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Total Synthesis of the Lycopodium Alkaloid Serratezomine A Using Free Radical-Mediated Vinyl Amination to Prepare a β-Stannyl Enamine Linchpin

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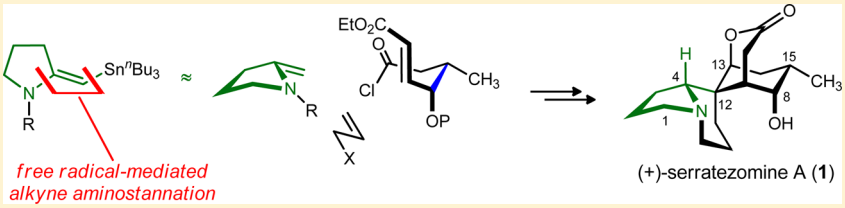
Supporting Information



ABSTRACT: Serratezomine A is a member of the structurally diverse class of compounds known as the *Lycopodium* alkaloids. The key supporting studies and successful total synthesis of serratezomine A are described in this account. Significant features of the synthesis include the first application of free radical mediated vinyl amination and Hwu's oxidative allylation in a total synthesis and an intramolecular lactonization via a transannular S_Ni reaction. Minimal use of protecting groups and the highly diastereoselective formation of a hindered, quaternary stereocenter using an umpolung allylation are also highlights from a strategy perspective. Observation of quaternary carbon epimerization via a *retro*-Mannich/Mannich sequence highlights the additional challenge presented by the axial alcohol at C8 in serratezomine A.

INTRODUCTION

Serratezomine A (**1**), a $C_{16}N$ alkaloid belonging to the fawcettimine class of *Lycopodium* alkaloids,[1,2] was isolated from the club moss *Lycopodium serratum* var. *serratum* in 2000 (Figure 1).[3] Serratezomine A exhibited moderate cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 9.7 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} >10 μg/mL) and demonstrated strong anticholinesterase activity. Of the *Lycopodium* alkaloids, huperzine A (**2**, Figure 1), a constituent alkaloid, has shown the most promising biological activity. It has been used for the treatment of neurodegenerative disorders relating to the neurotransmitter acetylcholine, including myasthenia gravis and Alzheimer's disease,[4−6] and is available as a dietary supplement to enhance memory.

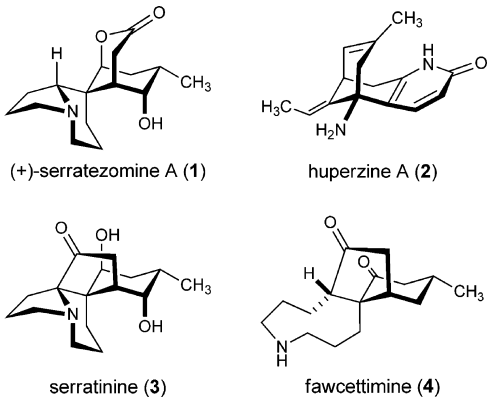


Figure 1. Serratezomine A (**1**) and representative *Lycopodium* alkaloids.

The complex framework of the *Lycopodium* alkaloids makes them challenging, yet attractive targets for total synthesis. Serratezomine A contains six contiguous stereocenters including a spirocyclic all-carbon center contained within a tetracyclic ring system. The structure of **1** was determined by ^{1}H and ^{13}C NMR, a combination of 2D NMR techniques, and from data obtained by the structurally similar serratinine (**3**).[3] In addition, serratinine (**3**) was converted to **1** via a biomimetic, one-pot modified Polonovski rearrangement.[7] The first total synthesis of **1** was recently completed by us,[8] and elegant syntheses of the structurally similar serratinine (**3**)[9,10] and fawcettimine (**4**)[11] have also been accomplished. Still other *Lycopodium* alkaloids have been the subject of recent publications.[12] In this report, our complete study leading to the successful preparation of (+)-serratezomine A through total chemical synthesis is described. The steric influence of the axial alcohol was evident in the discovery of an undesired

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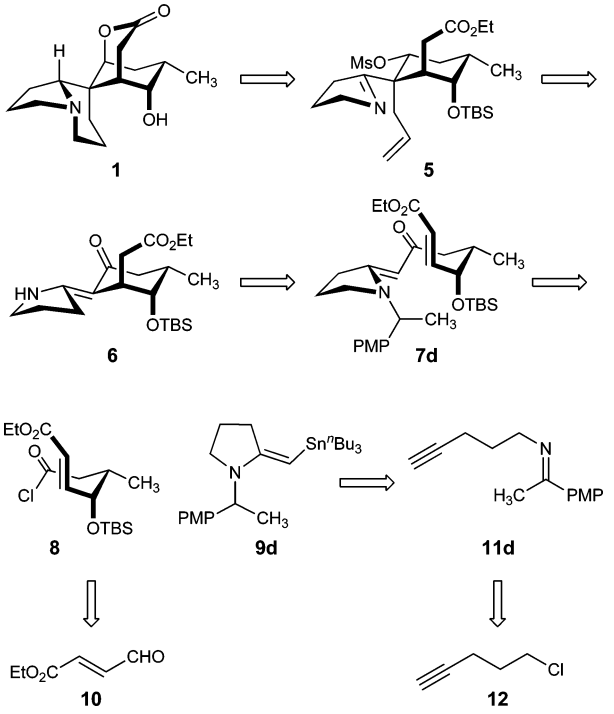
epimerization at the spirocyclic carbon, which was successfully overcome in the final synthetic route.

Our retrosynthetic approach to serratezomine A (**1**) is presented in Scheme 1. The first two disconnects involve the

Scheme 1. Retrosynthetic Analysis of 1

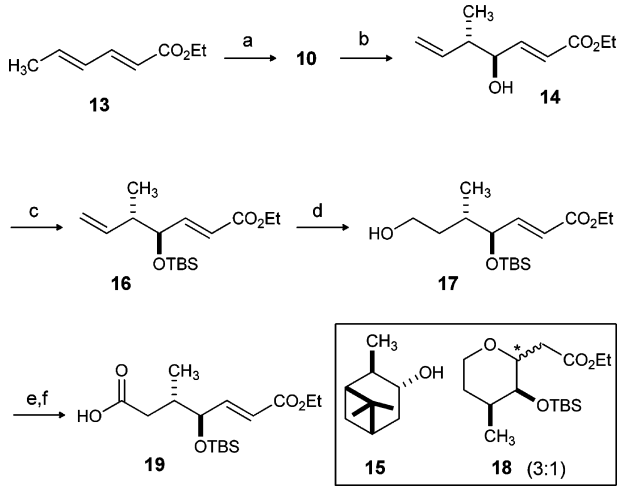


piperidine and lactone rings. The piperidine ring formation is evident after functionalization of the pendant alkene in **5** to provide a leaving group for imine cyclization and reduction to the bicyclic amine. The lactone ring is formed after saponification of the ester and displacement of the mesylate. Target **5** provides an intermediate that contains all of the carbons in the natural product. Installation of the allyl group was to be attempted through a diastereoselective allylation of vinylogous amide **6**. The cyclohexanone ring in **6** was anticipated to result from an intramolecular Michael addition of the vinylogous amide and α,β-unsaturated ester in **7d**. Selectivity in this step was projected to be the result of $A^{1,3}$-strain minimization[13] and favor an axial ethyl acetate substituent as depicted in **7d**. The *N*-protected vinylogous amide represents the convergent point in our synthesis. It was expected to be accessible via acylation of β-stannylenamine **9d** with acid chloride **8**. The β-stannylenamine was synthesized by methodology developed earlier by us, involving a nonconventional radical-mediated 5-*exo*-*trig* cyclization of an imine.[14,15] The required imine (**11d**) is accessible in three steps from the commercially available chloride **12** by a Gabriel amine synthesis. The acid chloride portion (**8**) was anticipated to be accessible from α,β-unsaturated aldehyde **10** using a Brown crotylation. The two stereocenters in **8** would be used to direct the formation of all remaining stereocenters in **1**.

RESULTS AND DISCUSSION

The synthesis began with selective ozonolysis of the terminal alkene in commercially available ethyl sorbate (**13**, Scheme 2).[16] The α,β-unsaturated aldehyde (**10**) was isolated after vacuum distillation in up to 93% yield.[17] Next, the homoallylic

Scheme 2. Synthesis of Carboxylic Acid 19[a]



[a](a) O_3, EtOH, −78 °C, then DMS, 93%: (b) (−)-Ipc-crotylborane, $BF_3{\cdot}OEt_2$, −60 °C, 7 d, then NaOOH, 79%, 93% *ee*, 11:1 *dr*; (c) TBSCl, imidazole, DMF, 95%; (d) 2-methyl-2-butene, $BH_3{\cdot}DMS$, THF, 0 °C, 4 h, then NaOOH, 82%; (e) Dess−Martin periodinane, CH_2Cl_2, 0 °C, 4 h, 97%; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene (95%).

alcohol was installed in the *anti*-configuration using a Brown crotylation. This reaction is especially difficult with unsaturated aldehydes and tends to provide lower yields and selectivities.[18] Fortunately, using a modification on multigram scale that included a large dry ice bath that could be maintained for an extended period, the desired product was formed with good enantioselectivity and yield (**14**, 93% ee, 79% yield). Careful temperature control was imperative to good stereoselection since considerable conversion could occur as the reaction mixture warmed during the quenching process. The structure of the main diastereomer was confirmed by formation of both (*R*)- and (*S*)-Mosher esters in which NMR analysis led to the determination of relative stereochemistry as depicted for alcohol **14**.[19] The majority of the terpene alcohol (**15**, a byproduct from the chiral auxiliary oxidation) could be fractionally distilled, and the crude reaction mixture containing the two alcohols (**14** and any remaining **15**) was subjected to TBS protection to afford the mixture of TBS ethers. The TBS group provided greater separation of the two products by column chromatography and allowed for the isolation of pure **16**. Using the optimized reaction conditions, the crotylation reaction could be performed on a 50 g scale to provide the silyl ether (**16**) in 75% yield over 2 steps.

After successful installation of the first two stereocenters, our attention focused on elaboration of the terminal alkene in **16**. Treatment with disiamylborane followed by oxidative work up afforded primary alcohol **17** in good yields (70−85%).[20] Subsequent oxidation of the primary alcohol **17** using Dess−Martin periodinane[21] gave the desired aldehyde in a quantitative yield, which then was carried through the Pinnick oxidation[22] to afford carboxylic acid **19**.

The stage was now set for the convergent coupling with a β-stannyl enamine linchpin. Starting from pentynyl chloride **12**, a Gabriel amine synthesis was utilized to form primary amine **20** in 85% yield (Scheme 3).[23] The protecting group on the amine was formed via transimination with benzophenone imine to form imine **11a**.[24] The protecting group on the nitrogen could be varied and is an important aspect for success of the free-

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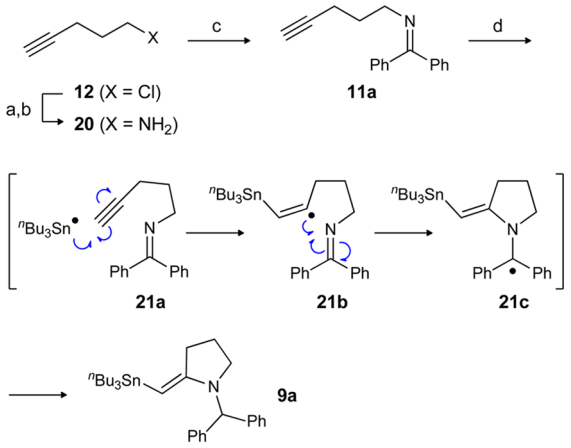
Scheme 3. Synthesis of the β-Stannyl Enamine Linchpin[a]



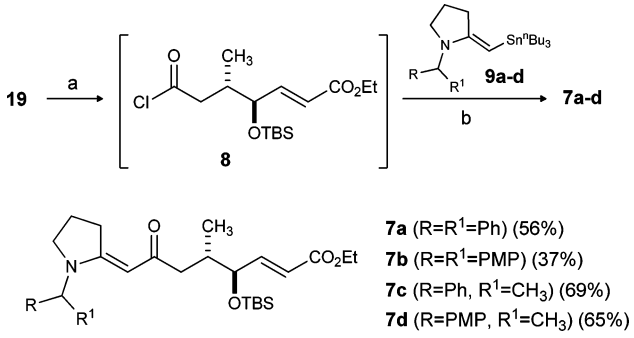
[a](a) phthalimide, DMF, 100%; (b) H_2NNH_2, MeOH, 85%; (c) benzophenone imine, 4 Å MS, CH_2Cl_2, 99%; (d) $^nBu_3SnH$, AIBN, C_6H_6, 90 °C, 70%.

radical mediated amination and future deprotection reaction (vide infra).

Free radical-mediated aminostannation was carried out using slow addition of $^nBu_3SnH$ and AIBN to a refluxing, degassed benzene solution of imine **11a** (Scheme 3).[14] The stannane radical adds to the terminal position of the alkyne (as in **21a**) to form the vinyl radical (**21b**). The 5-*exotrig* cyclization of the vinyl radical onto the azomethine nitrogen provides a stabilized tertiary carbon radical adjacent to two phenyl groups (**21c**).[25] This radical is quenched by $^nBu_3SnH$ to form β-stannylenamine **9a**, which is used in unpurified form for the subsequent coupling reaction with acid chloride **8**.

The acid chloride needed for the coupling was made by treating acid **19** with oxalyl chloride (Scheme 4). After removal

Scheme 4. Synthesis of *N*-Protected Vinylogous Amides[a]

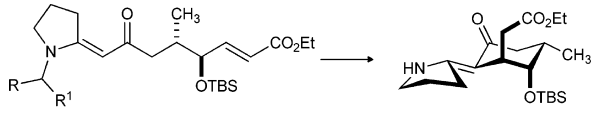


[a](a) oxalyl chloride, DMF, CH_2Cl_2, 0 °C; (b) **9a–d**, THF. PMP = *p*-$MeOC_6H_4$.

of volatile compounds, the crude acid chloride **8** was added to the β-stannyl enamine (**9a**), and the resulting oil was chromatographed to provide the coupled product (**7a**). Vinylogous amides (**7b**, **7c**, and **7d**), with different *N*-protecting groups, were synthesized utilizing the same protocol with β-stannyl enamines (**9b**, **9c**,[14c] and **9d**, respectively).

With vinylogous amides **7a–d** in hand, the intramolecular conjugate addition was attempted (Table 1). Various methods were initially investigated to effect the deprotection/cyclization using diphenylmethyl (DPM)-protected **7a**, such as complex-

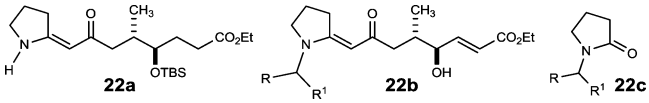
Table 1. Deprotection and Cyclization Attempts of Vinylogous Amides[a]



7a R=R1=Ph **7c** R=Ph, R1=CH3
7b R=R1=PMP **7d** R=PMP, R1=CH3

entry	vinylogous amide	reagent(s)	result
1	**7a**	NH_3CO_2H, Pd/C	**22a**[a]
2	**7a**	HCO_2H, Pd/C	NR
3	**7a**	Et_3SiH, TFA	NR
4	**7a**	Et_3SiH, TFA, PhSH	**22b**
5	**7a**	EtSH, $AlBr_3$ (30 equiv)	**22b**
6	**7a**	BCl_3	NR
7	**7a**	BBr_3	NR
8	**7a**	BBr_3 (5 equiv)	**22b**
9	**7a**	DDQ	**22c**
10	**7b**	DDQ	**22c**
11	**7b**	CAN	$(PMP)_2CO$[b]
12	**7b**	DDQ (pH = 7)	**22c**
13	**7b**	80% AcOH	**22b**
14	**7b**	EtSH, $AlBr_3$ (30 equiv)	**22b**
15	**7b**	KO^{t}Bu, DMSO	NR
16	**7b**	Li, NH_3	NR
17	**7c**	KO^{t}Bu, DMSO	NR
18	**7c**	EtSH, $AlBr_3$ (30 equiv)	**22b**
19	**7c**	EtSH, $AlBr_3$ (0.2 equiv)	NR
20	**7c**	Li, NH_3	NR
21	**7d**	DDQ	**22c**
22	**7d**	**CAN**	**6**
23	**7d**	$Ph_3C^+BF_4^-$	NR

[a]Deprotection only occurred post-reduction of the α,β-unsaturated system, as observed by crude ^1H NMR. [b]This indicates that the expected ketone from deprotection was isolated. However, the corresponding enamine/cyclized product was not isolated.



ation with Lewis acids with or without hydride reducing agents (entries 3–8) and metal-catalyzed reduction (entries 1–2).[19b] These reactions either did not occur or caused deprotection of the TBS group (to form **22b**). Oxidative removal of the *N*-protecting group using DDQ led to cleavage of the vinylogous amide to form lactam **22c** (entry 9). Oxidative deprotection methods attempted with the other vinylogous amides (**7b–7d**) also resulted in lactam **22c** (entries 10, 12, 21). Using CAN instead of DDQ provided the most interesting results with both **7b** (entry 11) and **7d** (entry 22). In both cases, the *N*-deprotection was successful and the ketone byproduct was observed (bis(PMP) ketone in entry 11 and PMP-CH_3 ketone in entry 22), but none of the deprotected product could be isolated (**22a**). Fortunately, using CAN with substrate **7d** (entry 22) provided the desired, cyclized product (**6**).

Only one diastereomer of the product (**6**) was observed, and this was expected on the basis of examination of the interactions within the transition state (Scheme 5). Developing $A^{1,3}$-strain between the large ethyl acetate substituent and the nitrogen protecting group in pretransition state assembly **23a** would disfavor the ethyl ester substituent in the equatorial

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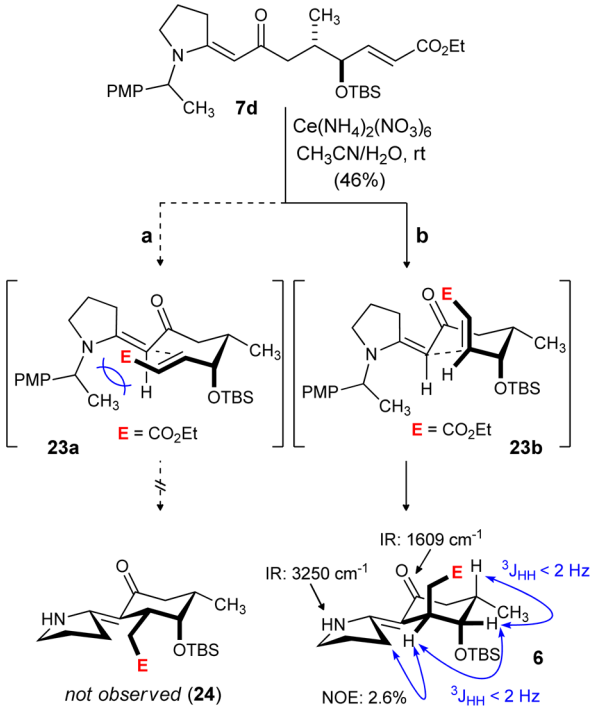
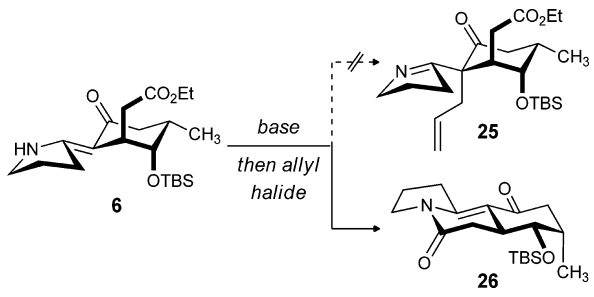
Scheme 5. Transition State Analysis of the Oxidative Deprotection and Michael Addition



position. Alternatively, pretransition state **23b** containing the axial ester would minimize this strain between the ester and the pyrrolidine ring and also between the vinyl hydrogen and large OTBS group. NOE studies were performed on the isolated product (**6**) to confirm the stereochemistry of the ester side chain as well as those created by the Brown crotylation. The vinylogous amide was established as *Z* on the basis of an NOE correlation between the equatorial hydrogen and a methylene of the pyrrolidine ring. Furthermore, the chair conformation of the cyclohexanone ring in solution was determined on the basis of coupling constant analysis. Under optimal conditions, the desired vinylogous amide could be isolated in up to 46% yield.

