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# Stereoselective Synthesis of 2,4,5-Trisubstituted Piperidines via Radical Cyclization

Maria-Eleni Ragoussi,[†] Stephen M. Walker,[†] Andrea Piccanello,[†] Benson M. Kariuki,[†,§]
Peter N. Horton,[‡] Neil Spencer,[†] and John S. Snaith*,[†]

[†] *School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, U.K., and* [‡] *EPSRC National Crystallography Service, School of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, U.K.* [§] *Current address: School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, U.K.*

*j.s.snaith@bham.ac.uk*

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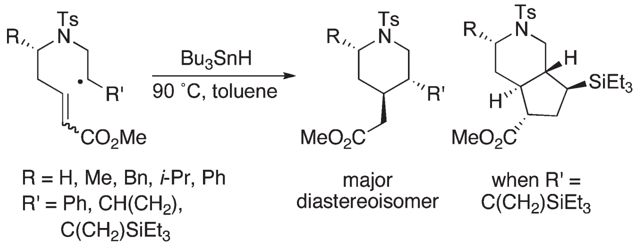

A novel approach to 2,4,5-trisubstituted piperidines is reported, involving the 6-*exo* cyclization of stabilized radicals onto $\alpha,\beta$-unsaturated esters. Only two of the four possible diastereoisomers are observed, with diastereomeric ratios ranging from 3:2 to 40:1 when the radical stabilizing group is vinyl or phenyl. Cyclization of a (triethylsilyl)vinyl-stabilized radical gives the corresponding piperidine radical as a single diastereoisomer that may either be trapped by tributyltin hydride to afford the 2,4,5-trisubstituted piperidine or undergo a second 5-*endo* cyclization onto the (triethylsilyl)vinyl substituent to produce the 3,5,7-trisubstituted octahydro[2]pyrindene as a single diastereoisomer.

## Introduction

Substituted piperidines occur widely in natural products[1] and feature in a number of successful pharmaceuticals, with the ring system being regarded as a privileged scaffold for drug discovery.[2,3] The biological importance of piperidines has led to the development of a multitude of synthetic approaches;[4] nevertheless, many piperidine substitution patterns remain difficult to access, a factor that continues to drive the search for new methodologies.[5]

Free radical cyclizations are one of the most useful techniques employed in ring construction and have played an important role in the synthesis of heterocycles[6] and natural products.[7] Nevertheless, there are relatively few reports of radical cyclizations leading to piperidines.[8−10]

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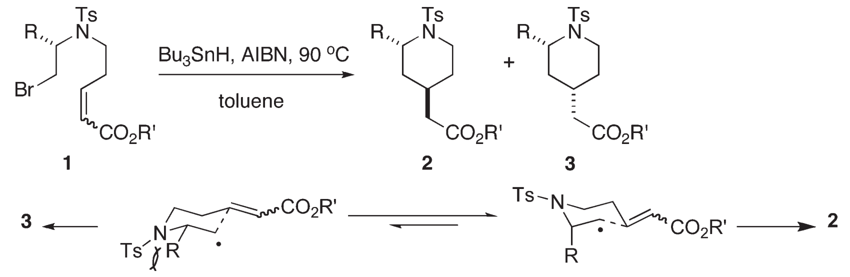

**FIGURE 1.** Stereocontrol models for the radical cyclization of 7-substituted-6-aza-8-bromooct-2-enoates to 2,4-disubstituted piperidines.[11]

We previously reported the radical cyclization of bromides of the type **1** to give 2,4-disubstituted piperidines that favored the *trans* diastereomer **2**.[11] However, the approach suffered from an inherently low stereoselectivity (between 3:1 and 6:1), giving significant amounts of the *cis* diastereomer **3** in which the 2-substituent was equatorial, Figure 1.

In piperidine sulfonamides the 2-substituent shows a marked preference to adopt the axial position as a result of torsional strain with the sulfonamide.[12] We reasoned that the modest axial:equatorial ratios in this case resulted from the rather early transition states for radical cyclization which allow distortion from the idealized chair.[13] This distortion, with the forming bond being rather elongated, means that factors such as the torsional strain which are important in the product are of less importance in the transition state, and other conformers are energetically accessible.

We hypothesized that a stabilized radical of the type **4**, Figure 2, should react through a later transition state, in accordance with the Hammond postulate.[14,15] In this later, more product-like transition state, in which the forming C−C bond is shorter, the steric interactions should be accentuated, hopefully resulting in an enhanced stereoselectivity.

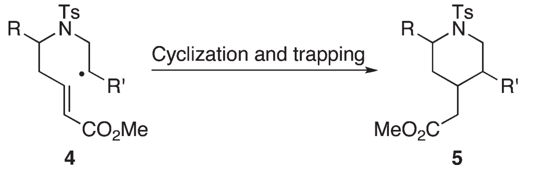

**FIGURE 2.** Cyclization of the stabilized radical **4**, where R′ is a radical-stabilizing group, to afford 2,4,5-trisubstituted piperidine **5**.

The cyclization of radicals of the type **4** would generate 2,4,5-trisubstituted piperidines **5**. A number of natural products have 2,4,5-trisubstituted piperidines at their core, where the 5-substituent is a vinyl group or an ethyl group, including hirsuteine, corynantheine, strychnofoline, and mitragynanine. The quinuclidine ring of quinine may also be viewed as a piperidine, and in Stork's 2001 synthesis a 2,4,5-trisubstituted piperidine was used as a late-stage intermediate.[16] In addition to natural products, there is pharmaceutical interest, with a recent report that 2,4,5-trisubstituted piperidines, including those bearing an aryl substituent at C-5, are highly potent renin inhibitors.[17] Stereocontrolled approaches to these ring systems are therefore of considerable interest.

## Results and Discussion

Our investigation started by exploring the use of a phenyl radical-stabilizing group in our system, which would become the substituent at position 5 of the piperidine after cyclization (Figure 3). Our starting materials were the amino alcohols (*S*)-alaninol **6a**, (*S*)-phenylalaninol **6b**, (*S*)-valinol **6c**, and (*S*)-phenylglycinol **6d**, affording cyclization precursors with a range of steric demands at the 2-position.

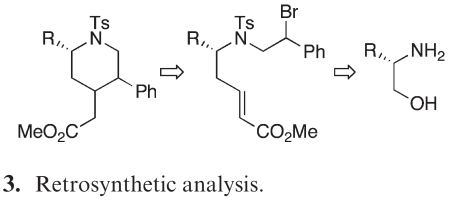

**FIGURE 3.** Retrosynthetic analysis.

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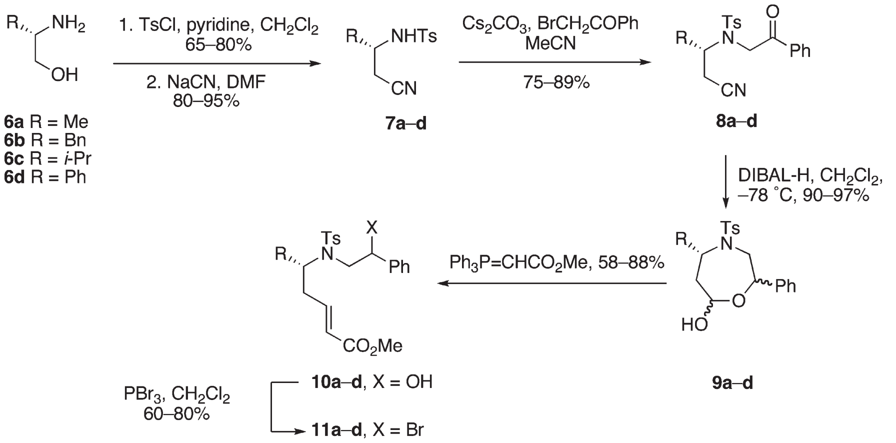
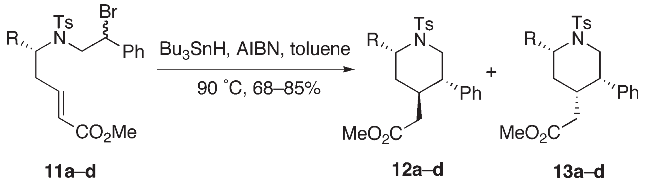
**SCHEME 1.** **Synthesis of Phenyl Bromide Precursors**



The desired bromide cyclization precursors were synthesized in a 6-step procedure. Ditosylation of the amino alcohols was followed by cyanide displacement of the *O*-tosyl group to form amino nitriles **7a−d** (Scheme 1).[18] *N*-Alkylation with 2-bromoacetophenone and $Cs_2CO_3$ as the base, giving nitriles **8a−d**, was followed by a DIBAL-H reduction to afford lactols **9a−d** as a mixture of diastereoisomers. These were directly subjected to Wittig olefination to give the corresponding $\alpha,\beta$-unsaturated esters **10a−d** in good yields, chiefly or exclusively as the (*E*)-diastereoisomer after column chromatography. In the case of lactol **9d** the olefination proceeded with poor *E*/*Z* selectivity; however, the isomers were separable and were taken forward separately. Subsequent bromination, using phosphorus tribromide, gave the target bromides **11a−d** in good yields.

With the bromide precursors in hand, we proceeded to study the radical cyclization. The reactions were performed in toluene, heated at 90 °C, with slow addition of tributyltin hydride and AIBN by syringe pump; the results are summarized in Table 1.

**TABLE 1.** **Radical Cyclizations of Phenyl-Stabilized Precursors**[a]



| entry | bromide | R | **12**:**13**[b] | yield (%)[c] |
|---|---|---|---|---|
| 1 | **11a** | Me | 7:3 | 85 |
| 2 | **11b** | Bn | 10:1 | 68 |
| 3 | **11c** | *i*-Pr | 40:1 | 73 |
| 4 | **11d** | Ph | 2.5:1 | 85 |

[a]Reactions performed by syringe pump addition of benzene or toluene solutions of $Bu_3SnH$ and AIBN to a solution of the bromide in toluene heated at 90 °C, final concentration typically 0.01−0.015 M. [b]Ratio determined by HPLC of the crude reaction mixture and/or $^1H$ NMR after chromatography to remove tin residues. [c]Isolated yields following chromatography.

