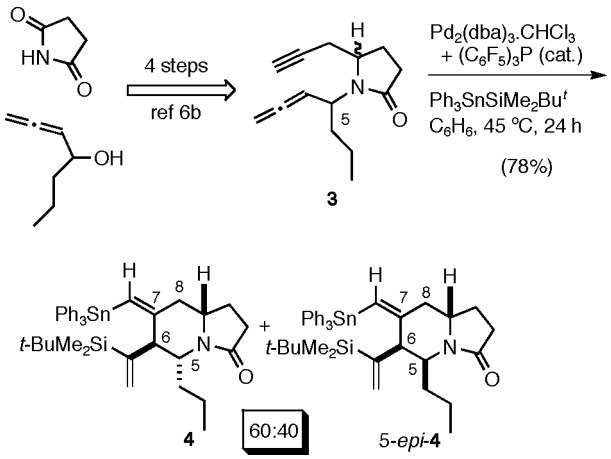


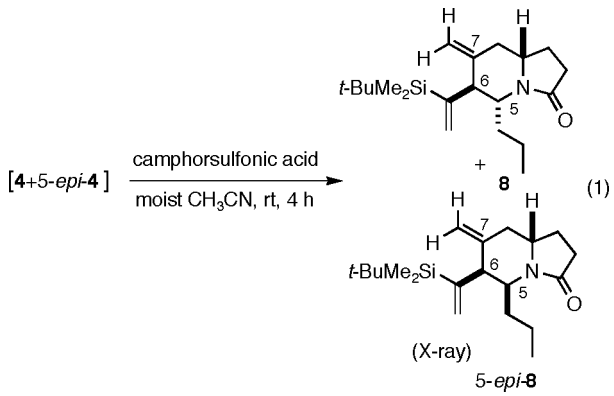
FIGURE 2. Original plans for the synthesis of 6-epi-indolizidine 223A.

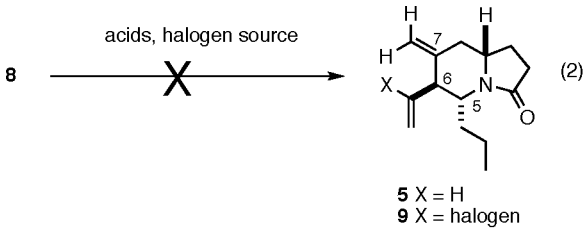
SCHEME 1. An Expeditious Entry into Alkylated Indolizidines

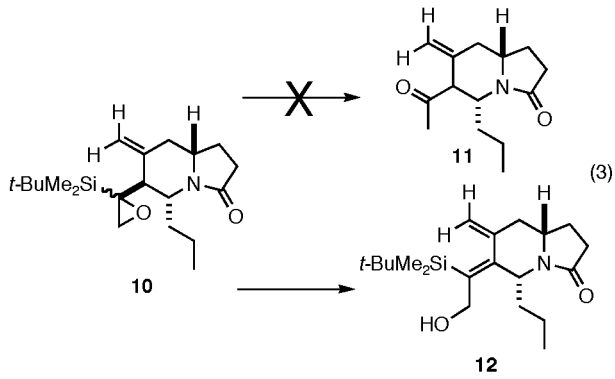


of an appropriately constructed allenyne **3** to build the core of indolizidine 223A, in the originally proposed structure **2**. Removal of Si and Sn from **4** would yield a diene **5**, which upon reduction of the lactam and the monosubstituted olefin, followed by ozonolysis would yield the ketone **6** (X = H_2), which is set up for alkylation under thermodynamic conditions to give **7**. Deoxygenation of **7** would complete the synthesis of **2**. Alternatively, ozonolysis of **5** would give an α-formyl ketone, which can be subjected to dialkylation[7] and deformylation to install the two equatorial ethyl substituents. In either case, this new annulation scheme was expected to significantly reduce the overall number of steps in the construction of this ring system vis-à-vis the more classical approaches.

To explore the above-described strategy, the allenyne **3** was synthesized as a mixture of diastereomers (**3** + C_5-epimer) from the 1,2-heptadiene-4-ol and succinic anhydride in four steps and 40% yield.[6b] Silylstannylation-cyclization with $Ph_3SnSiBu^tMe_2$ proceeds to give a mixture of only two compounds, identified as **4** along with the C_5-epimer (Scheme 1). The structures of the two compounds were established by rigorous NMR methods, and X-ray analysis of the destannylated derivative prepared from 5-epi-**4** (eq 1).[6b]







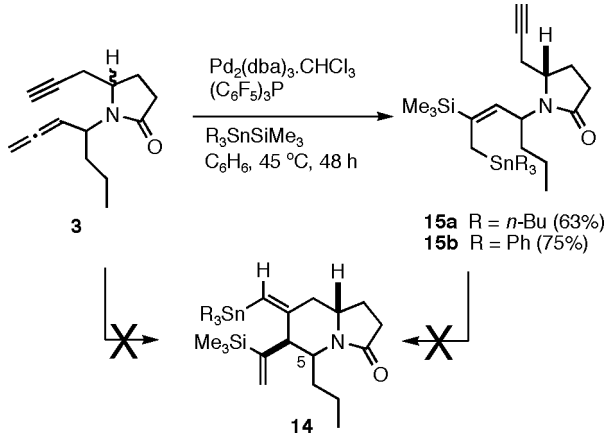
It is well-known that trimethylsilyl olefins are readily desilylated under a variety of electrophilic conditions.[8] Typically strong acids such as trifluoroacetic acid (TFA), aqueous HF, or other mineral acids are used for this reaction. However, repeated efforts to effect this protodesilylation on **8**, employing camphorsulfonic acid (CSA), TFA, aqueous HF, and HI or brominating agents such as $(PhO)_3P.Br_2$, NBS led only to the recovery (eq 2) or decomposition of the starting material. Treatment of **8** with tetrabutylammonium fluoride (TBAF) under a

(6) (a) Shin, S.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2001**, *123*, 8416. (b) Kumareswaran, R.; Shin, S.; Gallou, I.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 7157.

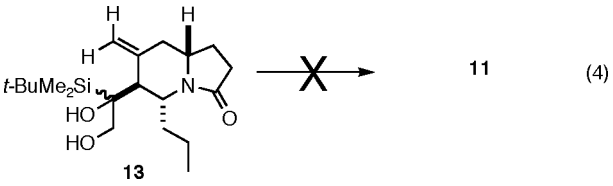
(7) (a) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, 1994. (b) The γ-alkylation and arylation of dianions of β-dicarbonyl compounds: Harris, T. M.; Harris, C. M. *Org. React.* **1969**, *17*, 155. See also: Thompson, C. M.; Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223. Several examples of dianion alkylation can be seen in: Ranganathan, S. In *Art in Organic Synthesis*; Wiley: New York, 1987.

(8) Koenig, K. B.; Weber, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 3416. (b) Utimoto, K.; Kitai, M.; Nozaki, H. *Tetrahedron Lett.* **1975**, 2825. (c) Fujikura, S.; Inoue, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1999. (d) Weber, W. P. In *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; Chapter 25.