The next desired step was the installation of an allyl group, which would provide the three carbons in the piperidine ring of serratezomine A. However, exposure of vinylogous amide **6** to a variety of bases (LDA, KO^{t}Bu, KHMDS, ^{n}BuLi) and allyl halides did not provide any of the desired substrate (**25**, Scheme 6). Under all conditions, either starting material was recovered or a new product was formed containing a strong UV active π-system and led to assignment of the new product as vinylogous imide **26**. The reaction gave the highest yield when

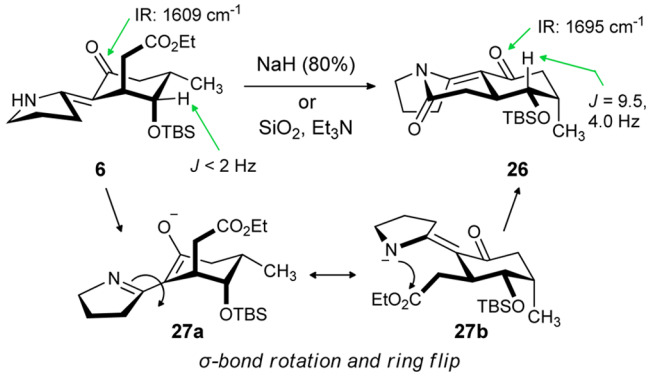
Scheme 6. Formation of a New Tricyclic Backbone (26)



using NaH and THF (80% yield) but can also occur simply by chromatography of **6** on Et_3N-treated silica gel.

A plausible mechanism for formation of imide **26** is outlined in Scheme 7. Deprotonation of the acidic pyrrolidine nitrogen

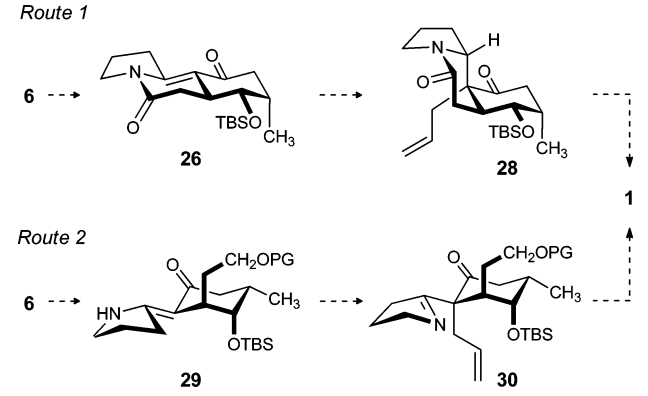
Scheme 7. Mechanism of the Base-Mediated Cyclization



in vinylogous amide **6** would lead to enolate **27a**. Rotation about the C−C σ-bond, nucleophilic attack by the vinylogous amide on the ester, and a cyclohexanone ring flip leads to **27b**. This ring flip locates the nitrogen in proximity to the ester side chain allowing for cyclization to form imide **26**. The fact that the transformation occurs on SiO_2 treated with Et_3N suggests the importance of base to enhance the nucleophilicity of the nitrogen N−H.

While this reaction course was unplanned, imide **26** appeared to be a viable intermediate to serratezomine A (**1**). Imide **26** was more stable over time, compared to **6**, and provided a rigid, tricyclic structure that might also be advanced to serratezomine A. A comparison of the two routes is shown in Scheme 8 (new

Scheme 8. Evaluation of a Second Approach to 1



= route 1, original = route 2).[26] For route 1, a reductive allylation (e.g., dissolving metal reduction) of vinylogous imide **26** would furnish **28**. The amide bond could act as a protecting group for the nitrogen until cyclization to form the piperidine ring was necessary, at which time the amide would be solvolyzed. Alternatively, if route 2 using vinylogous amide **6** was applied, then the ester functionality would have to be reduced prior to allylation to prevent imide formation (as in **29**). With **29** in hand, allylation would provide **30**. Both routes address the installation of the congested quaternary carbon, which we anticipated would be among one of the most challenging aspects of the synthesis, unusually so for

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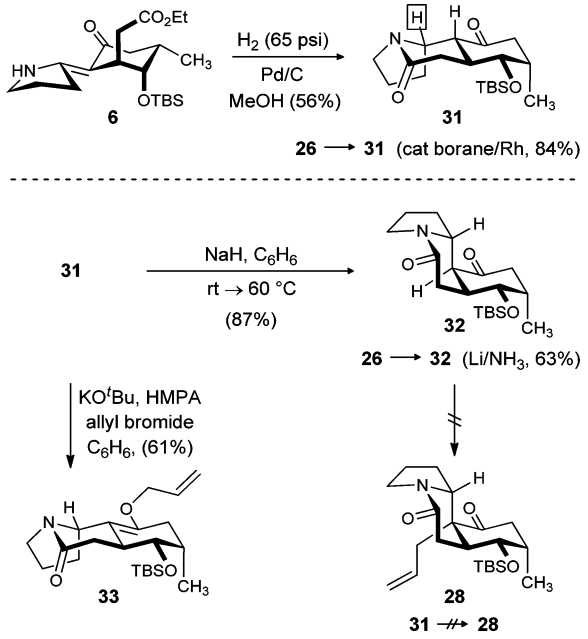
serratezomine A relative to other *Lycopodium* alkaloids because of its axial alcohol at C8. During the early studies investigating route 2, any reagents used to effect ester reduction still proved too basic and instead caused cyclization to imide **26**. At that point, the decision was made to investigate route 1.

Claisen Approach to Establish the C12 Quaternary Stereocenter (Route 1). To progress forward with this route, an allyl group would need to be installed adjacent to the ketone, as in **28**. Alkene reduction of **26** and a subsequent allylation provided a feasible sequence that might be adapted to a one step process.[27] Alkene reduction was achieved using metal-catalyzed hydrogenation on either vinylogous amide **6** or imide **26** (Scheme 9). Hydrogenation of **6** over Pd/C provided a 56%

Scheme 9. Formation and Reactions of the Tricyclic Backbone

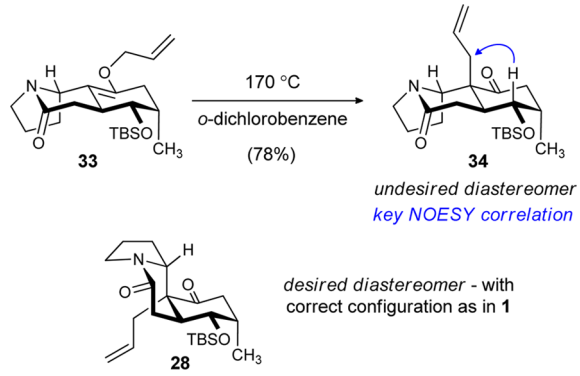


yield of ketone **31**, while PtO_2 provided over-reduction of the ketone as well (to form the α-OH, not shown).[28] Alternatively, imide **26** could be reduced using catecholborane in the presence of Wilkinson's catalyst to form ketone **31**.[29] Gratifyingly, the pyrrolidine stereocenter in both reductions was set in the correct orientation as is required in serratezomine A, indicating that substrate control provided the needed configuration.[30]

The stereocenter of the hydrogen adjacent to the ketone in **31**, however, is opposite to that of the desired allyl group (as in **28**). Epimerization was possible in the presence of bases that established thermodynamic conditions, such as NaH or ^{t}BuOK, to provide the ketone epimer with a *cis*-orientation of the 6,6-ring system (**32**, Scheme 9). Epimer **32** could also be formed in one step using a solution of lithium in NH_3 (**26** → **32**). If allylation could occur from the same face as protonation (see **28**), then successful installation of the quaternary center would be achieved. However, attempts to capture the enolate with allyl halides and a variety of bases did not result in any *C*-allylation (**28**) starting from either ketone epimer (**31** or **32**). Small amounts of *O*-allylated product **33** were isolated though and could be enhanced using KO^{t}Bu and HMPA (61% yield). Allyl vinyl ether **33** is significant since it could potentially be converted to the desired allylation product (**28**) via a Claisen rearrangement.

Pursuing this course, ether **33** was heated to 170 °C in a sealed tube. While the reaction was successful, it provided the undesired allyl epimer with the *trans*-decalone ring system (**34**, Scheme 10). The key NOESY correlation used in assigning the

Scheme 10. Claisen Rearrangement of 33



configuration was the 1,3-diaxial interaction between the geminal hydrogen to the OTBS group and one of the hydrogens of the methylene carbon in the allyl group. Modeling studies using Pcmodel showed that while the energy difference between non-allylated *trans*-decalone **31** and *cis*-**32** was relatively small (0.13 kcal/mol), the difference between allylated *trans*-decalone **34** and *cis*-**28** is much greater (2.4 kcal/mol) with *trans*-**34** being favored. Inspection of the bond angles in each 6-membered ring showed that the cyclohexanone ring suffered the most torsional strain in *cis*-decalone **28** due to the allyl group. This would explain why capture of a proton is possible to form the *cis*-decalone (**32**) but allylation in this same manner was never observed (**28**). It appeared that substrate control would not be easily overcome to obtain the desired allylation product. This realization encouraged us to further consider route 2 involving reduction of the ester to prevent cyclization to form imide **26** (see Scheme 8 for comparison of the two routes).

Oxidative Allylation Approach to Establish the Quaternary Stereocenter at C12 (Route 2). To explore route 2, the ester in **6** would need to be reduced to prevent the cyclization to the imide. As mentioned, many reducing agents were also sufficiently basic, causing cyclization to imide **26** (even $NaBH_4/CeCl_3$). The key reducing agent was eventually identified as Red-Al in toluene. It allowed reduction of the ester to form **35**, which was then protected as pivalate **36** in good yield (Scheme 11).

Different allylation reaction conditions were then attempted to install the three carbon chain necessary to form the piperidine ring (**36** → **37**, Scheme 11). These attempts focused on various base-mediated alkylation reactions but were not successful despite the possibility of *N*, *C*, or *O*-alkylation. Even metal-catalyzed hydrogenation, which worked well with imide **26**, did not work to provide any alkene reduction (in which an allyl group would be added in a second step). Unreacted starting material was isolated in all cases. Interestingly, if the allyl halide was exposed to Ag(I) salts, small amounts of allylated products were observed, which indicates that the vinylogous amide is inherently nucleophilic. An attempt to capitalize on this behavior was tested via exposure of **36** to two

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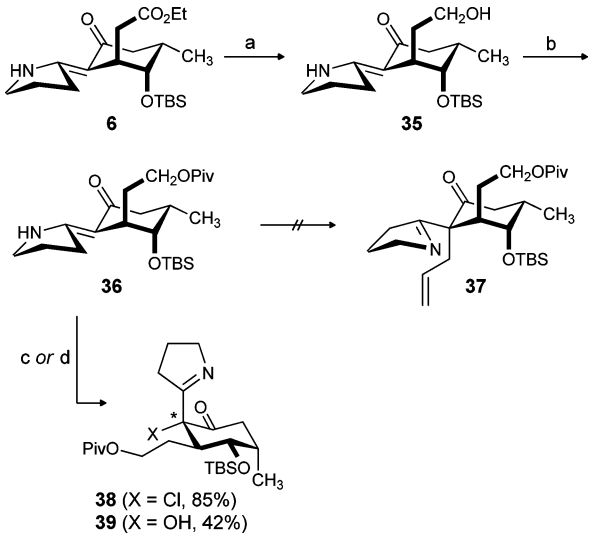
Scheme 11. Ester Reduction and Alkene Functionalization[a]



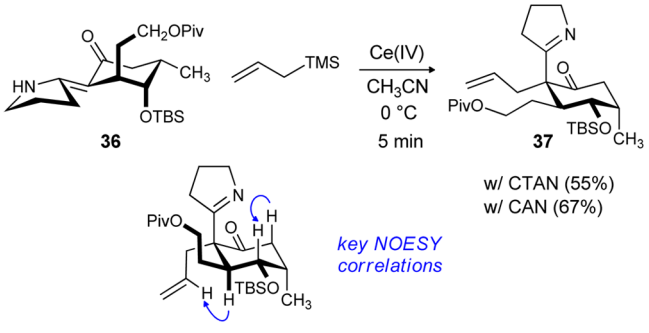
[a](a) Red-Al, toluene, 0 °C to rt, 81%; (b) pivalic anhydride, Et_3N, DMAP, CH_2Cl_2, rt, 40 h, 93%; (c) NCS, CH_2Cl_2, 15 min, 85% (**38a**); (d) MCPBA, CH_2Cl_2, rt, 30 min, 42% (**38b**, 63% brsm). *Stereocenter not confirmed.

oxidants, NCS[31] and MCPBA, providing the α-chloro ketimine (**38**)[32] and α-hydroxy ketimine (**39**), respectively.[33]

Both **38** and **39** were reasonable substrates to allow introduction of an allyl group by reductive enolate formation.[34] However, exposure of either compound to SmI_2 and allylbromide provided intractable mixtures. The use of either $Fe(acac)_3$[35] or HMPA[36] provided a cleaner reaction, but no allylated product (**37**) was observed and only reduced vinylogous amide **36** was isolated. This demonstrates that the α-carbon-heteroatom bond was reductively cleaved, but protonation followed rather than allylation.

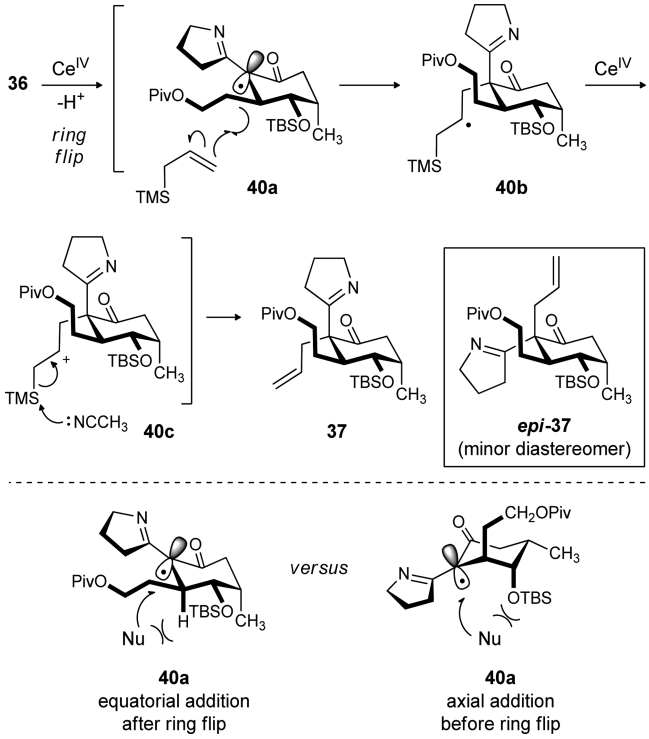
The insight gained from exposure of **36** to oxidants led us to the successful work from the Flowers' group utilizing a cerium-mediated oxidative allylation of vinylogous amides.[37] Their research used a more soluble source of Ce(IV) known as CTAN[38] ($Ce(NBu_4)_2(NO_3)_6$) along with allyl silane as the source of the three carbon chain. Initial allylation attempts using CTAN, allyl silane, and vinylogous amide **36** furnished a *C*-allyl product in only 20% yield. However, 2D NMR analysis indicated the product was indeed the desired diastereomer (**37**, Scheme 12). Optimization included increasing the amount of allyl silane to 2 equiv (45% yield) and degassing the CH_3CN solvent (55% yield). Degassing of CH_3CN likely improved the reaction because oxygen can react with a radical intermediate, leading to oxidation byproducts (one of which was identified as α-hydroxyketone **39**). A further improvement was made by switching CTAN to CAN, which gave the highest yields (58–67%) and diastereoselection (23:1, assigned on the basis of isolation of the minor diastereomer on large scale, *epi*-**37**).

Scheme 12. Oxidative Allylation Using Cerium(IV)



The mechanism of the oxidative allylation is believed to involve single electron oxidation of the vinylogous amide (**36**) by cerium(IV), forming radical cation **40a** (Scheme 13).[37a,39]

Scheme 13. Plausible Mechanism of the Cerium-Mediated Allylation



The radical cation then undergoes attack by the nucleophilic allyl silane, forming the quaternary center and a new secondary alkyl radical (**40b**). A second equivalent of Ce(IV) is then needed to oxidize the radical to a cation (**40c**). It was then proposed by the Flowers group that the nucleophilic solvent, CH_3CN, plays a role in displacement of the trimethylsilyl group, providing the terminal alkene in **37**.[37a]

The high diastereoselectivity observed during the allylation is surprising (Scheme 13). It is likely that the cyclohexanone ring flip occurs as soon as the radical cation is formed since the π-bond of the alkene in **36** is broken, resulting in the release of $A^{1,3}$-strain and allowing the large OTBS group to be equatorial. The main interactions an incoming allyl silane nucleophile would experience from the bottom face are a 1,2-interaction with an axial hydrogen in **40a**. From the top face, there would be two 1,3-diaxial interactions with hydrogen and a 1,2-interaction with the side chain in **40a**.

The all-carbon quaternary stereocenter was now established, and all carbons required in serratezomine A were in place. Our attention was then turned to accessing the piperidine ring by functionalizing the terminal alkene via hydroboration. To prevent selectivity issues, the ketone had to be reduced prior to hydroboration in which the β-alcohol was required as in the natural product. Reduction with $NaBH_4$ in THF at room

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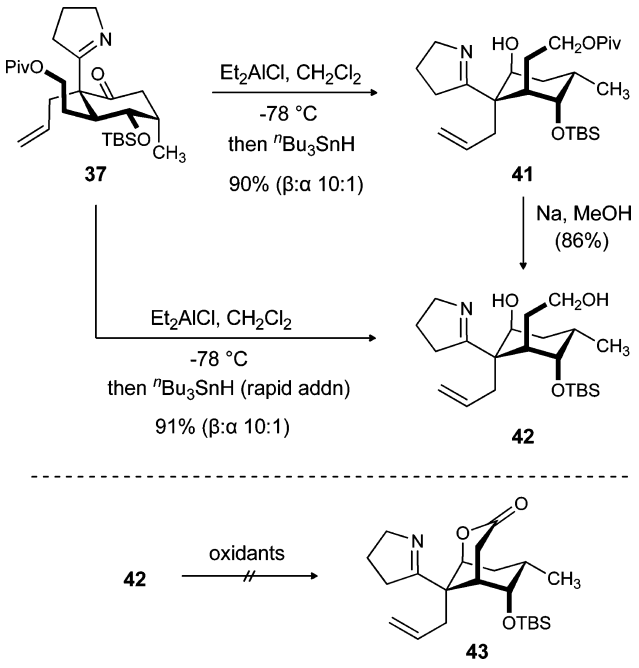
temperature provided more of the undesired α-alcohol in yields ranging from 45 to 58% (not shown), likely because of an imine-directed borane delivery to the top face. To direct hydride addition to the opposite face, chelating conditions were used to engage the imine nitrogen and ketone since this would effectively block the top face. Gratifyingly, using a bidentate Lewis acid (Et_2AlCl) and $^nBu_3SnH$ as a reducing agent afforded the desired β-alcohol in good yield and moderate diastereoselectivity (**41**, Scheme 14).[40] Rapid addition of $^nBu_3SnH$

Scheme 14. Installation of the β-Alcohol

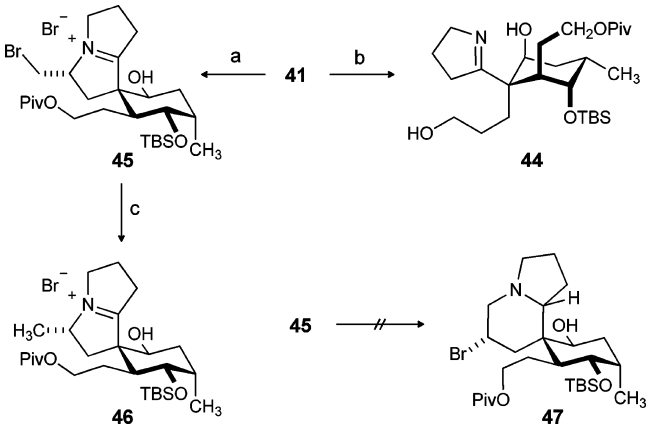


resulted in the simultaneous reduction of the ester to afford the diol (**42**) with similar diastereoselectivity. A two-step reduction/deprotection to diol **42** was also developed using the chelating reduction in the first step and then sodium metal in MeOH for the second step. The two-step protocol was advantageous since the alcohol diastereomers (α and β-**41**) could be separated by column chromatography after the reduction, whereas it was not straightforward to separate the diol diastereomers (α and β-**42**).

