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Application of the Aza-Achmatowicz Oxidative Rearrangement for the Stereoselective Synthesis of the *Cassia* and *Prosopis* Alkaloid Family

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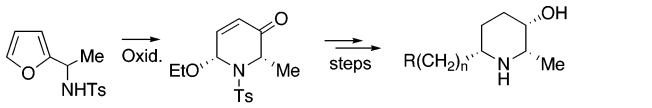

azimic acid; R = CO_2H; n = 5
deoxocassine; R = C_2H_5; n = 10
cassine; R = CH_3CO; n = 10
spicigerine; R = CO_2H; n = 11

cis-2-Methyl-6-substituted piperidin-3-ol alkaloids of the *Cassia* and *Prosopis* species are readily prepared by a combination of an aza-Achmatowicz oxidative rearrangement and dihydropyridone reduction followed by a stereoselective allylsilane addition to a *N*-sulfonyliminium ion. The stereochemical outcome of the reduction reaction can be attributed to steric hindrance between the pseudoaxially oriented 2,6-substituents and the equatorially approaching hydride reagent which explains the exclusive formation of the *cis*-alcohol by axial approach of the hydride. The unsaturation present in the (*E*)-methyl-pent-3-enoate side chain was removed by catalytic reduction, and the remaining ester group was converted to the corresponding Weinreb's amide. This key intermediate was utilized for the synthesis of azimic acid, deoxocassine, cassine, and spicigerine. The facile preparation of (*S*)-*N*-tosylamidofuran **16** and its conversion to the chiral Achmatowicz oxidation product **18** provide a formal chiral synthesis of these alkaloids.

Introduction

The piperidine ring system is a frequently encountered heterocyclic unit found in many naturally occurring and biologically important compounds.[1] In particular, 2,6-disubstituted piperidines have attracted much attention because they often appear in various ring forms and exhibit a broad range of biological activities.[2] As a consequence, numerous synthetic methods have been developed for the stereoselective synthesis of 2,6-disubstituted piperidines.[3] Most of the earlier procedures have been directed toward the synthesis of simple *cis*-[4] or *trans*-2,6-dialkylpiperidines.[5] The stereoselective synthesis of more complex polysubstituted piperidines still remains a substantial challenge in organic chemistry.[6] Among this class of products, 2,6-disubstituted 3-piperidinol alkaloids are frequently encountered in biologically active natural products (Figure 1).[7]

A small yet important subgroup of the piperidin-3-ol alkaloids which are of continuing interest to synthetic chemists are those of the *Cassia* and *Prosopis* species, found in leaves and twigs throughout the world.[8] The characteristic framework of these natural products is the *cis*-2-methyl-6-substituted piperidin-3-

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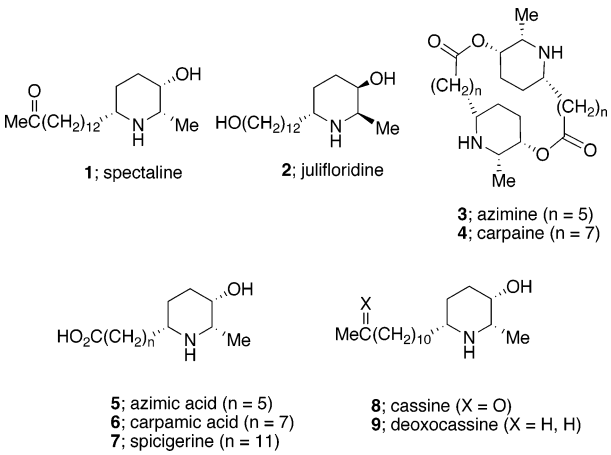

FIGURE 1. Some representative 2,6-disubstituted piperidin-3-ol alkaloids.

