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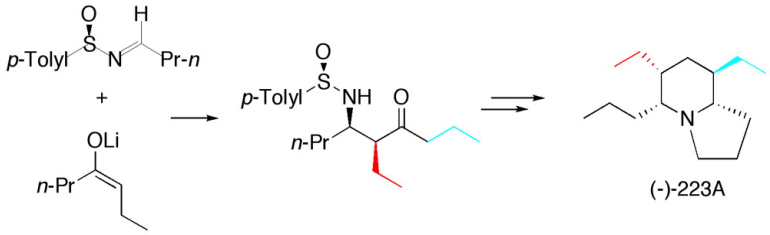

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Asymmetric Synthesis of α-Substituted β-Amino Ketones from Sulfinimines (*N*-Sulfinyl Imines). Synthesis of the Indolizidine Alkaloid (−)-223A

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Abstract: Of the possible four stereoisomers, addition of the lithium enolate of 4-heptanone to sulfinimines resulted in only the *syn*- and *anti*-α-substituted β-amino ketones. The formation of the major *syn*-β-amino ketone was rationalized in terms of addition of the *E*-enolate to the C−N double bond of the sulfinimine via a six-member chelated chairlike transition state. The enolates of 4-heptanone were generated using LiHMDS in THF where a 1:2.5 *E*:*Z* enolate ratio was noted. In diethyl ether the *E*:*Z* ratio was 15:1 in favor of the *E*-enolate and explained in terms of Ireland's transition state model. Here increased steric interactions between the ethyl group and the carbonyl-LiN(TMS)$_2$ moiety destabilize the transition state leading to the *Z*-enolate in the poorly coordinating diethyl ether solvent. This new synthesis of *syn*-α-substituted-β-amino ketones was applied to the concise enantioselective total synthesis of indolizidine (−)-223A, a 5,6,8-trisubstituted alkaloid isolated from the skin of the dendrobatide frog.

Substituted piperidines represent a common structural motif in numerous alkaloid natural products, bioactive compounds, drugs, and drug candidates. Although many methods have been devised to prepare this ring system, the continuing challenge is to develop concise procedures for establishing the piperidine ring stereocenters.[1] Our recent studies have demonstrated that the intramolecular Mannich reaction of aldehydes with the free amino group derived from *N*-sulfinyl δ-amino β-ketoesters is an important one-pot strategy for the stereoselective assembly of substituted piperidines in enantiopure form.[2,3] In previous work we applied this methodology to the concise asymmetric synthesis of the frog skin toxin (+)-241D,[4] a 2,4,6-trisubstituted piperidine, and the quinolizidine alkaloid (−)-epimyrtine.[5]

Using the intramolecular Mannich protocol, Troin and co-workers reported that the ketal of enantiopure 4-amino-2-pentanone (*S*)-(+)-**1** reacts with various aldehydes in the presence of acid to give *cis*-2,6-disubstituted piperidines **2** (Scheme 1).[6] However, the multistep synthesis of (+)-**1** requires either a classical resolution or a microbiological reduction as a key step and did not provide easy access to substituted derivatives.[6a,e]

Scheme 1

Sulfinimine-derived *N*-sulfinyl β-amino ketones **3** provided a general solution to the difficulty of preparing β-amino ketone ketals **4** in enantiomerically pure form. We found that treatment of **3** with *p*-toluenesulfinic acid (TsOH) and 1,3-propane diol resulted in *N*-sulfinyl deprotection and protection of the carbonyl group all in one pot (Scheme 2).[7] For example, this new methodology resulted in the synthesis of (*S*)-(+)-**1** in better than 72% yield. The β-amino ketones **3** were readily prepared by reaction of the potassium enolates of methyl ketones with sulfinimine **5**[7] or by treatment of the *N*-sulfinyl β-amino Weinreb amide **6** with Grignard reagents.[8] Significantly this new way of preparing β-amino ketone ketals means that, along with the intramolecular Mannich protocol, it will be possible to prepare diverse 2,3,4,6-tetrasubstituted piperidines in an efficient and highly stereoselective manner. Previously, we illustrated

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(2) For a review of the application of the Mannich reaction in alkaloid synthesis, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.
(3) For a review on sulfinimine chemistry that includes a discussion of *N*-sulfinyl δ-amino β-ketoesters, see: Zhou, P.; Chen, B.-C.; Davis, F. *Tetrahedron* **2004**, *60*, 8030.
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(8) (a) Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. *Org. Lett.* **2003**, *5*, 925. (b) Davis, F. A.; Nolt, B. M.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, *70*, 2184.

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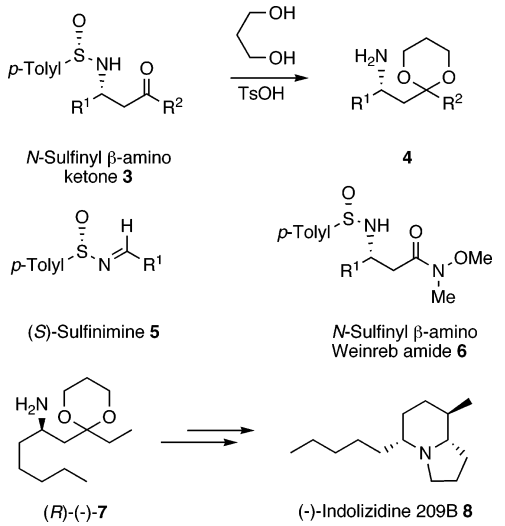
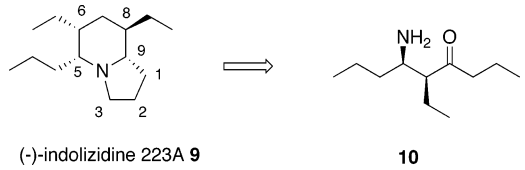
Scheme 2



Scheme 3



the potential of this methodology with a concise asymmetric synthesis of (−)-indolizidine 209B (**8**), an alkaloid isolated from the skin of the toxic dendrobatide frog, from the ketal of β-amino ketone (−)-**7** (Scheme 2).

The indolizidine alkaloid (−)-223A (**9**), like 209B (**8**), was isolated from the skin of the dendrobatide frog by Daly and co-workers (Scheme 3).[9] Indeed more than 500 alkaloids (pyrrolidines, piperidines, indolizidines, and quinolizidines) have been detected in the skin extracts of poisonous frogs and toads worldwide.[10] Many of these alkaloids exhibit interesting biological activity, including noncompetitive blockers for nicotinic channels.[11] However, due to the scarcity of the majority of these materials, their biological activities remain largely unexplored. While most of the isolated indolizidine alkaloids have the 3,5- or 5,8-disubstituted structure, e.g., **8**, (−)-223A (**9**) was the first trisubstituted indolizidine alkaloid to have been isolated from the dendrobatid frogs.[9] To prepare 223A (**9**) using the intramolecular Mannich protocol requires access to (5*S*,6*R*)-6-amino-5-ethylnonan-4-one (**10**), a *syn*-α-substituted β-amino ketone (Scheme 3). Described below are studies aimed at the asymmetric synthesis of *syn*-α-substituted β-amino ketones, which is highlighted in a concise asymmetric synthesis of (−)-indolizidine 223A (**9**).[12,13] In addition we report a novel and apparently not well-recognized effect of ether solvents on the stereoselectivity of aliphatic acyclic ketone *E*- and *Z*-enolate formation.

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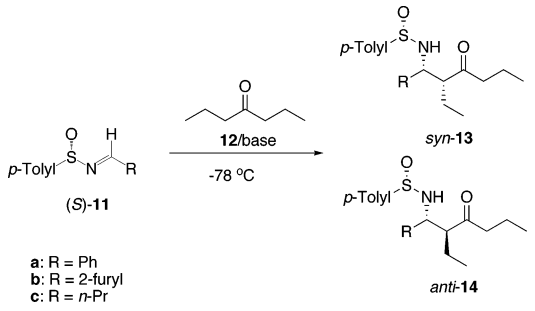
Scheme 4



Asymmetric Synthesis of *syn*-α-Substituted *β*-Amino Ketones. It appears that methods for the asymmetric synthesis of α-substituted β-amino ketones, where the amino group is attached to the stereogenic center, have not been previously described.[14,15] Among the procedures considered was the α-alkylation of β-amino ketones or β-amino ester enolates, but this would provide the *anti*-isomers.[14,16] Conversion of *syn*-α-substituted β-amino esters is another possibility but necessitates conversion into the ketone.[12b,17,18] Our recent success in the asymmetric synthesis of *syn*- and *anti*-α,β-diamino esters by addition of protected glycine enolates to sulfinimines (*N*-sulfinyl imines) encouraged us to devise a more direct method for the preparation of *syn*-α-ethyl β-amino ketone **10**.[19] This procedure involved the addition of the metal enolate derived from 4-heptanone (**12**) to sulfinimines **11** (Scheme 4).