Having β-diol **42** in hand led to us to attempt lactone ring formation, which would be followed by piperidine ring construction in separate synthetic operations. However, subjecting diol **42** to a variety of oxidation conditions including Ag_2CO_3/C_6H_6 (Fetizon oxidation),[41] Dess–Martin, PCC, and TEMPO proved fruitless, as no oxidation products were observed (**43**, Scheme 14). This was surprising since diol **42** is in the correct chair conformation to undergo lactonization. Our suspicion was that the nucleophilic imine nitrogen might be involved in the formation of side products that result once the primary alcohol in **42** is oxidized.[42,43]

Our attention was again focused on construction of the piperidine ring before the lactone ring. This would functionalize the nitrogen and allow us to proceed with the synthesis. Treatment of the alkene in **41** with either BH_3·THF or BH_3·DMS followed by oxidative workup provided the desired primary alcohol **44**, but in low yields (23–35% with up to 25% recovered **41**, Scheme 15). A survey of boron reagents, including 9-BBN, disiamylborane, and catecholborane with

Scheme 15. Alkene Conversions of 41[a]

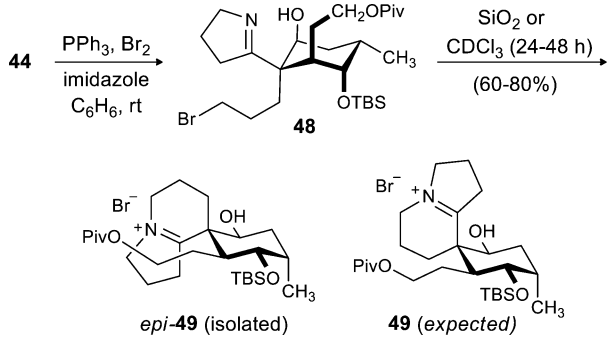


[a](a) NBS, CH_2Cl_2, rt, 51%; (b) BH_3·DMS, THF, 0 °C, then NaOH, H_2O_2, H_2O, 35%; (c) $^nBu_3SnH$, AIBN, 85 °C, 59%.

Wilkinson's catalyst [$RhCl(PPh_3)_3$], did not provide the desired hydroboration product (**44**). Increasing the borane amount, reaction time, or temperature proved to be even more detrimental to the yield. We thought that the imine may be binding irreversibly to the borane, so Lewis acids were added along with the borane. The primary alcohol was still formed but without any improvement in the yield. Therefore, an alternative approach was used with electrophilic bromination to form the piperidine ring directly via a bromonium intermediate and 6-*endo* cyclization (as in **47**). Instead a 5-*exo* cyclization was observed in the presence of NBS in either CH_2Cl_2 or MeOH to form **45**.[44] Efforts to reduce the iminium ion with $^nBu_3SnH$ or $NaBH_3CN$ were unsuccessful but did reduce the primary bromide in the former case. There is literature precedence for conversion of the 5-*exo* to 6-*endo* product via an intermediate aziridium ion (**45** → **47**), but attempts to implement this approach were met with failure, likely due to the inability to reduce the iminium ion in **45**.[45]

Despite low yields during the hydroboration, alcohol **41** provided our best access to serratezomine A and was carried forward to form the piperidine ring. Conversion of the alcohol to the primary bromide was successful using Br_2 and PPh_3 (**48**, Scheme 16). After column chromatography to isolate bromide **48**, a second compound of low R_f was also observed that was not initially seen by ^1H NMR analysis of the crude reaction mixture. This compound would form by allowing a pure sample of bromide **48** to stand at room temperature in $CDCl_3$. Surprisingly, the compound was not only cyclized to form the

Scheme 16. Unexpected Epimerization



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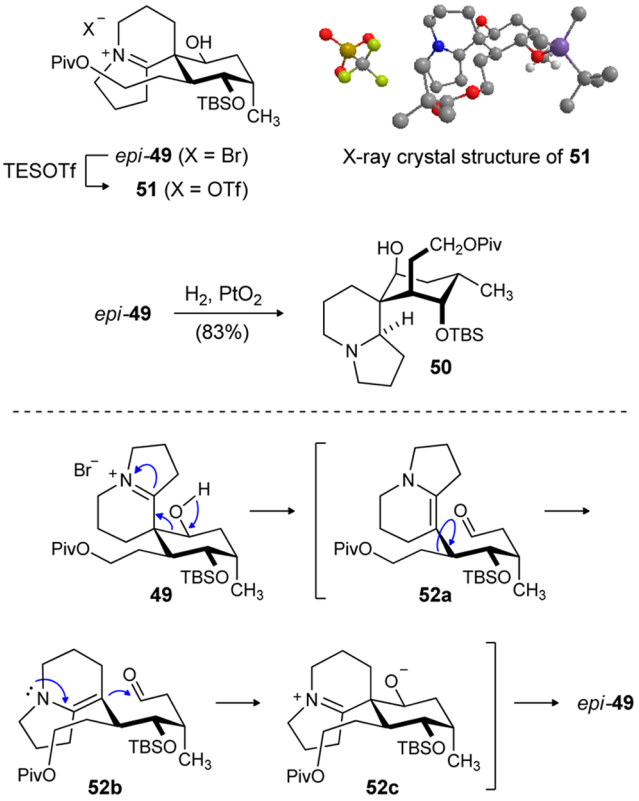
piperidinium ring, but was also epimeric at the quaternary center and was identified as *epi*-**49** instead of the expected product (**49**).

To ascertain the structure of *epi*-**49**, it was subjected to a PtO_2-catalyzed reduction to provide the amine as a single diastereomer (**50**, Scheme 17). At this point 2D NMR techniques more clearly highlighted the correlations with the new methine CH adjacent to the nitrogen.[46] Fortunately, a crystal structure of *epi*-**49** was also obtained by exchange of the bromide counterion to a triflate (using TESOTf, **51**). The crystal structure unambiguously confirmed the epimerization and solidified our previous stereochemical assignments. The epimerization likely occurs through an enamine *retro*-aldol reaction of the expected cyclized product (**49**) (as in Scheme 17).[47] First, a ring-opening of **49** forms the enamine-aldehyde (**52a**). Rotation about the C−C σ-bond in **52a** provides intermediate **52b** in which enamine addition to the aldehyde to reclose the ring would give **52c**. After protonation of the enolate, *epi*-**49** would result with an overall epimerization of the spirocyclic carbon.

Scheme 17. Studies to Support Epimerization Conclusion



The driving force to epimerize is less apparent. The isomerization may relieve some strain derived from the interaction of the methylene carbon in the pyrrolidine ring with the two axial hydrogens on the cyclohexanol ring in **49**. The epimerized product (*epi*-**49**) allows the pyrrolidine ring to be further away and thus minimizes the steric strain. The epimerization was an unfortunate finding so late in the synthesis but seems to be favored on the basis of substrate control. Several routes were then devised to prevent epimerization: reduction of the imine (to prevent formation of an iminium ion upon cyclization), protection of the β-OH (to prevent opening of the cyclohexanone ring), and formation of the α-OH (as an alternative strategy). The latter two are discussed here.

Routes Investigated to Prevent Epimerization. Protection of β-alcohol **41** was unexpectedly complicated. While silylation was successful (TESOTf or TIPSOTf), the addition of a larger protecting group, along with the fact that four of the six substituents were axial, provided compounds with broad peaks by NMR analysis and unclear conformational preferences. An idea to tether the β-OH with the primary alcohol, using diol **42**, was also met with failure.[48] A crystal structure of diol **42** was obtained, which revealed that a hydrogen bond existed between the imine nitrogen and the secondary alcohol (Figure 2). This could explain the observed unreactivity of the β-alcohol toward protecting group reaction conditions.

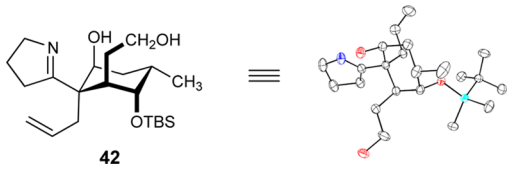
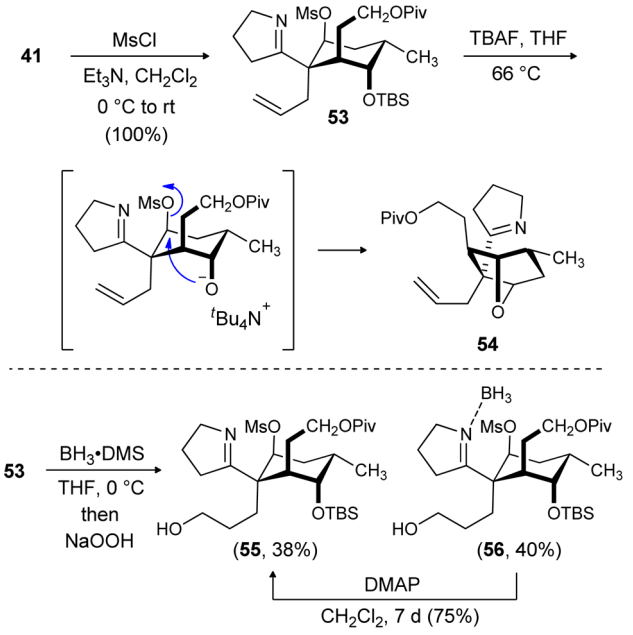


Figure 2. Crystal structure of diol **42**.

Fortunately, the sulfonation of the alcohol could be accomplished to form mesylate **53** in quantitative yield (Scheme 18). In an effort to increase the yield of the next step, hydroboration of the alkene, two tactics were pursued. The first was deprotection of the TBS group since it was speculated that the terminal alkene was sterically hindered by the large TBS group, thus leading to low yields of the primary alcohol. Treatment of **53** with TBAF at 66 °C provided an unexpected product, the bridged bicyclic ether (**54**), as a result of an intramolecular S_N2 displacement of the mesylate by the intermediate alkoxide formed from the TBS deprotection.

Scheme 18. Reactions of Mesylate 53



The second attempt to increase the yield of the hydroboration was to locate the mass balance. During chromatography, more polar fractions were present and accounted for

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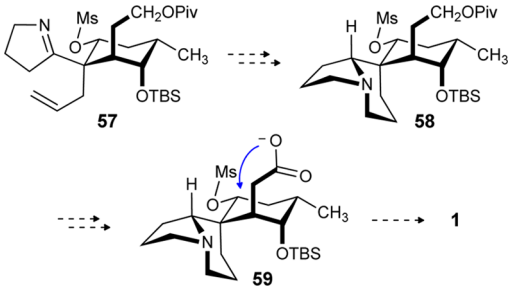
35−40% of the material. ^{1}H NMR analysis revealed a set of broad peaks different from the primary alcohol. Upon storage of this viscous oil for several days, the new compound converted to primary alcohol **55**. It was speculated that the broadness of the peaks may be a result of borane binding with the electron rich imine (as in **56**, Scheme 18). Furthermore, amine−borane complexes are known to be stable and isolable compounds at room temperature.[49,50] To test this hypothesis, a solution of the oil (presumed to be **56**) in CH_2Cl_2 was treated with an excess of DMAP for 7 days. DMAP, an electron rich amine, was expected to bind more strongly to borane than to the imine functionality, and thus would act as a borane scavenger. Indeed, purification of the resulting mixture afforded the pure primary alcohol (**55**). This study established the feasibility of alkene conversion to the terminal alcohol, but concerns related to sulfonate deprotection[51] and our inability to make forward progress with β-alcohol (**41**) led us to a new approach to serratezomine A, using the α-alcohol.

Originally, the β-alcohol was desired as an approach to lactone ring formation, but our numerous strategies were thwarted (vide supra). Since the alcohol was easily protected as the mesylate, it was envisioned that the α-mesylate could be used instead (**57**, Scheme 19).[52] Conversion of **57** to the

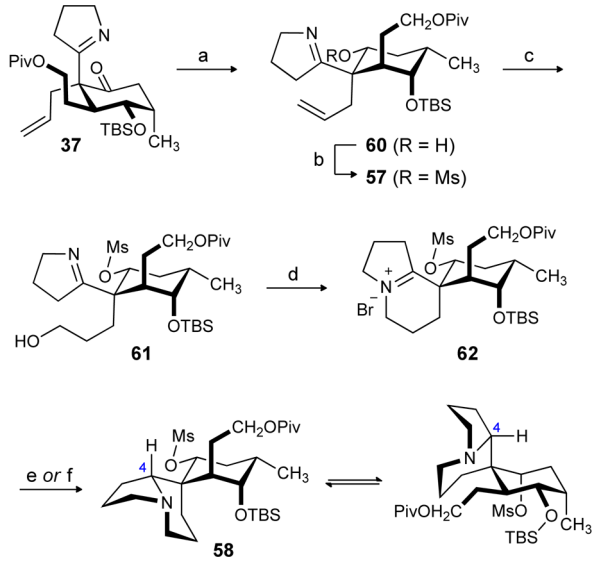
Scheme 19. Advancement of the α-Alcohol



piperidine ring could be accomplished in a similar manner as before to form **58**. Then a pivalate deprotection could be carried out, and the primary alcohol could be oxidized to a carboxylate (as in **59**). Cyclization of the carboxylate could occur via an S_Ni displacement of the mesylate to form the lactone ring, leaving only a TBS deprotection to complete the synthesis of **1**.

Advancement of the α-Alcohol As a New Strategy. To form the desired alcohol, ketone **37** was treated with $NaBH_4$ in THF to provide the α-alcohol (**60**, >23:1 dr), which was then protected as the mesylate in excellent yield (**57**, Scheme 20). The mesylate was subjected to the hydroboration conditions, and the resulting crude oil was treated as before with DMAP. Upon purification, the desired primary alcohol (**61**) was isolated. The alcohol was again treated with Br_2 and PPh_3 to afford the primary bromide, which cyclized slowly upon standing to afford the iminium salt (**62**). Subsequent reduction of iminium **62** was investigated by utilizing both hydride reducing agents and metal-catalyzed hydrogenation. The latter case proved superior in providing the amine (**58**). The ^{1}H NMR peaks of **58** were uniformly broad, suggesting two interconverting chair conformations as shown. As a result, 2D NMR analysis to determine the facial selectivity of the reduction step could not be conducted. However, the presence of only one set of peaks by NMR strongly suggested the reduction was highly stereoselective to provide the desired

Scheme 20. Advancement of α-Alcohol 60[a]

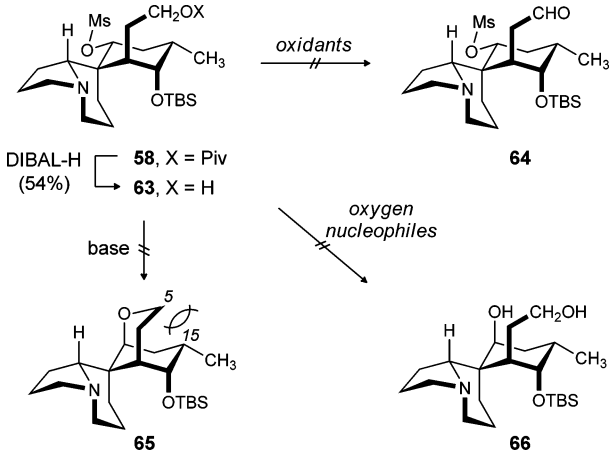


[a](a) $NaBH_4$, THF, 0 °C to rt, 55% (>23:1 dr); (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 98%; (c) BH_3·DMS, THF, 0 °C, then NaOOH, then DMAP, 7 d, 79%; (d) PPh_3, Br_2, imid., C_6H_6, rt, 76%; (e) PtO_2, H_2, 57%; (f) $NaBH_3CN$, 45%.

isomer, as a *syn*-pentane interaction between the pyrrolidine ring and ester side chain would highly disfavor the undesired isomer.[53]

With the piperidine ring in place (**58**), our attention turned toward oxidative adjustment of the primary alcohol to the carboxylate functionality to allow formation of the lactone ring. To accomplish this goal, deprotection of the pivalate protecting group was required. Treatment of **58** with DIBAL afforded the desired alcohol in good yield (**63**, Scheme 21). The alcohol was

Scheme 21. Attempts at Lactone Ring Formation



then subjected to a variety of oxidation conditions including Dess−Martin periodinane, Parikh−Doering,[54] and Swern oxidations. In all cases, decomposition of the starting material was observed, and no oxidation product could be isolated (**64**). It was believed that the lone pair of electrons on the nitrogen still exerted its effect by donating into the newly formed aldehyde, and that the resulting strained hemiaminal underwent a variety of fragmentation pathways, leading to the decomposition of **64**.[43]

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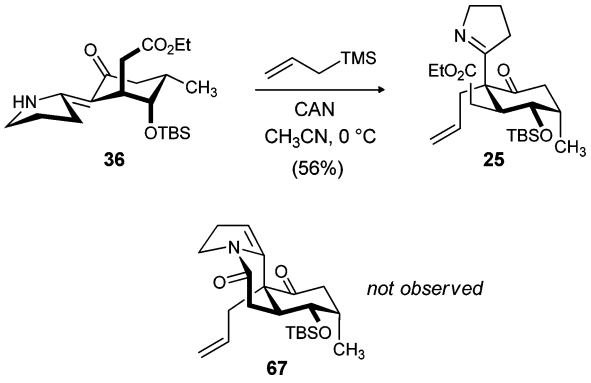
It was reasoned that serratezomine A might be accessed by a RuO_4-mediated oxidation of cyclic ether **65**.[55] The approach to **65** appeared straightforward via an intramolecular displacement of the mesylate by an alkoxide, generated by deprotonation of the primary alcohol. Surprisingly, alcohol **63** was inert to most basic reaction conditions including potassium *tert*-butoxide, sodium hydride, LiHMDS and LDA (Scheme 21). Exposure to ^{n}BuLi and ^{t}BuLi led to complete decomposition of the starting material. On the basis of the model studies, it was believed that the steric interactions between the two sp^3-hybridized carbons at C5 and C15 were too high to overcome in the cyclic ether (**65**). The S_N2 displacement of the mesylate by an exogenous oxygen nucleophile was also investigated to form diol **66**. It was hypothesized that the presence of the β-alcohol in diol **66** would lead to the formation of the desired lactone, via a lactol intermediate, using a Fetizon oxidation. The mesylate was treated with a variety of oxygen nucleophiles, including CsOAc,[56] $^n Bu_4N^{+-}NO_3$,[57] and KNO_2[58] at elevated temperatures (>100 °C) and for a long duration (10−20 h). However, the starting material was recovered in all cases. The inert nature of mesylate **63** could be attributed to its sterically hindered environment (both the adjacent quaternary center and the axial alcohol side chain).

Completion of the Synthesis and Reduction of the Overall Step Count. The use of an α-mesylate remained a promising strategy, and we encountered difficulties only during the late-stage oxidation in an attempt to form the lactone ring. This could be avoided if the pivaloate side chain was not reduced to the alcohol earlier in the synthesis (refer to Scheme 11). The ester reduction was used at the time to prevent formation of the tricyclic imide under basic conditions. With the cerium-mediated allylation developed, it was hypothesized that the product might withstand the nonbasic conditions and not undergo an undesired cyclization, thereby reducing the total step count by two.

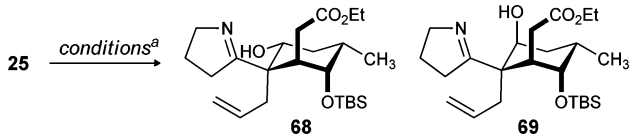
The CAN-mediated oxidative allylation of vinylogous amide **36** was carried out as before, but now with the ethyl ester in place to form **25** (Scheme 22). Fortunately, no cyclization of

Scheme 22. Cerium-Mediated Allylation with Ester Intact



the imine onto the pendant ester was observed in the product (**67**), and the high diastereoselectivity for the allylation was maintained. The ketone was then treated with an excess of $NaBH_4$ in THF to form the α-alcohol (**68**). The reaction was sluggish, but ultimately provided the desired alcohol in high diastereoselectivity (>20:1), albeit in low yields (**68**, Table 2, entry 1). In an attempt to increase the yield of the reduction step, a variety of reducing agents and reaction conditions were

Table 2. Optimization of Ketone Reduction



entry	reducing agent	solvent	time	α:β	conversion[b] (%)
1[c]	$NaBH_4$	THF	3 d	>20:1	30−45
2	$NaBH_4$	MeOH	1.5 h	0.8:1	100
3	**$NaBH_4$**	**1-propanol**	**1.5 h**	**3:1**	**100**
4[c]	$LiBH_4$	THF	2 d	>5:1	25
5	L-Selectride	THF	2 d		5
6[c]	L-Selectride	MeOH	2 d	4:1	25
7[c]	KBH_4	THF	1 d	4:1	15

[a]All reactions were performed at −3 °C and employed 1.4 equiv of reducing agent. [b]Conversions were measured using ^{1}H NMR of the crude reaction mixture. [c]Decomposition of the starting material was observed.

evaluated. Employing KBH_4, $LiBH_4$ and L-Selectride as reducing agents afforded α-alcohol **68** in high diastereoselectivity but with mainly decomposition of the starting material (entries 4−7). Gratifyingly, treatment of ketone **25** with $NaBH_4$ in MeOH led to complete conversion to α-alcohol **68**, but in low diastereoselectivity (entry 2). The solvent that ultimately provided the best combination of diastereoselectivity and yield was 1-propanol (entry 3). Performing the reaction at lower temperatures did not improve the diastereoselection in favor of the α-alcohol.[59]

With the ketone reduction in place, we turned toward formation of the piperidine ring. After some experimentation, we were pleased to find that the desired iminium salt could be formed in quantitative yield by mesylation of the primary alcohol, rather than formation of the corresponding bromide, followed by imine cyclization. After extended treatment of the reaction mixture with aqueous NH_4Cl, the crude NMR indicated complete conversion and cyclization to the iminium salt (**71**, Scheme 23). The crude reaction mixture was then treated with $NaBH_3CN$ to afford the tertiary amine (**72**) in quantitative yield.[60] The NMR peaks of **72** were uniformly broad, as in **58**, but indicated one diastereomer at C4 had formed, and this was carried onto the next step.