ol skeleton.[9,10] Structural variation is found in the long aliphatic side chain appended at C_6 which provides for a number of different stereochemical and oxygenation patterns (Figure 1). Typical representatives of this family include spectaline (**1**), julifloridine (**2**), azimine (**3**), and carpaine (**4**). The latter two structures correspond to macrocyclic dilactones containing two molecules of the characteristic 2-methyl-3-piperidinol skeleton with a carboxyl group as a terminal substituent at the C_6 position.[11,12] They are readily hydrolyzed to azimic (**5**) and carpamic acid (**6**), which are presumably their biological precursors. Since their discovery in the 1960s, much effort has been directed to the synthesis of these and other related alkaloids such as cassine (**8**) and deoxocassine (**9**).[13] Besides the interesting structural features, these alkaloids are also of pharmaceutical interest as they exhibit a wide range of biological activities.[14] The physiological effects stem from their ability to mimic carbohydrate substrates in a variety of enzymatic processes.

Because of their medicinal potential and characteristic all-cis relative stereochemistry, the *Cassia* and *Prosopis* alkaloids are of special synthetic significance, and many have been prepared using a wide variety of methods.[15,16] Methods also exist for the synthesis of the corresponding trans isomers.[17] One of the earliest routes to (±)-carpamic acid (**6**) relied on singlet oxygen addition to a functionalized pyridine as the key step.[18] More recently, Lee and co-workers demonstrated the usefulness of a two-carbon homologation of β-lactams to access the piperidine core.[19] Kumar and Datta reported a stereoselective total synthesis of (+)-azimic acid (**5**) starting with L-alanine.[20] Kibayashi demonstrated an elegant route to azimic acid (**5**) employing a hetero Diels−Alder cycloaddition.[21] Finally, Trost and co-workers reported a route to (+)-spectaline (**1**) using a hydrosilylation−oxidation strategy.[22]

Despite the availability of many synthetic methods for this class of compounds, there still exists a need to develop procedures more efficient than those currently in existence. In connection with our ongoing studies on natural product synthesis based on amidofuran chemistry,[23] we became interested in employing *N*-tosylaminofurans for the synthesis of various cis-2,3,6-trisubstituted piperidine alkaloids. Pioneering work by the Ciufolini group[24] demonstrated that the aza-Achmatowicz reaction can be used for the preparation of various nitrogenous ring systems. This novel oxidative ring expansion reaction has been employed for the synthesis of azasaccharides,[25] izidine structures,[26] β-lactam intermediates,[27] and unusual amino acids[28] and, we believe, possesses significant potential for the preparation of a variety of piperidinol alkaloids. In an earlier study from our laboratory,[29] we showed that the aza-Achmatowicz oxidation of a furyl-substituted benzenesulfonamide could be used for the synthesis of the putative indolizidine alkaloid 223A,

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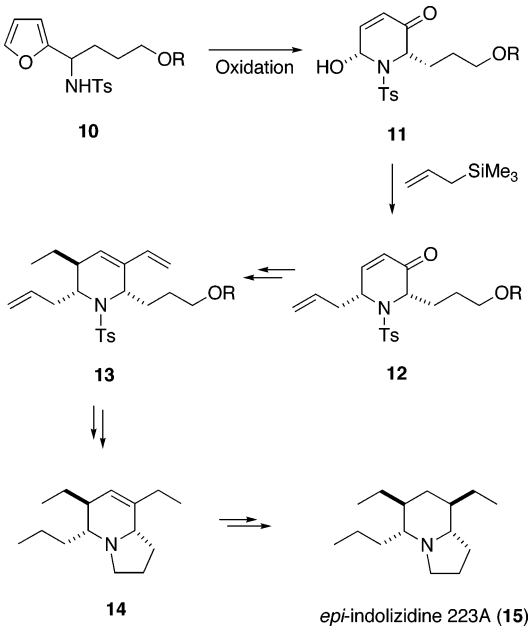
SCHEME 1. Synthesis of *epi*-Indolizidine 223A Using an Aza-Achmatowicz Oxidation