SCHEME 2. Attempted Silylstannylation/ Cyclization Using Trimethylsilystannanes



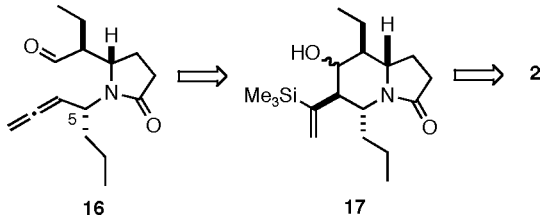
variety of conditions also led to no reaction. Epoxide formation of the vinylsilane (**10**) followed by acid treatment[9] gave none of the expected methyl ketone **11** but yielded dienyl alcohol **12** (eq 3). Peterson reaction via the diol **13**, prepared by OsO_4 mediated dihydroxylation of **8**, was also unsuccessful in removing the *tert*-butyldimethylsilyl (TBS) group (eq 4). These experiments strongly suggested that the bulky silyl group is resistant to removal, thereby precluding this approach.



Since the removal of the TBS group turned out to be a major impediment in our synthetic approach, we attempted cyclizations of allenyne **3** using other silyltin reagents that contain a trimethylsilyl (TMS) moiety as the silicon partner (Scheme 2). We reasoned that in the event of a successful cyclization, the product bearing a pendent vinyltrimethylsilyl group (**14**) will be formed and we may have a better chance of effecing the desilylation. Unfortunately, reaction of allenyne **3** with trimethylsilyltin reagents led only to uncyclized allylstannane adducts **15a,b**.[6b]

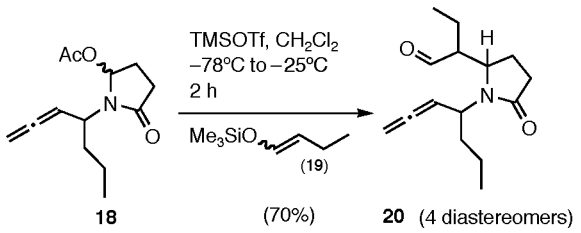
The formation of the open chain adducts in the above reactions not only lends credence to our proposed mechanism for the allenyne cyclization[6a] but also suggests the possibility of an intramolecular allylstannane addition to an alternate, better electrophilic acceptor.[10] Thus if we could replace the acetylene in **3** with an aldehyde, we should be able to achieve a cyclization. Such a reaction was briefly explored in our group previously,[11] and Kang et al.[12] have since published a version of the reaction. Encouraged by these results we imagined an aldehyde such as **16** (Scheme 3) bearing all the necessary appendages would give an advanced precursor **17** toward the synthesis of polyalkylated indolizidines. Our expectation of a rapid synthesis of target **2** from **17** was built on a possible reaction sequence involving desilylation, hydrogenation of the pendent olefin, and deoxygenation followed by lactam reduction.

SCHEME 3. An Approach to Indolizidines via Silylstannylation-Cyclization of an Allene-aldehyde



While our studies were in progress, the structure of the alkaloid 223A was revised from **2** to **1** (Figure 1) with a different configuration[3a] at C_6. At this point we turned our attention to the broader issues of the stereochemistry of the allene-aldehyde cyclization, fully realizing that the C_5-C_6 cis-relationship of the alkyl side chains in the revised structure would present difficulties in our approach involving the silylylstannylation/cyclization reactions and creative solutions would be needed to circumvent this problem. For our initial studies, we decided to proceed with racemic allene-aldehyde substrate(s) with the hope of constructing the indolizidine core and examining the stereochemical issues associated with the cyclization and subsequent transformations. The results of these studies are described in the rest of this paper.

Synthesis of Aldehyde Substrate for Allene-Aldehyde Cyclization. Synthesis of the requisite aldehyde substrate(s) **20** is shown in eq 5. The acetoxy lactam **18**



was prepared from succinic anhydride as described earlier.[6b] Lactam **18** was subsequently reacted with *n*-butanal-derived enolsilyl ether **19** (mixture of geometrical isomers, *E*/*Z* = 39:61) in the presence of TMSOTf (trimethylsilyl triflate) as a Lewis acid in CH_2Cl_2 at

(9) Isomerization of epoxytrimethylsilanes to carbonyl compounds was originally discovered by G. Stork and E. Colvin: (a) Stork, G.; Colvin, E. *J. Am. Chem. Soc.* **1971**, *93*, 2080. For some elegant applications of this chemistry, see also: (b) Grobel, B. T.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 83. (c) Cooke, F.; Roy, G.; Magnus, P. *Organometallics* **1982**, *1*, 893. (d) Paquette, L. A.; Galemmo, R. A., Jr.; Caille, J.-C.; Valpey, R. S. *J. Org. Chem.* **1986**, *51*, 686.

(10) Allylstannanes add intramolecularly to acetylenes under the catalysis of various electrophilic metal salts. Fernández-Rivas, C.; Méndez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *67*, 5197. (b) Montgomery and Kang have reported the preparation of homoallylic alcohols by cyclization of δ-allenylaldehydes initated by organozinc reagents. (c) Montgomery, J.; Song, M. *Org. Lett.* **2002**, *4*, 4009. (d) Kang, S.-K.; Yoon, S.-K. *Chem. Commun.* **2002**, 2634. For other related reactions, see: (e) Ha, Y.-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143. (f) Kang, S.-K.; Hong, Y.-T.; Lee, J.-H.; Lee, I.; Yu, C.-M. *Org. Lett.* **2003**, *5*, 2813. Catalyzed additions of 1,3-dienes to tethered carbonyl compounds: (g) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (h) Shibata, K.; Kimura, M.; Shimizu, M.; Tamura, Y. *Org. Lett.* **2001**, *3*, 2181.

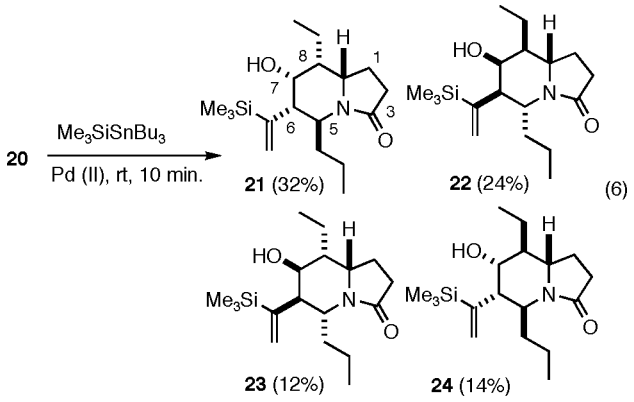
(11) Unpublished results: Shin, S.; Rhee, J. Ph.D. Dissertations, The Ohio State University.

(12) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 343.