The final efforts were focused on installing the bridged lactone by a tandem saponification/intramolecular cyclization strategy (Scheme 23). Employing different reagents for the saponification including NaOTMS,[61] K_2CO_3,[62] and LiOH led to either decomposition or formation of an alkene by facile elimination of the mesylate (**74**). Success was finally realized by treating **72** with aqueous NaOH at 34 °C for 10 h to afford a 1.1:1 mixture of lactone **73** and alkene **74**, as indicated by NMR analysis. Purification attempts of the crude mixture were unsuccessful because of coelution of the products. Therefore, the crude reaction mixture was instead exposed to TBAF at 40 °C for 20 h, which led to a separable 3:2 mixture of (+)-serratezomine A (**1**) and the fused lactone (**75**, from lactonization of **74**). The spectral data (^{1}H NMR, ^{13}C NMR, and IR) and optical rotation of synthetic **1** (syn. $[\alpha]_D$ +9.5 (*c* 0.3, MeOH)), were in agreement with the reported values (nat. $[\alpha]_D$ +13.0 (*c* 0.5, MeOH)), confirming the structural and absolute stereochemical assignments of **1** (for the complete, total synthesis scheme of **1**, see Scheme 24).

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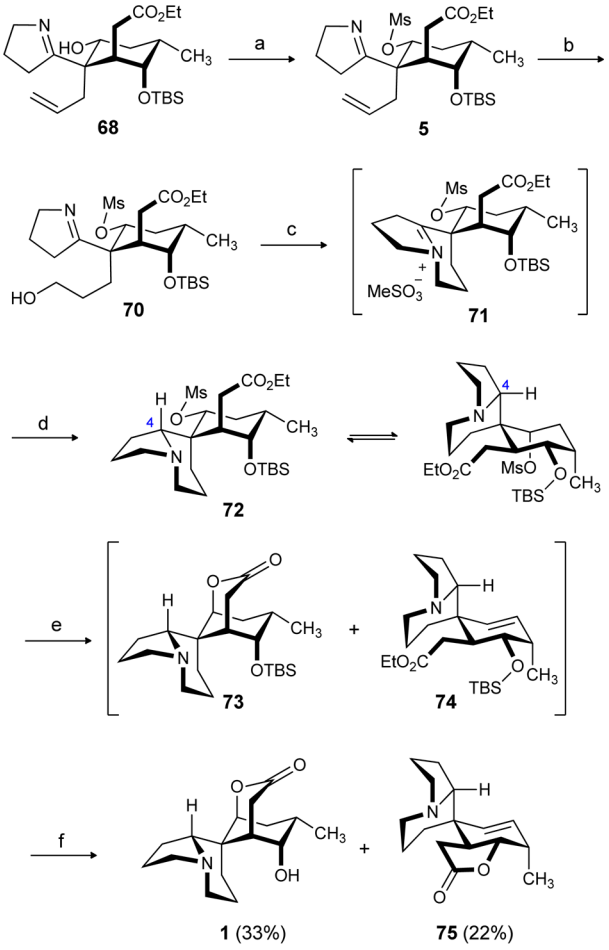
Scheme 23. Completion of the Synthesis[a]



[a](a) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 98%; (b) BH_3·DMS, THF, 0 °C, then NaOOH, then DMAP, CH_2Cl_2, 51% brsm; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, then satd aq NH_4Cl, rt, 20 h; (d) $NaBH_3CN$, MeOH, 98% over 2 steps; (e) NaOH, MeOH, 34 °C; (f) TBAF, THF, 40 °C, 33% over 2 steps.

CONCLUSIONS

In summary, the first total synthesis of (+)-serratezomine A was ultimately accomplished in 15 steps from a commercially available aldehyde. Notably, this is the only member of the *Lycopodium* alkaloids of the fawcettimine class bearing a substituent (OH) at C8 to be prepared other than the early synthesis of serratinine. The axial alcohol provided a powerful driving force for quaternary carbon epimerization when offered a pathway (**49** → *epi*-**49**). Fortunately, this challenge was overcome without sacrificing brevity in the current synthesis but did require several investigational lines to probe the reactivity inherent to this crowded system. Additional salient features of this synthesis include the following: (a) application of a free radical-mediated vinyl amination to construct the pyrrolidine ring; (b) a highly stereoselective intramolecular Michael addition to construct the cyclohexane ring; (c) the use of an oxidative allylation promoted by cerium(IV) to establish the all carbon quaternary stereocenter with the proper configuration; (d) a tandem saponification/intramolecular S_Ni cyclization to provide the bridged lactone; and (e) minimal use of protecting groups. Access to the β-stannyl enamine was particularly enabling, as it provided a platform for the convergent assembly of each unit in a sequence of three steps.

EXPERIMENTAL SECTION

General Methods. All glassware used for reactions was flame-dried under a vacuum, and reactions were run under an inert atmosphere of nitrogen or argon. All reagents and solvents were commercial grade and purified prior to use when necessary. Diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), benzene (C_6H_6), and acetonitrile (CH_3CN) were dried by passage through a column of activated alumina as described by Grubbs.[63] Benzene was additionally passed through a column containing activated Q-5 reactant. All other solvents were distilled over calcium hydride before use or are otherwise indicated differently. All organic layers collected from extractions were dried over $MgSO_4$ unless otherwise indicated. Reagents were used from the bottle unless otherwise noted within the experimental details. Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates, and flash chromatography utilized 230−400 mesh silica. Products were visualized using UV light and either ceric ammonium molybdate, ninhydrin, *p*-anisaldehyde, potassium iodoplatinate, or potassium permanganate solutions. Melting points were recorded on a capillary melting point apparatus and are reported uncorrected. For FTIR, liquids and oils were analyzed as neat films on a NaCl plate (transmission), whereas solids were applied to a diamond plate (ATR) if a thin film could not be prepared, and data are reported in wavenumbers (cm^{-1}). NMR were acquired on either a 400, 500, or 600 MHz instrument. Chemical shifts are measured relative to the residual solvent peaks as an internal standard set to δ 7.26 and δ 77.1 for ^1H and ^{13}C, respectively. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q) or combinations thereof, while higher coupling patterns are written out explicitly. HRMS data was obtained either by chemical ionization (CI), electron ionization (EI), or electrospray ionization (ESI) using an ion trap or by matrix-assisted laser desorption/ionization (MALDI) in either positive and negative ion modes using TOF. Combustion data analyzing C, H, and N were performed on select compounds. Compounds **5**, **7d**, **14**, **16**, **25**, **68**, **69**, **70**, and **72** were reported in an earlier publication[8] as well as **9c** and **11c**.[14c]

(+)-Serratezomine A (1) and (1*S*,5*S*,6*S*,7*S*,8′*S*,8a′*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-methylhexahydro-1′*H*-2-oxaspiro-[bicyclo[3.3.1]nonane-9,8′-indolizin]-3-one (73). To a solution of ester **72** (13.2 mg, 25.5 μmol) in MeOH (600 μL) at 0 °C was added sodium hydroxide (220 μL, 0.1 M in H_2O). The reaction was stirred for 30 min before being warmed to 34 °C and stirred for another 10 h. The solvent was removed in vacuo, and the resulting residue was dissolved in CH_2Cl_2. The organic layer was washed once with H_2O and then satd aq NH_4Cl and dried, filtered, and concentrated to a yellow oil. The crude oil could be purified and was characterized as the TBS protected intermediate (**73**, see data below). Alternatively, the crude oil could be carried on directly by dissolving in THF (300 μL) and adding TBAF (63.8 μL, 1.0 M in THF). The reaction was stirred for 15 min before being warmed to 40 °C and stirred for another 20 h. The solvent was evaporated, and the resulting crude oil was subjected to mass directed LC purification (15% CH_3CN/0.1% TFA) to afford (+)-serratezomine A **1** as a white solid (2.4 mg, 33%): R_f = 0.22 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ +9.5 (*c* 0.3, MeOH); IR (film) 3423, 2920, 2850, 1720, 1463, 1200, 1134 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 4.32 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.81 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.77 (dd, *J* = 3.6, 3.6 Hz, 1H), 3.54 (ddd, *J* = 9.6, 9.6, 9.6 Hz, 1H), 3.36−3.34 (m, 1H), 3.28−3.25 (m, 1H), 3.14 (dd, *J* = 20.0, 8.0 Hz, 1H), 2.98 (ddd, *J* = 13.2, 13.2, 3.6 Hz, 1H), 2.83 (br d, *J* = 13.6 Hz, 1H), 2.62−2.61 (m, 1H), 2.46 (d, *J* = 20.0 Hz, 1H), 2.29−2.13 (m, 4H), 2.05−1.99 (m, 1H), 1.85−1.74 (m, 4H), 1.40 (ddd, *J* = 13.6, 13.6, 3.2 Hz, 1H), 1.01 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, MeOD) ppm 173.2, 83.5, 76.2, 66.7, 56.0, 48.7, 37.3, 37.1, 34.3, 34.2, 27.0, 23.6, 22.0, 20.6, 19.7, 17.3. Data for **73**: R_f = 0.35 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ +3.5 (*c* 0.5, MeOH); IR (film) 2927, 2855, 1738, 1672, 1196, 1039 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.18 (s, 1H), 3.75 (s, 1H), 3.57 (br d, *J* = 9.0, 1H), 3.48 (br d, *J* = 9.6, 1H), 3.37 (dd, *J* = 20.4, 7.8 Hz, 1H), 3.17 (br s, 1H), 2.87 (d, *J* = 13.8 Hz, 1H), 2.79 (br s, 1H), 2.72 (d, *J* = 14.4 Hz, 1H), 2.63 (d, *J* = 10.8 Hz, 1H), 2.37 (d, *J* = 20.4 Hz, 1H), 2.28−2.25 (m, 1H), 2.16−2.04 (m, 4H), 1.85−1.82 (m, 2H),

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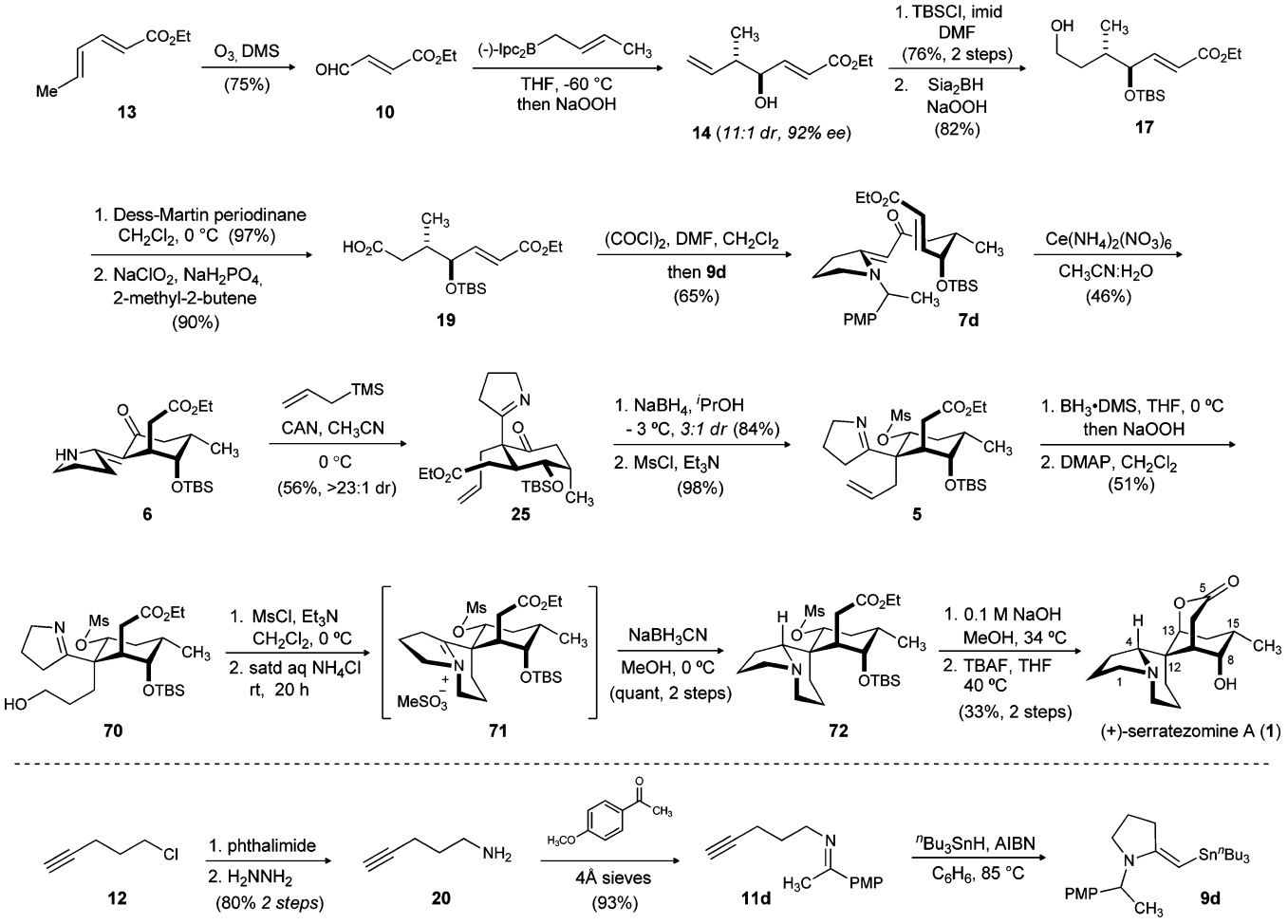
Scheme 24. Total Synthesis of 1



1.79−1.74 (m, 2H), 1.63−1.60 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.0, 81.3, 75.9, 64.0, 53.9, 46.6, 45.8, 35.7, 35.4, 33.4, 30.7, 26.0, 22.4, 21.0, 19.5, 18.0, 16.9, 14.1, −4.3, −5.2.

Ethyl 2-((1*S*,2*R*,3*S*,*Z*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-5-oxo-6-(pyrrolidin-2-ylidene)cyclohexyl)acetate (6). Ceric ammonium nitrate (16.8 g, 30.6 mmol) was added in one portion to **7d** (8.10 g, 15.3 mmol) in CH_3CN/H_2O (5:1, 765 mL) at rt. After 5 min, the reaction was quenched with satd aq $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed once with brine, and dried, filtered, and concentrated to an orange/brown oil. The crude oil was subsequently chromatographed (SiO_2, 10−32−38% ethyl acetate in hexanes) to provide **6** as a yellow/brown oil (2.8 g, 46%). This material was of sufficient purity to carry onto the next step, but to obtain an analytically pure compound for characterization, a second purification was performed (SiO_2, 35−50% ethyl acetate in hexanes) providing **6** as a dark yellow oil (2.5 g, 88% recovery, 40% after two purifications): R_f = 0.20 (50% EtOAc/hexanes); $[\alpha]_D^{21}$ + 50.0 (c 1.0, $CHCl_3$); IR (film) 2955, 2930, 2856, 1730, 1613, 1537 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (br s, 1H), 4.17 (dq, J = 10.9, 7.1 Hz, 1H), 4.10 (dq, J = 10.8, 7.1 Hz, 1H), 3.66 (br s, 1H), 3.59 (dt, J = 10.6, 6.9 Hz, 1H), 3.54 (dt, J = 10.6, 7.0 Hz, 1H), 2.95 (ddd, J = 9.4, 5.2, 2.8 Hz, 1H), 2.65−2.61 (m, 2H), 2.31−2.24 (m, 2H), 2.23 (dd, J = 17.0, 11.9 Hz, 1H), 2.18−2.05 (m, 2H), 2.05−1.96 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H), 0.81 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 194.7, 172.5, 167.8, 98.5, 72.6, 60.6, 47.7, 41.8, 41.0, 40.3, 30.6, 28.8, 25.9, 21.6, 18.7, 18.2, 14.4, −4.4, −4.8; HRMS (CI) Exact mass calcd for $C_{21}H_{37}NO_4Si$ $[M]^+$ 395.2486, found 395.2502. 1D NOE NMR studies to confirm the new stereocenter and to establish the alkene geometry are described in Supporting Information 2.

General Procedure for the Coupling Reaction to Prepare Vinylogous Amides (7a−d). The crude acid chloride (**8**, 1 equiv) was dissolved in THF (0.15 M), cooled to 0 °C, and then cannulated at a quick dropwise rate to a stirring solution of the β-stannyl enamine (**9a**−**9c** (1 equiv, small scale), **9d** (1.8 equiv, large scale)) in THF (0.14 M) also at 0 °C. After the addition was complete, the reaction was allowed to stir an additional 5 min at 0 °C and was then warmed to rt and stirred overnight (10−14 h). The solvent was removed in vacuo, and the crude oil was purified by column chromatography on SiO_2 (0−40% ethyl acetate in hexanes), and the fractions containing the product were resubmitted to a second column with 20−35% ethyl acetate in hexanes) to provide the coupled product (**7a**−**d**).

(2*E*,4*S*,5*S*,8*E*)-Ethyl 8-(1-Benzhydrylpyrrolidin-2-ylidene)-4-((*tert*-butyldimethylsilyl)oxy)-5-methyl-7-oxooct-2-enoate (7a). According to the general coupling procedure, **9a** was treated with **8** to provide the vinylogous amide as a brown viscous oil, which was chromatographed on SiO_2 (5−50% ethyl acetate in hexanes to provide **7a** as a pale orange oil (534 mg, 56% yield): R_f = 0.21, (30% EtOAc/hexanes); IR (film) 3063, 1638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 6H), 7.13 (m, 4H), 6.87 (dd, J = 15.6, 4.6 Hz, 1H), 5.99 (s, 1H), 5.93 (dd, J = 15.6, 1.8 Hz, 1H), 5.09 (s, 1H), 4.18 (m, 3H), 3.32 (t, J = 7.6 Hz, 2H), 3.09 (t, J = 7.3 Hz, 2H), 2.30 (dd, J = 14.5, 4.9 Hz, 1H), 2.19 (m, 1H), 2.00 (m, 1H), 1.93 (t, J = 7.3 Hz, 2H), 1.28 (t, J = 7.3 Hz, 3H), 0.89 (s, 9H), 0.81 (d, J = 6.7 Hz, 3H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 196.3, 166.8, 165.3, 149.5, 138.5, 128.9, 128.8, 128.7, 128.1, 121.2, 91.6, 75.3, 63.3, 60.5, 49.9, 46.0, 36.9, 33.7, 26.1, 21.3, 18.4, 15.7, 14.5, −4.4, −4.7; HRMS (CI) Exact mass calcd for $C_{34}H_{47}NO_4Si$ $[M]^+$, 561.3274. Found 561.3291.

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(2*E*,4*S*,5*S*,8*E*)-Ethyl 8-(1-(Bis(4-methoxyphenyl)methyl)-pyrrolidin-2-ylidene)-4-((*tert*-butyldimethylsilyl)oxy)-5-methyl-7-oxooct-2-enoate (7b). According to the general coupling procedure, **9b** was treated with **8** to provide the vinylogous amide as a brown viscous oil, which was chromatographed on SiO_2 (5−50% ethyl acetate in hexanes) to provide **7b** as an orange oil (241 mg, 28%): R_f = 0.11, (30% EtOAc/hexanes); IR (film) 2955, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, J = 8.6, 1.3 Hz, 4H), 6.88 (m, 5H), 5.94 (dd, J = 15.6, 1.6 Hz, 1H), 5.88 (s, 1H), 5.07 (s, 1H), 4.18 (m, 3H), 3.80 (s, 3H), 3.30 (dd, J = 7.5, 7.5 Hz, 2H), 3.06 (dd, J = 7.0, 7.0 Hz, 2H), 2.30 (dd, J = 14.5, 4.8 Hz, 1H), 2.20 (m, 1H), 2.01 (dd, J = 14.2, 9.1 Hz, 1H), 1.90 (ddd, J = 14.7, 7.5, 7.5 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.82 (d, J = 6.7 Hz, 3H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 196.2, 166.8, 165.3, 159.3, 149.6, 130.9, 130.8, 129.8, 129.7, 121.2, 114.1, 91.3, 75.3, 62.1, 60.5, 55.5, 49.7, 46.0, 36.9, 33.8, 26.1, 21.2, 18.4, 15.7, 14.5, −4.3, −4.7; HRMS (CI) Exact mass calcd for $C_{36}H_{51}NO_6Si$ $[M]^+$, 621.3486. Found 621.3476.