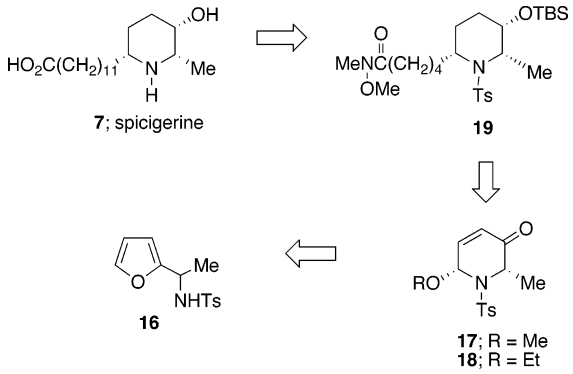
which had been isolated from the skin secretion of a neotropical frog.[30] The approach that we employed is shown in Scheme 1 and involved a flexible combination of an aza-Achmatowicz oxidative rearrangement followed by a stereoselective allylsilane addition to a *N*-sulfonyliminium ion and a subsequent 1,4-conjugate addition.

In this paper, we further describe the utility of the aza-Achmatowicz oxidation for the preparation of several members of the *Cassia* and *Prosopis* alkaloid family such as (±)-azimic acid. The synthesis also includes the generation of a versatile Weinreb amide that readily allows for the introduction of various side chains thereby providing quick access to several piperidinol alkaloids such as (±)-deoxocassine, (±)-cassine, and (±)-spicigerine. By making use of Davis' sulfilimine chemistry,[31] we were also able to generate a chiral *N*-tosylaminofuran allowing for a formal asymmetric synthesis of these alkaloids.

Results and Discussion

aza-Achmatowicz products incorporate functionality that is easily modified and can be utilized to construct complex nitrogen heterocycles. In his early studies of the aza-Achmatowicz reaction, Ciufolini reported that carbamate-protected furfurylamines are somewhat unstable and readily hydrolyze to 3-hydroxypiperidines under typical oxidation conditions.[24] Subsequent studies by Zhou[32] and Altenbach,[33] however, showed that a sulfonamide protecting group was completely compatible with the aza-Achmatowicz oxidation reaction. The earlier work by Hiemstra and Speckamp with *N*-tosyl-6-alkoxy-2,6-dihydro-1*H*-pyridin-3-ones also demonstrated that these systems undergo reaction with great stereoselectivity with various nucleophiles under the influence of $BF_3{\cdot}OEt_2$ to furnish

SCHEME 2. Key Disconnections for the Synthesis of the 3-Piperidinol Alkaloid System



2,6-cis-disubstituted dihydropyridinones.[34] Consequently, we chose to work with several related *N*-tosyl systems because of their robust nature, ease of purification of the resulting products,[35] and high stereoselectivity of reaction with an assortment of nucleophiles. Our retrosynthetic strategy for the synthesis of a 3-piperidinol alkaloid system such as spicigerine (**7**) is based on the earlier Hiemstra/Speckamp report[34] and envisages initial construction of the functionalized piperidino Weinreb amide **19** from a 6-alkoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one intermediate (i.e., **17** or **18**). The required dihydropyridone **17** (or **18**) is easily procured by the aza-Achmatowicz oxidation of furyl sulfonamide **16** (Scheme 2). The availability of the Weinreb amide intermediate **19** would also allow for the ready synthesis of cassine (**8**), deoxocassine (**9**), and spicigerine (**7**) by its reaction with an appropriate lithiate derived from either commercially available or easily synthesized alkyl halides.