−78 °C.[13] The enolsilane adds to the intermediate iminium ion resulting in the formation of the aldehyde(s) **20** in over 70% isolated yield. Aldehyde(s) **20** displayed four sets of peaks for C_2, C_3, C_8, and aldehydic protons in ^{1}H NMR and four peaks corresponding to each of the carbons in ^{13}C decoupled spectrum.[14] This suggests a virtually unbiased addition of **19** to produce all possible diastereomers of the adduct. These diastereomers were found to exist in a ratio of 1.0:0.7:0.5:0.6 on the basis of the integral intensity of the aldehyde proton signals at 27 °C. To gain further insight into possible restricted rotations in this molecule, we decided to monitor the ^{1}H NMR spectrum of the mixture in $CDCl_3$ at various temperatures. Our experiments ranging from 27 to − 60 °C showed further resolution of two of the aldehyde signals into two signals each at −60 °C and coalescence of these signals at −50 °C. This suggests some restricted conformational motion in these compounds. When the sample was heated to 70 °C, signals corresponding to aldehyde protons disappeared with the appearance of new peaks suggesting possible decomposition.

To assess the feasibility of improving the diastereoselectivity of this useful reaction, several Lewis acids that are known for the Mukaiyama aldol reactions were studied. The results are shown in Table 1. Best chemical yield (70%) was obtained using TMSOTf as the Lewis acid, and this reaction was used for preparative scale runs. Under optimized conditions we were able to produce **20** in up to 4 g in one pot without compromising the chemical yield or selectivity.

Allene-Aldehyde Cyclization. Having the required aldehyde in hand, our attention turned to the key cyclization to produce indolizidine precursors for our target structures. Since removal of the TBS group appeared to present problems as was the case in our earlier examples (eq 2, vide supra), we resorted to bifunctional reagents that contain a $SiMe_3$ group as the silyl partner, for the present cyclization reaction. To our delight, an extremely facile cyclization of **20** ensued upon treatment with 1.2 equiv of *n*-$Bu_3SnSiMe_3$ in the presence of a 5 mol % of $[(allyl)PdCl]_2$ in THF at room temperature (eq 6). Analysis of the reaction mixture by TLC indicated the



formation of four products (R_f on silica gel using ethyl acetate/hexane solvent, **22** > **23** > **21** > **24**) with disappearance of the starting material in about 10 min. Purification by flash column chromatography afforded the individual diastereomeric indolizidinols bearing five contiguous stereocenters, in a combined yield of 82%. Isomer **22** was a solid, whereas the others were isolated as viscous oils.

TABLE 1. Ratio of Products in Lewis Acid Mediated Addition of 19 to 18

entry	Lewis acid	dr of **20**	yield (%)
1	TMSOTf	0.7:1:0.5:0.6	70
2	$SnCl_2$	0.2:0.3:0.4:1.0	44
3	$Sc(OTf)_3$	0.7:0.8:1.1:0.8	67
4	$BF_3{\cdot}OEt_2$	complex mixture	
5	$SnCl_4$	complex mixture	
6	$TiCl_4$	complex mixture	
7	ZnI_2	no reaction	

TABLE 2. ^{1}H NMR Spectra of 21−24

	chemical shift δ, multiplicity, *J* (Hz)			
proton	**21**	**22**	**23**	**24**
C_5-H	4.30, m	3.67, ddd, 11.4, 11.4, 3.4	3.64, m	4.21, m
C_6-H	2.46, t, 4	2.51, dd, 11.3, 1.3	2.68, dd, 11.5, 2	2.59, dd, 12.5, 2.5
C_7-H	3.62, t, 1.5	3.62, br, s	4.07, t, 4.5	3.59, d, 3.5
C_8-H	1.83, q, 8.5	1.25, m	2.04, m	1.60, br

Structures of the Adducts. The structures of these compounds were unambiguously assigned by rigorous spectroscopic and X-ray crystallographic methods. All products were characterized by ^{1}H, ^{13}C, and 2D HMQC NMR and HRMS analysis. The C_5, C_6, C_7, and C_8 protons in all products were identified with the help of 2D COSY spectroscopy, and the details of the chemical shifts and coupling constants are presented in Table 2.

The assignments and relative stereochemistry of the stereogenic carbons in the solid product **22** were initially based on $^{1,3}J_H$ values and 2D NOESY spectroscopy. Strong cross-peaks between C_5-H and C_9-H, C_6-H and C_8-H, and C_6-H and C_7-H led to the assigned structure. Further, X-ray analysis of the crystals obtained from a CH_2Cl_2/hexanes (1:4) mixture proved the relative configurations of each of the carbons beyond any doubt as shown.[14]

The stereochemistry in **21** was established by a combination of $^{1,3}J_H$ values and a 2D NOESY spectrum. The structure was further confirmed by single-crystal X-ray analysis of the corresponding desilylated product **28**.[14]

In **23** the relative stereochemistry of the substituents could not be assigned from the 1D and 2D NMR data alone. However, removal of the trimethylsilyl group (vide infra, Scheme 6) gave a solid (**38**), which was recrystallized from CH_2Cl_2/hexanes (1:4). Analysis by X-ray diffraction unequivocally established the relative configuration of all carbons.[14]

The structure of **24** was assigned by comparison of its ^{1}H and 2D NOESY data with the rest.

The formation of four products in the present cyclization reaction should not be a point of concern since eventually the plan was to start with enantiopure **18** and conduct a stereoselective addition of a enol surrogate to the iminium ion[15] to make a single isomer of **20**. *Note that this is conceivable only because the allene-aldehyde*

(13) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717.

(14) See Supporting Information for details. Also included there are the ORTEP diagrams for **22**, **28**, and **38** and the corresponding crystallographic information as CIF files.

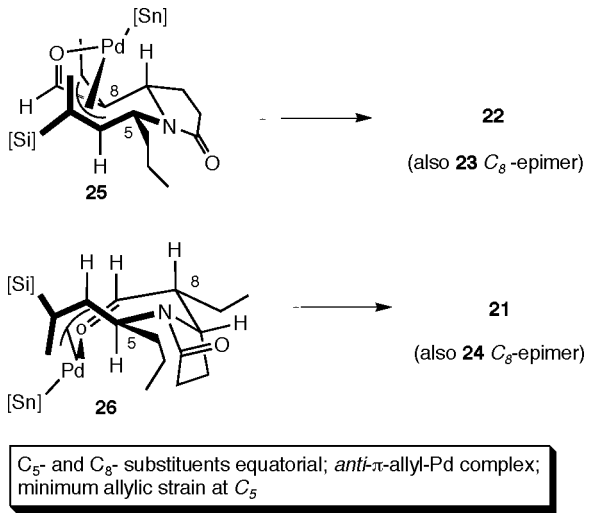


FIGURE 3. Favored transition states in the formation of **21** and **22**.

cyclization is completely stereoselective (C_5−C_6 trans; C_6−C_7 cis). Thus the stereoselectivity of all reactions in the sequence could in principle be controlled, opening a new, facile entry into highly alkylated indolizidines.