(2*E*,4*S*,5*S*,8*E*)-Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-5-methyl-7-oxo-8-(1-(1-phenylethyl)pyrrolidin-2-ylidene)oct-2-enoate (7c). According to the general coupling procedure, **9c** was treated with **8** to provide the vinylogous amide as a brown viscous oil, which was chromatographed on SiO_2 (5−50% ethyl acetate in hexanes) to provide **7c** as a pale orange oil (436 mg, 69%): R_f = 0.10 (30% EtOAc/hexanes); IR (film) 2955, 1718, 1544 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (unable to separate diastereomers) 7.35 (m, 2H), 7.28 (m, 1H), 7.22 (d, J = 7.3 Hz, 2H), 6.90 (m, 1H), 5.97 (ddd, J = 15.6, 4.8, 1.6, 1H), 5.17, (s, 1H), 4.95 (q, J = 7.0 Hz, 1H), 4.11−4.27 (m, 3H), 3.32 (m, 2H), 3.18 (m, 1H), 3.08 (m, 1H), 2.36 (m, 1H), 2.25 (m, 1H), 2.07 (dd, J = 11.7, 9.1 Hz, 1H), 1.88 (m, 2H), 1.57 (d, J = 7.0 Hz, 3H), 1.28 (td, J = 7.3, 3.0 Hz, 3H). 0.90 (s, 9H), 0.87 (m, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 196.1, 166.9, 165.4, 149.7, 140.2, 129.0, 127.9, 126.9, 126.8, 121.3, 90.6, 75.4, 60.5, 53.2, 47.3, 46.1, 37.0, 34.0, 26.1, 21.1, 18.4, 17.0, 16.9, 15.8, 14.5, −4.3, −4.7; HRMS (CI) Exact mass calcd for $C_{29}H_{45}NO_4Si$ $[M]^+$, 499.3118. Found 499.3112.

(4*S*,5*S*,*E*)-Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-7-chloro-5-methyl-7-oxohept-2-enoate (8). To carboxylic acid **19** (1 equiv) in CH_2Cl_2 (0.1 M) at 0 °C was added oxalyl chloride (3 equiv). After several minutes, catalytic DMF was added (5−10 μL). The reaction was stirred for 30 min at 0 °C and 15 min at rt. The volatiles were removed in vacuo, and the crude oil was placed under high vacuum for a short time and then used immediately in the coupling reactions above with **7a**−**7d**.

General Procedure for β-Stannyl Enamine Formation (9a−d). To a flame-dried round-bottom flask fitted with a reflux condenser was added the alkynyl imine (**11a**−**11d**, 1 equiv), and the flask was evacuated and backfilled with nitrogen three times. Benzene (0.04 M in imine) and ^{n}Bu$_3$SnH (0.22 equiv) were added, and the contents were heated in an oil bath to 85−90 °C. In a separate flask, AIBN (1 equiv)[64] was added, and the flask was evacuated and backfilled with nitrogen three times. Then benzene (0.25 M in imine) and ^{n}Bu$_3$SnH (1.98 equiv) were added, and the resulting solution was cannulated through the reflux condenser of the original reaction vessel at rate of one drop every 3−4 s. After the addition was complete, the reaction was stirred an additional 1 h before cooling to room temperature. The solvent was removed in vacuo to provide the crude β-stannyl enamines (**9a**−**d**), which were used in the coupling reaction with acid chloride **8**.[65] The scale varied between 1.5 and 15 mmol of **8**.

(*E*)-Ethyl 4-Oxobut-2-enoate (10). A 500 mL round-bottom flask equipped with a magnetic stir bar and ozonolysis glass-adapter fitting was charged with freshly distilled ethyl sorbate **13** (15 g, 0.107 mol) and absolute ethanol (430 mL). To this solution was added approximately 6 drops of a saturated solution of Sudan Red 7B dye in ethanol (resulting solution was magenta in color). The solution was cooled to −78 °C, and then O_2 was bubbled through the solution for 10 min, followed by the addition of O_3 until the solution turned a faint yellow color. At this point, the solution was purged with O_2 for an additional 10 min. Dimethyl sulfide (approximately 2.2 equiv) was then added dropwise at −78 °C and allowed to warm to rt overnight with stirring. The solution was concentrated, diluted with ether, washed with water and then satd aq $NaHCO_3$, and then dried (Na_2SO_4), filtered, and concentrated. The residue was distilled (75 °C/15 Torr) to give aldehyde **10** as a light yellow oil (13.7 g, 75%). All spectroscopic data was consistent with that reported in the literature.[66]

***N*-(Diphenylmethylene)pent-4-yn-1-amine (11a).** Alkynyl amine **20**[67] (3.5 g, 42.1 mmol), benzophenone imine[24] (7.25 g, 40.0 mmol), and 4 Å MS (2.0 g) were rapidly stirred in benzene (30 mL) at rt for 36 h. The solution was filtered through a pad of Celite, washed with ether, and concentrated to yield imine **11a** as a light yellow oil (9.76 g, 99%): IR (film) 3299, 3057, 1623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7.46 (m, 3H), 7.36 (m, 3H), 7.19 (m, 2H), 3.48 (t, J = 6.7 Hz, 2H), 2.33 (ddd, J = 7.3, 7.3, 2.7 Hz, 2H), 1.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.7, 140.1, 137.1, 130.1, 129.0, 128.7, 128.6, 128.3, 128.0, 84.6, 68.6, 52.6, 30.3, 16.6; HRMS (CI) Exact mass calcd for $C_{18}H_{16}N$ $[M - H]^+$, 246.1283, found 246.1283.

***N*-(Bis(4-methoxyphenyl)methylene)pent-4-yn-1-amine (11b).** Alkynyl amine **20**[67] (447 mg, 5.38 mmol), *p*-methoxybenzophenone imine[68] (865 mg, 3.60 mmol), and 4 Å MS (2.0 g) were rapidly stirred in benzene (10 mL) at rt for 48 h. The solution was filtered through a pad of Celite, washed with ether, and concentrated to yield imine **11b** as a light yellow oil (1.59 g, 96%): IR (film) 3297, 3002, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.9 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.9 Hz, 2H), 3.76 (s, 3H), 3.70 (s, 3H), 3.35 (dd, J = 6.7, 6.4 Hz, 2H), 2.18, (m, 2H), 1.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.0, 161.3, 159.7, 134.2, 133.4, 132.5, 130.2, 129.6, 129.4, 128.6, 115.0, 114.0, 113.5, 84.7, 68.5, 55.6, 55.5, 52.5, 30.5, 16.6; HRMS (CI) Exact mass calcd for $C_{20}H_{20}NO_2$ $[M - H]^+$, 306.1494, found 306.1484.

***(E)*-*N*-(1-(4-Methoxyphenyl)ethylidene)pent-4-yn-1-amine (11d).** Alkynyl amine **20**[67] (23.0 g, 270 mmol) was added to a flask containing *p*-methoxyacetophenone (27.0 g, 180 mmol) and 4 Å molecular sieves in C_6H_6 (360 mL). After 24 h, the reaction was filtered through Celite using minimal C_6H_6, and then more sieves were added, and the reaction was stirred another 24 h. The reaction was filtered, more sieves were added and also more amine **20** (4 g), and the reaction was stirred 24 h, filtered, more sieves added, 24 h, and then filtered and concentrated to a pale yellow oil. The crude oil (**11d**) contains less than 5% of the starting ketone (36.5 g, 94%). The imine was used crude below: IR (film) 3292, 2933, 1603, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 3.72 (s, 3H), 3.43 (t, J = 6.7 Hz, 2H), 2.27 (td, J = 7.0, 2.6 Hz, 2H), 2.12 (s, 3H), 1.87 (quintet, J = 6.8 Hz, 2H), 1.86 (t, J = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 164.8, 160.8, 134.1, 128.2, 113.6, 84.7, 68.4, 55.4, 50.5, 30.0, 16.5, 15.5; HRMS (FAB) Exact mass calcd for $C_{14}H_{17}NO$ $[M + H]^+$, 216.1388. Found 216.1389.

(4*S*,5*S*,*E*)-Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-7-hydroxy-5-methylhept-2-enoate (17). In a 200 mL round-bottom flask charged with BH_3·DMS (4.80 mL, 50.6 mmol) at 0 °C was added 2-methyl-2-butene dropwise (11.9 mL, 102 mmol). The colorless mixture was stirred for 15 min, warmed to rt for 1.5 h, and then recooled to 0 °C. To this mixture, a precooled solution of alkene **16** (12.6 g, 42.1 mmol) in THF (32.4 mL) was added slowly via cannula addition. The reaction was stirred for 4 h at 0 °C, with the last 30 min having minimal ice within the ice/water bath. The ice was recharged, and the reaction was quenched by slow dropwise addition via addition funnel of 3 N NaOH (36.2 mL, 1 drop per 3−4 s) and then addition of 30% H_2O_2 (25.1 mL) in the same fashion.[69] The reaction was stirred an additional 10 min and then allowed to warm to rt and stirred overnight (at least 10 h). Saturated aq $Na_2S_2O_3$ was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with satd aq NaCl, dried, filtered and concentrated to a cloudy white oil. Column chromatography (SiO_2, 5−10−20−30−45% ethyl acetate in hexanes) provided **17** as a colorless oil (10.5 g, 79%) along with a small amount of **18** as a colorless oil (1−5%). Data for **17**: R_f = 0.11 (20% EtOAc/hexanes); IR (film) 3442 (br), 2957, 2931, 2858, 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, J = 15.6, 4.9 Hz, 1H), 5.97 (dd, J = 15.6, 1.5 Hz, 1H), 4.25−4.20 (m, 1H), 4.21

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(qd, J = 7.1, 1.6 Hz, 2H), 3.77−3.69 (m, 1H), 3.66−3.58 (m, 1H), 1.90−1.81 (m, 1H), 1.68 (dtd, J = 13.9, 7.0, 4.6 Hz, 1H), 1.58 (br s, 1H), 1.44 (ddt, J = 14.4, 8.4, 6.2 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.95−0.91 (m, 3H), 0.93 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.4, 149.0, 121.2, 75.5, 60.5, 60.3, 36.1, 34.4, 25.8, 18.1, 15.4, 14.2, −4.5, −5.0; HRMS (ESI) Exact mass calcd for $C_{16}H_{32}O_4SiNa$ $[M + Na]^+$ 339.1968, found 339.1951.

Ethyl 2-((2*R*,3*S*,4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-methyltetrahydro-2*H*-pyran-2-yl)acetate (18). Data is for the major diastereomer only, ratio of major to minor is 3:1: R_f = 0.22 (10% EtOAc/hexanes); IR (film) 2957, 2931, 2857, 1740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (q, J = 7.1 Hz, 2H), 3.83 (ddd, J = 9.4, 9.4, 3.1 Hz, 1H), 3.65−3.61 (m, 2H), 3.48 (dd, J = 9.0, 4.9 Hz, 1H), 2.72 (dd, J = 15.0, 3.1 Hz, 1H), 2.26 (dd, J = 15.0, 9.7 Hz, 1H), 2.15−2.08 (m, 1H), 1.93−1.85 (m, 1H), 1.48 (ddd, J = 13.8, 5.1, 2.3 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 172.3, 73.4, 73.2, 62.5, 60.6, 38.5, 32.6, 31.9, 36.0, 18.2, 14.4, 11.5, −4.0, −4.8; HRMS (CI) Exact mass calcd for $C_{16}H_{33}O_4Si$ $[M + H]^+$ 317.2143, found 317.2136.

(3*S*,4*S*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-7-ethoxy-3-methyl-7-oxohept-5-enoic acid (19). Aldehyde **76** (9.7 g, 31 mmol) was added to CH_3CN/^{t}BuOH/2-methyl-2-butene (3:3:1, 760 mL) and cooled to 0 °C. In an Erlenmeyer flask, $NaH_2PO_4{\cdot}H_2O$ (33.9 g, 245 mmol) was dissolved in H_2O (210 mL) via stirring, and then $NaClO_2$ (31.3 g, 277 mmol, 80% tech grade) was added in small portions until it was completely dissolved (the solution turns from colorless to yellow). The solution in the Erlenmeyer flask was then poured into a pressure addition funnel and added dropwise to the stirred aldehyde solution. After 1 h at 0 °C, the reaction was warmed to rt for an additional 2.5 h. Ether was added, and the two layers were separated. The organic layer was washed once with satd aq $Na_2S_2O_3$ and then brine, and dried, filtered, and concentrated to a crude oil. Column chromatography (SiO_2, 10−15−25−40% ethyl acetate in hexanes) provided carboxylic acid **19** as a pale yellow oil (9.1 g, 90% yield): R_f = 0.10 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ +1.8 (c 0.8, $CHCl_3$); IR (film) 3100 (br), 2957, 2932, 2858, 1714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (dd, J = 15.6, 5.1 Hz, 1H), 5.97 (dd, J = 15.6, 1.4 Hz, 1H), 4.22−4.15 (m, 1H), 4.19 (qd, J = 7.0, 2.8 Hz, 2H), 2.50−2.43 (m, 1H), 2.20−2.12 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.2 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H), OH hydrogen was not observed; ^{13}C NMR (125 MHz, $CDCl_3$) ppm 179.0, 166.2, 148.5, 121.7, 74.7, 60.4, 36.1, 35.9, 25.7, 18.0, 16.2, 14.1, −4.5, −5.1; HRMS (ESI) Exact mass calcd for $C_{16}H_{30}O_5NaSi$ $[M + Na]^+$ 353.1760, found 353.1765.

(6*aS*,7*S*,8*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-methyl-2,3,6a,7,8,9-hexahydropyrrolo[2,1-a]isoquinoline-5,10(1*H*,6*H*)-dione (26). To a solution of vinylogous amide **6** (280 mg, 530 μmol) in toluene at 0 °C was added oil-free NaH (15.3 mg, 640 μmol, oil was removed by washing 3× with hexanes under an inert atmosphere). The reaction was stirred for 3 h at rt and then quenched with water. The mixture was extracted with EtOAc, and the organic layers were dried, filtered, and concentrated to a brown oil. Flash column chromatography (SiO_2, 50−65−100% ether in hexanes) yielded **26** as a cream-colored, powdery solid (184 mg, 72%): mp 136.5−138.0 °C; R_f = 0.47 (60% EtOAc/hexanes); IR (film) 2947, 2931, 2886, 2857, 1696, 1669, 1586 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (ddd, J = 11.7, 7.9, 6.1 Hz, 1H), 3.75 (dd, J = 9.5, 3.7 Hz, 1H), 3.62 (ddd, J = 11.6, 7.6, 7.6 Hz, 1H), 3.33−3.24 (m, 1H), 3.12 (dddd, J = 18.2, 8.9, 6.6, 2.6 Hz, 1H), 2.96−2.88 (m, 1H), 2.84 (dd, J = 16.1, 5.2 Hz, 1H), 2.50 (dd, J = 17.8, 5.3 Hz, 1H), 2.38 (dd, J = 17.7, 2.6 Hz, 1H), 2.19−2.11 (m, 2H), 2.06−1.92 (m, 2H), 1.01 (d, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 196.1, 169.5, 155.1, 106.6, 74.9, 45.6, 45.1, 36.0, 35.8, 33.7, 32.0, 25.7, 21.3, 17.9, 12.9, −4.4, −4.8; HRMS (CI) Exact mass calcd for $C_{19}H_{32}NO_3Si$ $[M + H]^+$ 350.2151, found 350.2154. Anal. calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.34; H, 8.99; N, 3.99.

(6*aS*,7*S*,8*S*,10*aR*,10*bR*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-methyloctahydropyrrolo[2,1-a]isoquinoline-5,10(6*H*,10a*H*)-dione (31). Vinylogous amide **6** (4.0 mg, 10 μmol) and 10% Pd/C (1.7 mg) in MeOH (200 μL) were combined in a small vial, placed into a metal chamber, and pressurized to 70 psi with hydrogen. The reaction mixture was stirred for 72 h before it was filtered, concentrated, and purified via flash column chromatography (SiO_2, 70−90−100% ethyl acetate in hexanes) to yield ketone **31** as a white, crystalline solid (2.0 mg, 56%) as well as unreacted **6** (1.5 mg, 38%): R_f = 0.43 (80% EtOAc/hexanes); mp 138.5−139.0 °C; IR (film) 2956, 2930, 2856, 1715, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (ddd, J = 12.2, 9.7, 6.2 Hz, 1H), 3.87 (dd, J = 9.2, 4.2 Hz, 1H), 3.63 (ddd, J = 11.4, 5.5, 5.5 Hz, 1H), 2.96 (ddd, J = 11.1, 11.1, 5.4 Hz, 1H), 2.79−2.70 (m, 2H), 2.62 (dd, J = 15.2, 5.1 Hz, 1H), 2.45−2.38 (m, 1H), 2.37 (dd, J = 15.2, 2.8 Hz, 1H), 2.34−2.26 (m, 1H), 2.18−2.09 (m, 2H), 1.92−1.78 (m, 2H), 1.17 (dddd, J = 11.7, 11.7, 9.9, 9.9 Hz, 1H), 0.98−0.87 (m, 12H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 206.6, 168.9, 75.0, 57.3, 49.7, 46.3, 42.9, 38.9, 36.2, 34.3, 27.0, 26.0, 21.9, 18.3, 12.9, −4.0, −4.4. HRMS (EI) Exact mass calcd for $C_{15}H_{24}NO_3Si$ $[M - C_4H_9]^+$ 294.1525, found 294.1530. An X-ray crystal structure of **31** was obtained in which cocrystallization occurred with an α-hydroxy compound (**S4**, not shown) as the minor component. See Supporting Information 2 for more details as well as detailed 2D NMR data.

Alternate Preparation of 31. Catecholborane (1.14 mL, 1.14 mmol) was added to a solution of vinylogous imide **26** (200 mg, 572 μmol) and Wilkinson's catalyst (26 mg, 29 μmol) in THF (2 mL) at 0 °C. The reaction was quenched after 30 min by the addition of MeOH and concentrated to a brown oil. Flash column chromatography (SiO_2, 60−80−100% ethyl acetate in hexanes) provided a ketone as a white solid (170 mg, 84%) whose analytical data and ^{1}H NMR matched **31**.

(6*aS*,7*S*,8*S*,10*aS*,10*bR*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-methyloctahydropyrrolo[2,1-a]isoquinoline-5,10(6*H*,10a*H*)-dione (32). Oil-free NaH (700 μg, 28.4 μmol, oil was removed by washing 3× with hexanes under an inert atmosphere) was added to a stirred solution of ketone **31** (10.0 mg, 28.4 μmol) in benzene (280 μL), and the reaction was heated to 60 °C for 30 min. The reaction was quenched with water and then extracted with EtOAc. The organic layers were dried, filtered, and concentrated to a yellow oil that was purified via flash column chromatography (70−90% ethyl acetate in hexanes) to give ketone epimer **32** as a colorless oil (8.7 mg, 87%): R_f = 0.20 (80% EtOAc/hexanes); IR (film) 2955, 2928, 2889, 2856, 1715, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19−4.12 (m, 1H), 3.78−3.69 (m, 2H), 3.40−3.32 (m, 1H), 2.96−2.94 (m, 1H), 2.54 (dd, J = 13.2, 13.2 Hz, 1H), 2.43 (dddd, J = 13.3, 6.8, 6.8, 3.4 Hz, 1H), 2.26 (dd, J = 13.8, 4.4 Hz, 1H), 2.21 (ddd, J = 15.5, 3.2, 1.4 Hz, 1H), 2.16−2.07 (m, 1H), 2.05−1.96 (m, 2H), 1.93 (dd, J = 14.3, 13.1 Hz, 1H), 1.90−1.81 (m, 1H), 1.46 (dddd, J = 11.4, 11.4, 11.4, 8.2 Hz, 1H), 1.04 (d, J = 6.7 Hz, 3H), 0.95 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 209.4, 168.6, 72.8, 54.2, 47.1, 44.0, 43.7, 41.6, 34.2, 34.2, 32.4, 26.0, 22.1, 18.3, 18.2, −4.2, −4.4; HRMS (CI) Exact mass calcd for $C_{19}H_{34}NO_3Si$ $[M + H]^+$ 352.2310, found 352.2308. Anal. calcd for $C_{19}H_{33}NO_3Si$: C, 64.91; H, 9.46; N, 3.98. Found: C, 65.01; H, 9.26; N, 3.70. Additional 2D data for **32** can be found in Supporting Information 2.