In all cases only two of the four possible diastereoisomers were produced. The major diastereoisomer was **12**, in which the 2-substituent is axial and the 4- and 5-substituents are equatorial (Figure 4). While separation could be achieved for all compounds on an analytical HPLC column, only **12d** and **13d** were separable by preparative HPLC, and the major diastereoisomer **12d** proved to be crystalline, allowing us to confirm the stereochemical assignment by single-crystal X-ray analysis (Figure S1 in Supporting Information). The other compounds were oils, but in the case of **12b** and **12c** the structure of the major diastereoisomer was confirmed by a combination of NOE experiments and analysis of the coupling constants in the $^1H$ NMR spectra of the diastereoisomeric mixtures.

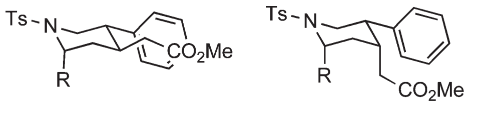

major diastereoisomer **12** minor diastereoisomer **13**

**FIGURE 4.** Structures of major and minor diastereoisomers.

The structure of the separated minor diastereoisomer **13d** was likewise secured from $^1H$ NMR coupling constants and NOE experiments, although **13d** was inseparable from a small amount of another piperidine that could not be identified. The structure of the minor isomer from the cyclization of **11b** was more difficult to determine as it was present in only small amounts, inseparable from the major isomer, with a number of resonances overlapping in the $^1H$ NMR spectrum. However, the 2-substituent was clearly identified as being axial,[19] and it is therefore reasonable to conclude that the 4-substituent is also axial, as in **13d**, since a significant energetic penalty would be incurred by an axial phenyl substituent at the 5-position. The same is assumed to hold true for **13c**, although the 40:1 product ratio meant that resonances from **13c** were very small in the $^1H$ NMR spectrum of the two diastereoisomers. For the cyclization of **11a** the situation was less clear-cut, since resonances from the two diastereoisomers were heavily overlapped in the $^1H$ NMR spectrum. Once again it was clear from the $^1H$ NMR spectrum that the 2-substituent was axial in the major and minor diastereoisomers. It is not unreasonable to assume

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(19) The equatorial proton at position 2 experiences significant deshielding by the tosyl group compared with an axial proton at the same site, resulting in the equatorial proton coming into resonance up to 1 ppm downfield of the axial proton. For other examples see ref 11.

that this compound would behave in a similar fashion to the others, and this, coupled with similarities in the $^1$H NMR spectra from all of the cyclizations, led us to assign the major and minor diastereoisomers for all cyclizations as **12** and **13**, respectively (Figure 4).

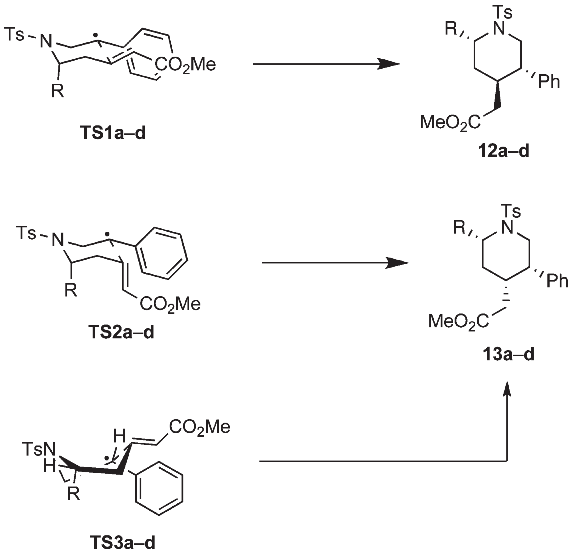

**FIGURE 5.** Proposed transition states leading to major and minor diastereoisomers.

Pleasingly, and in contrast to our earlier work on the 2,4-disubstituted systems, the 2-substituent is axial in both the major and minor diastereoisomers, suggesting that the stabilized radicals derived from **11a–d** react through later, more product-like transition states (**TS1**, Figure 5) in accordance with our original hypothesis. Also, in contrast to our earlier work, is the observation that the 4-substituent lies axial in the minor product, something that is likely to result from a gauche interaction between the α,*β*-unsaturated ester and the phenyl substituent, which presumably can be relieved either by the ester lying axial (**TS2**) or by cyclization through a twist boat (**TS3**). If formation of the minor diastereoisomer is through **TS2**, then the increasing 1,3-diaxial interaction between the ester and the axial 2-substituent on going from **TS2a** to **TS2c** would explain the increasing major:minor ratio. If the minor isomer is formed by cyclization through a twist boat (**TS3**), this is likely to introduce an element of torsional strain between the 2-substituent and the sulfonamide, increasing with the size of the 2-substituent from **TS3a** to **TS3c** and so disfavoring this TS, in line with the stereoselectivity trend. Rather more surprising is the very poor major:minor ratio in the cyclization of **11d**, which on the basis of the steric demand of the 2-substituent would be expected to display the highest stereoselectivity. It seems unlikely that this product ratio could result from cyclization through chairlike transition states, leading us to speculate that the exceptional steric demands of the phenyl substituent at the 2-position results in both the major and minor diastereoisomers being formed through boat-like transition states.

If the minor diastereoisomer results from cyclization through **TS2** it should be possible to disfavor this pathway by switching to the (*Z*)-alkene. In earlier work on 6-*exo-trig* cyclizations by Hanessian,[20] the geometry of the acceptor double bond was found to be an important feature in controlling the stereoselectivity of the cyclization. The (*Z*)-ester experienced greater 1,3-diaxial interactions when it adopted a pseudo axial position, resulting in preferential cyclization to the trans product (Figure 6).

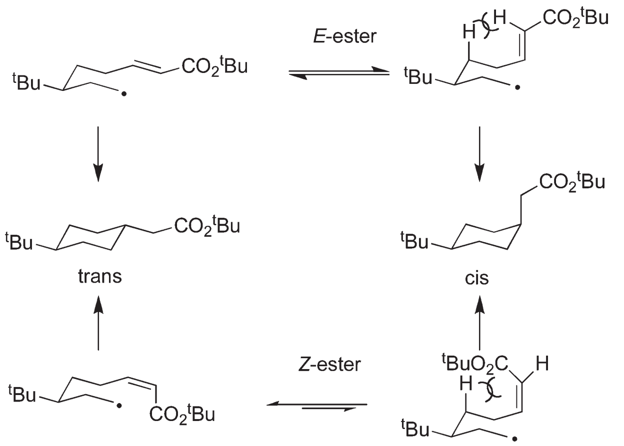

**FIGURE 6.** Improved selectivity for (*Z*)-esters in Hanessian's system.

To test this idea two (*Z*)-esters, **14b–c**, were prepared using the Still–Gennari-modified Horner–Wadsworth–Emmons reaction (Scheme 2).[21] The yield for both substrates was disappointingly low at around 20%, increasing to up to 50% based on recovered starting material. Elimination from the *β*-amino aldehyde was a significant competing pathway, and attempts to optimize the reaction conditions did not lead to any improvement. In addition, the (*Z*)-ester **14d** was available from the poorly *E*/*Z*-selective Wittig olefination of lactol **9d** (vide supra). Bromination of all compounds with PBr$_3$ gave the required (*Z*)-bromides **15b–d**.

The esters were cyclized under conditions identical to those used for the (*E*)-esters; the results are summarized in Table 2.

Surprisingly, **15b** and **15c** cyclized with stereoselectivities essentially identical to those of the corresponding (*E*)-esters, something which, in the light of Hanessian's results, argues against production of the minor diastereoisomer through **TS2** and adds weight to the twist boat **TS3** (Figure 5). For **15d** the major:minor ratio decreased slightly (but reproducibly), a result which is incompatible with chairlike transition states, where the ratio might be expected to increase.

Encouraged by the results of the phenyl-stabilized radical precursors, our attentions turned to the cyclization of vinyl-stabilized radicals. The synthesis of this family of compounds resembled the route to the phenyl series described previously, using nitriles **7a–d** as a starting point. Initially, nitrile **7a** was alkylated using allylbromide **16** bearing a benzoate ester, affording **17**. It was hoped that a DIBAL-H reduction of the nitrile to the aldehyde would result in concomitant ester removal, but disappointingly, none of the desired compound could be isolated from a complex mixture. Instead the benzoate was cleaved by transesterification with sodium methoxide and the resulting alcohol reprotected as the

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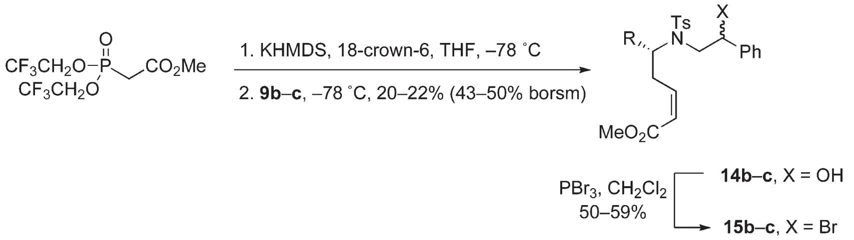
**SCHEME 2. Preparation of Z-Cyclization Precursors 15b,c**