In a typical experiment (*S*)-(+)-*N*-(benzylidine)-*p*-toluenesulfinamide (**11a**) was added to 1.5 equiv of the preformed sodium enolate of **12** at −78 °C. In this reaction the formation of four isomeric α-substituted β-amino ketones is possible. Significantly, the only two detected were the *syn*-**13a** and *anti*-**14a** isomers, isolated by flash chromatography in 66 and 24% yield, respectively (Table 1, entry 1). The best selectivities were observed for the lithium enolate generated using lithium bis(trimethylsilyl)amide (LiHMDS) in diethyl ether with the *syn*:*anti* ratios being dependent on the number of equivalents of the enolate (Table 1, entries 9 and 10). With 1.5 and 3.0 equiv of the lithium enolate of **12** the ratios of **13a** and **14a** were 9:1 and 18:1, respectively (Table 1, entries 9 and 10). These same trends were noted for the reaction of the lithium enolate of **12** with sulfinimines (*S*)-(+)-*N*-(2-furylmethylidene)-*p*-toluenesulfinamide (**11b**) and in particular (*S*)-(+)-*N*-(butylidene)-*p*-toluenesulfinamide (**11c**) necessary for the preparation of 223A (**9**). The major *syn* isomers **13b** and **13c** were isolated in 64 and 67% yields, respectively (Table 1, entries 13 and 15). An

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Table 1. Addition of the Enolate of 4-Heptanone to Sulfinimines at −78 °C[a]

entry	sulfinimine **11** (R =)	base	solvent	enolate *E*:*Z*[b,c] **15** (equiv)[d]	products	*syn*:*anti*[c,e] (% isolated yield)[f]
1	**11a** (Ph)	NaHMDS	Et_2O	3.5:1 (1.5)	**13a**:**14a**	3:1 (66):(21)
2			Et_2O[g]			3:1 (55):(18)
3			Et_2O	3.5:1 (0.9)		3:1 (36)
4			Et_2O[h]	(1.5)		1:1 (44):(44)
5			THF	1:45 (1.5)		2:1 (55):(24)
6		KHMDS	Et_2O	4:1 (1.5)		2:3 (34):(50)
7			THF	1:2.5 (1.5)		6:5 (52):(40)
8			PhMe	(1.5)		2:1 (48)
9		LiHMDS	Et_2O	15:1 (1.5)		9:1 (35)
10			Et_2O[i]	12:1 (3.0)		18:1 (71)
11			THF	1:2.5 (1.5)		6:1 (21)
12	**11b** (2-furyl)	NaHMDS	Et_2O	3.5:1 (1.5)	**13b**:**14b**	3:1 (62):(20)
13		LiHMDS	Et_2O	15:1 (3.0)		15:1 (64)
14	**11c** (*n*-Pr)	NaHMDS	Et_2O	3.5:1 (1.5)	**13c**:**14c**	3:1 (65):(21)
15		LiHMDS	Et_2O	15:1 (3.0)		12:1 (67)
16		LiHMDS	Et_2O[j]	15:1 (3.0)		10:1 (78):(8)
17		LiHMDS	THF	1:2.5 (1.5)		4:1 (20)

[a] Sulfinimine transferred to the enolate unless otherwise noted. [b] *E*:*Z* ratio of the enolate was determined by trapping experiments. [c] The % THF, from the LiHMDS solution, in diethyl ether was approximately the same. [d] Equivalents of enolate. [e] Determined by ^{1}H NMR on the crude reaction mixtures. [f] Isolated yields of major and minor isomers. [g] 4-Heptanone was added to **11a** and the base. [h] HMPA, 1.5 equiv added. [i] The % THF in Et_2O was approximately 3 times greater. [j] The preformed enolate added to the sulfinimine.

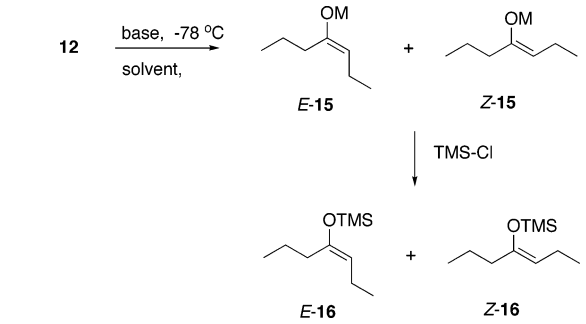
alternative procedure involved adding the enolate to the sulfinimine **11c**, and while this increased the yield of the major product, *syn*-**13c**, to 78%, it resulted in decreased selectivity (Table 1, entry 16).

Assignment of the absolute stereochemisty for the *syn*-**13** (major) and *anti*-**14** (minor) β-amino ketones was ultimately determined by the conversion of the enantiomer of *syn*-**13c** to (−)-223A **(9)** (see below). However, chemical shifts of the NH protons for the minor *anti* isomers **14** appeared about 0.6 to 0.9 ppm downfield from the major *syn* isomers **13**. There was no useful diagnostic correlation of the coupling constants for **13** and **14**. Interestingly, on TLC the minor isomers had higher R_f values compared to the major *syn* isomers.

Enolate Geometries. Pioneering studies by Heathcock and others on the aldol reaction have demonstrated that there is a strong correlation between the enolate geometry and the stereochemistry of the aldol product.[20] In our studies, the geometries of the acyclic enolates of 4-heptanone (**12**), generated using LiHMDS, NaHMDS, and KHMDS, were determined by trapping with trimethylsilyl chloride (TMS-Cl) at −78 °C to give the corresponding *E*- and *Z*-enol silanes **16** as previously described (Scheme 5).[20−22] The ratios of the *E*- and *Z*-enol silanes **16** were determined by integration of the characteristic triplets of the vinyl proton resonances on C-3 in the ^{1}H NMR of **16**.[21] In *E*-**16** the vinyl proton appears at δ 4.62 ppm and in *Z*-**16** it appears at δ 4.31 ppm in accordance with earlier studies. The enolate geometries thus determined are summarized in Table 1.

In all cases examined the *Z*-enolate, *Z*-**15**, was favored in THF solvent (Table 1). For example the sodium enolate gave a 1:45 *E*:*Z* ratio (Table 1, entry 5), whereas the *E*:*Z* ratios for the

Scheme 5



lithium and potassium enolates were much lower, i.e., 1:2.5 (Table 1, entries 7, 11, and 17). Earlier studies by Munchhof and Heathcock, which used LDA and THF to generate the enolate of **12**, also revealed a preference for the *Z*-enolate.[23] However, these workers observed that as the polarity of the solvent increased (hexane in THF), the portion of the *Z*-enolate decreased. Enhanced *E*:*Z* ketone enolate selectivity (50:1) has also been reported by Collum and others using hindered lithium bases and added lithium salts.[24] For ketone enolization the LiHMDS/THF base system usually results in the formation of the kinetic *Z*-enolate.[20,22,23,25] These results have generally been interpreted in terms of Ireland's transition model invoking steric and electronic effects (see below).

Significantly, in diethyl ether we observed a dramatic increase in selectivity for formation of the *E*-enolate (*E*-**15**) that has not previously been noted (Table 1). The highest *E*:*Z* ratio, 15:1, was observed for the lithium enolates generated using LiHMDS (Table 1, entries 9, 10, 13, 15, and 16). With one exception, the sodium, potassium, and lithium enolates of **12**, on addition to sulfinimines (*S*)-**11**, preferentially formed the *syn*-β-amino α-ethyl β-amino ketones **13**. The *syn*:*anti* **13**:**14** ratios were 2:1 for the sodium enolates in THF, whereas the enolate **15** had a

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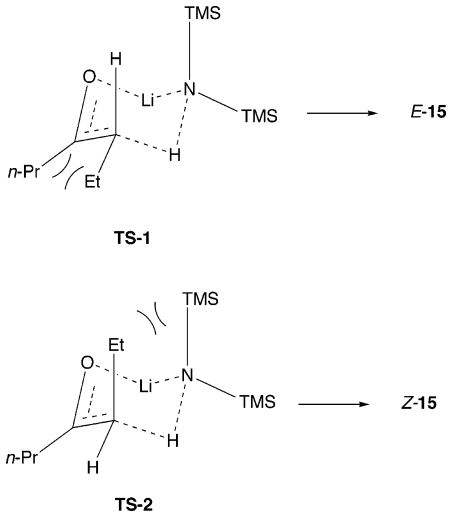


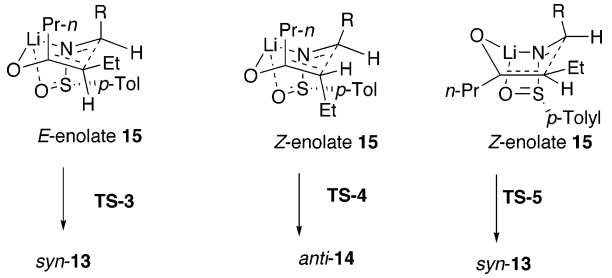
Figure 1. Ireland transition state models for the formation of *E*- and *Z*-enolates.

1:45 *E*:*Z* ratio (Table 1, entry 5). Only the potassium enolate of **12** in diethyl ether afforded more *anti* product **14a** on addition to **11a** (Table 1, entry 6). Importantly, the *syn*:*anti* ratios improved from 9:1 to 18:1 for the lithium enolates in diethyl ether (Table 1, entries 10, 13, 15, and 16).

Mechanism. Particularly intriguing is why the *E*-enolate of **12** (*E*-**15**) is so dramatically favored in LiHMDS/diethyl ether (*E*:*Z*, 15:1) compared to this base in THF (*E*:*Z*, 1:2.5). The well-known Ireland transition model for formation of *E*- and *Z*-enolates, applied to the deprotonation of 4-heptanone (**12**), may offer an explanation (Figure 1).[26] In Ireland's transition state model the formation of *E*- and *Z*-enolates is determined by the energy differences between transition state **TS-1** and **TS-2** and dependent on steric and electronic factors within these structures. A more demanding steric interaction between the Et group and the carbonyl-LiN(TMS)$_2$ moiety in **TS-2** is expected to result in an increase in the formation of the *E*-enolate. Because ethyl ether is a poorer coordinating solvent than THF, this could result in a tighter transition state and greater interaction between the Et group and the carbonyl-LiN(TMS)$_2$ moiety, which could destabilize **TS-2** and favor **TS-1**.[27] Collum and co-workers have reported that, in the formation of ketone enolates, LiHMDS acts as a dimer in ether solvents and a monomer in THF,[28,29] which has even greater impact on the stability of **TS-2** vs **TS-1**. Thus the effective size of the carbonyl-Li group should be much larger in diethyl ether than in THF, which further destabilizes **TS-2** (Figure 1).