Alternate Preparation of 32. NH_3 (9 mL) was condensed into a two-necked flask at −78 °C. Oil-free lithium wire (9 mg, washed once with hexanes to remove the oil) was added, and the reaction was stirred until a blue color persisted for at least 10 min. A solution of vinylogous imide **26** (75.3 mg, 214 μmol), ^{t}BuOH (20.5 μL, 214 μmol), and THF (600 μL) were added dropwise. After 20 min the reaction was quenched by the addition of water and was warmed to rt to evaporate the NH_3. The crude reaction was then extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Flash column chromatography (SiO_2, 70−90−100% ethyl acetate in hexanes) yielded a colorless oil identical in analytical data and matching ^{1}H NMR to ketone epimer **32** (47.3 mg, 63%).

(6*aS*,7*S*,8*S*,10*bR*)-10-(Allyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-8-methyl-1,2,3,6a,7,8,9,10b-octahydropyrrolo[2,1-a]isoquinolin-5(6*H*)-one (33). Ketone **31** (20.0 mg, 56.9 μmol) was added to a stirred mixture of KO^{t}Bu (7.0 mg, 63 μmol) and HMPA (49 μL, 284 μmol) in C_6H_6 (600 μL) at 0 °C. After 10 min, the

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reaction was warmed to rt and stirred for an additional 2 h before quenching with satd aq $NaHCO_3$. The mixture was extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated to a brown oil. Flash column chromatography (50−70−100% ethyl acetate in hexanes) yielded **33** as a colorless oil (13 mg, 58%): R_f = 0.33 (65% EtOAc/hexanes); IR (film) 2956, 2929, 2885, 2856, 1653, 1647, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (dddd, J = 15.8, 10.5, 5.2, 5.2 Hz, 1H), 5.29 (dd, J = 17.2, 1.6 Hz, 1H), 5.20 (dd, J = 10.5, 1.4 Hz, 1H), 4.27−4.22 (m, 3H), 3.70 (ddd, J = 12.0, 8.7, 8.7 Hz, 1H), 3.43 (dd, J = 7.6, 3.6 Hz, 1H), 3.35−3.27 (m, 1H), 2.65 (dd, J = 15.2, 3.7 Hz, 1H), 2.44−2.30 (m, 3H), 2.11−2.07 (m, 1H), 2.04−1.98 (m, 1 H), 1.94−1.85 (m, 2H), 1.82−1.78 (m, 1H), 1.36 (dddd, J = 11.6, 11.6, 11.6, 8.2 Hz, 1H), 0.96 (d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) led to decomposition in the time needed to acquire the data and did not allow for characterization; HRMS (CI) Exact mass calcd for $C_{22}H_{38}NO_3Si$ $[M + H]^+$ 392.2621, found 392.2611.

(6*aS*,7*S*,8*S*,10*aR*,10*bR*)-10a-Allyl-7-((*tert*-butyldimethylsilyl)oxy)-8-methyloctahydropyrrolo[2,1-a]isoquinoline-5,10(6*H*,10a*H*)-dione (34). A solution of freshly prepared allyl vinyl ether **33** (37.0 mg, 94.5 μmol) in *o*-dichlorobenzene (1.2 mL) was heated at 170 °C in a sealed tube for 3.5 h. The reaction was concentrated, and the crude oil was purified by flash column chromatography (SiO_2, 40−60% ethyl acetate in hexanes) to give **34** as a colorless oil (29 mg, 78%): R_f = 0.38 (60% EtOAc/hexanes); IR (film) 2956, 2929, 2885, 2856, 1653, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50 (dddd, J = 17.1, 10.3, 7.2, 7.2 Hz, 1H), 5.13 (d, J = 9.4 Hz, 1H), 5.12 (d, J = 18.3 Hz, 1H), 4.16 (ddd, J = 12.2, 9.5, 5.6 Hz, 1H), 4.13−4.07 (m, 1H), 3.42 (dd, J = 11.7, 4.9 Hz, 1H), 2.88 (ddd, J = 11.9, 10.3, 6.3 Hz, 1H), 2.66 (dd, J = 14.8, 5.2 Hz, 1H), 2.70−2.61 (m, 1H), 2.57−2.53 (m, 2H), 2.37−2.27 (m, 4H), 2.25 (dd, J = 14.8, 2.4 Hz, 1H), 1.91−1.75 (m, 2H), 1.27−1.14 (m, 1H), 0.94 (d, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^1H NMR (400 MHz, C_6D_6—*for use with 2D NMR*) δ 5.38 (dddd, J = 17.8, 10.0, 7.8, 6.8 Hz, 1H), 4.95 (d, J = 9.5 Hz, 1H), 4.85 (dd, J = 16.8, 1.3 Hz, 1H), 4.30 (ddd, J = 13.1, 9.6, 5.2 Hz, 1H), 3.78 (dd, J = 9.9, 4.8 Hz, 1H), 3.27 (dd, J = 11.6, 4.9 Hz, 1H), 2.85−2.74 (m, 1H), 2.57 (ddd, J = 10.2, 10.2, 6.2 Hz, 1H), 2.32−2.06 (m, 6H), 1.97 (dd, J = 14.8, 2.6 Hz, 1H), 1.93−1.86 (m, 1H), 1.38−1.15 (m, 2H), 0.95 (s, 9H), 0.80 (d, J = 7.1 Hz, 3H), 0.74−0.62 (m, 1H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 208.9, 169.0, 131.3, 120.4, 71.0, 62.1, 51.8, 45.0, 43.1, 36.6, 36.4, 35.8, 32.8, 26.7, 26.2, 22.2, 18.4, 13.1, −3.9, −4.3; HRMS (EI) Exact mass calcd for $C_{22}H_{38}NO_3Si$ $[M + H]^+$ 392.2621, found 392.2611. 2D NMR data was obtained to support the assignment of the allyl group; see Supporting Information 2 for details.

(3*S*,4*R*,5*S*,*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(2-hydroxyethyl)-5-methyl-2-(pyrrolidin-2-ylidene)cyclohexanone (35). A 1.67 M stock solution of Red-Al (13 mL, 65 wt % in toluene) in toluene (13 mL) was cooled to 0 °C. Of this stock solution, a portion (18.5 mL, 30.9 mmol) was added rapidly to ester **6** (5.10 g, 12.9 mmol) stirring in toluene (103 mL) also at 0 °C.[70] After 30 min, the reaction was warmed to rt and stirred an additional 30 min. It was then cooled to 0 °C before quenching with Rochelle's salt (200 mL) and then warmed again to rt for 20 min. The crude reaction was extracted with EtOAc, and the combined organic layers were washed with brine, dried, filtered, and concentrated to a yellow/green oil. Column chromatography (SiO_2, 50−70−90% ethyl acetate in hexanes) provided alcohol **35** as a yellow, flaky solid (3.2 g, 70%): R_f = 0.18 (90% EtOAc/hexanes); mp 87.9−89.5 °C; IR (film) 3269 (br), 2953, 2928, 2856, 1603, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.74 (br s, 1H), 3.72 (br s, 1H), 3.69 (t, J = 6.3 Hz, 2H), 3.59 (ddd, J = 10.5, 7.8, 6.2 Hz, 1H), 3.52 (ddd, J = 10.4, 7.3, 7.3 Hz, 1H), 2.72 (ddd, J = 16.7, 8.7, 6.5 Hz, 1H), 2.62−2.58 (m, 1H), 2.57 (ddd, J = 16.7, 8.6, 7.1 Hz, 1H), 2.22 (dd, J = 17.5, 12.1 Hz, 1H), 2.14 (dd, J = 17.3, 5.7 Hz, 1H), 2.13−2.06 (m, 1H), 2.01−1.92 (m, 2H), 1.66−1.52 (m, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 194.9, 167.6, 99.9, 73.0, 61.2, 47.6, 41.4, 40.6, 39.5, 30.8, 29.0, 25.9, 21.9, 18.9, 18.3, −4.2, −4.5; HRMS (CI) Exact mass calcd for $C_{19}H_{36}NO_3Si$ $[M + H]^+$ 354.2464, found 354.2454. Anal. Calcd for $C_{19}H_{35}NO_3Si$: C, 64.54; H, 9.98; N, 3.96. Found: C, 64.53; H, 10.04; N, 3.96.

2-((1*S*,2*R*,3*S*,*Z*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-5-oxo-6-(pyrrolidin-2-ylidene)cyclohexyl)ethyl pivalate (36). Trimethylacetic anhydride (2.02 mL, 10.0 mmol) was added to alcohol **35** (1.76 g, 4.98 mmol), DMAP (183 mg, 1.50 mmol), and Et_3N (4.2 mL, 30 mmol) in CH_2Cl_2 (25 mL) at rt and stirred for ∼40 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine and then dried, filtered, and concentrated to a yellow oil. Flash column chromatography (SiO_2, 50−70−90% ether in hexanes) provided pivalate **36** as a yellow oil (2.04g, 93%), which upon standing in the refrigerator became a cream-colored solid: R_f = 0.35 (60% EtOAc/hexanes); mp 54.5−57.0 °C; $[\alpha]_D^{20}$ +20.1 (*c* 1.0, $CHCl_3$); IR (film) 2956, 2929, 2856, 1727, 1611, 1534 cm^{-1}. Data in $CDCl_3$: ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (br s, 1H), 4.12 (ddd, J = 11.2, 7.7, 5.9 Hz, 1H), 4.09−4.01 (m, 1 H), 3.74 (dd, J = 2.7, 1.6 Hz, 1H), 3.61 (ddd, J = 10.4, 7.7, 6.1 Hz, 1H), 3.53 (ddd, J = 10.4, 7.9, 6.4 Hz, 1H), 2.64 (ddd, J = 16.7, 8.8, 6.6 Hz, 1H), 2.59−2.52 (m, 2H), 2.23 (dd, J = 17.6, 12.3 Hz, 1H), 2.19−2.06 (m, 2H), 2.03−1.93 (m, 2H), 1.75−1.56 (m, 2H), 1.22 (s, 9H), 0.96 (d, J = 6.5 Hz, 3H), 0.82 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 195.0, 178.9, 167.5, 99.7, 72.8, 63.1, 47.8, 41.9, 50.7, 39.1, 35.6, 30.9, 29.1, 27.6, 26.0, 21.9, 19.1, 18.4, −4.1, −4.4. Data in C_6D_6 (for use with 2D NMR): ^1H NMR (500 MHz, C_6D_6) δ 11.1 (br s, 1H), 4.21 (dt, J = 11.0, 6.6 Hz, 1H), 4.10 (dt, J = 11.3, 6.0 Hz, 1H), 3.75 (br s, 1H), 2.84 (dt, J = 10.6, 7.2 Hz, 1H), 2.75 (dt, J = 10.6, 7.2 Hz, 1H), 2.67 (ddd, J = 7.2, 7.2, 3.0 Hz, 1H), 2.62 (dd, J = 17.8, 12.1 Hz, 1H), 2.53 (dd, J = 17.4, 6.4 Hz, 1H), 2.45−2.38 (m, 2H), 2.01 (dddq, J = 6.3, 6.3, 6.3, 6.3 Hz, 1H), 1.62 (dt, J = 6.8, 6.8 Hz, 2H), 1.36 (quintet, J = 7.1 Hz, 2H), 1.31 (s, 9H), 1.02−0.96 (m, 12H), 0.16 (s, 3H), 0.14 (s, 3H); HRMS (CI) Exact mass calcd for $C_{24}H_{44}O_4NSi$ $[M + H]^+$ 438.3040, found 438.3023. 2D NOESY data supporting the *cis*-assignment of the vinylogous amide was performed and is in Supporting Information 2.

2-((1*S*,2*S*,5*S*,6*S*)-2-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-5-methyl-3-oxocyclohexyl)ethyl pivalate and epimer (37 and *epi*-37). Ceric ammonium nitrate[64] (2.5 g, 4.6 mmol) was added to a stirring solution of vinylogous amide **36** (1.0 g, 2.3 mmol) and allyltrimethylsilane (3.6 mL, 23 mmol) in degassed CH_3CN[71] (76 mL) at 0 °C. The reaction was quenched after 10 min by the addition of satd aq $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were dried, filtered, and concentrated to provide a crude brown oil. Subsequent column chromatography (SiO_2, 8−15% ethyl acetate in hexanes) yielded the major diastereomer (**37**) as a colorless oil (750 mg, 67%), as well as a small amount of the allyl diastereomer (*epi*-**37**) as a colorless oil (22 mg, 2% yield). Data for major diastereomer **37**: R_f = 0.55 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ −83.9 (*c* 1.0, $CHCl_3$); IR (film) 2957, 2931, 2858, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (dddd, J = 17.0, 9.4, 5.1, 5.1 Hz, 1H), 5.14 (d, J = 17.0 Hz, 1H), 5.09 (d, J = 10.1 Hz, 1H), 4.65 (dd, J = 9.4, 3.9 Hz, 1H), 4.06−4.00 (m, 2H), 3.89−3.77 (m, 2H), 3.01 (dd, J = 13.9, 5.1 Hz, 1H), 2.84 (dd, J = 15.2, 6.2 Hz, 1H), 2.50−2.32 (m, 3H), 2.25−2.18 (m, 2H), 2.00−1.94 (m, 1H), 1.84−1.63 (m, 4H), 1.17 (s, 9H), 0.92−0.86 (m, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 208.9, 178.4, 176.5, 134.1, 118.8, 73.9, 64.7, 71.8, 60.9, 43.9, 40.4, 38.5, 37.5, 36.4, 35.4, 29.2, 27.1, 25.9, 22.0, 18.0, 13.4, −4.4, −4.6; HRMS (CI) Exact mass calcd for $C_{27}H_{48}NO_4Si$ $[M + H]^+$ 478.3347, found 478.3335. Data for minor diastereomer (*epi*-**37**): R_f = 0.32 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ −3.3 (*c* 1.0, $CHCl_3$) IR (film) 2958, 2931, 2858, 1728, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80−5.70 (m, 1H), 4.98 (d, J = 17.0 Hz, 1H), 4.93 (d, J = 10.1 Hz, 1H), 4.06 (dd, J = 8.1, 3.8 Hz, 1H), 4.00 (t, J = 7.5 Hz, 2H), 3.93−3.74 (m, 2H), 2.90−2.81 (m, 1H), 2.70−2.61 (m, 1H), 2.52−2.34 (m, 4H), 2.32−2.23 (m, 2H), 1.97−1.77 (m, 2H), 1.74−1.59 (m, 1H), 1.67 (dddd, J = 14.3, 14.3, 7.3, 7.3 Hz, 1H), 1.18 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 209.7, 178.5, 177.7, 134.8, 116.7, 73.9, 63.9, 60.8, 60.5, 44.8, 42.2, 38.8, 36.0, 35.9, 35.1, 27.6, 27.4, 26.2, 22.9, 18.4, 14.7, −4.1, −4.0; HRMS (CI) Exact mass calcd for $C_{27}H_{48}NO_4Si$ $[M + H]^+$ 478.3347, found

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478.3352. 2D NMR data supporting the assignments of both the major and minor diastereomers is discussed in Supporting Information 2.

2-((1*R*,5*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-5-methyl-3-oxocyclohexyl)ethyl pivalate (38). *N*-Chlorosuccinimide (6.1 mg, 45.7 μmol)[64] was added to a stirring solution of the vinylogous amide **36** (20.0 mg, 45.7 μmol) in CH_2Cl_2 (450 μL) at rt. After 15 min, the reaction was quenched with satd aq $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated to a white oily solid. Flash column chromatography (SiO_2, 5−10% ethyl acetate in hexanes) provided the α-chloro ketone **38** as a colorless oil and single diastereomer (18.3 mg, 85%). However, while the chair conformation could be determined by ^{1}H NMR and 2D NMR, the newly set stereocenter could not be identified by NOESY correlations: R_f = 0.69 (40% EtOAc/hexanes); IR (film) 2959, 2931, 2859, 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.11−4.05 (m, 1H), 4.01 (ddd, *J* = 10.6, 8.9, 6.4 Hz, 1H), 3.97−3.91 (m, 2H), 3.24 (dd, *J* = 14.3, 5.4 Hz, 1H), 2.87 (ddd, *J* = 9.7, 5.4, 5.4 Hz, 1H), 2.76−2.59 (m, 2H), 2.38−2.26 (m, 1H), 2.30 (dd, *J* = 13.6, 4.6 Hz, 1H), 1.96 (quintet, *J* = 7.8 Hz, 2H), 1.84−1.76 (m, 2H), 1.16 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.6, 178.6, 175.1, 74.2, 63.9, 61.6, 48.7, 42.9, 41.9, 39.0, 37.1, 35.5, 30.1, 27.6, 26.2, 23.3, 18.4, 13.7, −4.0, −4.2; HRMS (CI) Exact mass calcd for $C_{24}H_{43}ClNO_4Si$ [M + H]$^+$ 472.2650, found 472.2632.

2-((1*R*,5*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-hydroxy-5-methyl-3-oxocyclohexyl)ethyl pivalate (39). MCPBA[64] (30.0 mg, 171 μmol) was added to vinylogous amide **36** (75.0 mg, 171 μmol) in CH_2Cl_2 (1.7 mL) at rt. After 25 min, the reaction was quenched with satd aq $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated to an oil. Flash column chromatography (SiO_2, 5−10−20% ethyl acetate in hexanes) furnished α-hydroxyketone **39** as a colorless oil as one diastereomer (32.7 mg, 42%), along with recovered starting material (25 mg, 33%). As with the **38** above, the exact diastereomer could not be established: R_f = 0.69 (50% EtOAc/hexanes); IR (film) 3464, 2958, 2930, 2858, 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (dd, *J* = 10.3, 4.6 Hz, 1H), 4.42 (br s, 1H), 4.19 (ddd, *J* = 10.6, 8.7, 6.5 Hz, 1H), 4.12 (ddd, *J* = 10.6, 8.9, 6.1 Hz, 1H), 4.04−3.85 (m, 2H), 3.38 (dd, *J* = 13.4, 5.8 Hz, 1H), 2.76−2.66 (m, 1H), 2.47−2.34 (m, 2H), 2.30 (dd, *J* = 13.4, 2.9 Hz, 1H), 1.99 (ddd, *J* = 11.3, 7.0, 4.9 Hz, 1H), 1.95−1.66 (m, 4H), 1.18 (s, 9H), 0.95−0.87 (m, 12H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 209.4, 178.7, 178.2, 83.4, 72.2, 64.5, 62.6, 48.3, 41.7, 39.0, 37.3, 36.8, 28.0, 27.6, 26.2, 21.8, 18.4, 13.0, −3.9, −4.4; HRMS (CI) Exact mass calcd for $C_{24}H_{44}NO_5Si$ [M + H]$^+$ 454.2989, found 454.2976.

2-((1*S*,2*S*,3*S*,5*S*,6*S*)-2-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-3-hydroxy-5-methylcyclohexyl)-ethyl pivalate (41). To a solution of ketone **37** (1.18 g, 2.47 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added Et_2AlCl (3.43 mL, 6.18 mmol, 1.8 M in toluene) slowly via syringe. The reaction mixture was stirred for 30 min at −78 °C, and then ^{n}Bu$_3$SnH (1.33 mL, 4.94 mmol) was added over 45 min via syringe pump. The reaction mixture was stirred for 1 h at −78 °C, warmed gradually to rt over 1 h, and then for another 1.5 h at rt. The reaction mixture was cooled to 0 °C, quenched with satd aq NH_4OH, and stirred for an additional 30 min at rt. Water was added, and the crude reaction was extracted with EtOAc, and the combined organic layers were washed with brine and then dried, filtered, and concentrated to a pale yellow oil. Flash column chromatography (2× SiO_2, 4−10−20% ethyl acetate in hexanes) yielded the desired β-alcohol (**41**) as a colorless oil (900 mg, 76%): R_f = 0.65 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ +48.9 (*c* 1.0, $CHCl_3$); IR (film) 3515−3234, 3076 (w), 2957, 2929, 2857, 1729, 1621, 1463, 1282, 1251, 1154, 1051, 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (br s, 1H), 5.50−5.38 (m, 1H), 5.02−4.91 (m, 2H), 4.23 (br s, 1H), 4.06−3.98 (m, 2H), 3.97−3.88 (m, 1H), 3.82−3.73 (m, 2H), 3.37−3.27 (m, 1H), 2.62−2.44 (m, 2H), 2.30−2.21 (m, 1H), 2.18−2.09 (m, 1H), 1.92−1.76 (m, 5H), 1.58−1.47 (m, 1H), 1.44−1.34 (m, 1H), 1.20 (s, 9H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 184.0, 178.7, 134.8, 117.0, 73.9, 69.7, 63.7, 59.8, 48.8, 44.8, 41.9, 38.9, 34.0, 30.4, 29.9, 27.5, 26.2, 25.4, 20.1, 18.7, 18.3, −3.5, −4.6; HRMS(CI) exact mass calcd for $C_{27}H_{50}NO_4Si$ [M + H]$^+$ 480.3504 Found 480.3521. Anal. calcd for $C_{27}H_{49}NO_4Si$: C, 67.59; H, 10.29; N, 2.92. Found: C, 67.37; H, 10.23; N, 2.86. 2D NMR data of **41** supporting the assignment of the stereochemistry of the reduction is presented in Supporting Information 2.