**SCHEME 3. Synthesis of Vinyl Bromide Precursors**

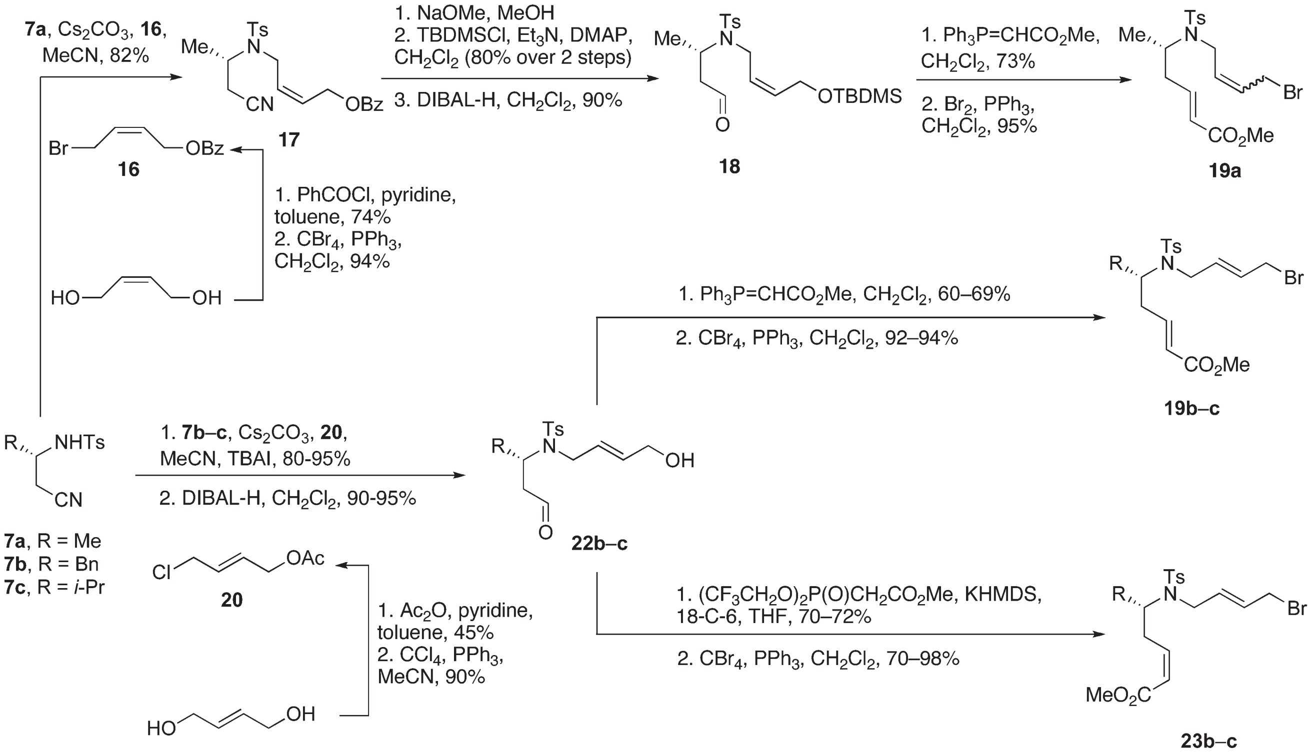
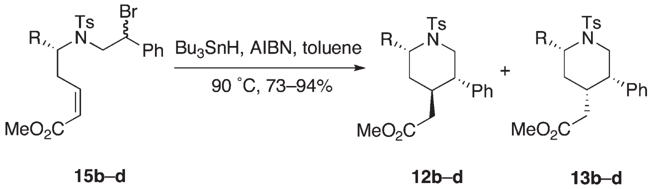


**TABLE 2. Cyclizations of (*Z*)-Esters 15b–d**[a]



| entry | bromide | R | 12:13[b] | yield (%)[c] |
|---|---|---|---|---|
| 1 | **15b** | Bn | 10:1 | 94 |
| 2 | **15c** | *i*-Pr | 40:1 | 73 |
| 3 | **15d** | Ph | 1.7:1 | 84 |

[a] Reactions performed by syringe pump addition of toluene solutions of Bu$_3$SnH and AIBN to a solution of the bromide in toluene heated at 90 °C, final concentration typically 0.01–0.015 M. [b] Ratio determined by HPLC of the crude reaction mixture and/or $^1$H NMR after chromatography to remove tin residues. [c] Isolated yields following chromatography.

*tert*-butyldimethylsilyl ether in 80% yield over 2 steps. DIBAL-H reduction proceeded smoothly to give aldehyde **18** in 90% yield, and Wittig olefination introduced the α,*β*-unsaturated ester in 77% yield as a separable 14:1 *E*/*Z* mixture. Concomitant silyl ether removal and bromination occurred on treatment with triphenylphosphine and bromine,[22] giving the target bromide **19a** in 95% yield as an inconsequential 1:1 mixture of *E*/*Z* diastereomers at the allyl double bond (Scheme 3).

The failure of the DIBAL-H reduction of the benzoate ester led us to examine the corresponding acetate. The required alkylating agent **20**, prepared in two steps from (*E*)-but-2-ene-1,4-diol, smoothly alkylated amino nitriles **7b**–**c** to afford **21b**–**c**. These compounds reacted cleanly with DIBAL-H to give the aldehyde alcohols **22b**–**c**; Wittig reaction and bromination proceeded uneventfully to yield the required bromides **19b**–**c**. A Still–Gennari-modified Horner–Wadsworth–Emmons olefination gave the (*Z*)-esters in a satisfactory 63–70% yield, and these were brominated as before to give **23b**–**c**. Attempts to alkylate **7d** were very low yielding, apparently as a result of the *N*-alkylated aminonitrile undergoing a facile *β*-elimination of the amine to give the fully conjugated cinnamonitrile, and so this compound was not pursued further.

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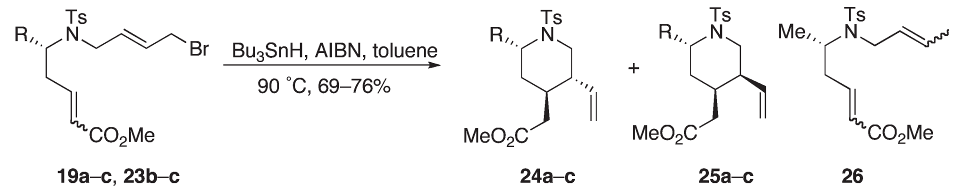
[22] Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941–4943.

**TABLE 3. Cyclizations of Vinyl-Stabilized Precursors**[a]



| entry | bromide | R | *E* or *Z* | **24**:**25**[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **19a** | Me | *E* | 3:2 | 76[d] |
| 2 | **19b** | Bn | *E* | 3:1 | 72 |
| 3 | **23b** | Bn | *Z* | 3:1 | 69 |
| 4 | **19c** | *i*-Pr | *E* | 10:1 | 70 |
| 5 | **23c** | *i*-Pr | *Z* | 10:1 | 71 |

[a] Reactions performed by syringe pump addition of toluene solutions of Bu$_3$SnH and AIBN to a solution of the bromide in toluene heated at 90 °C, final concentration typically 0.01−0.015 M. [b] Ratio determined by HPLC of the crude reaction mixture and/or $^1$H NMR after chromatography to remove tin residues. [c] Isolated yields following chromatography. [d] Combined yield of **24a**, **25a**, and **26**.

The radical cyclization was performed under the previously optimized conditions; the results are summarized in Table 3.

As before, only two of the possible four diastereoisomers were formed. In the cyclization of **19a**, a significant amount of the inseparable reduction product **26** was also formed. This was surprising and contrasted with **19b−c** and **23b−c** where direct reduction was not observed, but given the poor stereoselectivity of this substrate, optimization to favor cyclization over reduction was not attempted.

In each case the two diastereoisomers had such similar retention times on HPLC that preparative separation was not possible. Nevertheless, the major and minor diastereoisomers were identified by NOE experiments and analysis of the $^1$H NMR spectrum of the 3:1 mixture of **24b** and **25b**. In the major diastereoisomer the 2-substituent occupied the expected axial position, while the 4- and 5-substituents were equatorial; the minor diastereomer differed by having the 5-substitent axial (Figure 7).

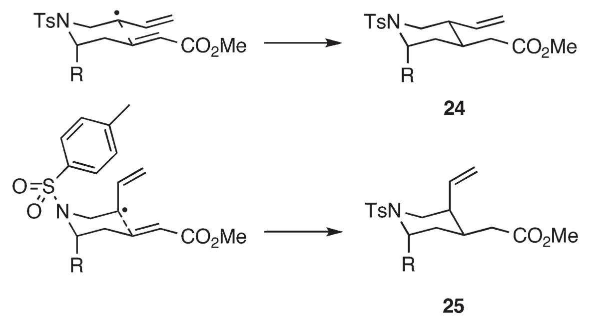


**FIGURE 7.** Transition state models for formation of major and minor diastereoiosmers **24** and **25**.

The observation that the 2-substituent was axial in both the major and minor diastereoisomers suggested that, like before, cyclization was occurring through a later, more product-like transition state. However, stereocontrol at the 5-position was modest. By adopting an axial position the relatively sterically undemanding vinyl 5-substituent is able to relieve the gauche interaction with the α,β-unsaturated ester, at the expense of a 1,3-diaxial interaction with the 3-hydrogen and a steric clash with the aromatic ring of the sulfonamide. As the 2-substituent increases in size, it is expected that the conformation will distort from a regular chair, forcing the sulfonamide closer to the axial vinyl substituent and so disfavoring this minor diastereoisomer.

It was apparent that the small size of the vinyl 5-substituent resulted in only a modest energetic penalty when it occupied the axial position, thereby eroding the stereoselectivity of the cyclization. In an attempt to overcome this, we decided to study cyclization of the corresponding (triethylsilyl)vinyl-stabilized radical. The (triethylsilyl)vinyl group has significantly greater steric demands yet can be viewed as synthetically equivalent to the vinyl group via protodesilylation.

To test whether the additional bulk of the radical stabilizing group would have an effect, we prepared the four cyclization precursors **29b−c** and **30b−c**, incorporating differing steric demands at the 2-position, as well as *E*- and *Z*-acceptor double bonds. Alkylation of amino nitriles **7b−c** was performed using allyl chloride **27**;[23] subsequent DIBAL-H reduction, Wittig olefination, and bromination proceeded as before to give the (*E*)-bromides **29b−c** (Scheme 4). The (*Z*)-bromides **30b−c** were prepared, as before, by the Still−Gennari-modified Horner−Wadsworth−Emmons procedure in a disappointing 27−32% yield, with a 4:1 ratio in favor of the desired (*Z*)-olefin. A major side reaction, which could not be suppressed, was base-induced elimination of the amine from the β-aminoaldehyde. The Ando-modified Horner−Wadsworth−Emmons procedure[24] fared even worse; under the standard conditions, using KHMDS as base, a yield of around 20% of the desired olefins was obtained, in a very disappointing 2:1 *E*/*Z* ratio, while using the less basic DBU and LiCl conditions developed for base-sensitive aldehydes in the Horner−Wadsworth−Emmons procedure by Masamune and Roush[25] increased the yield a little to around 30% but left the *E*/*Z* ratio unchanged.