(±)-Azimic Acid Synthesis. Our studies began by subjecting the readily available furyl sulfonamide **16**[36] to the aza-Achmatowicz oxidative ring expansion[37] with *m*CPBA. The initially formed hemiaminal was immediately treated with trimethyl orthoformate and catalytic $BF_3{\cdot}OEt_2$ which furnished aminal **17** in 85% yield. Whereas the hemiaminal was difficult to purify, the resulting *N*-tosyl-*O*-methylaminal **17** was a stable crystalline solid that could be stored for extended periods of time. A similar procedure was also utilized to transform **16** into the corresponding *O*-ethyl aminal **18** by making use of triethyl orthoformate. Even though both procedures worked well, the synthesis of **18** from **16** proceeded in a somewhat higher yield (95% vs 85%). Also, the synthetic steps following the aza-Achmatowicz oxidation were higher yielding with the ethoxy substituent, leading us to routinely adopt this more efficient protocol over our previously reported conditions.[35] The exclusive cis orientation of the substituent group in **17**/**18** can be rationalized by assuming that $A^{1,3}$-strain of the tosyl group forces the alkoxy and methyl groups to adopt a pseudoaxial orientation. Reduction of **17** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ (Luche conditions)[38] stereoselectively produced alcohol **20** (Scheme 3), whose configuration was elucidated by NMR

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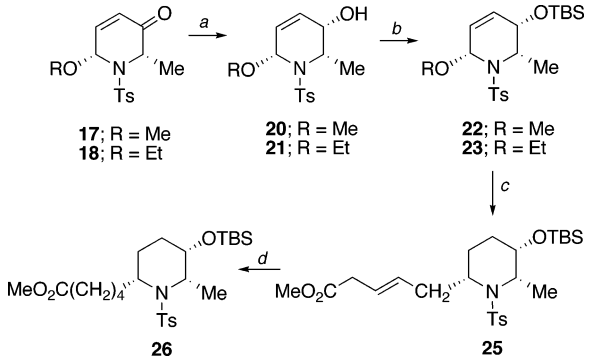
SCHEME 3. Synthesis of the Cis-Trisubstituted Core[a]



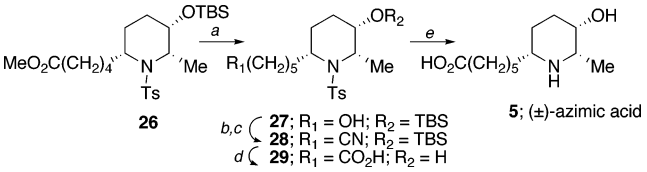
[a] Reagents: (a) $NaBH_4$, $CeCl_3$, MeOH, −40 °C, 60%; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 25 °C, 86%; (c) methyl 3-(trimethylsilyl)-4-pentenoate (**24**), BF_3OEt_2, CH_2Cl_2, −78 °C; (d) H_2, PtO_2, MeOH, 87% (two steps).

studies. The reduction proved to be remarkably stereospecific, providing the desired *cis*-alcohol **20** in pure diastereomeric form and in 60% isolated yield. This result may be attributed to the steric hindrance between the pseudoaxially oriented 2,6-bulky substituents and the incoming hydride reagent thus favoring formation of the *cis*-alcohol by the less sterically demanding axial attack.[39] Alcohol **20** was converted into the corresponding TBS ether **22** using TBSCl and imidazole in 86% yield. A similar set of experiments was also carried out with **18**, and this compound was easily converted in the TBS ether **23** in 66% overall yield (vs 49% overall yield for formation of **22**).

The reaction of the TBS ether **22** or **23** with methyl 3-(trimethylsilyl)-4-pentenoate (**24**) in the presence of $BF_3{\cdot}OEt_2$ led to the somewhat labile allylic ester **25**, which was immediately hydrogenated (H_2, PtO_2, MeOH) to give the key intermediate **26** in 57% or 87% yield, respectively. The choice of the hydrogenation catalyst proved to be crucial for the success of the reduction. Our first attempts used palladium on carbon (Pd/C) as in ethanol; however, the desired product was only isolated in low yield with a nearly equal amount of the isomerized *N*-tosyl enamine. On the other hand, the use of PtO_2 (Adams catalyst) afforded the desired saturated piperidine **26** as the exclusive product, with no evidence of epimerization at C_6. As suggested by Hiemstra and Speckamp,[34] the preference for the cis substitution pattern in **26** can be rationalized by assuming that the steric bulk associated with the tosyl group directs the attack of the allylsilane on the iminium ion to the side of the C_2-methyl group, thereby leading to the formation of the all-cis stereochemistry.