(1*S*,2*S*,3*S*,4*S*,5*S*)-2-Allyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-3-(2-hydroxyethyl)-5-methylcyclohexanol (42). Na metal (72 mg, 3.1 mmol, washed 3× with hexanes prior to use under an inert atmosphere) was added to pivalate **41** (150 mg, 313 μmol) in MeOH (6.3 mL) at 0 °C. The reaction was stirred an additional 10 min at 0 °C before warming to rt and stirring for 16 h. The reaction was quenched with 1 N HCl until a pH of 5−6, and then the MeOH was removed in vacuo. The remaining oil was extracted with ether, and the combined organic layers were dried, filtered, and concentrated. Column chromatography (SiO_2, 40−65% ethyl acetate in hexanes) provided the desired β-diol (**42**) as a colorless, thick oil (108 mg, 87%): R_f = 0.16 (40% EtOAc/hexanes); $[\alpha]_D^{21}$ +44.3 (*c* 0.7, $CHCl_3$); IR (film) 3400 (br), 2954, 2930, 2859 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (br s, 1H), 5.48−5.38 (m, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 10.1 Hz, 1H), 4.20 (br s, 1H), 3.93−3.85 (m, 1H), 3.80−3.72 (m, 1H), 3.74 (br s, 1H), 3.66 (ddd, *J* = 10.7, 6.8, 4.6 Hz, 1H), 3.57−3.50 (m, 1H), 3.28 (dd, *J* = 14.7, 8.3 Hz, 1H), 2.60−2.45 (m, 2H), 2.28−2.13 (m, 2H), 1.89−1.69 (m, 5H), 1.63 (br s, 1H), 1.48 (br d, *J* = 13.4 Hz, 1H), 1.34−1.26 (m, 1H), 0.94−0.90 (m, 12H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 184.3, 135.0, 116.9, 74.4, 69.9, 62.1, 59.7, 48.8, 44.4, 41.9, 34.3, 34.1, 30.5, 26.2, 25.4, 22.2, 18.7, 18.3, −3.6, −4.8; HRMS (CI) Exact mass calcd for $C_{22}H_{42}NO_3Si$ [M + H]$^+$ 396.2934, found 396.2916. See Supporting Information 2 for X-ray data of **42** supporting an intramolecular hydrogen bond between the β-OH hydrogen and imine nitrogen.

Alternate Preparation of 42 along with (1*R*,2*S*,3*S*,4*S*,5*S*)-2-Allyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-3-(2-hydroxyethyl)-5-methylcyclohexanol (S2). To a stirred solution of ketone **37** (125 mg, 262 μmol) in CH_2Cl_2 (4.0 mL) at −78 °C was added Et_2AlCl (728 μL, 1.31 mmol, 1.8 M solution in toluene) slowly dropwise. The reaction mixture was stirred for 30 min at −78 °C, and then ^{n}Bu$_3$SnH (282 μL, 1.05 mmol) was added rapidly. The reaction mixture was stirred for 30 min at −78 °C and then for 3 h at rt (with slow warming of the reaction from −78 °C to rt) before being treated with NH_4OH with stirring for 30 min. The aluminum salt was filtered off and washed with CH_2Cl_2. The resulting solution was concentrated, and the residue was purified by column chromatography (SiO_2, 30−50 ethyl acetate in hexanes) to furnish β-diol **42** as a colorless oil (86 mg, 83%) along with the α-diol diastereomer (**S2**) as a colorless oil (8 mg, 8%). Data for α-diol **S2**: R_f = 0.08 (33% EtOAc/hexanes); IR (film) 3410 (br), 2953, 2928, 2855 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03−5.93 (m, 1H), 4.84 (d, *J* = 17.2 Hz, 1H), 4.78 (d, *J* = 10.0 Hz, 1H), 4.16 (dd, *J* = 12.1, 4.1 Hz, 1H), 3.77 (br t, *J* = 7.6 Hz, 2H), 3.70−3.58 (m, 2H), 3.69 (br s, 1H), 3.41 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.58−2.39 (m, 2H), 2.19 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.04−1.89 (m, 2H), 1.85−1.70 (m, 2H), 1.69−1.56 (m, 2H), 1.44−1.21 (m, 4H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 184.1, 138.3, 114.1, 73.7, 71.7, 61.9, 59.4, 51.2, 45.7, 39.6, 34.3, 32.3, 32.0, 31.5, 26.0, 22.1, 18.3, 18.1, −3.8, −5.0; HRMS (CI) Exact mass calcd for $C_{22}H_{42}NO_3Si$ [M + H]$^+$ 396.2928 Found 396.2948.

2-((1*S*,2*S*,3*S*,5*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-3-hydroxy-2-(3-hydroxypropyl)-5-methylcyclohexyl)ethyl pivalate (44). BH_3·DMS (116 μL, 1.25 mmol) was added to alkene **41** (300 mg, 625 μmol) in THF (6.3 mL) at 0 °C. After 3.5 h, the reaction was quenched by the addition of 3 N NaOH (2.3 mL) and 30% H_2O_2 (1.5 mL) and was allowed to stir at rt overnight. The reaction was extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated to an oily solid. Column chromatography (SiO_2, 15−30−45−60% ethyl acetate in hexanes) yielded alcohol **44** as a colorless oil (87.1 mg, 28%), as well as recovered starting material (**41**) (65.8 mg, 22%). Data for **44**: R_f = 0.21 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ +28.6 (*c* 1.8, $CHCl_3$); IR (film)

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3403 (br), 2956, 2930, 2856, 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (br s, 1H), 4.30 (br s, 1H), 4.07−4.00 (m, 2H), 4.00−3.92 (m, 1H), 3.80 (ddd, J = 15.3, 7.7, 7.7 Hz, 1H), 3.77 (br s, 1H), 3.61 (ddd, J = 12.3, 6.4, 6.4 Hz, 1H), 3.55−3.47 (m, 1H), 2.68−2.56 (m, 2H), 2.53−2.44 (m, 1H), 2.32−2.23 (m, 1H), 1.96−1.75 (m, 5H), 1.57−1.44 (m, 2H), 1.43−1.33 (m, 2H), 1.22 (s, 9H), 1.12−1.01 (m, 1H), 0.97−0.90 (m, 12H), 0.08 (s, 6H), primary OH hydrogen was not observed; ^{13}C NMR (125 MHz, $CDCl_3$) ppm 184.0, 178.5, 73.6, 69.0, 63.5, 63.2, 59.6, 48.7, 45.2, 38.6, 33.6, 33.4, 30.4, 30.3, 28.3, 27.2, 25.9, 25.3, 21.8, 18.4, 18.0, −3.9, −5.0; HRMS (EI) Exact mass calcd for $C_{27}H_{52}NO_5Si$ $[M + H]^+$ 498.3610, found 498.3609.

(1*S*,2*S*,3*S*,3′*R*,4*S*,6*S*)-3′-(Bromomethyl)-3-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-4-methyl-2-(2-(pivaloyloxy)ethyl)-3′,5′,6′,7′-tetrahydro-2′*H*-spiro[cyclohexane-1,1′-pyrrolizin]-4′-ium bromide (45). NBS (83.0 mg, 463 μmol) was added to alkene **41** (117 mg, 244 μmol) in CH_2Cl_2 (2.4 mL) at 0 °C, and the reaction was stirred for 25 min. The solvent was concentrated in vacuo, and the residual oil was purified via flash column chromatography (SiO_2, 7−15% ethyl acetate in hexanes) to yield **45** as a colorless oil (72 mg, 46% yield): R_f = 0.54 (30% EtOAc/hexanes); IR (film) 2958, 2931, 2857, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39−4.33 (m, 1H), 4.34 (dd, J* = 10.2, 5.4 Hz, 1H), 4.11−4.04 (m, 2H), 3.89−3.76 (m, 2H), 3.81 (dd, J* = 13.4, 3.8 Hz, 1H), 3.52 (dd, J = 10.1, 5.6 Hz, 1H), 3.39 (dd, J = 10.1, 6.6 Hz, 1H), 2.68−2.59 (m, 1H), 2.52−2.44 (m, 1H), 2.47 (dd, J = 9.6, 6.6 Hz, 1H), 2.22−2.14 (m, 1H), 2.07−1.98 (m, 1H), 2.01 (ddd, J* = 12.8, 12.8, 5.2 Hz, 1H), 1.85−1.73 (m, 4H), 1.70 (dd, J = 12.7, 8.1 Hz, 1H), 1.67 (ddd, J = 10.2, 4.8, 4.8 Hz, 1H), 1.20 (s, 9H), 1.03 (d, J = 7.6 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H), OH hydrogen was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 178.8, 176.9, 81.8, 78.1, 73.8, 65.2, 60.7, 56.0, 44.8, 43.3, 38.9, 38.4, 36.1, 34.2, 30.5, 29.5, 27.5, 26.2, 22.4, 18.3, 13.6, −4.0, −4.5; HRMS (CI) Exact mass calcd for $C_{27}H_{48}Br^{81}BrNO_4Si$ $[M - H]^+$ 638.1693, found 638.1696. J* indicates that the coupling constant was obtained using a 1D-TOCSY to separate overlapping peaks. 2D NMR assignments of **45** can be found in Supporting Information 2.

(1*S*,2*S*,3*S*,3′*S*,4*S*,6*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-3′,4-dimethyl-2-(2-(pivaloyloxy)-ethyl)-3′,5′,6′,7′-tetrahydro-2′*H*-spiro[cyclohexane-1,1′-pyrrolizin]-4′-ium bromide (46). To a stirred solution of bromide **45** (6.0 mg, 9.4 μmol) in C_6H_6 (1 mL) was added ^{n}Bu_3SnH (7.6 μL, 28 μmol) and AIBN (3.1 mg, 18.8 μmol), and the reaction mixture was heated at 80 °C for 30 min. After cooling to rt, the reaction mixture was treated with 1 N NaOH (0.5 mL) with vigorous stirring for 30 min. The product was extracted with Et_2O, and the combined organic layers were dried, filtered and concentrated to yellow oil. Flash column chromatography (SiO_2, 8−15% ethyl acetate in hexanes) yielded **46** as colorless oil (2.7 mg, 59%): R_f = 0.55 (25% EtOAc/hexanes); $[\alpha]_D^{22}$ +18.0 (c 0.3, $CHCl_3$); IR (film) 2960, 2925, 2858, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (dd, J = 10.4, 5.6 Hz, 1H), 4.31−4.24 (m, 1H), 4.12−4.02 (m, 2H), 3.89−3.78 (m, 2H), 3.77 (dd, J = 13.2, 3.6 Hz, 1H), 2.69−2.61 (m, 1H), 2.52−2.44 (m, 1H), 2.38 (dd, J = 12.4, 6.8 Hz, 1H), 2.21−2.14 (m, 1H), 2.05−1.97 (m, 2H), 1.86−1.79 (m, 1H), 1.78−1.70 (m, 3H), 1.67−1.61 (m, 1H), 1.57 (br s, 1H); 1.48 (dd, J = 12.4, 8.0 Hz, 1H), 1.29 (d, J = 6.2 Hz, 3H), 1.20 (s, 9H), 1.04 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 178.8, 177.6, 80.1, 74.8, 73.8, 65.4, 60.7, 56.1, 46.0, 45.0, 38.9, 38.4, 34.3, 30.7, 29.4, 27.5, 26.2, 22.6, 22.4, 18.4, 13.7, −4.0, −4.5; HRMS (CI) Exact mass calcd for $C_{27}H_{50}NO_4Si$ $[M - Br]^+$ 480.3504, found 480.3506. 2D NMR assignments of **46** can be found in Supporting Information 2.

(1*R*,2*S*,3*S*,4*S*,6*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-4-methyl-2-(2-(pivaloyloxy)ethyl)-1′,2′,3′,5′,6′,7′-hexahydrospiro[cyclohexane-1,8′-indolizin]-4′-ium bromide (*epi*-49). Bromine (4.9 μL, 97 μmol) was added to a stirred solution of alcohol **44** (24.1 mg, 48.4 μmol), PPh_3 (25 mg, 97 μmol), and imidazole (6.6 mg, 97 μmol) in benzene (1 mL) at rt. After 8 min, the reaction was quenched with satd aq $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated in vacuo to provide a colorless oily solid. The crude was dissolved in $CDCl_3$ for ^1H NMR analysis and after was allowed to sit for 1−2 d (until TLC revealed the disappearance of the primary bromide, **48**, not isolated). Column chromatography (SiO_2, 80% ethyl acetate in hexanes then 5−12% methanol in dichloromethane) provided *epi*-**49** as a colorless oil (21.8 mg, 78%): R_f = 0.15 (10% MeOH/CH_2Cl_2); IR (film) 3417 (br), 2958, 2930, 2857, 1721, 1669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.55 (br s, 1H), 4.89−4.81 (m, 1H), 4.39 (br t, J = 7.5 Hz, 1H), 4.24−4.12 (m, 2H), 4.11 (ddd, J = 10.3, 10.3, 6.5 Hz, 1H), 3.99 (ddd, J = 10.1, 10.1, 5.3 Hz, 1H), 3.87−3.80 (m, 1H), 3.68 (dd, J = 10.5, 4.9 Hz, 1H), 3.57−3.49 (m, 1H), 3.30−3.20 (m, 1H), 2.80−2.72 (m, 1H), 2.58−2.49 (m, 1H), 2.32 (ddd, J = 13.9, 6.5, 6.5 Hz, 1H), 2.26−2.16 (m, 1H), 2.13−2.06 (m, 1H), 1.98−1.93 (m, 1H), 1.90−1.81 (m, 3H), 1.75−1.67 (m, 1H), 1.57 (ddd, J = 14.3, 9.7, 4.8 Hz, 1H), 1.16 (s, 9H), 1.04 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), OH not observed; ^{13}C NMR (125 MHz, $CDCl_3$) ppm 194.2, 178.6, 73.5, 68.2, 64.2, 63.1, 53.2, 48.5, 38.8, 38.7, 36.0, 34.7, 33.9, 29.9, 27.1, 25.9, 20.5, 19.4, 18.2, 18.1, 11.9, −4.2, −4.8; HRMS (CI) Exact mass calcd for $C_{27}H_{50}NO_4Si$ $[M]^+$ 480.3504, found 480.3519.

2-((1*R*,2*S*,4*S*,5*S*,6*S*,8*a*′*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-4-methylhexahydro-1′*H*-spiro[cyclohexane-1,8′-indolizin]-6-yl)ethyl pivalate (50). PtO_2 (8.0 mg, 36 μmol) was added to salt *epi*-**49** (10.0 mg, 17.8 μmol) in MeOH (500 μL), and 1 atm of hydrogen (H_2) was administered via a balloon. After 5 h, the reaction was complete as indicated by TLC and was filtered through Celite, rinsing with MeOH and then concentrated. The crude oil was chromatographed (SiO_2, 5−10% methanol in dichloromethane) to provide amine **50** as a colorless oil (7.2 mg, 83%): R_f = 0.30 (10% MeOH/CH_2Cl_2); IR (film) 3380 (br), 2957, 2929, 2856, 1726 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) δ 12.10−11.75 (br s, 1H), 4.89−4.83 (s, 1H), 4.06 (ddd, J = 11.2, 5.9, 5.9 Hz, 1H), 4.02−3.92 (m, 2H), 3.71 (s, 1H), 3.39−3.28 (m, 2H), 3.13−3.06 (m, 1H), 2.62−2.56 (m, 1H), 2.42−2.35 (m, 1H), 2.33 (d, J = 13.4 Hz, 1H), 2.25−2.14 (m, 2H), 2.14−2.09 (m, 1H), 2.07−1.96 (m, 3H), 1.96−1.90 (m, 1H), 1.74−1.69 (m, 1H), 1.66−1.61 (m, 1H), 1.58−1.52 (m, 2H), 1.20 (s, 9H), 1.10 (dd, J = 13.2, 12.9 Hz, 1H), 0.93−0.88 (m, 12H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 178.5, 74.7, 67.3, 66.2, 64.0, 54.2, 46.0, 44.1, 39.6, 38.7, 31.9, 27.9, 27.2 (3C), 26.0 (3C), 24.6, 23.1, 22.0, 18.35, 18.31, 18.2, 17.9, −3.3, −4.5; HRMS (CI) Exact mass calcd for $C_{27}H_{51}NO_4Si$ $[M]^+$ 481.3582, found 481.3589.

(1*R*,2*S*,3*S*,4*S*,6*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-4-methyl-2-(2-(pivaloyloxy)ethyl)-1′,2′,3′,5′,6′,7′-hexahydrospiro[cyclohexane-1,8′-indolizin]-4′-ium trifluoromethanesulfonate (51). Upon stirring *epi*-**49** in CH_2Cl_2 with excess TESOTf, the bromide counterion could be exchanged for a triflate counterion resulting in **51**: R_f = 0.20 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ +4.0 (c 0.05, $CHCl_3$); IR (film) 3424 (br), 2959, 2932, 2858, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.69−4.61 (m, 1H), 4.30 (dd, J = 10.2, 6.2 Hz, 1H), 4.29−4.20 (m, 1H), 4.10 (ddd, J = 10.3, 10.3, 6.3 Hz, 1H), 3.99 (ddd, J = 10.2, 10.2, 5.4 Hz, 1H), 3.90−3.83 (m, 1H), 3.78−3.67 (m, 1H), 3.70 (dd, J = 10.4, 5.0 Hz, 1H), 3.59−3.51 (m, 1H), 3.36−3.27 (m, 1H), 2.70−2.60 (m, 1H), 2.50−2.41 (m, 1H), 2.37−2.26 (m, 2H), 2.17−2.10 (m, 1H), 1.96−1.86 (m, 4H), 1.76−1.67 (m, 1H), 1.53 (ddd, J = 14.7, 10.8, 4.6 Hz, 1H), 1.20 (s, 9H), 1.09−1.03 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), OH not observed; ^{13}C NMR (125 MHz, $CDCl_3$) ppm 193.8, 178.7, 73.3, 68.6, 64.2, 62.5, 53.0, 48.5, 39.0, 38.6, 34.9, 34.5, 33.8, 29.5, 27.1, 25.8, 20.2, 19.3, 18.0, 17.8, 11.8, −4.3, −4.8. The $CF_3SO_3^-$ (triflate) carbon was not observed by ^{13}C NMR, but a peak was observed at −76.5 ppm in the ^{19}F NMR. HRMS (ESI) Exact mass calcd for $C_{27}H_{50}NO_4Si$ $[M]^+$ 480.3509, found 480.3510. A crystal structure of triflate salt **51**, which supports the expected epimerization at the spirocyclic carbon, can be found in Supporting Information 2.