Cyclization of all four compounds afforded two products in each case, separable by HPLC, both of which had the same relative stereochemistry around the piperidine ring (Table 4). The major products from the cyclizations of **29b** and **29c** were the expected piperidines **31b** and **31c**, Figure 8. Although the compounds were not crystalline, analysis of the $^1$H NMR spectra provided unambiguous proof of the relative stereochemistry. The minor products, formed by

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[23] Thorimbert, S.; Giambastiani, G.; Commandeur, C.; Vitale, M.; Poli, G.; Malacria, M. *Eur. J. Org. Chem.* **2003**, 2702–2708.

[24] Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408.

[25] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

**SCHEME 4. Synthesis of the (Triethylsilyl)vinyl Bromide Precursors**

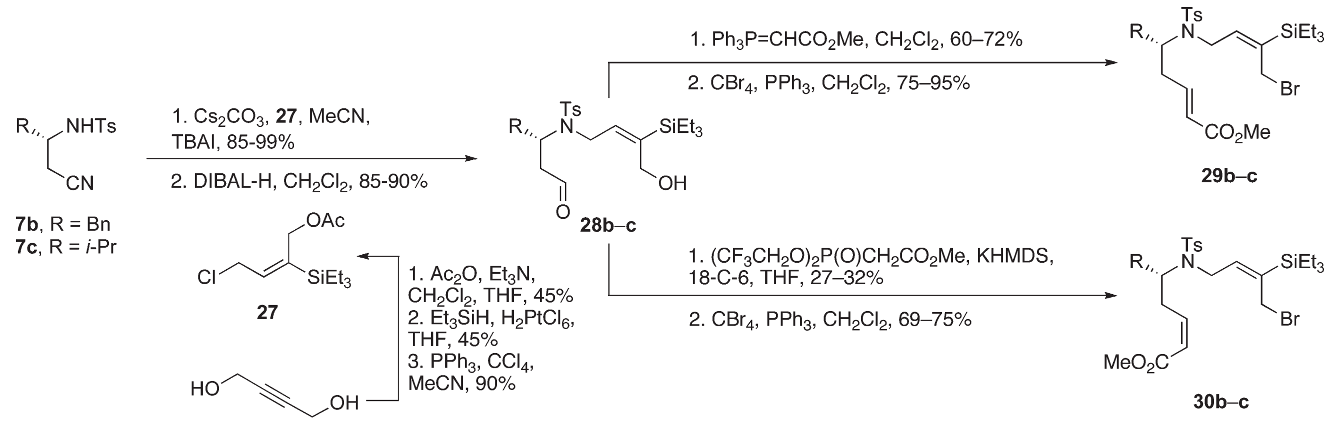
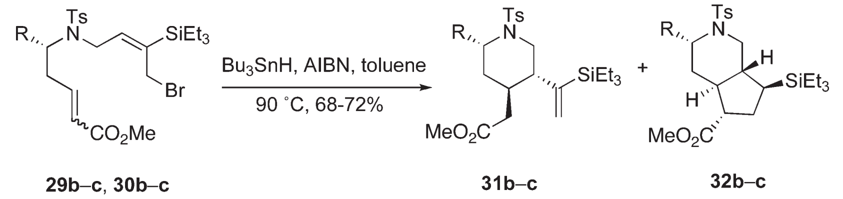


**TABLE 4. Cyclizations of the (Triethylsilyl)vinyl-Stabilized Precursors**[a]



| entry | bromide | R | *E* or *Z* | **31**:**32**[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **29b** | Bn | *E* | 5:4 | 70 |
| 2 | **30b** | Bn | *Z* | 1:4 | 71 |
| 3 | **29c** | *i*-Pr | *E* | 2:1 | 68 |
| 4 | **30c** | *i*-Pr | *Z* | 1:4 | 72 |

[a] Reactions performed by syringe pump addition of toluene solutions of $Bu_3SnH$ and AIBN to a solution of the bromide in toluene heated at 90 °C, final concentration typically 0.01−0.015 M. [b] Ratio determined by HPLC of the crude reaction mixture and/or $^1H$ NMR after chromatography to remove tin residues. [c] Isolated yields of the mixture following chromatography. The compounds were separable by HPLC.

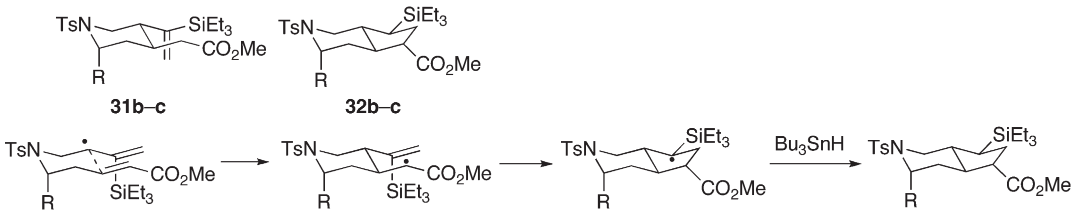


**FIGURE 8.** Products from the cyclization of the (triethylsilyl)vinyl-stabilized radical precursors, and the proposed tandem 6-*exo-trig* and 5-*endo-trig* cyclizations leading to their formation.

tandem 6-*exo-trig* and 5-*endo-trig* cyclizations that give complete control of the four new stereogenic centers, were the octahydropyrindenes **32b** and **32c**, the structures of which were confirmed by NOE studies. Octahydropyrindenes are interesting synthetic targets and have been exploited, among other things, as HIV-1 protease inhibitors.[26]

Interestingly, the (*Z*)-esters gave significantly more of the bicyclic product than the (*E*)-esters. It is tempting to suggest that the steric clash between the ester and the triethylsilyl group favors **TS1** over **TS2**, Figure 9. The (triethylsilyl)vinyl group in **TS1** is correctly oriented to undergo 5-*endo-trig* attack, while in **TS2** the bulky (triethylsilyl)vinyl group will have to rotate through 180°, a process which is likely to be slow relative to radical trapping by tributyltin hydride.

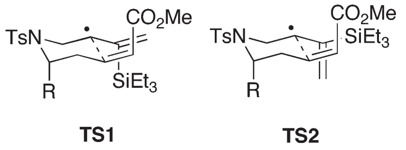


**FIGURE 9.** Proposed transition states for cyclization of the radicals derived from **30b**−**c**.

Intrigued by the differences between the vinyl- and (triethylsilyl)vinyl-stabilized radicals, we decided to compare them in the cyclization of radicals lacking the substituent at the 2-position to see if simpler systems would also undergo stereoselective tandem 6-*exo-trig* and 5-*endo-trig* cyclizations.

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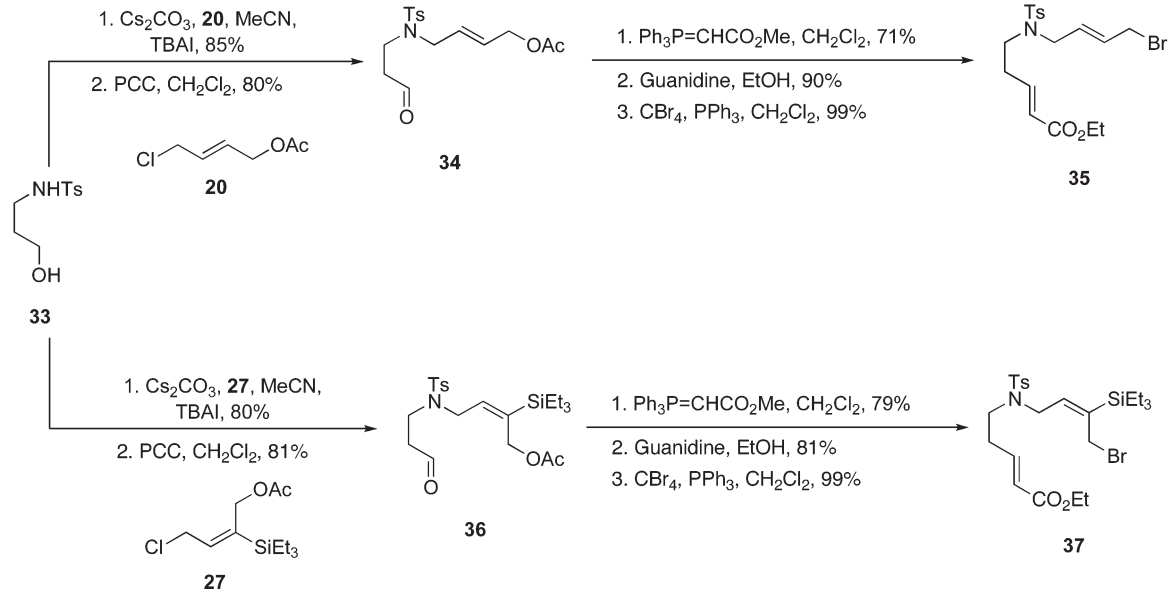
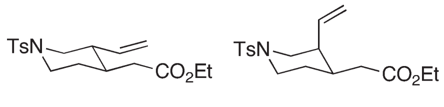
[26] Ghosh, A. K.; Lee, H. Y.; Thompson, W. J.; Culberson, C.; Holloway, K. M.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Smith, A. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 1177–1188.

**SCHEME 5. Synthesis of Achiral Vinyl-Stabilized and (Triethylsilyl)vinyl-Stabilized Radical Precursors 35 and 37**



The required cyclization precursors were readily prepared from 3-(tosylamino)propan-1-ol **33**, Scheme 5. Alkylation with allyl chlorides **20** or **27** gave **34** and **36**, respectively. PCC oxidation followed by Wittig olefination gave exclusively the (*E*)-esters after chromatography. Hydrolysis of the acetate groups proved troublesome. Use of $K_2CO_3$ in methanol[27] or KCN in methanol[28] led to extensive fragmentation by removal of the ester $\gamma$-proton and elimination of the sulfonamide. Fortunately the acetate could be cleanly removed by the use of guanidine in MeOH or EtOH.[29] The reaction in EtOH was preferred as it gave a higher yield, although under these conditions the $\alpha,\beta$-unsaturated ester also underwent transesterification to the ethyl ester. Finally, bromination was straightforwardly carried out using carbon tetrabromide and triphenylphosphine to afford bromides **35** and **37** in excellent yields.