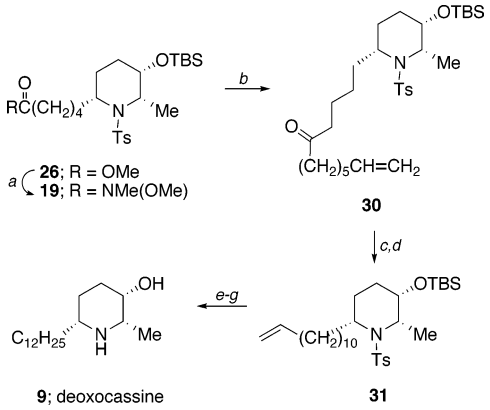
Having achieved a reliable preparation of the key piperidine intermediate **26**, we proceeded to use this compound for the synthesis of azimic acid (**5**). Our approach to **5** began with the $LiAlH_4$ reduction of ester **26** which afforded the corresponding alcohol **27** in 97% yield (Scheme 4). Conversion of **27** to the mesylate followed by cyanide displacement (NaCN, DMF) provided nitrile **28** which was hydrolyzed to carboxylic acid **29** in 89% yield. Deprotection of the TBS group occurred during the basic hydrolysis conditions used to convert **28** into **29** (NaOH, MeOH). Removal of the tosyl group with Li/NH_3 gave (±)-azimic acid (**5**) in 70% yield. The spectral data were in good agreement with those reported in the literature.[15]

SCHEME 4. Total Synthesis of (±)-Azimic Acid[a]



[a] Reagents: (a) $LiAlH_4$, THF, 0 °C, 97%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) NaCN, DMF, 50 °C, 68% (two steps); (d) NaOH, MeOH, 70 °C, 89%; (e) Li, NH_3, THF, −78 °C, 70%.

SCHEME 5. Total Synthesis of (±)-Deoxocassine (9)[a]



[a] Reagents: (a) MeNH(OMe)·HCl, *i*-PrMgCl, THF, −20 °C, 85%; (b) $CH_2{=}CH(CH_2)_5I$, *t*-BiLi, heptane, −78 °C, 56%; (c) $TsNHNH_2$, EtOH, 25 °C; (d) DIBAL-H, NaOH, CH_2Cl_2, 0 °C, 40% (two steps); (e) H_2 PtO_2, MeOH; (f) TBAF, THF, 0 °C, 92% (two steps); (g) Li, NH_3, THF, −78 °C, 100%.

(±)-Deoxocassine Synthesis. Having successfully obtained azimic acid (**5**) from piperidine **26**, we extended the above strategy to the synthesis of deoxocassine (**9**). Accordingly, the ester functionality present in piperidine **26** was converted (85% yield) into the corresponding Weinreb amide **19** with methoxymethylamine hydrochloride and isopropylmagnesium chloride. Although *N*-methoxy-*N*-methylamides are generally prepared from the ester using an aluminum-based reagent,[40] we found that the use of *i*-PrMgCl[41] gave higher yields and resulted in a cleaner overall reaction. Treatment of **19** with 6-heptenyllithium in heptane at −78 °C provided the expected ketone **30** in 56% unoptimized yield (Scheme 5). The terminal π-bond present in **30** can be utilized for a synthesis of either deoxocassine (**9**) or cassine (**8**) depending on the experimental conditions. Reduction of the carbonyl group in **30** proved more difficult than we originally anticipated. A Wolff−Kishner reduction of **30** provided a complex, intractable mixture of products. Instead, ketone **30** was converted to the corresponding tosylhydrazone and then treated with DiBAL-H/NaOH[42] which afforded **31** in reasonable yield. After hydrogenation of the double bond with PtO_2, the TBS protecting group was removed with TBAF and the tosyl group was cleaved using Li/NH_3 to furnish deoxocassine (**9**) in 92% yield for the three-step sequence.