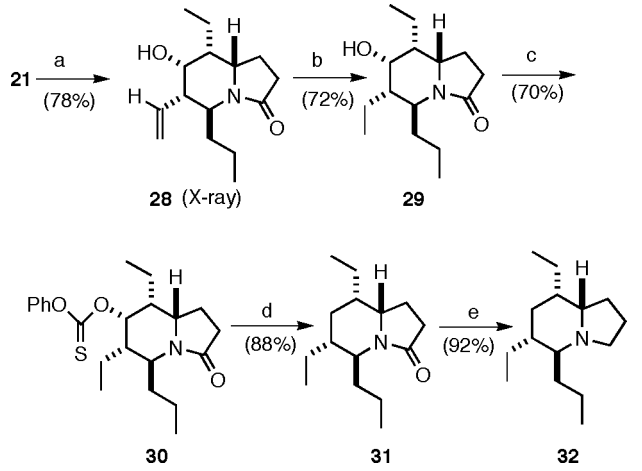
The observed diastereoselectivity (trans-C_5,C_6 and cis-C_6,C_7 substitution pattern) during the above cyclization can be rationalized by invoking a pair of chairlike transition states (**25** and **26**) shown in Figure 3. The structures **25** and **26** are characterized by (i) equatorial orientation of the C_5 and C_8 substituents, (ii) the most stable (anti) arrangement of the π-allyl Pd complex, and (iii) minimum of 1,3-allylic strain at C_5. With such constraints, intramolecular coordination of carbonyl oxygen to palladium dictates the cis orientation of the C_6 and C_7 substituents.

Substrate Choices for Natural Indolizidine 223A Synthesis. Having developed a concise route for the synthesis of advanced indolizidine precursors, our next goal was to complete the synthesis by choosing one of four diastereomeric indolizidines, **21**−**24**. However, comparison of the stereochemical features of these materials with the revised structure of the natural indolizidine 223A (**1**) reveals an obvious mismatch, which raises the challenge of maneuvering the stereochemistry in the most appropriate candidate in hand. Before attempting to do so, we decided to explore some of the chemistry of the major isomers in order to uncover the impending problems in stereochemical and functional group manipulations during the rest of the synthesis.

An Efficient Synthesis of Indolizidine 5,8-epi-223A. The major indolizidinol **21**, isolated in 32% yield, was our immediate choice to explore the chemistry of this bicyclic ring system. We envisioned a five-step sequence that involves removal of silicon, hydrogenation of the olefin, deoxygenation, and lactam reduction (Scheme 4). Our initial efforts to remove the trimethylsilyl moiety via protodesilylation returned only the starting material, presumably because of the primary nature of the incipient β-carbonium ion involved in the reaction. However, use of TBAF in a THF/DMSO (2:1) solvent mixture at

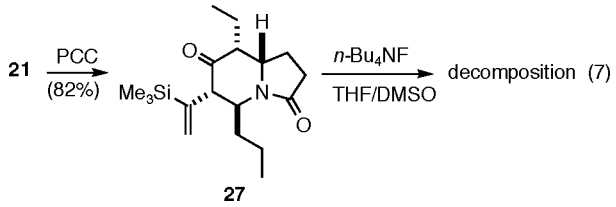
(15) For a recent attempt, see: Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187.

SCHEME 4. Synthesis of 5,8-Epi-indolizidine 223A[a]



[a] (a) TBAF in THF, THF/DMSO (2:1), 75 °C, 2.5−3.0 h. (b) 10% Pd−C, H_2 (60 psi), EtOH, 3−4 h. (c) PhOC(S)Cl, DMAP, CH_2Cl_2, rt, 3 d. (d) *n*-Bu_3SnH, AIBN (cat.), toluene, 95−100 °C, 2.5 h. (e) BH_3·THF, THF, rt, 24 h.

75 °C effected a smooth cleavage to give the desired olefin **28** as a solid in 78% yield. Intramolecular assistance of a hydroxyl group during the cleavage of silicon attached to olefin is known in the literature.[16] Oxidation of **21** to ketone **27** using pyridinium chlorochromate (PCC) followed by prolonged heating with TBAF under the above reaction conditions led only to the decomposition of the substrate (eq 7), thereby suggesting that indeed an



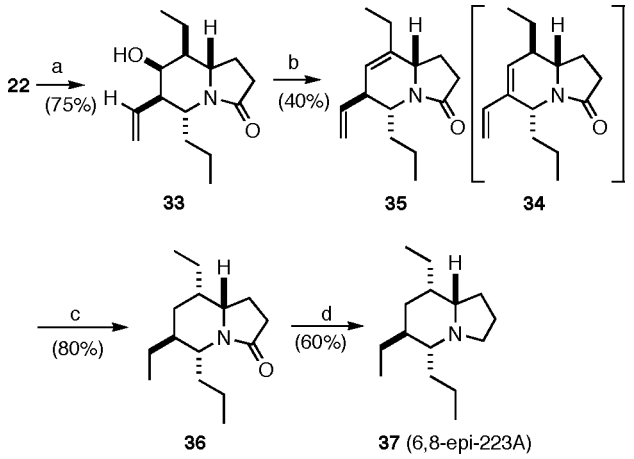
intramolecular hydroxy-assisted cleavage of the Si−C bond maybe taking place in **21**.

Crystallization of **28** from a 4:1 mixture of hexanes and CH_2Cl_2 yielded colorless needles whose analysis by X-ray crystallography established the structure as shown. Further, hydrogenation of olefin in **28** using 5% Pd−C in EtOH set the stage for Barton's deoxygenation. Our initial attempts to deoxygenate **29** via the corresponding imidazolylthionocarbonate intermediate gave only poor results. However, reaction of **29** with phenyl chlorothionoformate under Robins conditions[17] to form phenyl thionocarbonate **30** and the subsequent reduction using tri-*n*-butyltin hydride to the desired lactam **31** proceeded in very good yield. With bicyclic lactam **31** in hand, all that remained to get to the target was reduction of the lactam function to the amine. Submission of **31** to 3 equiv of borane in THF at room temperature effected a smooth reduction giving the indolizidine **32** as a solid in high yield. Analysis by ^1H and ^{13}C NMR and gas chromatog-

(16) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K. *Tetrahedron* **1985**, *41*, 3257.

(17) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059. Formation of **30** was equally slow in acetonitrile as a solvent.

SCHEME 5. Synthesis of 6,8-Epi-Indolizidine 223A[a]

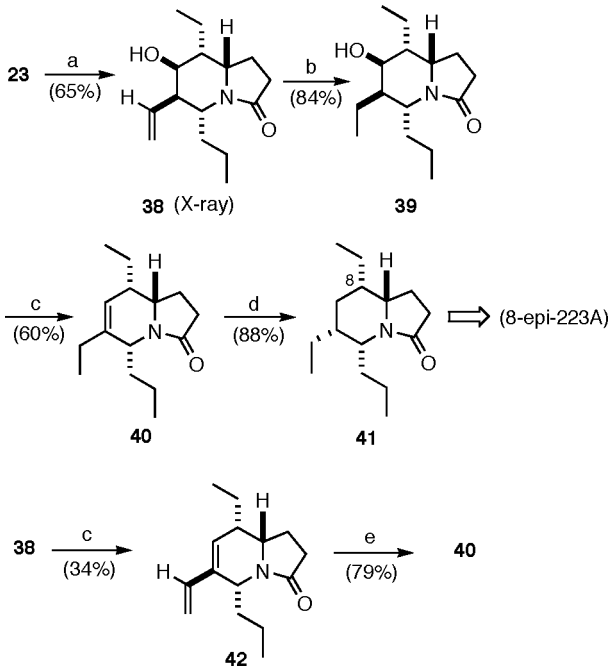


[a] (a) TBAF in THF, THF/DMSO (2:1), 75 °C, 2.5−3.0 h. (b) C_6F_5OCSCl, DMAP, CH_2Cl_2, reflux, 18 h. (c) 5% PtO_2/C, H_2, EtOH, 3−4 h. (d) BH_3·THF, THF, rt, 24 h.

raphy confirmed the homogeneity of the sample. Thus we established a facile route to the indolizidine ring system, completing a synthesis of an unnatural indolizidine in yield of 32% from **21** (10 linear steps from succinimide in 4% overall yield).