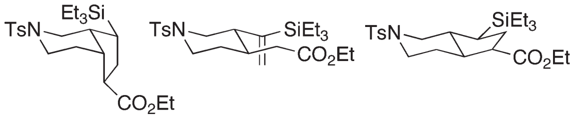
Cyclization of **35** and **37** was performed under the conditions used previously. In both cases the reaction took significantly longer to reach completion than had been the case for the 2-substituted examples, likely the result of the additional substituent reducing the entropy of activation.[30] Cyclization of **35** gave a 3:2 inseparable mixture of the two expected diastereoisomers **38** and **39**, Figure 10.



**38** **39**

**FIGURE 10.** The two piperidines isolated from cyclization of **35**.

On the other hand, cyclization of **37** gave a 4:1:1 mixture of three compounds, inseparable by column chromatography. Purification of a portion by HPLC afforded two fractions. The larger fraction was the cis-fused octahydropyrindene **40** which was crystalline, and single-crystal X-ray analysis confirmed the structure (Figure S2, Supporting Information). The smaller fraction comprised a 1:1 mixture of piperidine **41** and trans-fused octahydropyrindene **42**, Figure 11.



**40** **41** **42**

**FIGURE 11.** Products isolated from cyclization of **37**.

Thus, in the absence of a 2-substituent, the cyclizations display an inherently low stereoselectivity, with a significant fraction cyclizing through transition states that give rise to the cis products **39** and **40**.

In conclusion, we have demonstrated a diastereoselective radical route to 2,4,5-trisubstituted piperidines. All stabilized radicals underwent 6-*exo-trig* cyclization to afford the corresponding piperidines in good yields, with the acyclic reduction product isolated in only one instance. The major diastereoisomer in all cases could be accounted for by cyclization through a chairlike transition state in which the 2-substituent is pseudo axial, thereby minimizing torsional strain with the sulfonamide, and the 4- and 5-substituents are pseudo equatorial, although cyclization through a boat-like transition state is likely in at least some cases. Model reactions with cyclization precursors lacking the 2-substituent suggested that the inherent stereocontrol between the 4- and 5-positions is low. Inclusion of the 2-substituent gave better stereocontrol, with the minor diastereoisomer disfavored either as a result of a 1,3-diaxial interaction between the 2- and 4-substituents or from a repulsive interaction between the axial 5-substituent and the sulfonamide, the latter experiencing torsional strain with the 2-substituent. In the case of the 5-phenyl examples, a minor isomer was obtained which had an axial 4-susbtituent, whereas for the 5-vinyl examples the relatively sterically undemanding vinyl group

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(27) Robarge, M. J.; Husbands, S. M.; Kieltyka, A.; Brodbeck, R.; Thurkauf, A.; Newman, A. H. *J. Med. Chem.* **2001**, *44*, 3175–3186.

(28) Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.* **1986**, *51*, 727–730.

(29) Kunesch, N.; Miet, C.; Poisson, J. *Tetrahedron Lett.* **1987**, *28*, 3569–3572.

(30) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305–329.

occupied the axial position in the minor diastereomer. Exchanging the vinyl group for the more bulky (triethysilyl)-vinyl substituent led solely to isolation of products in which the 2-substituent was axial and the 4- and 5-substituents were equatorial. As well as the expected piperidine products, octahydropyrindenes were also isolated as single stereoisomers, resulting from an unexpected 5-*endo* cyclization of the piperidine radical onto the (triethysilyl)vinyl substituent. The cyclization of stabilized radicals appears to proceed through later, more piperidine-like transition states, giving rise to improved diastereoselectivities over the analogous unstabilized examples that we have previously reported.

## Experimental Section

**(*R*)-4-Aza-3-isopropyl-6-oxo-6-phenyl-4-(*p*-toluenesulfonyl)-hexanenitrile (8c).** Cesium carbonate (1.81 g, 5.56 mmol) was added to a solution of (3*R*)-(*p*-toluenesulfonyl)amino-4-methylpentanenitrile (1.14 g, 4.28 mmol) in anhydrous MeCN (15 mL). The reaction mixture was stirred at ambient temperature for 30 min before a solution of 2-bromoacetophenone (1.02 g, 5.12 mmol) in MeCN (7 mL) was added dropwise. The resulting mixture was stirred for 18 h before the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and poured into water. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a pale yellow oil that was purified by flash column chromatography (toluene/$Et_2O$, 15:1) to afford (*R*)-4-aza-3-isopropyl-6-oxo-6-phenyl-4-(*p*-toluenesulfonyl)hexanenitrile as a white solid (1.23 g, 75%): $R_f = 0.16$; mp 159−162 °C; $[\alpha]^{20}_{D} = +112.3$ (*c* 1.0, $CHCl_3$); IR (film) 3020, 2972, 2249, 1706, 1598 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.73 (d, $J$ = 6.6, 2H), 0.95 (d, $J$ = 6.6, 2H), 1.92−2.04 (m, 1H), 2.42 (s, 3H), 2.67 (dd, $J$ = 5.1, 17.3, 1H), 2.87 (dd, $J$ = 3.3, 17.3, 1H), 3.52−3.59 (m, 1H), 4.61 (d, $J$ = 18.7, 1H), 5.10 (d, $J$ = 18.7, 1H), 7.31 (d, $J$ = 8.3, 2H), 7.44−7.49 (m, 2H), 7.56−7.61 (m, 1H), 7.77 (d, $J$ = 8.3, 2H), 7.94 (d, $J$ = 8.3, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 19.6, 21.5, 21.8, 29.3, 49.6, 59.0, 117.6, 127.8, 127.9, 128.7, 129.5, 133.6, 134.7, 136.9, 143.8, 194.4; MS (electrospray) *m*/*z* 407.1 (100%, $[M + Na]^+$). HRMS (electrospray) calcd for $C_{21}H_{24}N_2O_3NaS$: 407.1405, found 407.1425.

**(6*R*)-5-Aza-1-hydroxy-6-isopropyl-2-oxa-3-phenyl-4-(*p*-toluenesulfonyl)cycloheptane (9c).** DIBAL (1.5 M solution in toluene, 1.46 mL, 2.18 mmol) was added dropwise to a solution of nitrile **8c** (0.35 g, 0.91 mmol) in $CH_2Cl_2$ (15 mL) under argon at −78 °C. After stirring at −78 °C for 1 h, MeOH (1 mL) was added, and the reaction allowed to warm to ambient temperature. $H_2SO_4$ (1 M solution, 10 mL) was added, and the mixture was stirred vigorously for 15 min before the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford the crude lactol (6*R*)-5-aza-1-hydroxy-6-isopropyl-2-oxa-3-phenyl-4-(*p*-toluenesulfonyl)cycloheptane as an orange oil (0.32 g, 90%), which was used without any further purification: IR (film) 3465, 3027, 2967, 2929, 1598, 1494 $cm^{-1}$; MS (electrospray) *m*/*z* 412.1 (100%, $[M + Na]^+$), 444.1 (25%, $[M + Na + MeOH]^+$). HRMS (electrospray) calcd for $C_{21}H_{27}NO_4NaS$: 412.1559, found 412.1567. The $^1H$ NMR and the $^{13}C$ NMR spectra of the sample were complex due to the presence of four diastereoisomers as well as a small amount of the open-chain aldehyde.

**Methyl (5*R*,*E*)-6-Aza-8-hydroxy-5-isopropyl-8-phenyl-6-(*p*-toluenesulfonyl)oct-2-enoate (10c).** Methyl (triphenylphophoranylidene)acetate (0.34 g, 1.02 mmol) was added to a solution of lactol **9c** (0.36 g, 0.92 mmol) in $CH_2Cl_2$ (15 mL) at room temperature and was stirred overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography (hexane/EtOAc, 5:1) to give methyl (5*R*,*E*)-6-aza-8-hydroxy-5-isopropyl-8-phenyl-6-(*p*-toluenesulfonyl)oct-2-enoate as a mixture of two epimers in a 10:1 ratio as a colorless oil (0.25 g, 60%): $R_f = 0.22$; IR (film) 3464, 3028, 2962, 2926, 1718, 1646, 1598, 1494 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.77 (d, $J$ = 6.6, 3H), 0.98−1.00 (m, 3H major, 6H minor), 1.78−1.92 (m, 1H major, 1H minor), 2.23−2.50 (m, 5H major, 5H minor), 3.14−3.32 (m, 2H major, 2H minor), 3.62−3.70 (m, 4H major, 4H minor), 3.90 (br s, 1H major, 1H minor), 4.93−4.96 (m, 1H major), 5.04−5.08 (m, 1H minor), 5.63 (d, $J$ = 15.6, 1H major), 5.73 (d, $J$ = 15.6, 1H minor), 6.65−6.75 (m, 1H major), 6.80−6.90 (m, 1H minor), 7.26−7.40 (m, 7H major, 7H minor), 7.71 (d, $J$ = 8.2, 2H major, 2H minor); $^{13}C$ NMR (75 MHz, $CDCl_3$, mixture of epimers) $\delta$ 20.4, 20.7, 21.4, 31.9, 32.9, 34.5, 35.6, 51.3, 53.0, 64.7, 73.1, 73.4, 122.7, 125.7, 127.4, 127.8, 128.5, 129.6, 129.8, 136.7, 142.0, 143.7, 146.0, 146.2, 166.2; MS (electrospray) *m*/*z* 468.2 (100%, $[M + Na]^+$). HRMS (electrospray) calcd for $C_{24}H_{31}NO_5NaS$: 468.1821, found 468.1809.