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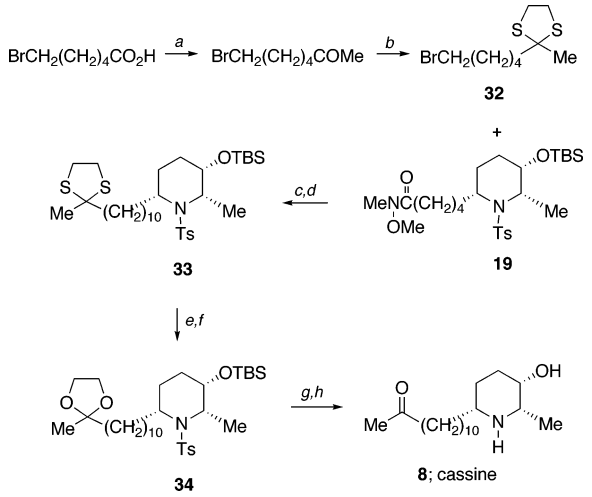
SCHEME 6. First-Generation Synthesis of (±)-Cassine (8)[a]

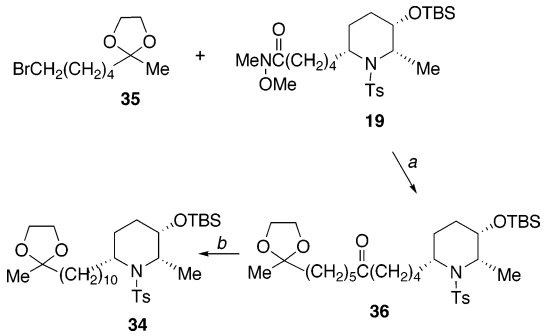


[a] Reagents: (a) MeLi, THF, −78 °C, 65%; (b) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 89%; (c) *t*-BuLi, pentane/TBME, −78 °C, 70%; (d) $TsNHNH_2$, EtOH, rt, then DIBAL-H, NaOH, CH_2Cl_2, 0 °C, 57%; (e) MeI, $CaCO_3$, CH_3CN/H_2O, 55 °C, quantitative; (f) ethylene glycol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 93%; (g) Li, NH_3, THF, −78 °C, 94%; (h) 3 N HCl, THF, rt, 59%.

(±)-Cassine Synthesis. With these encouraging results in hand, the total synthesis of (±)-cassine (**8**) was next undertaken. We realized that it should be possible to obtain **8** by a Wacker oxidation[43] of the piperidinyl-substituted alkene **31** but thought it would be more convergent to employ a side chain that already contained a protected keto group. With this in mind, we prepared 2-(5-bromopentyl)-2-methyl-[1,3]dithiolane (**32**) in two steps from commercially available 6-bromohexanoic acid. Thus, slow addition of 2.2 equiv of methyllithium to the above acid at −78 °C in THF afforded 65% yield of the requisite bromopentyl methyl ketone.[44] The ketone was then allowed to react with 1,2-ethanedithiol in CH_2Cl_2 with $BF_3{\cdot}OEt_2$ to give bromodithiolane **32** in 89% yield. Treating **32** with *t*-BuLi at −78 °C followed by reaction of the resulting lithiate with Weinreb's amide **19** afforded the expected coupled ketone which was subsequently reduced with $TsNHNH_2$-DiBAL-H/NaOH[42] to furnish [1,3]-dithiolane **33** in 45% overall yield. Hydrolysis of **33** afforded the expected methyl ketone in quantitative yield which was subsequently protected as the dioxolane **34** by reaction with ethylene glycol. Conversion of **34** to (±)-cassine (**8**) was then accomplished by a series of reactions involving Li/NH_3 removal of the tosyl group and deprotection of the TBS ether in 55% overall yield (Scheme 6).