The absolute stereochemistry for the product of addition of enolates to sulfinimines is controlled by the *N*-sulfinyl group and predicted by a six-membered chairlike transition state.[3] For the addition of α-substituted ester enolates to *tert*-butyl sulfinimines Ellman evoked a six-member chairlike transition state to explain the preferred formation of the *syn*-α-substituted-β-amino esters.[17a] The enolate geometry is presumed to be *E*. The addition of the *E*- and *Z*-enolate of **12** to sulfinimines (*S*)-**11** results in exclusive *re* face addition, which affords the *syn*-**13** and *anti*-**14** β-amino ketones via transition states **TS-3** and **TS-4**, respectively (Scheme 6). The fact that *syn*-**13** is favored in nearly all cases suggests that the *E*-enolate *E*-**15** is more reactive and more selective toward addition to the sulfinimine than is the *Z*-enolate. Consistent with this idea is the observation that the *E*:*Z*-enolate ratio of **12** is lower than the *syn*:*anti* selectivity, particularly at higher concentrations of the enolate. Here the *E*-enolate *E*-**15** reacts at a faster rate with sulfinimine **13** and favors the *syn*-**13** product. However, the possibility that the *Z*-enolate could also give some of the *syn* product via boatlike transition state **TS-5** cannot be ruled out at this time. Indeed if this were correct, it could explain the unusually high yield of *syn*-**11a** (55%) despite the fact that the *E*:*Z* ratio is 1:45 (Table 1, entry 5).

Scheme 6



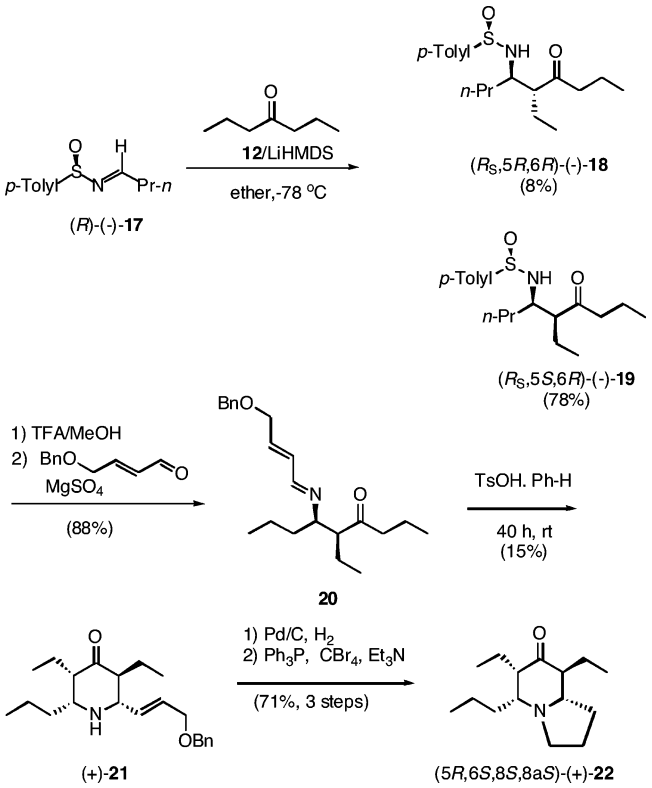
Asymmetric Synthesis of (−)-223A. To prepare alkaloid (−)-223A (**9**) using the intramolecular Mannich protocol requires the enantiomer of *syn*-**13c**, (R_S,5*S*,6*R*)-(−)-**19**, which was readily prepared from sulfinimine (*R*)-(−)-**17** as outlined in Scheme 7. The *N*-sulfinyl β-amino ketone (−)-**19** was deprotected with TFA/MeOH, and the product was passed through a short pad of silica gel and treated with *E*-4-benzyloxybut-2-enal in the presence of anhydrous $MgSO_4$ to give the crude imine **20** in ca. 88%. Attempted isolation of the imine by chromatography resulted in decomposition. However, the intramolecular Mannich cyclization, which involves stirring the crude imine in benzene with 2 equiv of TsOH for 40 h, resulted in only a 15% yield of the desired 2,3,5,6-tetrasubstituted piperidin-4-one (+)-**21**. Considerable decomposition was noted under these conditions, and we speculated that this might be due to the liability of the benzyloxy group under the acidic conditions. To affect the cyclization of (+)-**21** to (+)-**22**, the former was hydrogenated (H_2/Pd) and the intermediate alcohol (not shown) was subjected to cyclization with CBr_4/Ph_3P/Et_3N, affording the indolizidine (+)-**22** in 71% yield for the three steps (Scheme 7).[7]

In an effort to circumvent the poor yields in the Mannich cyclization step when using imine **20**, a ring-closing metathesis strategy was next explored to install the indolizidine structure. Here (−)-**19**, after removal of the *N*-sulfinyl group, was treated with crotonaldehyde to give the crude imine **23** in better than 93% yield (Scheme 8). Treatment of **23** with TsOH for 40 h resulted in two piperidines, (2*S*,3*S*,5*S*,6*R*)-(+)-**24** and (2*R*,3*S*,5*S*,6*R*)-(+)-**25**, in 58 and 18% isolated yields, respectively (Scheme 8). Importantly, no epimerization was noted at C-5 during the acid-catalyzed Mannich cyclization.

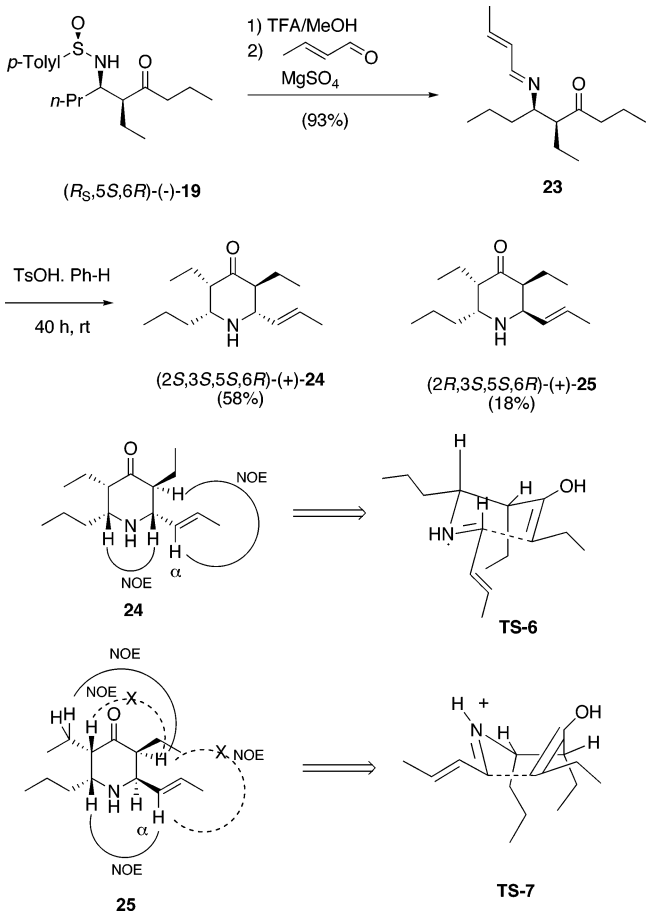
The stereochemistry features of (+)-**24** and (+)-**25** were based on 1D NOE studies and ultimately the conversion of (+)-**24**

(26) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Moreland, D. W.; Dauben, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2264. (c) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 4119. (d) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.
(27) Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *1035*, 5.
(28) (a) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008. (b) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411. (c) Zhao, P.; Lucht, B. L.; Kenkre, S. L.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 242. (d) Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 3113.
(29) See also: Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829.

Scheme 7



Scheme 8



into (−)-223A (**9**) (see below). In **24**, the observed NOE between the C-2 and C-6 methine protons indicates a *cis* orientation for the 6-propyl and 2-propenyl groups. Another NOE was observed between the C-3 methine proton and the H_α of the propenyl group, which indicates the *trans* relationship between the propenyl group on C-2 and the ethyl group on C-3. In (+)-**25** the 1D NOE revealed an interaction between the methine proton at C-6 and the H_α of the propenyl group at C-2, which signifies the *trans* relationship between the groups on C-2 and C-6. No NOE was observed between the two methine protons on C-2 and C-6 and provides additional evidence for the *trans* relationship of these groups. The observed NOE between the C-3 methine proton and the methylene protons in the ethyl group on C-5 suggests that the C-3 ethyl group has a *trans* relationship with the C-5 substituent. Again no NOE was detected between the C-3 methine proton and the H_α on the 2-propenyl group, which provides further evidence for the *cis* relationship between the groups on C-2 and C-3 (Scheme 8).