**Methyl (5*R*,*E*)-6-Aza-8-bromo-5-isopropyl-8-phenyl-6-(*p*-toluenesulfonyl)oct-2-enoate (11c).** $PBr_3$ (1 M solution in $CH_2Cl_2$, 0.35 mL, 0.35 mmol) was added dropwise to a solution of ester **10c** (0.13 g, 0.29 mmol) in $CH_2Cl_2$ (8 mL) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 1 h, after which it was poured into water and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated before being purified by column chromatography (hexane/EtOAc, 4:1) to afford bromide methyl (5*R*,*E*)-6-aza-8-bromo-5-isopropyl-8-phenyl-6-(*p*-toluenesulfonyl)oct-2-enoate as a mixture of epimers in a 5:1 ratio as a colorless oil (0.12 g, 80%): $R_f = 0.34$; IR (film) 3063, 3028, 2961, 2874, 1721, 1656, 1598, 1494 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.40 (d, $J$ = 6.6, 3H major), 0.68 (d, $J$ = 6.6, 3H minor), 0.73 (d, $J$ = 6.6, 3H major), 0.86 (d, $J$ = 6.6, 3H minor), 2.04−2.15 (m, 1H major, 1H minor), 2.29−2.43 (m, 5H major, 5H minor), 3.24−3.31 (m, 1H major), 3.34−3.40 (m, 1H minor), 3.58−3.82 (m, 5H major, 5H minor), 5.36−5.41 (m, 1H minor), 5.47−5.61 (m, 2H major, 1H minor), 6.50−6.60 (m, 1H major, 1H minor), 7.28−7.37 (m, 5H major, 5H minor), 7.44−7.47 (m, 2H major, 2H minor), 7.68 (d, $J$ = 8.3, 2H major, 2H minor); $^{13}C$ NMR (75 MHz, $CDCl_3$, mixture of epimers) $\delta$ 20.1, 20.3, 20.6, 21.1, 21.5, 32.2, 32.7, 35.1, 51.38, 51.41, 52.4, 52.7, 53.9, 65.3, 122.1, 122.5, 127.7, 128.2, 128.5, 128.7, 128.8, 128.9, 129.6, 129.7, 136.1, 139.4, 143.9, 146.1, 146.3, 166.2; MS (electrospray) *m*/*z* 530.2 (40%, $[M(^{79}Br) + Na]^+$), 532.3 (35%, $[M\,(^{81}Br) + Na]^+$), 450.3 (100%, $[M + Na - HBr]^+$). HRMS (electrospray) calcd for $C_{24}H_{30}NO_4NaS^{79}Br$: 530.0977, found 530.0970.

**(2*R*,4*R*,5*S*)-2-Isopropyl-4-(methoxycarbonylmethyl)-5-phenyl-1-(*p*-toluenesulfonyl)piperidine (12c) and (2*R*,4*S*,5*S*)-2-Isopropyl-4-(methoxycarbonylmethyl)-5-phenyl-1-(*p*-toluenesulfonyl)piperidine (13c).** A solution of bromide **11c** (0.10 g, 0.20 mmol) in toluene (5 mL) was deoxygenated by bubbling nitrogen through it for 15 min. The solution was heated to 90 °C, and deoxygenated solutions of $Bu_3SnH$ (0.11 g, 0.10 mL, 0.39 mmol) and AIBN (0.006 g, 0.04 mmol) in toluene (both in 5 mL) were added simultaneously *via* syringe pump over 8 h. Stirring was continued for a further 8 h. The reaction mixture was cooled to room temperature, concentrated, and purified by column chromatography (hexane 100% to remove the tin residues and then toluene/$Et_2O$, 20:1 to obtain the product) to afford the mixture of (2*R*,4*R*,5*S*)-2-isopropyl-4-(methoxycarbonylmethyl)-5-phenyl-1-(*p*-toluenesulfonyl)piperidine and (2*R*,4*S*,5*S*)-2-isopropyl-4-(methoxycarbonylmethyl)-5-phenyl-1-(*p*-toluenesulfonyl)-piperidine in a 40:1 ratio, as determined by analytical HPLC, as a colorless oil (0.063 g, 73%): analytical HPLC (from water/TFA 99.95:0.05 to MeOH/TFA 99.95:0.05 over 60 min) $t_R$ = 53.48 min (**13c**), 54.20 min (**12c**); $R_f = 0.39$; IR (film) 3029, 2963, 1730, 1599, 1494 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, only major diastereoisomer reported) δ 0.93 (d, *J* = 6.6, 3H), 0.99 (d, *J* = 6.6, 3H), 1.12 (dt, *J* = 5.1, 13.6, 1H), 1.68 (dd, *J* = 10.0, 15.9, 1H), 1.95−2.00 (m, 1H), 2.03−2.13 (m, 2H), 2.16−2.39 (m, 2H), 2.43 (s, 3H), 3.02 (dd, *J* = 12.1, 14.9, 1H), 3.50 (s, 3H), 3.67 (dd, *J* = 3.6, 9.9, 1H), 3.78 (dd, *J* = 4.5, 14.9, 1H), 7.06 (d, *J* = 7.1, 2H), 7.19−7.32 (m, 5H), 7.74 (d, *J* = 8.2, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$, only major diastereoisomer reported) δ 19.7, 20.3, 21.5, 26.8, 31.4, 32.0, 38.3, 46.8, 47.0, 51.4, 59.5, 127.0, 127.3, 127.7, 128.8, 129.6, 138.6, 140.2, 143.0, 172.7; MS (electrospray) *m*/*z* 452.2 (100%, $[M + Na]^+$). HRMS (electrospray) calcd for $C_{24}H_{31}NO_4NaS$: 452.1872, found 452.1863.

**(*R*,*E*)-8-Acetoxy-4-aza-3-isopropyl-4-(*p*-toluenesulfonyl)oct-6-enenitrile.** $Cs_2CO_3$ (0.61 g, 1.86 mmol) was added to a solution of nitrile **7c** (0.45 g, 1.69 mmol) in MeCN (15 mL) at room temperature. The resulting suspension was stirred for 30 min and cooled to 0 °C, and a solution of chloride **20** (0.30 g, 2.02 mmol) in MeCN (10 mL) was added dropwise, followed by TBAI (0.44 g, 1.18 mmol). The mixture was allowed to warm to room temperature and was stirred for 12 h, after which it was concentrated, and the residue was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a yellow oil that was purified by column chromatography (EtOAc/hexane, 1:2) to give (*R*,*E*)-8-acetoxy-4-aza-3-isopropyl-4-(*p*-toluenesulfonyl)oct-6-enenitrile as a pale yellow oil (0.51 g, 95%): $R_f$ = 0.56; $[\alpha]^{18}_{D}$ = −35.6 (*c* 1.0, $CHCl_3$); IR (film) 3021, 2969, 2877, 2246, 1737, 1598, 1494 $cm^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.6, 3H), 0.92 (d, *J* = 6.6, 3H), 1.86−1.99 (m, 4H), 2.35 (s, 3H), 2.48 (dd, *J* = 4.4, 17.3, 1H), 2.58 (dd, *J* = 7.4, 17.3, 1H), 3.65−3.72 (m, 1H), 3.86 (dd, *J* = 5.1, 16.6, 1H), 3.97 (dd, *J* = 5.5, 16.6, 1H), 4.47−4.62 (m, 2H), 5.49−5.64 (m, 2H), 7.25 (d, *J* = 7.7, 2H), 7.68 (d, *J* = 7.7, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 19.8, 20.3, 20.8, 21.2, 21.4, 30.8, 41.4, 59.4, 60.8, 117.8, 126.1, 127.4, 129.7, 130.9, 137.2, 143.7, 170.5; MS (electrospray) *m*/*z* 401.1 (100%, $[M + Na]^+$). HRMS (electrospray) calcd for $C_{19}H_{26}N_2O_4SNa$: 401.1511, found 401.1500.

**(*R*,*E*)-4-Aza-8-hydroxy-3-isopropyl-4-(*p*-toluenesulfonyl)oct-6-enal (22c).** To a solution of (*R*,*E*)-8-acetoxy-4-aza-3-isopropyl-4-(*p*-toluenesulfonyl)oct-6-enenitrile (0.50 g, 1.32 mmol) in $CH_2Cl_2$ (20 mL) at −78 °C was added DIBAL (1 M solution in toluene, 3.96 mL, 3.96 mmol), and the reaction was stirred at −78 °C for 2 h before MeOH (2 mL) was added. After warming to room temperature, $H_2SO_4$ 1 M (5 mL) was added, and the mixture was stirred vigorously for 15 min before being extracted with $CH_2Cl_2$, washed with brine, dried over $MgSO_4$, and concentrated to give (*R*,*E*)-4-aza-8-hydroxy-3-isopropyl-4-(*p*-toluenesulfonyl)oct-6-enal as a pale yellow oil, which was used without further purification (0.43 g, 95%): $[\alpha]^{18}_{D}$ = −7.6 (*c* 1.0, $CHCl_3$); IR (film) 3485, 2963, 2938, 2882, 1721, 1600, 1470 $cm^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.7, 3H), 0.80 (d, *J* = 6.7, 3H), 1.69−1.81 (m, 1H), 2.37 (s, 3H), 2.64 (dd, *J* = 6.4, 17.0, 1H), 3.70−4.24 (m, 6H), 5.43−5.53 (m, 1H), 5.65−5.73 (m, 1H), 7.24 (d, *J* = 8.0, 2H), 7.65 (d, *J* = 8.0, 2H), 9.53 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 19.8, 20.3, 21.4, 31.9, 41.4, 46.8, 57.8, 59.0, 127.2, 128.6, 129.5, 131.0, 137.4, 143.4, 199.7; MS (electrospray) *m*/*z* 362.1 (100%, $[M + Na]^+$), 394.2 (15%, $[M + Na + MeOH]^+$). HRMS (electrospray) calcd for $C_{17}H_{25}NO_4NaS$: 362.1402, found 362.1408.