Synthesis of Indolizidine 6,8-epi-223A. Elaboration of Indolizidinol 22. This second most abundant cyclization product has all but the correct C_6 configuration for a projected synthesis of the indolizidine 223A. The transformation requires a four-step sequence involving removal of the trimethylsilyl group, regioselective dehydration with the formation of the C_6-C_7 double bond, and hydrogenation of this double bond, followed by reduction of the lactam functionality (Scheme 5). This strategy was based on the reasonable presumption that alcohol **33** bearing C_6 and C_8 axial hydrogens should undergo a preferential dehydration through the elimination of the C_6 hydrogen under appropriate conditions to give conjugated diene **34** (possibly mixed with **35**), whose reduction from the more exposed top face should lead to the correct configuration at C_6 for indolizidine 223A. In the event, removal of the TMS group from **22** using TBAF in THF/DMSO solvent mixture gave substrate **33** for the critical dehydration. Reaction of **33** with pentafluorophenyl chlorothionoformate in CH_2Cl_2 gave a mixture of dienes in 40% yield, the major component (~95%) of which was identified as **35**, not **34**. The structure was confirmed by careful analysis of various NMR spectra and subsequent reactions. Further, reduction of the diene [5% PtO_2, H_2 (60 psi) in EtOH] followed by reduction of the lactam (BH_3·THF, THF, rt) gave mostly **37**, identified as indolizidine 6,8-epi-223A. Analysis of this mixture by ^1H and ^{13}C NMR and comparison with the literature data[3−5] indicated that no trace of indolizidine 223A or indolizidine 6-epi-223A was present, thereby confirming the absence of any elimination reaction with the formation of **34**. Gas chromatography and NMR of the final product indicated the presence of a sideproduct (<5%), which has not been identified. Our attempts to prepare the key diene **34** by dehydration of **33** with other reagents such as Tf_2O and $POCl_3$ in pyridine gave only disappointingly low (10−15%) yields of elimination products, and this line of research was not pursued further.

SCHEME 6. Synthesis of 8-Epi-indolizidine 223A[a]



[a] (a) TBAF in THF, THF/DMSO (2;1), 75 °C, 2.5−3.0 h. (b) 5% Pd−C, H_2 (60 psi), EtOH, rt,7 h. (c) $POCl_3$, py, rt, 6 h. (d) 5% PtO_2/C/H_2 (60 psi), EtOH, rt, overnight. (e) 5 mol % [Ir(COD)py-(PCy_3)]$^+PF_6^-$, H_2 (200 psi), CH_2Cl_2, rt, 12 h.

Regioselective Dehydration of 23. Adduct **23** has stereochemical features making it attractive for the synthesis of yet another indolizidine. Since the axial alcohol in **39** bears only one trans-axial β proton (on C_6), we expected a selective dehydration to get **40**, setting the stage for a stereoselective hydrogenation en route to an unnatural indolizidine 8-epi-223A (Scheme 6). As expected, desilylation of **23** proceeded smoothly to give **38** in good yield. Hydrogenation followed by treatment of **39** with $POCl_3$ in pyridine yielded **40** as the only isomer exclusively via E_2 elimination. Further, hydrogenation using 5% PtO_2/H_2 (60 psi), surprisingly, led to the formation of an inseparable mixture of two compounds of which the structure of the major component was established as **41**. Reduction of the lactam function in **41** was not attempted since it is known to be a secure reaction from our previous studies with **31** and **36**. Incidentally, **40** can also be produced by dehydration of **38** and chemoselective hydrogenation with Crabtree's catalyst {[Ir(COD)Py(PCy_3)]$^+PF_6^-$, H_2 (200 psi) CH_2Cl_2, rt, 12 h}. The intermediate **42** appeared to be an exceptionally unstable product, which may explain why **34** was not seen in the dehydration of **33** (Scheme 5).

In conclusion, we have established a fundamentally new, relatively short route for the synthesis of highly alkylated indolizidines in less than 12 steps from readily available starting materials. Although a stereoselective addition of enolsilyl ether (or other enolate surrogates) to iminium ions remains to be explored,[18] the stereochemical issues associated with C_5 configuration can be solved by starting with the correct enantiomer of the allenyl alcohol,[19] since it is known that the Mitsunobu

(18) For a recent attempt, see: Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187.

reaction goes with clean inversion.[20] Our initial goals of assembling the carbon skeleton and exposing some of the functional group transformations and nontrivial stereochemical issues have been met. We plan to investigate solutions for the remaining stereochemical problems.

Experimental Section

General Methods. For general methods, see ref 6b. Procedures for the synthesis of **4** using allenyne cyclization as a key step and its subsequent protiodestannylation to get **8** have been described in our previous paper.[6b] Enolsilyl ether **19** was prepared in multigram quantities following the literature procedure.[21]

2-(1-(Octa-6, 7-dien-4-yl)-5-oxopyrrolidin-2-yl)butanal (20). In a two-necked flask equipped with a rubber septum, stirring bar, and a N_2 inlet were placed acetoxylactam **18**[6b] (20 mmol, 4.74 g) and silyl ether **19** (8 mL) in 40 mL of CH_2Cl_2 at −78 °C. Trimethylsilyl triflate (40 mmol, 7.23 mL) was added as a neat reagent dropwise slowly. The resulting mixture was warmed to −25 °C and stirred for 2 h. Aqueous $NaHCO_3$ was added to quench the reaction and extracted thoroughly with CH_2Cl_2 (3 × 30 mL). The combined organic part was washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (25% EtOAc in hexanes) afforded pure **20** (3.486 g, 70%) as a mixture of four diastereomers: IR (thin film) 2965, 2360, 2341, 1956, 1718, 1683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 and 9.78, 9.75 and 9.74 (2d, 2s, J = 1.5 Hz, 1H), 5.4, 5.29 and 5.23 (dq, q and q, J = 16, 7, 6.7, and 6.7 Hz, 1H), 4.8−4.76 (m, 2H), 4.58−4.51, 4.21 and 4.06 (m, qt and qt, J = m, 8, 2 Hz and 7.5, 2 Hz, 1H), 4.14, 4.89 and 3.82 (dt, J = 9, 2.9 Hz, 9, 3.5 and 9, 3.5 Hz, 1H), 2.83−2.79, 2.7, 2.66−2.62 and 2.56 (m, dm, m, dm, J = m, 11, m Hz, m, 11, m Hz, 1H), 2.36−2.25 (m, 2H), 2.11−1.95 (m, 1H), 1.9−1.59 (m, 4H), 1.51−1.42 and 1.4−1.2 (2m, 3H), 1−0.92 and 0.92−0.87 (2m, 6H); ^{13}C NMR (125 MHz) δ 208.9, 208.7, 208.5 and 208.3 (1C), 203.7, 203.7, 203.3 and 203.2 (1C), 175.9, 175.7, 175.4 and 175.2 (1C), 91.7, 91.4, 89.8 and 89.7 (1C), 77.7, 77.6, 77.1 and 76.9 (1C), 59.8, 58.3, 57.6 and 57.3 (1C), 57, 55.8, 55.5 and 55.1 (1C), 54,1, 53.8, 50.8 and 50 (1C), 35.8, 35.5, 32.9 and 32 (1C), 31.2, 30.8, 32.75 and 30.5 (1C), 20.8, 20,7, 20.67, 20.62, 20.62, 20.3, 20.1, 19.97, 19.6, 15.8 (4C), 13.98, 12.64, 12.61 and 12.5 (1C).