The formation of the major product (2*S*,3*S*,5*S*,6*R*)-(+)-**24** can be rationalized by a six-member chairlike transition state **TS-6** (Scheme 8). Here the 2-(1-propenyl), 3-ethyl, and 6-propyl all occupy equatorial positions, while the 5-ethyl is forced into an axial orientation. As shown in **TS-6**, the enol is assumed to have the *Z* configuration and is similar to transition state models proposed by Troin et al. in their syntheses of *cis*-2,6-disubstituted piperidin-4-ones from *β*-amino ketal (*S*)-(+)-**1**.[6] A boatlike transition state **TS-7** can be used to rationalize the formation of the minor product (2*R*,3*S*,5*S*,6*R*)-(+)-**25**, where the ethyl group at C-5 and the propyl group at C-6 both assume pseudoaxial positions. The 1-propenyl group on C-2 and the ethyl group on C-3 both have pseudoequatorial orientations. Another possibility that cannot be ruled out at this time is that the *E*-imine **23** isomerizes to the *Z*-imine under the acidic reaction conditions.[30]

Applying the intramolecular Mannich protocol to the minor *anti* isomer (S_S,5*R*,6*R*)-(−)-**18** resulted in the formation of two piperidin-4-ones, (2*S*,3*S*,5*R*,6*R*)-(+)-**26** and (2*R*,3*R*,5*R*,6*R*)-(−)-**27**, in 65 and 18% yields, respectively, for the three-step sequence (Scheme 9). Considering the axial alignment of the C-5 ethyl group in (2*S*,3*S*,S*R*,6*R*)-**24**, we anticipated that base-induced epimerization at C-5 would result in (2*S*,3*S*,5*R*,6*R*)-(+)-**26**. Indeed, refluxing (+)-**24** in the presence of sodium methoxide in MeOH for 24 h afforded (+)-**26** in 55% yield (Scheme 9). This transformation provides further support for the stereochemistry of (+)-**26**. The structure of (−)-**27** is supported by NOE studies.

With the requisite tetrasubstituted piperidin-4-one (+)-**24** in hand we found heating **24** with allyl bromide/Na_2CO_3 afforded diene (+)-**28** in 91% yield (Scheme 10). Ring-closing metathesis using 5 mol % of the Grubbs "first generation" catalyst,[31] followed by hydrogenation (Pd/H_2), gave indolizidine (+)-**22** in 72% yield for two steps (Scheme 10). All that remains is to remove the 7-oxo group in (+)-**22** and our target indolizidine (−)-223A (**9**) would be in hand. However, attempts to form the thioketal of (+)-**22** using ethanedithiol/BF_3, as we had previously found successful in our synthesis of indolizidine 209B (**8**),[7] resulted in extensive decomposition. A Clemenson reduction with Zn/HCl resulted in no reaction. Reduction of

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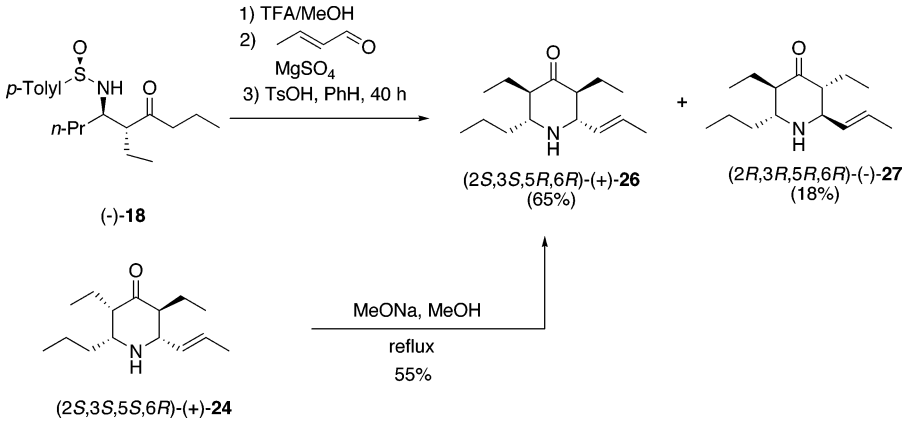
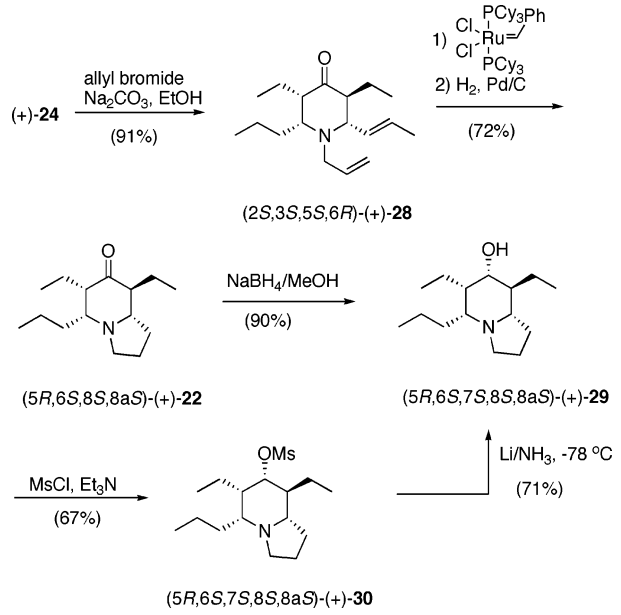
(31) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1999**, *54*, 4413. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 1751.

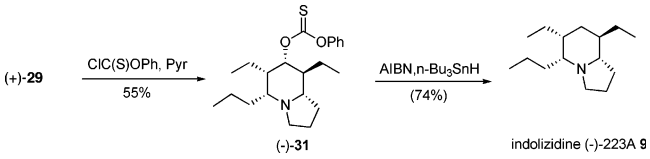
Scheme 9



Scheme 10



Scheme 11



(+)-**22** with $NaBH_4$ gave a 90% yield of alcohol (+)-**29** as a single isomer. The two vicinal diaxial coupling constants of 10.5 Hz between the C-7 proton and the C-8 methine protons in (+)-**29** support the equatorial orientation for the hydroxy group and are consistent with approach of hydride from the least hindered axial position; so the next plan was to convert (+)-**29** into its mesylate (+)-**30** followed by a reductive deoxygenation as previously reported.[32] Unfortunately, reduction of the mesylate with Li/NH_3 simply regenerated the alcohol (Scheme 10). Attempts to convert the alcohol into the corresponding diethyl phosphonate or *N*,*N*,*N*′*N*′-tetramethylphosphoradiamidates for reductive deoxygenation, as described by Ireland,[33] was also unsuccessful. Our inability to remove the 7-oxy/hydroxy groups in these transformations is likely the result of steric congestion in the regions of these moieties in (+)-**22** and (+)-**29**, respectively.

A radical deoxygenation protocol proved to be successful. Treatment of indolizidine alcohol (+)-**29** with phenylthionochloroformate and pyridine in dichloromethane afforded the phenylthionocarbonate (−)-**31** in 55% isolated yield (Scheme 11).[34] Reaction of *tri*-*n*-butyltin hydride and AIBN in benzene with (−)-**31** furnished indolizidine (−)-223A (**9**) in 74% yield with properties consistent with literature values.[12]

Summary and Conclusions. Of four possible stereoisomers, addition of the lithium enolate of 4-heptanone (**12**) to sulfinimines (*S*)-**11** results in only the *syn*-**13** and *anti*-**14** α-ethyl β-amino ketone isomers being formed. These results were interpreted in terms of the *E*-enolate of **12**, *E*-**15**, adding to the *re* face of the sulfinimine C−N double bond via six-member chelated transition state **TS-3**, affording *syn*-**13** as the major product. Trapping of the enolate of **12**, generated using LiHMDS, with TMS-Cl revealed an unexpected effect of solvent on the enolate geometry. In THF the *E*:*Z* ratio of enolates generated using this base was 1:2.5, as observed by a number of others. However, in diethyl ether the enolate geometry dramatically changes to 15:1 in favor of the *E*-enolate. These results were rationalized in terms of Ireland's transition state model wherein increased steric interaction between the Et group and the carbonyl-$LiN(TMS)_2$ moiety results in destabilized of **TS-2** (*Z*-enolate formation) relative to **TS-1** (*E*-enolate formation) (Figure 1). The increased interaction between the Et group and the carbonyl-$LiN(TMS)_2$ was suggested to result from a tighter transition state and the dimeric nature of LiHMDS in the poorly coordinating diethyl ether solvent compared to THF. This new methodology for α-substituted β-amino ketone synthesis was applied in a concise asymmetric synthesis of indolizidine 223A (**9**), a 5,6,8-trisubstituted indolizidine. The key step in this synthesis was the intramolecular Mannich cyclization of the crotonaldehyde imine of *syn*-α-ethyl β-amino ketone **10** to give 2,3,5,6-tetrasubstituted piperidine (+)-**24** in 58% yield. The synthesis of (−)-223A (**9**) was accomplished in approximately nine steps (9.3% overall yield) from sulfinimine (*R*)-(−)-**17** and represents the most concise synthesis of this alkaloid to date.

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(34) (a) Berninger, J.; Krauss, R.; Weinig, H.; Koert, U.; Ziemer, B.; Harms, K. *Eur. J. Org. Chem*. **1999**, 875. (b) Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J.; Colapret, J. A. *J. Org. Chem*. **1989**, *54*, 2209.

Experimental Section

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid. Melting points were recorded on a Mel-Temp apparatus and were uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter, and IR spectra were recorded, using NaCl plates, on a Mattson 4020 FTIR. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400, operating at 400 and 100 MHz, respectively. HRMS were performed in the Department of Chemistry, Drexel University, Philadelphia, PA, using a Fissions ZAB HF double-focusing mass spectrometer.