**Methyl (*R*,*E*,*E*)-6-Aza-10-hydroxy-5-isopropyl-6-(*p*-toluenesulfonyl)deca-2,8-dienoate.** Methyl (triphenylphophoranylidene)-acetate (0.31 g, 0.93 mmol) was added to a solution of aldehyde **22c** (0.29 g, 0.85 mmol) in $CH_2Cl_2$ (15 mL), and the resulting solution was stirred for 12 h. The solution was concentrated before being purified by column chromatography (hexane/EtOAc, 1:1) to give methyl (*R*,*E*,*E*)-6-aza-10-hydroxy-5-isopropyl-6-(*p*-toluenesulfonyl)deca-2,8-dienoate as a colorless oil (0.20 g, 60%): $R_f$ = 0.35; IR (film) 3433, 3027, 2962, 2875, 1721, 1657, 1598 $cm^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, *J* = 6.5, 3H), 0.90 (d, *J* = 6.5, 3H), 1.69−1.80 (m, 1H), 2.20−2.49 (m, 5H), 2.64 (br s, 1H), 3.57−3.66 (m, 4H), 3.79 (d, *J* = 4.9, 2H), 4.17 (d, *J* = 6.2, 2H), 5.41−5.49 (m, 1H), 5.61−5.69 (m, 2H), 6.65−6.76 (m, 1H), 7.21 (d, *J* = 7.9, 2H), 7.63 (d, *J* = 7.9, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.5, 21.4, 31.5, 34.6, 40.8, 51.4, 57.9, 64.0, 122.9, 127.2, 128.9, 129.4, 130.7, 137.9, 143.1, 146.0, 166.3; MS (electrospray) *m*/*z* 418.2 (100%, $[M + Na]^+$). HRMS (electrospray) calcd for $C_{20}H_{29}NO_5SNa$: 418.1664, found 418.1667. Anal. Calcd for $C_{20}H_{29}NO_5S$: C, 60.73; H, 7.39; N, 3.54. Found: C, 60.75; H, 7.23; N, 3.24.

**Methyl (*R*,*E*,*E*)-6-Aza-10-bromo-5-isopropyl-6-(*p*-toluenesulfonyl)-deca-2,8-dienoate (19c).** To a stirred solution of methyl (*R*,*E*,*E*)-6-aza-10-hydroxy-5-isopropyl-6-(*p*-toluenesulfonyl)deca-2,8-dienoate (0.12 g, 0.30 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added $PPh_3$ (0.12 g, 0.45 mmol) followed by $CBr_4$ (0.15 g, 0.45 mmol). The solution was heated at reflux for 4 h, concentrated, and purified by column chromatography (hexane/EtOAc, 4:1) to give methyl (*R*,*E*,*E*)-6-aza-10-bromo-5-isopropyl-6-(*p*-toluenesulfonyl)deca-2,8-dienoate as a colorless oil (0.13 g, 94%): $R_f$ = 0.62; $[\alpha]^{23}_{D}$ = −31.7 (*c* 0.7, $CHCl_3$); IR (film) 2972, 2959, 1727, 1659, 1598, 1448, 1336, 1158 $cm^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.7, 3H), 0.94 (d, *J* = 6.7, 3H), 1.74−1.86 (m, 1H), 2.22−2.54 (m, 5H), 3.65−3.72 (m, 4H), 3.75−3.87 (m, 2H), 3.95 (d, *J* = 8.5, 2H), 5.48−5.56 (m, 1H), 5.67−5.78 (m, 2H), 6.68−6.78 (m, 1H), 7.23 (d, *J* = 8.1, 2H), 7.65 (d, *J* = 8.1, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.6, 21.4, 25.7, 31.7, 34.6, 40.3, 51.4, 64.2, 123.0, 126.6, 127.3, 129.5, 132.2, 137.8, 143.2, 145.9, 166.1; MS (electrospray) *m*/*z* 480.1 (100%, $[M(^{79}Br) + Na]^+$), 482.1 (90%, $[M(^{81}Br) + Na]^+$), 400.2 (30%, $[M + Na - HBr]^+$). HRMS (electrospray) calcd for $C_{20}H_{28}NO_4NaS^{79}Br$: 480.0820, found 480.0830.

**(2*R*,4*R*,5*R*)-2-Isopropyl-4-(methoxycarbonylmethyl)-1-(*p*-toluenesulfonyl)-5-vinylpiperidine (24c) and (2*R*,4*R*,5*S*)-2-Isopropyl-4-(methoxycarbonylmethyl)-1-(*p*-toluenesulfonyl)-5-vinylpiperidine (25c).** This compound was prepared in the same way as **12c** using bromide **19c** (0.11 g, 0.24 mmol) in toluene (5 mL) and solutions of $Bu_3SnH$ (0.14 g, 0.13 mL, 0.48 mmol) and AIBN (0.008 g, 0.05 mmol) in toluene (both in 5 mL). Purification by flash column chromatography (hexane 100% to remove the tin residues and then toluene/$Et_2O$, 19:1 to obtain the product) afforded a mixture of (2*R*,4*R*,5*R*)-2-isopropyl-4-(methoxycarbonylmethyl)-1-(*p*-toluenesulfonyl)-5-vinylpiperidine and (2*R*,4*R*,5*S*)-2-isopropyl-4-(methoxycarbonylmethyl)-1-(*p*-toluenesulfonyl)-5-vinylpiperidine in a 10:1 ratio, as determined by $^{1}$H NMR, as a colorless oil (0.064 g, 70%): $R_f$ = 0.35; IR (film) 2956, 2927, 2877, 1734, 1603, 1456 $cm^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$, only major diastereoisomer reported) δ 0.88−1.02 (m, 7H), 1.60−1.67 (m, 1H), 1.72 (dd, *J* = 9.6, 15.7, 1H), 1.83−1.91 (m, 2H), 2.00−2.11 (m, 1H), 2.37−2.43 (m, 4H), 2.80 (dd, *J* = 11.8, 14.9, 1H), 3.60−3.74 (m, 5H), 4.99−5.11 (m, 2H), 5.33−5.45 (m, 1H), 7.29 (d, *J* = 8.3, 2H), 7.71 (d, *J* = 8.3, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, only major diastereoisomer reported) δ 19.8, 20.3, 21.6, 26.6, 30.9, 31.5, 38.5, 45.1, 45.2, 51.5, 59.5, 118.5, 127.1, 129.7, 137.4, 138.7, 143.1, 173.0; MS (electrospray) *m*/*z* 402.1 (100%, $[M + Na]^+$). HRMS (electrospray) calcd for $C_{20}H_{29}NO_4NaS$: 402.1715, found 402.1711.

**(*R*,*E*)-8-Acetoxy-4-aza-3-isopropyl-4-(*p*-toluenesulfonyl)-7-[(triethyl)silyl]oct-6-enenitrile.** $Cs_2CO_3$ (3.62 g, 11.11 mmol) was added to a solution of nitrile **7c** (2.70 g, 10.1 mmol) in MeCN (50 mL) at room temperature. The resulting suspension was stirred for 30 min and cooled to 0 °C, and a solution of chloride **27** (2.65 g, 12.12 mmol) in MeCN (50 mL) was added dropwise, followed by TBAI (2.24 g, 6.06 mmol). The mixture was allowed to warm to room temperature and was stirred for 12 h, after which it was concentrated, and the residue was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a yellow oil that was purified by column chromatography (EtOAc/hexane, 1:3) to give (*R*,*E*)-8-acetoxy-4-aza-3-isopropyl-4-(*p*-toluenesulfonyl)-7-[(triethyl)-silyl]oct-6-enenitrile as a pale yellow oil (4.95 g, 99%): $R_f$ = 0.35; $[\alpha]^{23}_{D}$ = −24.8 (*c* 1.0, $CHCl_3$); IR (film) 3021, 2956, 2876, 2247, 1732, 1599 cm$^{-1}$; $^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.53 (q, $J$ = 7.7, 6H), 0.85 (t, $J$ = 7.7, 9H), 0.91 (d, $J$ = 6.6, 3H), 0.98 (d, $J$ = 6.6, 3H), 1.88−2.01 (m, 4H), 2.40 (s, 3H), 2.53 (d, $J$ = 5.3, 2H), 3.80−3.88 (m, 1H), 4.06 (dd, $J$ = 5.7, 9.9, 2H), 4.58 (d, $J$=12.8, 1H), 4.69 (d, $J$ = 12.8, 1H), 5.74 (t, $J$ = 5.7, 1H), 7.29 (d, $J$ = 8.1, 2H), 7.76 (d, $J$ = 8.1, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 3.0, 7.3, 20.0, 20.5, 21.0, 21.1, 21.6, 31.0, 42.5, 61.2, 62.2, 117.9, 127.7, 129.8, 135.6, 137.7, 141.8, 143.9, 170.7; MS (electrospray) *m*/*z* 515.2 (100%, [M + Na]$^+$). HRMS (electrospray) calcd for $C_{25}H_{40}N_2O_4SSiNa$: 515.2376, found 515.2382. Anal. Calcd for $C_{25}H_{40}N_2O_4SSi$: C, 60.94; H, 8.18; N, 5.69. Found: C, 60.69; H, 8.48; N, 5.54.

**(*R*,*E*)-4-Aza-8-hydroxy-3-isopropyl-4-(*p*-toluenesulfonyl)-7-[(triethyl)silyl]oct-6-enal (28c).** Aldehyde **28c** was prepared in the same way as **22c**, from (*R*,*E*)-8-acetoxy-4-aza-3-isopropyl-4-(*p*-toluenesulfonyl)-7-[(triethyl)silyl]oct-6-enenitrile (1.00 g, 2.03 mmol) and DIBAL (1 M solution in toluene, 6.1 mL, 6.1 mmol), giving (*R*,*E*)-4-aza-8-hydroxy-3-isopropyl-4-(*p*-toluenesulfonyl)-7-[(triethyl)silyl]oct-6-enal as a pale yellow oil (0.83 g, 90%) that was used without further purification: IR (film) 3500.1, 3023.0, 2956.3, 2911.2, 2875.0, 1724.1, 1598.8 cm$^{-1}$; $^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.54 (q, $J$ = 7.7, 6H), 0.78 (t, $J$ = 7.7, 9H), 0.83 (d, $J$ = 6.6, 3H), 0.86 (d, $J$ = 6.6, 3H), 1.67−1.79 (m, 1H), 2.26−2.34 (m, 4H), 2.59 (dd, $J$ = 6.3, 17.3, 1H), 3.77−3.85 (m, 1H), 3.94−4.04 (m, 2H), 4.19 (m, 2H), 5.70 (t, $J$ = 6.2, 1H), 7.21 (d, $J$ = 8.1, 2H), 7.63 (d, $J$ = 8.1, 2H), 9.51 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 3.0, 7.5, 19.9, 20.5, 21.5, 32.1, 42.8, 46.8, 59.2, 60.1, 127.4, 129.7, 137.7, 140.2, 140.4, 143.5, 199.8; MS (electrospray) *m*/*z* 508.2 (100%, [M + MeOH + Na]$^+$), 476.1 (25%, [M + Na]$^+$). HRMS (electrospray) calcd for $C_{23}H_{39}NO_4SSiNa$: 476.2267, found 476.2253.