Although the above synthesis served to define the viability of the critical Weinreb amide coupling step, the added protection−deprotection steps and the modest yield in formation of the lithiate derived from dithiolane **32** resulted in a sequence that was less efficient than what we had envisioned. In considering a more direct approach to piperidinyl-ketal **34**, we became intrigued by the prospect of generating a lithium reagent directly from 2-(5-bromopentyl)-2-methyl-1,3-dioxolane (**35**).[45] This led us to reinvestigate the key coupling step using ketal **35** and the Weinreb amide **19** (Scheme 7). Although the critical coupling step required some optimization, it ultimately proceeded in good yield to give ketone **36**. Conversion of the keto group to the corresponding tosylhydrazone was followed by reduction with DiBAL-H/NaOH to give the same piperidinyl dioxolane **34** as had previously been prepared. This latter route represents a considerable improvement over the earlier approach. Thus, a complete synthesis of (±)-cassine (**8**) is now possible in four short steps starting from the Weinreb amide intermediate **19**.

SCHEME 7. Second-Generation Synthesis of (±)-Cassine (8)[a]



[a] Reagents: (a) *t*-BuLi, pentane/TBME, −78 °C, 72%; (b) $TsNHNH_2$, EtOH, rt, then DIBAL-H, NaOH, CH_2Cl_2, 0 °C, 67%.

(±)-Spicigerine Synthesis. (±)-Spicigerine (**7**) represents another member of the piperidinol alkaloid family, was isolated in minute amounts from *Prosopis spicigera*, and possesses noteworthy antibiotic and anesthetic properties.[46] Surprisingly, only two syntheses of (±)-spicigerine have been reported to date,[47] perhaps as a consequence of the presence of the terminal carboxylic acid functionality. The considerable potential of using Weinreb's amide **19** for the synthesis of various *Prosopis* alkaloids motivated us to undertake the synthesis of spicigerine. We reasoned that an efficient approach toward this particular alkaloid would involve an oxidative cleavage of the piperidinyl alkene **38**, which in turn should be easily available from Weinreb's amide **19** (Scheme 8). Thus, we extended our earlier two-step strategy and treated Weinreb's amide **19** with 8-octenyllithium, and this was followed by reduction of the resulting ketone **37** via its tosylhydrazone to give **38**. Several different conditions were examined for the oxidation of the terminal π-bond of **38** into the carboxylic acid functionality of **40**. The most successful method was a one-pot dihydroxylation/oxidation step using OsO_4 and Oxone.[48] Although this method allowed for a one-step synthesis of **40** from **38**, the yields were generally poor with the highest being only 53%. Instead, a much higher yield of **40** was obtained (92%) using a two-step sequence where **38** was first oxidized to aldehyde **39**[49] followed by a subsequent oxidation to **40** with sodium chlorite.[50] In line with our expectations, exposure of **40** to the TBAF and Li/NH_3 conditions effects deprotection of the TBS and tosyl groups producing (±)-spicigerine in 64% isolated yield.

Asymmetric Approach. The construction of versatile chiral building blocks for the efficient synthesis of biologically active

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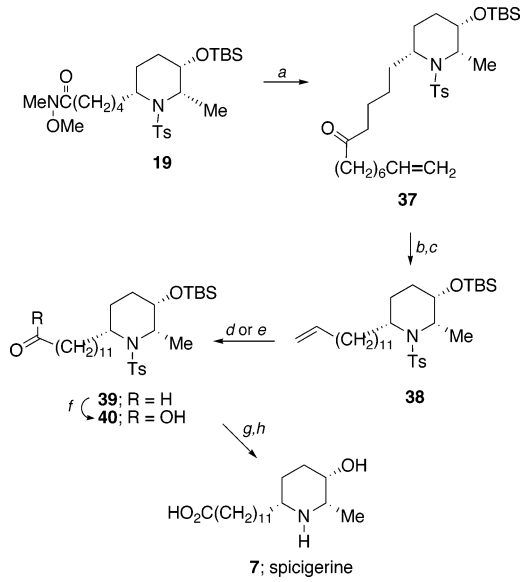
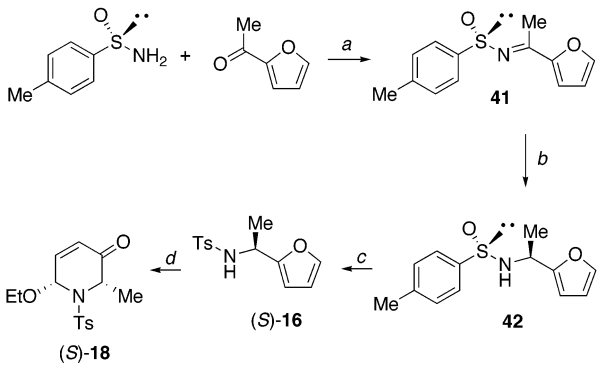
SCHEME 8. Total Synthesis of (±)-Spicigerine (7)[a]