Anhydrous and oxygen-free dichloromethane, toluene, Et_2O, and THF were obtained from a Schlenk manifold with purification columns packed with activated alumina and supported copper catalyst (Glass Contour, Irvine, CA). Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. Sulfinimines (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**11a**), (*S*)-(+)-*N*-(2-furylmethylidene)-*p*-toluenesulfinamide (**11b**), and (*S*)-(+)-*N*-(butylidene)-*p*-toluenesulfinamide (**11c**) were prepared as previously decribed.[35]

Determination of the Enolate Geometry of 4-Heptanone. General Procedure for Trapping the Enolate with Trimethylsilyl Chloride.[21] In a 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 2.89 mmol of the appropriate base (LiHMDS, NaHMDS, 1 M solution in THF, KHMDS, 0.5 M solution in toluene) in 30 mL of the specified solvent (diethyl ether or THF) at −78 °C. To the solution was slowly added 4-heptanone (**12**) (0.37 mL, 2.63 mmol) via syringe. The reaction was kept stirring at −78 °C for 1 h, and 0.33 mL (2.63 mmol) of chlorotrimethylsilane was added dropwise via syringe. The reaction was allowed to warm to room temperature over 0.5 h, and after stirring for an additional 0.5 h, the reaction mixture was partitioned between hexane and saturated $NaHCO_3$, The organic phase was dried (Na_2SO_4) and concentrated. Inspection of the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture was used to determine the ratio of *E*/*Z* silyl enol ethers **16**. Integrations of the vinyl protons at δ 4.62 and 4.31 ppm in the ^{1}H NMR were used to determined the *E*:*Z* ratios, respectively.

((*E*)-Hept-3-en-4-yloxy)trimethylsilane (*E*-16): ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9 H), 0.90 (t, J = 7.6 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H), 1.47 (m, 2 H), 1.94 (t, J = 7.6 Hz, 2 H), 2.02 (t, J = 7.2 Hz, 2 H), 4.62 (t, J = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.6, 13.9, 15.6, 20.4, 20.5, 33.3, 109.4, 150.4.

((*Z*)-Hept-3-en-4-yloxy)trimethylsilane (*Z*-16): ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9 H), 0.78 (m, 6 H), 1.34 (m, 2 H), 1.85 (m, 4 H), 4.31 (t, J = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.8, 13.9, 14.7, 18.8, 20.4, 38.8, 110.5, 150.0.

(*R*)-(−)-*N*-(Butylidene)-*p*-toluenesulfinamide (17). In a 250 mL, one-necked, round-bottomed flask equipped with magnetic stirring bar and argon balloon was placed 3.0 g (19.3 mmol) of (*R*)-(−)-*p*-toluenesulfinamide (Aldrich) in dichloromethane (100 mL). To this solution were added 1.73 mL (19.3 mmol) of butyraldehyde and 20.3 mL (96.6 mmol) of titanium tetraethoxide at room temperature. The reaction mixture was stirred for 3 h and poured into a 500 mL beaker containing 80 mL of an ice−water mixture, and the solution was vigorously stirred for 10 min. At this time dichloromethane (50 mL) was added and the solution was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum to give 3.4 g (84%) of a colorless oil: $[\alpha]^{20}_D$ −385.4 (*c* 0.6, $CHCl_3$); IR (neat) 2961, 2873, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.6 Hz, 3 H), 1.64 (m, 2 H), 2.39 (s, 3 H), 2.46 (m, 2 H), 7.30 (d, J = 7.6 Hz, 2 H), 7.56 (d, J = 7.6 Hz, 2 H), 8.22 (t, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.0, 21.6, 38.0, 124.7, 130.0, 141.8, 142.1, 167.3; HRMS calcd for $C_{11}H_{15}NOS$ (M + H) 210.0952, found 210.0949. Spectral properties were identical to (*S*)-(+)-*N*-(butylidene)-*p*-toluenesulfinamide (**11a**).[35]

Typical Procedure of the Addition of the Enolate of 4-Heptanone (12) to Sulfinimines. In a 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.48 mL (0.48 mmol) of NaHMDS (1.0 M solution in THF) in diethyl ether (5 mL). The % of THF in the diethyl ether was approximately the same as that used in the enolate trapping experiments. The solution was cooled to −78 °C, and 0.063 mL (0.45 mmol) of 4-heptanone (**12**) was added dropwise via syringe. The reaction was stirred for 1 h at this temperature, and 0.3 mmol of appropriate sulfinimine, **11a**, **11b**, or **11c**, in ether (1 mL) was added dropwise via cannula. After 0.5 h the reaction mixture was quenched at −78 °C by addition of saturated NH_4Cl solution (1.5 mL), and H_2O (6 mL) was added. The solution was extracted with EtOAc (2 × 10 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (20% EtOAc/hexane) was used to purify the products. The first to elute was *anti*-**14**, followed by *syn*-**13**.

***syn*-(*S*$_S$,1*R*,2*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-1-amino-2-ethyl-1-phenylhexan-3-one (13a).** Purification (20% EtOAc/hexane) afforded 0.072 g (66%) of a white solid: mp 90−91 °C; $[\alpha]^{20}_D$ +33.8 (*c* 0.8, $CHCl_3$); IR (neat) 3195, 2963, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.71 (dt, J = 7.5, 1.0 Hz, 3 H), 0.78 (t, J = 7.5 Hz, 3 H), 1.36 (m, 2 H), 1.62 (m, 1 H), 1.68 (m, 1 H), 2.04 (dt, J = 18.0, 7.5 Hz, 1 H), 2.16 (dt, 18.0, 7.5 Hz, 1 H), 2.41 (s, 3 H), 2.81 (m, 1 H), 4.57 (d, J = 3.5 Hz, 1 H), 4.62 (dd, J = 7.5, 3.5 Hz, 1 H), 7.30 (m, 3 H), 7.36 (m, 4 H), 7.55 (d, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.2, 12.9, 15.7, 20.5, 20.8, 46.4, 58.2, 59.0, 124.8, 127.4, 127.5, 128.1, 129.1, 139.3, 141.0, 141.8, 212.2; HRMS calcd for $C_{21}H_{27}NO_2S$ (M + H) 358.1841, found 358.1851.

***anti*-(*S*$_S$,1*R*,2*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-1-amino-2-ethyl-1-phenylhexan-3-one (14a).** Purification (20% EtOAc/hexane) afforded 0.023 g (21%) of a white solid: mp 83−84 °C; $[\alpha]^{20}_D$ +135.3 (*c* 0.53, $CHCl_3$); IR (neat) 3197, 2963, 1701 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.70 (t, J = 7.5 Hz, 3 H), 0.82 (t, J = 7.5 Hz, 3 H), 1.34 (m, 2 H), 1.55 (m, 1 H), 1.65 (m, 1 H), 1.86 (dt, J = 22.0, 9.0 Hz, 1 H), 2.16 (dt, J = 10.0, 22.0 Hz, 1 H), 2.39 (s, 3 H), 2.80 (m, 1 H), 4.58 (t, J = 7.5 Hz, 1 H), 5.36 (d, J = 8.0 Hz, 1 H), 7.24−7.35 (m, 7 H), 7.52 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.1, 13.9, 16.6, 21.8, 23.7, 47.2, 59.5, 59.7, 125.9, 127.4, 128.0, 129.0, 129.9, 141.7, 141.8, 142.6, 215.2; HRMS calcd for $C_{21}H_{27}NO_2S$ (M + H) 358.1841, found 358.1842.

***syn*-(*S*$_S$,1*R*,2*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-1-amino-2-ethyl-1-(2-furyl)hexan-3-one (13b).** Purification (20% EtOAc/hexane) afforded 0.065 g (62%) a colorless oil: $[\alpha]^{20}_D$ +76.3 (*c* 1.74, $CHCl_3$); IR (neat) 3192, 2964, 1709 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.78 (t, J = 7.5 Hz, 6 H), 1.42 (m, 2 H), 1.61 (m, 2 H), 2.09 (dt, J = 6.8, 17.8 Hz, 1 H), 2.20 (dt, J = 7.2, 17.8 Hz, 1 H), 2.40 (s, 3 H), 2.88 (dt, J = 8.0, 5.6 Hz, 1 H), 4.59 (t, J = 7.4 Hz, 1 H), 4.64 (d, J = 7.4 Hz, 1 H), 6.25 (d, J = 3.1 Hz, 1 H), 6.32 (dd, J = 2.0, 3.1 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 2 H), 7.37 (d, J = 2.0 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.7, 13.6, 16.4, 21.4, 21.6, 45.9, 52.4, 57.2, 108.3, 110.6, 125.6, 129.6, 141.6, 141.8, 142.1, 153.1, 212.2; HRMS calcd for $C_{19}H_{25}NO_3S$ (M + Na) 370.1453, found 370.1449.

***anti*-(*S*$_S$,1*R*,2*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-1-amino-2-ethyl-1-(2-furyl)hexan-3-one (14b).** Purification (20% EtOAc/hexane) afforded 0.021 g (20%) of a colorless oil: $[\alpha]^{20}_D$ +94.6 (*c* 1.14, $CHCl_3$); IR (neat) 3192, 2964, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.5 Hz, 3 H), 0.80 (t, J = 7.5 Hz, 3 H), 1.46 (m, 3 H), 1.59 (m, 1 H), 2.16 (dt, J = 17.6, 7.1 Hz, 1 H), 2.28 (dt, J = 17.6, 7.3 Hz, 1 H), 2.41 (s, 3 H), 2.95 (dt, J = 7.6, 6.0 Hz, 1 H), 4.57 (dd, J = 6.0, 7.7 Hz, 1 H), 5.27 (d, J = 7.7 Hz, 1 H), 6.28 (d, J = 3.3 Hz, 1 H), 6.34 (dd, J = 1.8, 3.3 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.37 (d, J = 1.8 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.7, 13.6, 16.5, 21.4, 22.6, 46.3, 53.0, 55.9, 108.0, 110.6, 125.7, 129.6, 141.4, 141.8, 142.0, 154.0, 214.1; HRMS calcd for $C_{19}H_{25}NO_3S$ (M + Na) 370.1452, found 370.1454.