Cyclization of 20 to 8-Ethyl-7-hydroxy-5-propyl-6-(1-trimethylsilanyl-vinyl)-hexahydro-indolizin-3-one (21−24). In a two-necked flask equipped with a rubber septum, stirring bar, and a N_2 inlet were placed **20** (11 mmol, 2.739 g) and $Me_3SiSnBu_3$-*n* (13.2 mmol, 4.8 g) in 60 mL of dry THF at room temperature. Allyl palladium chloride dimer (0.55 mmol, 202 mg) was added, and the resultant dark mixture was stirred for 10 min at which time the disappearance of the starting material was confirmed by TLC. Aqueous NH_4Cl (3 mL) was added to quench the reaction, and the mixture was filtered through a pad of $MgSO_4$. The filtrate was concentrated to get a dark residue that was purified by flash column chromatography (10%, 25%, and 40% EtOAc in hexanes) to get **21** (1.14 g, 32%), **22** (847 mg, 24%), **23** (426 mg, 12%), and **24** (498 mg, 14%). **Data for 21**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 6.79 (d, J = 1.5 Hz, 1H), 4.32−4.28 (m, 1H), 3.97 (q, J = 8.5 Hz, 1H), 3.63 (t, J = 1.5 Hz, 1H), 2.46 (t, J = 4 Hz, 1H), 2.36−2.28 (m, 2H), 2.22−2.12 (m, 1H), 1.98−1.93 (m, 1H), 1.84 (q, J = 8 Hz, 1H), 1.63 (qu, J = 7 Hz, 2H), 1.51 (s, 1H), 1.45−1.39 (m, 1H), 1.3−1.2 (m, 3H), 0.98 (t, J = 7 Hz, 3H), 0.89 (t, 7 Hz, 3H), 0.1 (s, 9H); ^{13}C NMR (125 MHz) δ 174.2, 152.5, 129.3, 67.8, 54.1, 51.9, 50, 42.3, 38.6, 31.6, 23.1, 21.4, 20.1, 14.2, 12.7, −1.2. **Data for 22**: mp 127−129° C; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (d, J = 2 Hz, 1H), 5.64 (d, J = 2 Hz, 1H), 3.67 (ddd, J = 11.4, 11.4, 3.4 Hz, 1H), 3.62 (br s, 1H), 3.51 (dt, J = 11.5, 6.5 Hz, 1H), 2.51 (dd, J = 11.3, 1.3 Hz, 1H), 2.38−2.25 (m, 2H), 2.12−2.05 (m, 2H), 2.01−1.93 (m, 1H), 1.69 (br s, exchangeable with D_2O, 1H), 1.68−1.6 (m, 1H), 1.5−1.42 (m, 2H), 1.32−1.21 (m, 3H), 0.94 (t, J = 7 Hz, 3H), 0.87 (t, J = 7 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz) δ 175.3, 152.6, 126.7, 65.6, 59.5, 54.3, 49.9, 47.5, 32.4, 30.1, 22.8, 20.6, 19.8, 14.4, 11.3, −1.8; HRMS (EI/CI) calcd for $C_{18}H_{33}NO_2SiNa^+$ 346.217274, found 346.21882. **Data for 23**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (d, J = 2 Hz, 1H), 5.7 (d, J = 2 Hz, 1H), 4.07 (t, J = 4.5 Hz, 1H), 3.64−3.62 (m, 2H), 2.68 (dd, J = 11.5, 2 Hz, 1H), 2.4−2.2 (m, 3H), 2.07 (br s, exchangeable with D_2O, 1H), 1.81−1.7 (m, 2H), 1.6−1.48 (m, 3H), 1.32−1.24 (m, 3H), 0.99 (t, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz) δ 152.4, 127.1, 67.6, 57.8, 55.4, 47, 45.6, 44.1, 33.3, 30.2, 20.7, 20.6, 18.1, 14.3, 13.1, −1.3; HRMS (EI/CI) calcd for $C_{18}H_{33}NO_2SiNa^+$ 346.217274, found 346.21669. **Data for 24**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (s, 1H), 5,68 (d, J = 2 Hz, 1H), 4.24−4.2 (m, 1H), 3.6 (br d, J = 3.5 Hz, 1H), 3.35 (ddd, J = 11, 8, 3.5 Hz, 1H), 2.59 (dd, J = 12.5, 2.5 Hz, 1H), 2.47−2.33 (m, 2H), 2.26−2.18 (m, 1H), 1.76−1.7 (m, 1H), 1.60 (br, 1H), 1.51 (d, J = 5 Hz, 1H), 1.48−1.27 (m, 6H), 0.99 (t, J = 7 Hz, 3H), 0.89 (t, J = 7 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz) δ 174.7, 151.2, 127.4, 71.2, 56.3, 50.2, 48.4, 44.6, 35.3, 30.4, 25, 23.7, 19.8, 14.4, 11.7, −1.2; HRMS (EI/CI) calcd for $C_{18}H_{33}NO_2SiNa^+$ 346.217274, found 346.21884.