**Methyl (*R*,*E*,*E*)-6-Aza-10-hydroxy-5-isopropyl-6-(*p*-toluenesulfonyl)-9-[(triethyl)silyl]deca-2,8-dienoate.** This compound was prepared in the same way as methyl (*R*,*E*,*E*)-6-aza-10-hydroxy-5-isopropyl-6-(*p*-toluenesulfonyl)deca-2,8-dienoate, from aldehyde **28c** (0.50 g, 1.10 mmol) and methyl (triphenylphosphoranylidene)acetate (0.40 g, 1.21 mmol). Purification by column chromatography (hexane/EtOAc, 5:2) afforded methyl (*R*,*E*,*E*)-6-aza-10-hydroxy-5-isopropyl-6-(*p*-toluenesulfonyl)-9-[(triethyl)silyl]deca-2,8-dienoate as a colorless oil (0.34 g, 60%): $R_f$ = 0.31; $[\alpha]^{20}_{D}$ = +9.2 (*c* 1.0, CHCl$_3$); IR (film) 3523, 3022, 2954, 2875, 1720, 1658, 1598 cm$^{-1}$; $^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.55 (q, $J$ = 7.7, 6H), 0.87 (t, $J$ = 7.7, 9H), 0.93 (d, $J$ = 6.6, 6H), 1.71−1.83 (m, 1H), 2.00 (s, 1H), 2.17−2.27 (m, 1H), 2.30−2.50 (m, 4H), 3.65−3.73 (m, 4H), 3.95 (t, $J$ = 5.9, 2H), 4.22 (s, 2H), 5.66−5.71 (m, 2H), 6.68−6.78 (m, 1H), 7.22 (d, $J$ = 8.1, 2H), 7.66 (d, $J$ = 8.1, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 3.0, 7.5, 20.4, 20.7, 21.6, 31.8, 34.7, 42.2, 51.6, 60.3, 64.1, 123.1, 127.5, 129.7, 138.3, 140.1, 140.6, 143.3, 146.1, 166.4; MS (electrospray) *m*/*z* 532.2 (100%, [M + Na]$^+$). HRMS (electrospray) calcd for $C_{26}H_{43}NO_5SSiNa$: 532.2529, found 532.2512.

**Methyl (*R*,*E*,*E*)-6-Aza-10-bromo-5-isopropyl-6-(*p*-toluenesulfonyl)-9-[(triethyl)silyl]deca-2,8-dienoate (29c).** Bromide **29c** was prepared in the same way as **19c**, from methyl (*R*,*E*,*E*)-6-aza-10-hydroxy-5-isopropyl-6-(*p*-toluenesulfonyl)-9-[(triethyl)silyl]-deca-2,8-dienoate (0.14 g, 0.27 mmol), PPh$_3$ (0.11 g, 0.41 mmol), and CBr$_4$ (0.13 g, 0.41 mmol). Purification by column chromatography (hexane/EtOAc, 2:1) afforded methyl (*R*,*E*,*E*)-6-aza-10-bromo-5-isopropyl-6-(*p*-toluenesulfonyl)-9-[(triethyl)silyl]-deca-2,8-dienoate as a colorless oil (0.15 g, 95%): $R_f$ = 0.80; $[\alpha]^{20}_{D}$ = +30.4 (*c* 1.0, CHCl$_3$); IR (film) 2954, 2875, 1724, 1659, 1599 cm$^{-1}$; $^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.55 (q, $J$ = 7.7, 6H), 0.87 (t, $J$ = 7.7, 9H), 0.92 (d, $J$ = 6.6, 3H), 0.95 (d, $J$ = 6.6, 3H), 1.73−1.85 (m, 1H), 2.19−2.29 (m, 1H), 2.38 (s, 3H), 2.44−2.53 (m, 1H), 3.69 (s, 3H), 3.73−3.81 (m, 1H), 3.87−4.07 (m, 4H), 5.67−5.76 (m, 2H), 6.68−6.78 (m, 1H), 7.23 (d, $J$ = 8.1, 2H), 7.66 (d, $J$ = 8.1, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 2.7, 7.3, 20.5, 20.8, 21.6, 28.3, 31.8, 34.4, 41.7, 51.5, 64.4, 123.1, 127.5, 129.7, 135.7, 138.2, 143.3, 145.3, 146.1, 166.2; MS (electrospray) *m*/*z* 596.1 (20%, [M($^{81}$Br) + Na]$^+$), 594.1 (15%, [M($^{79}$Br) + Na]$^+$), 514.2 (100%, [M + Na − HBr]$^+$). HRMS (electrospray) calcd for $C_{26}H_{42}NO_4SSiNa^{79}Br$: 594.1685, found 594.1676. Anal. Calcd for $C_{26}H_{42}NO_4SSiBr$: C, 54.53; H, 7.39; N, 2.45. Found: C, 54.48; H, 7.54; N, 2.10.

**(2*R*,4*R*,5*R*)-2-Isopropyl-4-(methoxycarbonylmethyl)-1-(*p*-toluenesulfonyl)-5-[1-{(triethyl)silyl}vinyl]piperidine (31c) and (3*R*,4a*R*,5*S*,7*S*,7a*R*)-3-Isopropyl-5-methoxycarbonyl-1-(*p*-toluenesulfonyl)-7-[(triethyl)silyl]octahydro-1*H*-[2]pyrindene (32c).** This reaction was performed in the same way as the cyclization of **11c** using bromide **29c** (0.12 g, 0.21 mmol) in toluene (5 mL) and solutions of Bu$_3$SnH (0.12 g, 0.11 mL, 0.42 mmol) and AIBN (0.007 g, 0.04 mmol) in toluene (both in 5 mL). Purification by flash column chromatography (hexane 100% to remove the tin residues and then toluene/Et$_2$O 16:1 to obtain the product) afforded a mixture of (2*R*,4*R*,5*R*)-2-isopropyl-4-(methoxycarbonylmethyl)-1-(*p*-toluenesulfonyl)-5-[1-{(triethyl)silyl}vinyl]-piperidine and (3*R*,4a*R*,5*S*,7*S*,7a*R*)-3-isopropyl-5-methoxycarbonyl-1-(*p*-toluenesulfonyl)-7-[(triethyl)silyl]octahydro-1*H*-[2]pyrindene in a 2:1 ratio, as determined by analytical HPLC, as a colorless oil (0.07 g, 68%): $R_f$ = 0.45; analytical HPLC (water/MeCN/TFA 20:79.95:0.05) $t_R$ = 25.38 min (**32c**) and 27.17 min (**31c**). A portion was separated by HPLC.

Data for **31c**: $[\alpha]^{18}_{D}$ = +7.7 (*c* 1.5, CHCl$_3$); IR (film) 2952, 2875, 1735, 1661, 1461 cm$^{-1}$; $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.54 (q, $J$ = 7.9, 6H), 0.89−0.97 (m, 15H), 1.07 (dt, $J$ = 5.0, 13.2, 1H), 1.61 (dd, $J$ = 10.8, 15.6, 1H), 1.72 (dt, $J$ = 4.2, 11.5, 1H), 1.93 (d, $J$ = 13.5, 1H), 2.07−2.13 (m, 1H), 2.21−2.26 (m, 1H), 2.43−2.48 (m, 4H), 2.61 (dd, $J$ = 11.8, 14.8, 1H), 3.56−3.62 (m, 5H), 5.52 (s, 1H), 5.76 (s, 1H), 7.27 (d, $J$ = 8.1, 2H), 7.72 (d, $J$ = 8.1, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 2.6, 7.2, 19.7, 20.2, 21.4, 26.7, 31.2, 31.6, 38.1, 44.0, 46.7, 51.4, 59.5, 127.2, 127.5, 129.5, 138.7, 142.9, 148.3, 173.0; MS (electrospray) *m*/*z* 516.4 (100%, [M + Na]$^+$). HRMS (electrospray) calcd for $C_{26}H_{43}NO_4NaSiS$: 516.2580, found 516.2572.

Data for **32c**: $[\alpha]^{21}_{D}$ = +27.9 (*c* 0.6, CHCl$_3$); IR (film) 2953, 2874, 1733, 1157 cm$^{-1}$; $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.45−0.46 (m, 4H), 0.50−0.63 (m, 2H), 0.85−0.99 (m, 17H), 1.05−1.11 (m, 1H), 1.61−1.68 (m, 1H), 1.76−1.84 (m, 1H), 1.93−2.11 (m, 4H), 2.42 (s, 3H), 2.67−2.81 (m, 1H), 3.67 (s, 3H), 3.77 (dd, $J$ = 4.7, 10.5, 1H), 3.93 (d, $J$ = 11.3, 1H), 7.27 (d, $J$ = 8.1, 2H), 7.72 (d, $J$ = 8.1, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 2.8, 7.7, 19.8, 20.5, 21.4, 24.6, 26.9, 29.8, 30.1, 45.1, 45.3, 46.9, 48.3, 51.6, 59.7, 127.1, 129.5, 138.9, 142.8, 175.7; MS (electrospray) *m*/*z* 516.2 (100%, [M + Na]$^+$). HRMS (electrospray) calcd for $C_{26}H_{43}NO_4NaSiS$: 516.2580, found 516.2589.

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**Supporting Information Available:** Experimental procedures, NMR spectra, and full characterization for all compounds, as well as CIF files and ORTEP diagrams for the X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.