(35) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.

(S_S,5*R*,6*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-6-amino-5-ethylnonan-4-one (13c). Purification (20% EtOAc/hexane) afforded 0.063 g (65%) of a colorless oil: $[\alpha]^{20}_D$ +63.7 (*c* 0.67, $CHCl_3$); IR (neat) 3214, 2960, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 0.95 (t, J = 7.5 Hz, 3 H), 1.37 (m, 1 H), 1.48−1.71 (m, 7 H), 2.35 (m, 2 H), 2.41 (s, 3 H), 2.63 (dt, J = 9.0, 5.0 Hz, 1 H), 3.48 (m, 1 H), 4.13 (d, J = 7.5 Hz, 1 H), 7.30 (d, J = 7.8 Hz, 2 H), 7.57 (d, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.2, 13.9, 14.0, 16.9, 19.8, 21.2, 21.6, 35.1, 46.0, 55.8, 57.7, 125.7, 129.7, 141.5, 142.7, 213.6; HRMS calcd for $C_{18}H_{29}NO_2S$ (M + Na) 346.1816, found 346.1821.

(S_S,5*R*,6*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-6-amino-5-ethylnonan-4-one (14c). Purification (20% EtOAc/hexane) afforded 0.026 g (21%) of a colorless oil: $[\alpha]^{20}_D$ +107.7 (*c* 0.96, $CHCl_3$); IR (neat) 3214, 2963, 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.1 Hz, 3 H), 0.87 (t, J = 7.6 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H), 1.33−1.57 (m, 7 H), 1.66 (m, 1 H), 2.35 (m, 2 H), 2.41 (s, 3 H), 2.55 (m, 1 H), 3.41 (m, 1 H), 5.05 (d, J = 8.6 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 2 H), 7.60 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.4, 13.7, 13.9, 16.7, 19.8, 21.4, 21.8, 37.6, 46.8, 55.8, 56.4, 125.7, 129.5, 141.2, 142.6, 215.0; HRMS calcd for $C_{18}H_{29}NO_2S$ (M + Na) 346.1816, found 346.1821.

(R_S,5*S*,6*R*)-(−)-*N*-(*p*-Toluenesulfinyl)-6-amino-5-ethylnonan-4-one (19). In a 500 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed diethyl ether (150 mL), the solution was cooled to −78 °C, and 23.6 mL (23.6 mmol) of LiHMDS (1.0 M solution in THF) was added. After 10 min 3.0 mL (21.5 mmol) of **12** was added via syringe and the reaction mixture was stirred for 1 h. In a separate 500 mL, one-necked, round-bottomed flask equipped with magnetic stirring bar and argon balloon was placed 1.50 g (7.16 mmol) of sulfinimine (*R*)-(−)-**17** in diethyl ether (40 mL), and the solution was cooled to −78 °C. At this time the preformed lithium enolate was added via cannula to the sulfinimine over 30 min, the solution was stirred for 1 h, and then the reaction was quenched at this temperature by addition of saturated NH_4Cl (30 mL) and H_2O (60 mL). The solution was extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. On chromatography (8%, EtOAc/hexane), the first to elute was (R_S,5*R*,6*R*)-(−)-**18**, 0.19 g (21%) of a colorless oil: $[\alpha]^{20}_D$ −110.3 (*c* 0.66, $CHCl_3$). Spectral properties were identical to (+)-**14**. HRMS: calcd for $C_{18}H_{29}NO_2S$ (M + H) 324.2000, found 324.2000.

The second to elute was *syn*-**19**, 1.81 g (78%) as a colorless oil: $[\alpha]^{20}_D$ −64.9 (*c* 0.67, $CHCl_3$). Spectra properties were identical to (+)-**13c**. HRMS: calcd for $C_{18}H_{29}NO_2S$ (M + Na) 346.1817, found 346.1826.

(2*S*,3*S*,5*S*,6*R*)-(+)-2-((*E*)-3-(Benzyloxy)prop-1-enyl)-3,5-diethyl-6-propylpiperidin-4-one (21). In a 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.29 g (0.9 mmol) of (−)-**19** in of anhydrous methanol (15 mL). The solution was cooled to 0 °C, and 0.28 mL of TFA (3.6 mmol) was added via syringe. After warming to room temperature the solution was stirred for 2 h, the solution concentrated, and the crude mixture passed through a short silica gel pad eluting with 30% EtOAc/hexane to remove the *p*-toluenesulfinyl byproducts. Elution with methanol gave the crude ammonium triflate salt, which was concentrated and placed in a 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon. Dichloromethane (15 mL) was added at room temperature followed by addition of 0.16 g (0.9 mmol) of 4-benzyloxylbutenal via syringe, and then 0.5 g of anhydrous $MgSO_4$ was added. The reaction mixture was stirred at room temperature for 2 h, concentrated, and washed with saturated $NaHCO_3$ (8 mL). The solution was extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4), and concentrated to give 0.27 g (88%) of an oil. In a separate 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.27 g (0.8 mmol) of the crude imine and anhydrous benzene (20 mL) was added, followed by 0.33 g (1.6 mmol) of *p*-toluenesulfonic acid monohydrate. After stirring at room temperature for 40 h, the solvent was concentrated and the residue was washed with saturated $NaHCO_3$ (2 × 5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (10% EtOAc/hexane, 1% Et_3N) afforded 0.041 g (15%) of a pale brown oil: $[\alpha]^{20}_D$ +65.6 (*c* 0.6, $CHCl_3$); IR (neat), 2956, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, J = 7.6 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H), 1.24−1.37 (m, 3 H), 1.43 (m, 2 H), 1.61 (m, 3 H), 1.85 (m, 1 H), 2.25 (m, 2 H), 2.90 (m, 1 H), 3.05 (dd, J = 8.1, 10.6 Hz, 1 H), 4.03 (d, J = 5.3 Hz, 2 H), 4.53 (m, 2 H), 5.70−5.82 (m, 2 H), 7.25−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.5, 12.5, 14.3, 18.0, 18.2, 19.4, 35.0, 53.5, 57.2, 59.7, 64.9, 70.3, 72.6, 127.8, 127.9, 128.6, 130.0, 134.0, 138.3, 213.6; HRMS calcd for $C_{22}H_{33}NO_2$ (M + H) 344.2589, found 344.2594.

(5*R*,6*S*,8*S*,8a*S*)-(+)-6,8-Diethyl-hexahydro-5-propylindolizin-7(1*H*)-one (22). In a 50 mL, one-necked, round-bottomed flask equipped with magnetic stirring bar was placed 0.030 g (0.09 mmol) of **21** in anhydrous methanol (5 mL). Wet 10% Pd/C (0.05 g) was slowly added to the solution, the reaction vessel was evacuated, and an H_2 balloon was attached. After stirring at room temperature for 8 h, the solution was filtered through a pad of Celite, and the filter cake was washed with methanol (2 × 5 mL). The filtrate was concentrated to give 0.020 g of the crude alcohol. The alcohol was dissolved in dichloromethane (5 mL) and transferred into a 25 mL, one-necked, round-bottom flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C, and 0.039 g (0.12 mmol) of CBr_4 and 0.041 g (0.16 mmol) of triphenyl phosphine were added. The reaction mixture was warmed to room temperature and stirred for 2 h, and 0.033 mL (0.24 mmol) of triethylamine was added. The reaction mixture was stirred for 0.5 h, washed with aqueous saturated $NaHCO_3$ (5 mL), and extracted with dichloromethane (2 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (10% EtOAc/0.5% Et_3N/hexane) gave 0.015 g (71%) of a colorless oil: $[\alpha]^{20}_D$ +10.5 (*c* 0.56, $CHCl_3$); IR (neat) 2960, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, J = 7.7 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H), 0.92 (t, J = 7.1 Hz, 3 H), 1.16 (m, 1 H), 1.29 (m, 2 H), 1.47−1.72 (m, 6 H), 1.81−2.03 (m, 5 H), 2.22 (m, 1 H), 2.27 (br, 1 H), 2.38 (m, 1 H), 3.17 (m, 1 H); ^{13}C NMR δ ($CDCl_3$) 11.3, 12.5, 14.4, 18.6, 18.8, 18.9, 21.4, 30.2, 33.0, 50.8, 54.2, 54.6, 64.8, 70.1, 217.5; HRMS calcd for $C_{15}H_{27}NO$ (M + H) 238.2171, found 238.2169.