Desilylation of 21 to 8-Ethyl-7-hydroxy-5-propyl-6-vinyl-hexahydro-indolizin-3-one (28). In a two-necked flask equipped with a reflux condenser attached to N_2 inlet and a stirring bar was placed **21** (2 mmol, 646 mg) in 3 mL of THF and 1.5 mL of DMSO at room temperature. A 1 M solution of TBAF in THF (6 mmol, 6 mL) was added dropwise, and the resulting mixture was heated at 75 °C for 2.5−3 h. The reaction mixture was concentrated in a rotary evaporator and dissolved in 50 mL of ether. It was transferred into a separatory funnel, washed successively with H_2O and brine, dried ($MgSO_4$), and concentrated to get a crude product. Purification by flash column chromatography (25% EtOAc in hexanes) afforded pure **28** (392 mg, 78%) as a solid: mp 104−106 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79−5.71 (m, 1H), 5.19 (dt, J = 7, 1 Hz, 1H), 5.17 (d, J = 1 Hz, 1H), 4.22 (ddd, J = 9, 9, 2.5 Hz, 1H), 4.01−3.98 (m, 1H), 3.88 (q, J = 6 Hz, 1H), 2.42−2.38 (m, 2H), 2.36−2.33 (m, 1H), 2.07−2.01 (m, 1H), 1.81−1.78 (m, 2H), 1.63−1.43 (m, 4H),1.33−1.21 (m, 3H), 0.99 (t, J = 7 Hz, 3H), 0.91 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 174.8, 137.6, 118, 69.7, 55.2, 50.6, 48.9, 46.1, 35, 31.2, 21.3, 20, 18.5, 15.7, 14.2; HRMS (EI/CI) calcd for $C_{15}H_{25}NO_2Na^+$ 274.177747, found 274.17778.

Hydrogenation of 28 to 6,8-Diethyl-7-hydroxy-5-propyl-hexahydro-indolizin-3-one (29). To a suspension of 5% Pd−C in 2 mL of EtOH in a pressure tube was added **28** (0.96 mmol, 241 mg) in 3 mL of EtOH at room temperature. The reaction tube was alternatively evacuated and refilled (twice) with H_2 at 60 psi pressure. After stirring for 4 h, the reaction mixture was filtered through a pad of $MgSO_4$, and the pad was washed with hot MeOH (50 mL). Concentration of the filtrate and purification by flash column chromatography (40% EtOAc in hexanes) afforded pure **29** (175 mg, 72%) as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 3.97−3.93 (m, 2H), 3.91 (q, J = 7.5 Hz, 1H), 2.33 (dd, J = 9.2, 6.8 Hz, 2H), 2.07 (m, 2H), 1.72 (qd, J = 7, 2.7 Hz, 1H), 1.65−1.22 (m, 10 H), 0.98 (t, J = 7.5 Hz, 3H), 0.95 (t, 7.5 Hz, 3H), 0.9 (t, J = 8 Hz, 3H); ^{13}C NMR (125 MHz) δ 174.8, 69.8, 55.1, 50.7, 47.6, 44.4, 37.1, 31.5, 23.9, 22.5, 20.1, 19.5, 14.3, 14.2, 12.9; HRMS (EI/CI) calcd for $C_{15}H_{27}NO_2Na^+$ 276.193397, found 276.194716.

Conversion of 29 to *O*-6,8-Diethyl-octahydro-3-oxo-5-propylindolizin-7-yl Benzothioate (30). In a single-necked flask equipped with a stirring bar and a one-way stopcock attached to N_2 was placed **29** (0.69 mmol, 175 mg) in 4 mL of CH_2Cl_2 at room temperature. A solution of phenyl chlo-

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(20) (a) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *26*, 3255. (c) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 1956.

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rothionoformate (7 mmol, 970 μL) in 1 mL of CH_2Cl_2 and DMAP (7 mmol, 854 mg) were added successively. The reaction mixture was evacuated quickly, refilled with N_2, and stirred for 3 d to see the disappearance of most of the starting material. The reaction mixture was concentrated and purified by flash column chromatography (30% EtOAc in hexanes) to afford **30** (171 mg of **30** and 15 mg of **29**, 70% based on recovered **29**) as a thick oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, J = 7 Hz, 2H), 7.31 (t, J = 7 Hz, 1H), 7.09 (d, J = 7 Hz, 2H), 5.83 (t, J = 4 Hz, 1H), 4.15 (td, J = 7.5, 2.5 Hz, 1H), 3.98 (q, J = 7 Hz, 1H), 2.37 (td, J = 9, 2 Hz, 2H), 2.2−2.16 (m, 1H), 2.15−2.01 (m, 1H), 1.96−1.9 (m, 1H), 1.8−1.78 (m, 1H), 1.68−1.5 (m, 4H), 1.41−1.26 (m, 4H), 1.04 (t, J = 7 Hz, 3H), 1.02 (t, J = 7 Hz, 3H), 0.97 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 195.1, 174.6, 153.5, 129.9, 126.9, 122.1, 83.5, 54.7, 50.4, 45.5, 43.3, 36.2, 31.1, 23.3, 21.5, 20.1, 19.1, 14.9, 14.2, 13.2.

Reduction of 30 to 6,8-Diethyl-5-propyl-hexahydro-indolizin-3-one (31). In a two-necked flask equipped with a reflux condenser attached to N_2, stirring bar, and a rubber septum was placed TBTH (0.44 mmol, 58 μL) in 1 mL of toluene at 80 °C. A mixture of **30** (0.44 mmol, 171 mg) and AIBN (0.5 mmol, 82 mg) in 6 mL of toluene was introduced slowly over a period of 30 min with the help of a syringe pump. Another portion of TBTH (58 μL) was injected quickly, and the mixure was heated at 100 °C for 2.5 h. The reaction mixture was concentrated and purified by flash column chromatography (16% EtOAc in hexanes) to get **31** (92 mg, 88%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88−3.84 (m, 2H), 2.34−2.29 (m, 2H), 1.94−1.87 (m, 1H), 1.77−1.68 (m, 2H), 1.58−1.49 (m, 2H), 1.44−1.15 (m, 9H), 0.93 (t, J = 7 Hz, 3H), 0.9 (t, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 174.7, 56.1, 52, 42.5, 38.6, 38, 32.1, 29.5, 29, 23.4, 21.8, 20.3, 14.4, 13, 12.3; HRMS (EI/CI) calcd for $C_{15}H_{27}NONa^+$ 260.198482, found 260.19887.

Reduction of Lactam 31 to 5,8-Epi-indolizidine 223A (32). In a two-necked flask equipped with a rubber septum, stirring bar, and a N_2 inlet was placed **31** (0.34 mmol, 81 mg) in 3 mL of THF at room temperature. Borane·THF (1.36 mmol, 1.36 mL) was added dropwise, and the mixture was stirred for 24 h. Water (2 mL) was added slowly dropwise to quench the reaction and diluted with 30 mL of CH_2Cl_2. It was transferred into a separatory funnel, washed with brine, dried ($MgSO_4$), and concentrated and purified by flash column chromatography (3% EtOAc in hexanes) to get **32** (70 mg, 92%) as a colorless solid: mp 82−84 °C; GC conditions: 100 °C for 10 min then 10 °C/min up to 250 °C, t_R = 20.58 min (100%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (ddd, J = 13, 10, 2.5 Hz, 1H), 3.27−3.22 (m, 1H), 2.96−2.9 (m, 1H), 2.35−2.3 (m, 1H), 2.14−2.08 (m, 1H), 2.08−1.95 (m, 2H), 1.9−1.7 (m, 4H), 1.65−1.53 (m, 2H), 1.45−1.35 (m, 3H), 1.3−1.13 (m, 4H), 0.94−0.91 (m, 9H); ^{13}C NMR (125 MHz) δ 73.3, 63.4, 60.5, 39.7, 33.4, 33.2, 29.9, 27, 25.9, 25.2, 21.5, 19, 14.5, 11.7, 11.6; HRMS (EI/CI) calcd for $C_{15}H_{29}NH^+$ 224.237275, found 224.23739.