2-((1*S*,2*S*,3*S*,5*S*,6*S*)-2-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-5-methyl-3-((methylsulfonyl)oxy)-cyclohexyl)ethyl pivalate (53). To a stirred solution of alcohol **41** (400 mg, 834 μmol) and triethylamine (255 μL, 1.83 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added methanesulfonyl chloride (124 μL, 1.08 mmol). The reaction was stirred for 30 min before it was warmed to rt and stirred for 15 min. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were

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dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2, 10−20% ethyl acetate in hexanes) provided the mesylate **53** as a pale yellow oil (464 mg, 100%): R_f = 0.70 (50% EtOAc/hexanes); $[\alpha]_D^{24}$ +18.0 (*c* 1.0, $CHCl_3$); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48−5.38 (m, 1H), 5.20 (br s, 1H), 4.98−4.90 (m, 2H), 4.10−3.98 (m, 2H), 3.89−3.80 (m, 1H), 3.78 (br s, 1H), 3.78−3.71 (m, 1H), 3.34 (dd, *J* = 15.0, 9.0 Hz, 1H), 3.07 (s, 3H), 2.71−2.62 (m, 1H), 2.41 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1H), 2.30 (br s, 1H), 2.17 (dd, *J* = 15.0, 4.0 Hz, 1H), 1.98 (br d, *J* = 11.5 Hz, 1H), 1.93−1.82 (m, 3H), 1.81−1.64 (m, 2H), 1.50−1.40 (m, 1H), 1.20 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 178.4, 177.0, 133.2, 117.6, 83.3, 73.1, 63.3, 59.7, 49.0, 44.5, 41.4, 38.8, 38.7, 33.7, 30.3, 30.0, 27.2, 25.9, 25.7, 22.4, 18.0 (2C), −3.9, −4.9; HRMS (ESI) Exact mass calcd for $C_{28}H_{52}NO_6SSi$ $[M + H]^+$ 558.3285, found 558.3278.

2-((1*S*,2*S*,3*S*,4*R*,6*S*)-3-Allyl-3-(3,4-dihydro-2*H*-pyrrol-5-yl)-6-methyl-7-oxabicyclo[2.2.1]heptan-2-yl)ethyl pivalate (54). TBAF (80.0 μL, 80.0 μmol) was added to silyl ether **53** (15.0 mg, 26.8 μmol) in THF (0.5 mL), and the reaction was refluxed for 2 h, quenched with satd aq $NaHCO_3$, and extracted with ether. The combined organic layers were dried, filtered, and concentrated to a crude oil that was purified via column chromatography (SiO_2, 12−25−50% ethyl acetate in hexanes) to furnish cyclic ether **54** as a yellow oil (7.5 mg, 81%): R_f = 0.60 (50% EtOAc/hexanes); $[\alpha]_D^{24}$ −12.6 (*c* 1.5, $CHCl_3$); IR (film) 2956, 2928, 2858, 1744, 1709 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.56 (dddd, *J* = 16.8, 10.2, 7.8, 6.6 Hz, 1H), 5.04 (d, *J* = 16.8 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 4.28 (d, *J* = 5.4 Hz, 1H), 4.07 (d, *J* = 4.8 Hz, 1H), 4.04−3.95 (m, 2H), 3.84−3.74 (m, 2H), 2.55−2.49 (m, 2H), 2.33−2.25 (m, 3H), 2.13 (dddd, *J* = 9.0, 6.6, 6.6, 3.6 Hz, 1H), 2.06 (ddd, *J* = 5.4, 5.4, 5.4 Hz, 1H), 1.95 (dd, *J* = 12.0, 8.4 Hz, 1H), 1.81−1.70 (m, 3H), 1.20 (s, 9H), 1.16 (ddd, *J* = 12.6, 5.4, 4.2 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 178.7, 177.7, 133.8, 117.8, 86.8, 84.2, 64.3, 60.5, 53.6, 47.2, 45.4, 38.7, 37.5, 35.5, 29.7, 27.4, 27.2, 22.2, 21.2; HRMS (ESI) Exact mass calcd for $C_{21}H_{34}NO_3$ $[M + H]^+$ 348.2539, found 348.2533.

2-((1*S*,2*S*,3*S*,5*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-(3-hydroxypropyl)-5-methyl-3-((methylsulfonyl)oxy)cyclohexyl)ethyl pivalate (55). BH_3·DMS (34.1 μL, 353 μmol) was added to alkene **53** (93.0 mg, 168 μmol) in THF (1.7 mL) at 0 °C. The reaction was stirred for 2 h before being warmed to rt and stirred for another 1 h. The reaction was cooled to 0 °C, quenched by the addition of 3 N NaOH (650 μmol) and 30% H_2O_2 (500 μmol) and was allowed to stir at rt overnight. The reaction was extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated to an oily solid. The residue was redissolved in CH_2Cl_2 (1 mL) and treated with DMAP (205 mg, 1.68 mmol) at rt for 7 d before it was filtered, concentrated, and purified via flash column chromatography (SiO_2, 20−35%-50% ethyl acetate in hexanes) to afford alcohol **55** as a colorless oily solid (48 mg, 50%) in addition to recovered starting material (**53**) (22 mg, 23%): R_f = 0.30 (50% EtOAc/hexanes); $[\alpha]_D^{24}$ −20.0 (*c* 0.6, $CHCl_3$); IR (film) 2956, 2928, 2858, 1744, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (br s, 1H), 3.96 (br s, 1H), 3.85−3.81 (m, 2H), 3.68−3.63 (m, 2H), 3.48 (br s, 1H), 3.08 (s, 1H), 3.07 (br s, 1H), 2.81 (br s, 1H), 2.55−2.50 (m, 2H), 2.50−2.45 (m, 1H), 2.07−2.84 (m, 7H), 1.87−1.84 (m, 1H), 1.40−1.36 (m, 1H), 1.19−1.16 (m, 10H), 0.95−0.91 (m, 15H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 178.4 (2C), 83.6, 72.5, 63.5, 63.0, 59.8, 48.5, 39.3, 38.7, 34.2, 32.9, 32.0, 31.3, 30.3, 28.1, 27.2, 26.0, 22.3, 18.0, 17.9, 14.2, −3.8, −4.9; HRMS (ESI) Exact mass calcd for $C_{28}H_{54}NO_7SSi$ $[M + H]^+$ 576.3390, found 576.3378.

2-((1*S*,2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-5-methyl-3-((methylsulfonyl)oxy)-cyclohexyl)ethyl pivalate (57). To a solution of alcohol **60** (283 mg, 590 μmol) and triethylamine (181 μL, 1.30 mmol) in CH_2Cl_2 (7.0 mL) at 0 °C was added methanesulfonyl chloride (60.1 μL, 767 μmol). The reaction was stirred for 30 min at 0 °C and then for 15 min at rt. The reaction was quenched with satd aq NH_4Cl, extracted with CH_2Cl_2, and the combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2, 10−20% ethyl acetate in hexanes) provided mesylate **57** as a thick colorless oil (291 mg, 89%): R_f = 0.68 (50% EtOAc/hexanes); $[\alpha]_D^{24}$ −44.8 (*c* 1.45, $CHCl_3$); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (dddd, *J* = 17.0, 10.0, 8.0, 6.0 Hz, 1H), 5.31 (dd, *J* = 12.0, 5.0 Hz, 1H), 4.94 (d, *J* = 16.5, Hz, 1H), 4.87 (d, *J* = 10.0 Hz, 1H), 3.98−3.95 (m, 2H), 3.84−3.70 (m, 2H), 3.65 (br s, 1H), 3.48 (br s, 1H), 3.07 (s, 3H), 2.55 (ddd, *J* = 8.5, 8.5, 8.5 Hz, 1H), 2.40 (ddd, *J* = 8.5, 8.5, 8.5 Hz, 1H), 2.33 (dd, *J* = 8.5, 8.0 Hz, 1H), 2.10−1.88 (m, 3H), 1.84−1.78 (m, 2H), 1.65 (br s, 1H), 1.50−1.38 (m, 2H), 1.19 (s, 9H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 178.4 (2C), 136.9, 115.5, 83.1, 72.5, 62.1, 59.6, 49.6, 47.9, 40.4, 39.3, 38.7, 34.6, 32.7, 31.1, 27.9, 27.2, 26.0, 22.4, 18.0 (2C), −3.8, −4.9; HRMS (ESI) Exact mass calcd for $C_{28}H_{52}NO_6SSi$ $[M + H]^+$ 558.3285, found 558.3287.

2-((1*S*,2*R*,4*S*,5*S*,6*S*,8*a*′*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-2-((methylsulfonyl)oxy)-hexahydro-1′*H*-spiro[cyclohexane-1,8′-indolizin]-6-yl)ethyl pivalate (58). PtO_2 (71.0 mg, 313 μmol) was added to salt **62** (91.1 mg, 143 μmol) in MeOH (4.0 mL), and a balloon atmosphere of hydrogen (H_2) was administered. After 5 h, the reaction was complete as indicated by TLC and was filtered through Celite using MeOH and then concentrated. The crude oil was chromatographed (SiO_2, 5−10% methanol in dichloromethane) to provide amine **58** as a colorless oil (45.3 mg, 57%): R_f = 0.30 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ −11.4 (*c* 1.4, $CHCl_3$); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.24 (br s, 1H), 4.14−4.06 (m, 2H), 3.88 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.09 (s, 3H), 3.05 (br s, 1H), 2.15−2.14 (m, 1H), 2.12−2.06 (m, 1H), 2.02 (ddd, *J* = 14.4, 4.2, 4.2 Hz, 1H), 1.95 (ddd, *J* = 6.6, 6.6, 6.6 Hz, 1H), 1.91−1.70 (m, 12H), 1.59 (br s, 1H), 1.49 (dddd, *J* = 13.8, 7.2, 7.2, 4.8 Hz, 1H), 1.19 (s, 9H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 178.6, 82.0, 71.6, 64.8, 63.6, 53.1, 46.7, 42.0, 40.9, 39.2, 31.3, 30.2, 29.7, 27.2, 25.9, 25.8, 25.7, 23.7, 18.9 (2C), 18.5, 17.9, −3.6, −4.9; HRMS (ESI) Exact mass calcd for $C_{28}H_{54}NO_6SSi$ $[M + H]^+$ 560.3434, found 560.3441.

2-((1*S*,2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-3-hydroxy-5-methylcyclohexyl)-ethyl pivalate (60). To ketone **37** (100 mg, 209 μmol) in THF (2 mL) at 0 °C was added $NaBH_4$ (40 mg, 1.1 mmol), and the reaction was stirred for 10 min before being warmed to rt and stirred for 72 h. The reaction was cooled to 0 °C, quenched with butyraldehyde (103 μL, 1.20 mmol), and allowed to warm to rt for 20 min before adding satd aq NH_4OH. The reaction mixture was extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2, 10−15−20−25% ethyl acetate in hexanes) provided α-alcohol **60** (55.5 mg, 55%), the epimeric β-alcohol (**41**) (12 mg, 12%), and recovered starting material (**37**) (5.4 mg, 5%). Data for **60**: R_f = 0.27 (30% EtOAc/hexanes); IR(film) 2956, 2932, 2855, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02−5.93 (m, 1H), 4.96 (br s, 1H), 4.85 (d, *J* = 17.0 Hz, 1H), 4.78 (d, *J* = 9.9 Hz, 1H), 4.17 (dd, *J* = 12.1, 3.9 Hz, 1H), 4.05−4.00 (m, 2H), 3.84−3.71 (m, 2H), 3.68 (br s, 1H), 3.40 (dd, *J* = 15.3, 5.7 Hz, 1H), 2.56 (ddd, *J* = 16.4, 9.4, 5.4 Hz, 1H), 2.43 (ddd, *J* = 16.8, 9.4, 7.6 Hz, 1H), 2.17 (dd, *J* = 15.3, 8.8 Hz, 1H), 1.99−1.88 (m, 2H), 1.87−1.79 (m, 1H), 1.76 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H), 1.76−1.70 (m, 1H), 1.60 (ddd, *J* = 12.8, 3.8, 3.8 Hz, 1H), 1.47 (dddd, *J* = 16.0, 11.7, 4.8, 4.8 Hz, 1H), 1.37−1.30 (m, 1H), 1.20 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 184.0, 178.7, 138.4, 114.4, 73.3, 71.7, 63.5, 60.7, 51.3, 46.2, 39.9, 39.0, 34.3, 32.1, 31.7, 38.7, 27.5, 26.2, 22.3, 18.6, 18.3, −3.5, −4.7; HRMS (CI) Exact mass calcd for $C_{27}H_{50}NO_4Si$ $[M + H]^+$ 480.3504, found 480.3501. 2D NMR spectra of α-alcohol **60** are described in the Supporting Information 2.

2-((1*S*,2*S*,3*R*,5*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-(3-hydroxypropyl)-5-methyl-3-((methylsulfonyl)oxy)cyclohexyl)ethyl pivalate (61). BH_3·DMS (102 μL, 1.06 mmol) was added to alkene **57** (279 mg, 504 μmol) in THF (5.0 mL) at 0 °C. The reaction was stirred for 2 h before being warmed to rt and stirred for another 1 h. The reaction was cooled to 0

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°C, quenched by the addition of 3 N NaOH (2.0 mL) and 30% H_2O_2 (1.5 mL) and was allowed to stir at rt overnight. The reaction was extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated to an oily solid. The residue was redissolved in CH_2Cl_2 (3 mL) and treated with DMAP (610 mg, 5.01 mmol) at rt for 7 d before it was filtered, concentrated, and purified via flash column chromatography (SiO_2, 20−40−60% ethyl acetate in hexanes) to yield alcohol **61** as a colorless, thick oil (228 mg, 79%): R_f = 0.24 (50% EtOAc/hexanes); $[\alpha]_D^{24}$ −18.2 (*c* 0.55, $CHCl_3$); IR (film) 2956, 2928, 2858, 1744, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (br s, 1H), 3.96 (br s, 1H), 3.85−3.81 (m, 2H), 3.68−3.63 (m, 2H), 3.48 (br s, 1H), 3.08 (s, 1H), 3.07 (br s, 1H), 2.81 (br s, 1H), 2.55−2.50 (m, 2H), 2.50−2.45 (m, 1H), 2.07−2.84 (m, 7H), 1.87−1.84 (m, 1H), 1.40−1.36 (m, 1H), 1.19−1.16 (m, 10H), 0.95−0.91 (m, 15H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 178.4 (2C), 83.6, 72.5, 63.5, 63.0, 59.8, 48.5, 39.3, 38.7, 34.2, 32.9, 32.0, 31.3, 30.3, 28.1, 27.2, 26.0, 22.3, 18.0, 17.9, 14.2, −3.8, −4.9; HRMS (ESI) Exact mass calcd for $C_{28}H_{54}NO_7SSi$ $[M + H]^+$ 576.3390, found 576.3395.

(1*S*,2*S*,3*R*,4*S*,6*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-6-((methylsulfonyl)oxy)-2-(2-(pivaloyloxy)ethyl)-1′,2′,3′,5′,6′,7′-hexahydrospiro[cyclohexane-1,8′-indolizin]-4′-ium bromide (62). Bromine (25.2 μL, 493 μmol) was added to a solution of alcohol **61** (142 mg, 247 μmol), PPh_3 (67 mg, 249 μmol), and imidazole (33.5 mg, 493 μmol) in benzene (8 mL) at rt. After 10 min, the reaction was quenched with satd aq $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated in vacuo to provide a pale yellow oily solid. The crude was dissolved in $CHCl_3$ (5 mL) and allowed to sit for 1 d (until TLC revealed the disappearance of the primary bromide). The solvent was removed, and the resulting crude oil was purified by column chromatography (SiO_2, 80% ethyl acetate in hexanes then 5−12% methanol in dichloromethane) to afford **62** as a colorless oil (120 mg, 76%): R_f = 0.12 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ −21.4 (*c* 1.05, $CHCl_3$); IR (film) 2956, 2928, 2858, 1744, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (dd, *J* = 9.0, 4.0 Hz, 1H), 4.85 (dd, *J* = 12.5, 9.0 Hz, 1H), 4.34−4.20 (m, 2H), 4.18 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 4.10 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 3.98 (dd, *J* = 16.0, 7.0 Hz, 1H), 3.75 (br s, 1H), 3.75−3.62 (m, 1H), 3.39 (s, 3H), 3.35−3.22 (m, 1H), 3.01 (br d, *J* = 13.5 Hz, 1H), 2.52−2.40 (m, 2H), 2.34−2.26 (m, 1H), 2.22 (ddd, *J* = 12.5, 9.0, 9.0 Hz, 1H), 2.18−2.11 (m, 2H), 2.07 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 2.03−1.90 (m, 2H), 1.82−1.73 (m, 1H), 1.71−1.63 (m, 1H), 1.19 (s, 9H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.98 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 193.0, 178.3, 78.2, 72.2, 62.9, 62.3, 49.6, 47.4, 45.8, 40.9, 39.1, 38.7, 31.0, 30.4, 29.7, 28.7, 27.1, 25.7, 19.9, 19.0, 17.9, 16.8, −3.7, −5.0; HRMS (ESI) Exact mass calcd for $C_{28}H_{52}NO_6SSi$ $[M - Br]^+$ 558.3285, found 558.3292.

(1*S*,2*S*,3*S*,4*S*,6*R*,8*a*′*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-(2-hydroxyethyl)-4-methylhexahydro-1′*H*-spiro[cyclohexane-1,8′-indolizin]-6-yl methanesulfonate (63). To a solution of pivalate **58** (42.2 mg, 75.0 μmol) in CH_2Cl_2/toluene (1:1, 4.0 mL) at 78 °C was added DIBAL (375 μL, 375 μmol, 1.0 M solution in toluene). The reaction was stirred for 30 min before being warmed to −5 °C and stirred for 5 h. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated to a pale yellow oil. Column chromatography (SiO_2, 10−15% methanol in dichloromethane) provided alcohol **63** as a yellow oil (18.0 mg, 54%): R_f = 0.11 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ −32.1 (*c* 0.95, $CHCl_3$); IR (film) 3396 (br), 2956, 2928, 2858, 1628 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.72 (br d, *J* = 6.0 Hz 1H), 3.82 (br d, *J* = 10.8 Hz 1H), 3.70 (s, 1H), 3.65 (dd, *J* = 7.8, 2.4 Hz, 1H), 3.40 (br s, 1H), 3.35−3.31 (m, 1H), 3.06 (s, 3H), 2.79 (br d, *J* = 18.0 Hz, 1H), 2.71 (br s, 1H), 2.60 (br t, *J* = 10.8 Hz, 1H), 2.35−2.28 (m, 2H), 2.22−1.85 (m, 7H), 1.72−1.60 (m, 5H), 0.94 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.88−0.81 (m, 1H), 0.28 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 82.2, 73.4, 65.2, 60.6, 53.0, 46.8, 42.0, 41.4, 40.8, 31.9, 31.3, 31.2, 30.4, 26.0, 22.7, 19.1, 18.0 (2C), 14.1, −3.9, −5.0; HRMS (EI) Exact mass calcd for $C_{23}H_{46}NO_5SSi$ $[M + H]^+$ 476.2866, found 476.2863.

(4*S*,5*S*,*E*)-Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-5-methyl-7-oxohept-2-enoate (S1). Dess−Martin periodinane[72] (30.5 g, 71.9 mmol) was added to alcohol **17** (11.4 g, 36.0 mmol) in CH_2Cl_2 (200 mL) at rt and stirred for 2 h. By TLC, the reaction was complete and therefore quenched by the addition of an aqueous solution containing 2:1 satd aq $Na_2S_2O_3$:$NaHCO_3$ and was stirred until both layers became clear (∼20 min). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried, filtered, and concentrated to a cloudy oil (**S1**), which was pure enough for characterization and could be carried on directly to form **19** (11.0 g, 97%). Data for **S1**: R_f = 0.40 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ −5.1 (*c* 0.5, $CHCl_3$); IR (film) 2957, 2932, 2887, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79−9.77 (m, 1H), 6.88 (dd, *J* = 15.6, 5.2 Hz, 1H), 6.00 (dd, *J* = 15.6, 1.6 Hz, 1H), 4.23 (qd, *J* = 7.1, 1.7 Hz, 2H), 4.22−4.19 (m, 1H), 2.57−2.50 (m, 1H), 2.31 (ddd, *J* = 16.1, 8.4, 2.1 Hz, 1H), 2.31−2.24 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 201.9, 166.2, 148.6, 121.8, 75.1, 60.4, 45.8, 34.1, 25.8, 18.1, 16.6, 14.1, −4.4, −5.0; HRMS (CI) Exact mass calcd for $C_{16}H_{30}O_4NaSi$ $[M + Na]^+$ 337.1811, found 337.1798.

■ ASSOCIATED CONTENT

Supporting Information

Includes ^1H and ^{13}C NMR spectra of all new compounds not previously reported including the title compound (**1**), **S1** (precursor to **19**), and **S2** (formed along with **42**), along with X-ray data (CIF) for **31** (co-crystallized with **S4**), **42**, and **51**, and select 2D data used for structural assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(70) To add the Red-Al/toluene rapidly, after pulling the correct amount of stock solution into the syringe, the needle was removed as well as the septum from the reaction flask, and the Red-Al was added directly to the reaction in one portion. The 1.67 M stock solution manages to dilute the Red-Al some, but it is still a relatively thick solution, and best yields were obtained by this method.

(71) CH_3CN was degassed by three cycles of freeze−pump−thaw under a high vacuum and back-filling with either argon or nitrogen.

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