(5*S*,6*R*,6*E*)-(−)-6-((*E*)-But-2-enylideneamino)-5-ethylnonan-4-one (23). In a 100 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 1.75 g (5.4 mmol) of (−)-**19** in anhydrous methanol (50 mL). The solution was cooled to 0 °C, 1.67 mL (21.6 mmol) of TFA was added via syringe, and the solution was warmed to room temperature and stirred for 2 h. At this time the solution was concentrated and the crude produce was subjected to a short silica gel pad elution with 30% EtOAc/hexane to remove the *p*-toluenesulfinyl byproducts. Elution with methanol gave the ammonium triflate salt, which was concentrated and placed in a 100 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon. To the flask were added dichloromethane (50 mL), 1.5 g of anhydrous $MgSO_4$, and 2.24 mL (27.1 mmol) of crotonaldehyde via syringe. The reaction was mixture stirred at room temperature for 2 h, the solution concentrated, and the residue washed with saturated $NaHCO_3$ (20 mL). At this time the solution was extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4), and concentrated. Chromatography gave 0.45 g (35%) of a colorless oil: $[\alpha]^{20}_D$ −38.9 (*c* 0.62, $CHCl_3$); IR (neat) 2961, 1707, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (t, J = 7.5 Hz, 3 H), 0.81 (t, J = 7.3 Hz, 3 H), 0.83 (m, 1 H), 0.92 (t, J = 7.5 Hz, 3 H), 1.01 (m, 1 H), 1.17 (m, 1 H), 1.31 (m, 1 H), 1.37−1.49 (m, 3 H), 1.59 (m, 2 H), 1.88 (d, J = 5.0 Hz, 3 H), 3.37−2.51 (m, 2 H), 3.04 (dt, J = 2.5, 9.4 Hz, 1 H), 6.22 (m, 2 H), 7.73 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.5, 13.7, 13.8, 16.6, 18.4, 19.7, 23.1, 36.1, 47.6, 58.5, 72.0, 131.7, 141.0, 162.5, 214.4; HRMS calcd for $C_{15}H_{27}NO$ (M + H) 238.2171, found 238.2168.

(2*S*,3*S*,5*S*,6*R*)-(+)-3,5-Diethyl-2-((*E*)-prop-1-enyl)-6-propylpiperidin-4-one (24). In a 250 mL, one-necked, round-bottomed flask

equipped with a magnetic stirring bar and argon balloon was placed 1.28 g (5.41 mmol) of crude imine **23**. Anhydrous benzene (120 mL) and 2.06 g (10.8 mmol) of *p*-toluenesulfonic acid monohydrate were added. After stirring for 40 h, the solution was concentrated, and the residue was washed with saturated $NaHCO_3$ solution. The solution was next extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (10% EtOAc/hexane, 1% Et_3N) afforded 0.74 g (58% from (−)-**19**) of a colorless oil: $[\alpha]^{20}_D$ +54.8 (*c* 0.73, $CHCl_3$); IR (neat) 3332, 2960, 1706 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.79 (t, J = 7.5 Hz, 3 H), 0.86 (t, J = 7.5 Hz, 3 H), 0.90 (t, J = 7.5 Hz, 3 H), 1.23−1.35 (m, 4 H), 1.42 (m, 2 H), 1.59 (m, 2 H), 1.69 (dd, J = 6.5, 1.7 Hz, 3 H), 1.82 (m, 1 H), 2.21 (m, 2 H), 2.86 (dt, J = 3.2, 6.8 Hz, 1 H), 2.95 (dd, J = 8.4, 10.3 Hz, 1 H), 5.42 (m, 1 H), 5.62 (dq, J = 6.5, 15.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.4, 12.5, 14.2, 17.8, 18.11, 18.13, 19.4, 35.0, 53.7, 57.2, 59.5, 65.5, 128.8, 132.5, 213.9; HRMS calcd for $C_{15}H_{27}NO$ (M + H) 238.2171, found 238.2170.

(2*R*,3*S*,5*S*,6*R*)-(+)-3,5-Diethyl-2-((*E*)-prop-1-enyl)-6-propylpiperidin-4-one (25). This compound was second to elute; 0.19 g (18% from (−)-**19**) of a colorless oil: $[\alpha]^{20}_D$ +62.7 (*c* 1.31, $CHCl_3$); IR (neat) 3336, 2960, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85−1.00 (m, 9 H), 1.20−1.92 (m, 12 H), 2.47 (dt, J = 5.3, 4.6 Hz, 1 H), 2.60 (dt, J = 8.4, 5.8 Hz, 1 H), 3.31 (m, 1 H), 3.78 (d, J = 5.5, 8.1 Hz, 1 H), 5.52 (m, 1 H), 5.67 (dq, J = 15.2, 6.2 Hz, 1 H); ^{13}C ($CDCl_3$) NMR δ 11.70, 11.73, 14.1, 18.0, 18.4, 19.1, 19.2, 32.7, 54.2, 55.5, 55.6, 59.8, 128.4, 128.8, 214.6; HRMS calcd for $C_{15}H_{27}NO$ (M + H) 238.2170, found 238.2181.

(2*S*,3*S*,5*R*,6*R*)-(+)-3,5-Diethyl-2-((*E*)-prop-1-enyl)-6-propylpiperidin-4-one (26). In a 100 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.38 g (1.2 mmol) of (−)-**18** in anhydrous methanol (20 mL). The solution was cooled to 0 °C, and 0.36 mL of TFA (4.7 mmol) was added via syringe. After warming to room temperature the reaction mixture was stirred for 2 h, the solution was concentrated, and the crude product was passed through a short silica gel pad eluting with 30% EtOAc/hexane to remove the *p*-toluenesulfinyl byproducts. Elution with methanol gave the ammonium triflate salt, which was concentrated and placed in a 100 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon. Dichloromethane (20 mL) was added at room temperature followed by the addition of 0.46 mL (5.7 mmol) of crotonaldehyde via syringe. Anhydrous $MgSO_4$, 1.5 g was added, and the reaction mixture was stirred at room temperature for 2 h, concentrated, and washed with saturated $NaHCO_3$ (15 mL). The solution was extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), and concentrated to give 0.26 g (93%) of the crude imine as a colorless oil. In a separate 100 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was place the crude imine, and anhydrous benzene (40 mL) was added, followed by 0.39 g (2.31 mmol) of *p*-toluenesulfonic acid monohydrate. After stirring at room temperature for 40 h, the solvent was concentrated, the residue was washed with saturated $NaHCO_3$ (2 × 8 mL), and the organic phase was extracted with EtOAc (3 × 8 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (10% EtOAx/hexane, 1% Et_3N) afford 0.18 g (65%, from (−)-**18**) of a colorless oil: $[\alpha]^{20}_D$ +19.4 (*c* 2.28, $CHCl_3$); IR (neat) 3334, 2959, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H), 0.93 (t, J = 7.4 Hz, 3 H), 1.29−1.68 (m, 9 H), 1.71 (dd, J = 1.4, 6.4 Hz, 3 H), 2.12 (m, 2 H), 2.63 (m, 1 H), 3.00 (dd, J = 8.6, 10.3 Hz, 1 H), 5.43 (m, 1 H), 5.62 (dq, J = 6.4, 15.4 Hz, 1 H); ^{13}C NMR δ ($CDCl_3$) 12.1, 12.3, 14.2, 17.7, 17.8, 18.5, 18.7, 36.4, 57.6, 57.7, 60.6, 65.2, 128.7, 132.5, 211.1; HRMS calcd for $C_{15}H_{27}NO$ (M + H) 238.2171, found 238.2163.

(2*R*,3*R*,5*R*,6*R*)-(−)-3,5-Diethyl-2-((*E*)-prop-1-enyl)-6-propylpiperidin-4-one (27). Second to elute, 0.5 g (18% from (−)-**18**) of a colorless oil; $[\alpha]^{20}_D$ −57.6 (c 1.06, $CHCl_3$); IR (neat) 3334, 2960, 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H), 0.91 (t, J = 7.1 Hz, 3 H), 1.24−1.67 (m, 8 H), 1.69 (dd, J = 6.5, 1.4 Hz, 3 H), 1.82 (m, 1 H), 2.09 (ddd, J = 4.7, 6.1, 9.0 Hz, 1 H), 2.20 (dt, J = 3.5, 8.5 Hz, 1 H), 3.01 (dt, J = 4.0, 8.5 Hz, 1 H), 3.26 (t, J = 8.2 Hz, 1 H), 5.44 (m, 1 H), 5.59 (dq, J = 6.5, 15.1 Hz, 1 H); ^{13}C ($CDCl_3$) NMR δ 12.0, 12.2, 14.0, 17.8, 19.3, 19.4, 23.7, 35.3, 54.3, 57.2, 57.5, 59.2, 128.1, 132.7, 213.7; HRMS calcd for $C_{15}H_{27}NO$ (M + H) 238.2171, found 238.2180.

(2*S*,3*S*,5*R*,6*R*)-(+)-3,5-Diethyl-2-((*E*)-prop-1-enyl)-6-propylpiperidin-4-one (26) from (+)-24. In a 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar was placed 0.12 g of sodium (previously washed with hexane), and anhydrous MeOH (6 mL) was slowly added. The solution was stirred at room temperature for 1 h, and 0.10 g of (+)-**24** (0.42 mmol) was added. The solution was stirred at 65 °C for 24 h and concentrated, and the residue was treated with H_2O (2 mL). The solution was extracted with EtOAc (3 × 3 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (10% EtOAc/hexane, 1% Et_3N) afforded 0.055 g (55%) of a colorless oil identical in all respects to (+)-**26** prepared previously (see above).