Desilylation of 22 to 8-Ethyl-7-hydroxy-5-propyl-6-vinyl-hexahydro-indolizin-3-one (33). Experimental procedure is the same as for the desilylation of **21** to **28**. Heating of **22** (1 mmol, 323 mg) with TBAF in THF (3 mmol, 3 mL) in THF (4 mL) and DMSO (2 mL) for 3 h followed by workup and purification by flash column chromatography (20% EtOAc in hexanes) afforded **33** (187 mg, 75%) as a solid: mp 127−129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (dt, J = 16, 10 Hz, 1H), 5.23, 5.2 and 5.17 (d, s, s, J = 1.5 Hz, 2H), 3.96 (br s, 1H), 3.54−3.49 (m, 2H), 2.32 (t, J = 7 Hz, 2H), 2.25 (t, J = 9.5 Hz, 1H), 2.12−1.98 (m, 3H), 1.65−1.6 (m, 2H), 1.51−1.38 and 1.38−1.2 (m, 5H), 0.95 and 0.9 (2t, J = 7 Hz, 2 × 3H); ^{13}C NMR (125 MHz) δ 175.1, 137.9, 118.4, 70.4, 59.6, 54.4, 51.1, 48.1, 32.3, 30.9, 23, 19.9, 19.3, 14.5, 11.3; HRMS (EI/CI) calcd for $C_{15}H_{25}NO_2Na^+$ 274.177747, found 274.17772.

Dehydration of 33 to 6,8-Diethyl-5-propyl-1,5,8,8a-tetrahydro-2*H*-indolizin-3-one (35). In a two-necked flask equipped with a rubber septum, a reflux condenser attached to N_2, and a stirring bar were placed **33** (1 mmol, 253 mg) and DMAP (1.3 mmol, 159 mg) in 2 mL of CH_2Cl_2 at room temperature. Pentafluorophenyl chlorothionoformate was introduced neat through a syringe, and the resultant yellow mixture was refluxed for 18 h. Concentration followed by purification by flash column chromatography (14% EtOAc in hexanes) afforded **35** as the major product contaminated with another as yet unidentified component (94 mg, 40%). **35**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.6 (dt, J = 16, 8 Hz, 1H from the contaminant), 5.48 (dt, J = 16, 8 Hz, 1H from the major isomer), 5.36 (q, J = 2 Hz, 1H), 5.21 (dd, J = 16, 4 Hz, 1H), 5.12−5.06 (m, 2H), 4.09 (t, J = 7 Hz, 1H from contaminant), 3.69 (t, J = 7 Hz, 1H from the major isomer), 3.23−3.28 (m, 1H from the major isomer), 3.18−3.12 (m, 1H from the contaminant), 3.08−3 (m, 1H), 2.51−2.32, 2.31−2.27 (2m, 5H), 2.22−2 (m, 4H), 1.98−1.81 (m, 1H), 1.8−1.72 (m, 2H), 1.71−1.52 (m, 5H), 1.41−1.28 (m, 3H), 1.05 (t, J = 7 Hz, 3H), 0.94−0.89 (m, 9H); ^{13}C NMR (125 MHz): *minor component* 174.5, 141.7, 137, 119.8, 65, 61.8, 59.7, 49.5, 32, 31.9, 23.2, 21.5, 19.9, 9.3, quartenary olefinic carbon not seen. **35**: 174.5, 139.1, 123.5, 116.5, 60.7, 58.9, 45, 32.8, 32.5, 24.9, 24.4, 20.9, 14.3, 12.5, quartenary olefinic carbon not seen.

Hydrogenation of 35 to 6,8-Diethyl-5-propyl-hexahydro-indolizin-3-one to 36. In a pressure tube containing 50 mg of 5% Pt/C was added **35** (0.47 mmol, 110 mg) in 4 mL of EtOH. The resulting mixture was stirred under H_2 at 60 psi pressure for 12 h. Filtration through a pad of $MgSO_4$ and washing of the pad with hot MeOH (25 mL) followed by concentration of the filtrate and purification by flash column chromatography (18% EtOAc in hexanes) gave **36** (89 mg, 80%) contaminated with an inseparable component as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57 (qu, J = 4 Hz, 1H from the minor contaminant), 3.03 (q, J = 5.5 Hz, 1H from the major isomer), 2.95 (q, J = 5.5 Hz, 1H from the major isomer), 2.85 (td, J = 7, 4 Hz, 1H from the minor contaminant), 2.32−2.28 (m, 2H), 2.22−2.01 (m, 2H), 1.82−1.74 (m, 1H), 1.71−1.6 (m, 1H), 1.45−1.6 (m, 5H), 1.4−1.1 (m, 5H), 0.92−0.8 (m, 9H). **36**: ^{13}C NMR (125 MHz) δ 174.7, 64.4, 60.8, 42.5, 39.9, 34.3, 32.3, 32, 26.5, 25.4, 23.8, 20.2, 14.5, 11.3, 11.2.

Reduction of 36 to Indolizidine 6,8-epi-223A (37). In a two-necked flask equipped with a N_2 inlet, rubber septum, and a stirring bar was placed the lactam **36** (0.152 mmol, 36 mg) in 1.5 mL of THF at room temperature. A 1 M solution of BH_3·THF was added slowly and the mixture was stirred overnight. Water (1 mL) was added dropwise, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic part was washed with brine, dried ($MgSO_4$), and concentrated to get a crude product, which upon chromatographic purification (2% EtOAc in hexanes) afforded **37** contaminated with <5% (GC) of another compound in 59% (20 mg) yield. **Data for 37**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48 (td, J = 7, 2.5 Hz, 1H), 2.95−2.8 (m, 1H), 2.65−2.55 (m, 1H), 2.3 (q, 8 Hz, 1H), 2.25−2 (m, 5H), 1.9−1.7 (m, 3H), 1.71−1.22 (m, 7H), 1.22−1.13 (m, 1H), 1.1−0.89 (m, 9H); ^{13}C NMR (125 MHz) δ 78.2, 77.4, 63.7, 39.8, 36.1, 35.9, 33.7, 26.5, 25.9, 25.8, 24.5, 19.8, 14.7, 11.8, 11; HRMS (EI/CI) calcd for $C_{15}H_{29}NH^+$ 224.237275, found 224.23734; GC conditions HP-ultra-1 cross-linked methyl silicone capillary column, 25 m length × 0.2 mm i.d.) run with program 100 °C for 10 min, then 10 °C/min heated to up to 250 °C, unidentified component t_R = 19.64 min, 5%; **37** t_R = 19.7 min, 95%.

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Supporting Information Available: Full experimental details for the preparation of starting materials not listed in the printed version; silylstannylation, distannylation, and related reactions of these substrates; and spectroscopic, crystallographic, and chromatographic data for characterization of compounds, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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