(2*S*,3*S*,5*S*,6*R*)-(+)-1-Allyl-3,5-diethyl-2-((*E*)-prop-1-enyl)-6-propylpiperidin-4-one (28). In a 100 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and condenser was placed 0.42 g (1.76 mmol) of (+)-**24** in anhydrous EtOH (30 mL). To the reaction mixture were added allyl bromide (1.53 mL) and anhydrous solid Na_2CO_3 (2.8 g), and the reaction mixture was refluxed for 6 h. At this time the solution was cooled to room temperature, filtered, and concentrated. Water (10 mL) was added to the residue, and the solution was extracted with dichloromethane (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (6% EtOAc/hexane) afforded 0.44 g (91%) of a colorless oil: $[\alpha]^{20}_D$ +85.4 (*c* 0.56, $CHCl_3$); IR (neat) 2961, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, J = 7.4 Hz, 3 H), 0.85 (t, J = 7.5 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H), 1.21−1.38 (m, 5 H), 1.53 (m, 1 H), 1.65 (m, 1 H), 1.72 (dd, J = 6.5, 1.5 Hz, 3 H), 1.86 (m, 1 H), 2.17 (ddd, J = 4.0, 7.2, 10.0 Hz, 1 H), 2.47 (ddd, J = 4.8, 5.8, 10.5 Hz, 1 H), 2.90 (m, 1 H), 3.18 (t, J = 9.3, 1 H), 3.36 (m, 2 H), 5.11−5.24 (m, 3 H), 5.51 (dq, J = 15.4, 6.5 Hz, 1 H), 5.84−5.92 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.1, 11.8, 14.4, 17.7, 18.7, 19.6, 20.6, 34.5, 52.7, 53.3, 54.5, 59.9, 65.3, 117.8, 128.2, 132.9, 134.3, 214.2; HRMS calcd for $C_{18}H_{31}NO$ (M + H) 278.2484, found 278.2476.

(5*R*,6*S*,8*S*,8a*S*)-(+)-6,8-Diethylhexahydro-5-propylindolizin-7(1*H*)-one (22) via RCM. In a 100 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon were placed 0.22 g of (+)-**28** and dichloromethane (30 mL). To the solution was added 0.032 g (5 mol %) of the Grubbs "first generation" catalyst, and the solution was refluxed for 2 h. At this time the solution was concentrated, anhydrous methanol (20 mL) was added, followed by 0.050 g of 10% Pd/C, and the argon balloon was replaced by a hydrogen-filled balloon. The reaction mixture was stirred at room temperature for 4 h, the solution was filtered through a Celite pad, and the pad was washed with methanol (3 × 10 mL). The solution was concentrated, and the residue was purified by column chromatography (1% Et_3N, 15% EtOAc/hexane) to afford 0.135 g (71%) of a colorless oil identical in all respects to (+)-**22** prepared previously (see above).

(5*R*,6*S*,7*S*,8*S*,8a*S*)-(+)-6,8-Diethyloctahydro-5-propylindolizin-7-ol (29). In a 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.10 g (0.42 mmol) of (+)-**22** in anhydrous MeOH (20 mL). The solution was cooled to −78 °C, and 0.024 g (0.63 mmol) of $NaBH_4$ was added. After 2 h the reaction mixture was warmed to room temperature and concentrated. To the residue was added water (10 mL), the solution was extracted with dichloromethane (3 × 15 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (1% Et_3N, 30% EtOAc/hexane) afforded 0.9 g (90%) of a white solid: mp 121−122 °C; $[\alpha]^{20}_D$ +56.5 (*c* 0.69, $CHCl_3$); IR (neat) 3331, 2951 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 6 H), 0.94 (t, J = 7.6 Hz, 3 H), 1.12 (m, 1 H), 1.28−1.85 (m, 16 H), 1.91 (b, 1 H), 3.03 (m, 1 H), 3.47 (dd,

J = 4.9, 10.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.6, 14.8, 17.1, 17.6, 20.1, 21.2, 21.5, 29.3, 33.6, 44.3, 45.5, 51.6, 65.8, 68.0, 76.6; HRMS calcd for $C_{15}H_{29}NO$ (M + H) 238.2171, found 238.2166.

(5*R*,6*S*,7*S*,8*S*,8a*S*)-(+)-6,8-Diethyloctahydro-5-propylindolizin-7-yl Methanesulfonate (30). In a 25 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.024 g (0.1 mmol) of (+)-**29** in dichloromethane (5 mL). To the solution were added 0.031 mL (0.4 mmol) of methanesulfonyl chloride and 0.055 mL (0.4 mmol) of triethylamine, and the reaction mixture was stirred at room temperature for 4 h. At this time the reaction was quenched by addition of saturated $NaHCO_3$ (1 mL) and water (5 mL). The solution was extracted with dichloromethane (2 × 3 mL), and the organic phases were combined, dried (Na_2SO_4), and concentrated. Chromatography (1% Et_3N, 15% EtOAc/hexane) afforded 0.021 g (67%) of a colorless oil: $[\alpha]^{20}_D$ +17.9 (*c* 0.56, $CHCl_3$); IR (neat) 2962, 2875, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H), 0.93 (t, J = 7.8 Hz, 3 H), 1.02 (t, J = 7.3 Hz, 3 H), 1.17−2.12 (m, 17 H), 3.04 (s, 3 H), 3.09 (m, 1 H), 4.61 (dd, J = 5.0, 10.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.1, 14.6, 16.1, 17.6, 19.9, 21.0, 21.2, 29.1, 33.3, 39.1, 42.4, 42.5, 43.8, 51.1, 65.0, 67.6; HRMS calcd for $C_{16}H_{31}NO_3S$ (M − H) 316.1946, found 316.1939.

Lithium Ammonia Reduction of (5*R*,6*S*,7*S*,8*S*,8a*S*)-(+)-30. In a 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, argon balloon, and ammonia dry ice condenser cooled to −78 °C in a dry ice/acetone bath was collected about 5 mL of liquid ammonia. Approximately 0.10 g (14 mmol) of lithium wire cut into pieces was added to the solution, and the mixture was stirred until the lithium was completely dissolved (15 min). Mesylate (+)-**30** (0.010 g, 0.03 mmol) in THF (0.5 mL) was added dropwise, and the solution was stirred at −78 °C for 30 min. At this time the reaction mixture was quenched by addition of 0.002 g of solid NH_4Cl. After evaporation of the ammonia, the mixture was partitioned between saturated $NaHCO_3$ (5 mL) and ether (5 mL), and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (20% EtOAc/hexane) afforded 0.05 g (71%) of alcohol (+)-**29**.

***O*-(5*R*,6*S*,7*S*,8*S*,8a*S*)-(−)-Indolizidine Carbonothioate (31).** In a 50 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.072 g (0.30 mmol) of (+)-**29** in dichloromethane (20 mL). To the solution was added 0.20 mL (1.8 mmol) of pyridine, and the solution was cooled to 0 °C. To the solution was added 0.20 mL (1.5 mmol) of phenyl chlorothionoformate, and the reaction was warmed to room temperature and stirred for 24 h. At this time the reaction was quenched by addition of water (15 mL) and extracted with dichloromethane (3 × 10 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography afforded 0.057 g (55%) of a pale yellow oil: $[\alpha]^{20}_D$ −3.6 (c 0.88, $CHCl_3$); IR (neat) 2959, 1255, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91−1.05 (m, 9 H), 1.20−1.99 (m, 15 H), 2.10 (br, 1 H), 2.28 (br, 1 H), 3.11 (br, 1 H), 5.21 (dd, J = 5.0, 11.1 Hz, 1 H), 7.08−7.47 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.3, 14.4, 15.8, 17.6, 19.6, 21.06, 21.09, 28.9, 33.2, 40.2, 41.8, 51.1, 64.5, 67.5, 89.4, 122.1, 126.5, 129.5, 153.4, 194.7; HRMS calcd for $C_{22}H_{33}NO_2S$ (M − H) 374.2154, found 374.2161.

Alkaloid (−)-223A (9) DCl Salt. In a 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and condenser was placed 0.04 g (0.11 mmol) of (−)-**31** in benzene (25 mL). Argon was bubbled through the solution for 10 min, and 0.085 mL (0.53 mmol) of tributyltinhydride and 0.005 g of AIBN were added to the solution. The reaction mixture was refluxed for 4 h and concentrated, and the residue was treated with 5 mL of 2 N potassium fluoride in dichloromethane (10 mL). After stirring for 20 min the mixture was extracted with dichloromethane (3 × 5 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (3% Et_3N, 15% EtOAc/hexane) afforded 0.018 g (74%) of a colorless volatile oil. To the oil was added 1 mL of DCl in diethyl ether solution (1.0 N), and the solution was shaken and concentrated to give 0.02 g (74%) of a colorless oil: $[\alpha]^{20}_D$ −36.8 (*c* 0.45, $CHCl_3$) [lit.[12a] $[\alpha]^{25}_D$ −40.9 (*c* 0.25, $CHCl_3$); lit.[12b] $[\alpha]^{15}_D$ −38.4 (*c* 0.3, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.82−0.89 (m, 9 H), 1.10−1.21 (m, 4 H), 1.30−1.73 (m, 7 H), 1.82−2.00 (m, 3 H), 2.06 (dd, J = 13.2, 2.5 Hz, 1 H), 2.28 (m, 1 H), 2.84 (dt, J = 18.0, 6.2 Hz, 1 H), 2.95 (q, J = 9.0 Hz, 1 H), 3.15 (dt, J = 15.0, 3.8 Hz, 1 H), 3.58 (m, 1 H); ^{13}C NMR (D_2O) δ 9.5, 11.2, 12.8, 16.6, 17.5, 18.3, 24.4, 26.5, 29.6, 29.8, 35.2, 35.3, 51.2, 66.4, 72.0. The ^{1}H NMR and ^{13}C NMR spectra data were consistent with the literature values.[12]

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

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