[a] Reagents: (a) CH_2═$CH(CH_2)_6Br$, *t*-BuLi, heptane, −78 °C, 59%; (b) $TsNHNH_2$, EtOH, 25 °C; (c) DIBaH, NaOH, CH_2Cl_2, 0 °C, 76% (two steps); (d) OsO_4, $NaIO_4$, dioxane/H_2O, 25 °C, 93%; (e) OsO_4, Oxone, DMF, 25 °C, 53%; (f) $NaClO_2$, *t*-BuOH, 25 °C, 99%; (g) TBAF, THF, 0 °C, 77%; (h) Li, NH_3, THF, −78 °C, 64%.

natural products is a topic of current interest.[51] A large number of methods leading to the synthesis of chiral piperidine, decahydroquinoline, indolizidine, and quinolizidine systems have already been developed.[52] Several methods for the stereoselective construction of 2,6-disubstituted piperidinols have also been reported.[53] In earlier work, the Ciufolini group demonstrated that a chemoenzymatic hydrolysis of N-protected furanylglycine methyl esters could be used to prepare chiral furan derivatives.[54] The resolved furylglycines were shown to be excellent substrates for the synthesis of trans-2,6-disubstituted piperidines by subjecting them to an aza-Achmatowicz oxidation reaction.[55] However, no example of an asymmetric synthesis of a cis-2,6-disubstituted piperidin-3-ol has appeared to date. As a consequence of our earlier synthetic work in this area, we wondered whether the aza-Achmatowicz oxidation could also be used for the enantiocontrolled synthesis of various members of the *Cassia* and *Prosopis* family of alkaloids. To this end, we examined a new strategy for the asymmetric construction of tosylaminofuran **16** by making use of the elegant sulfilimine chemistry developed independently by the Davis[31] and Ellman groups.[56] Our synthesis of (*S*)-**16** (Scheme 9) began by condensing (*S*)-(+)-*p*-toluenesulfinimide with 2-acetylfuran in the presence of $Ti(OEt)_4$ using a modification of the conditions reported by Davis.[5757] Stereoselective reduction of the resulting

SCHEME 9. Synthetic Route to Chiral (*S*)-*N*-Tosylaminofuran 16[a]



[a] Reagents: $Ti(OEt)_4$, $CHCl_3$, reflux, 69%; (b) $LiAlH(O^tBu)_3$, THF, −78 to −55 °C; (c) *m*CPBA, CH_2Cl_2, −30 to 0 °C, 35% (two steps); (d) *m*CPBA, CH_2Cl_2, rt, $CH(OEt)_3$, *p*-TsOH, rt, 95%.

sulfilimine was carried out at low temperatures (−78 to −55 °C) with $LiAlH(O^tBu)_3$, and this was followed by an immediate oxidation with *m*CPBA to give the desired *N*-tosylaminofuran **16** in >75% ee as determined by chiral HPLC. Comparison of the optical rotation of (*S*)-**16** ($[\alpha]^{20}_D$ −63.5 (*c* 1.0, EtOH)) with that reported by Zhou and co-workers[58] clearly indicates that hydride delivery occurred on the *si* face of the imine as expected for a sulfoxide-directed addition.[56] Having a sample of (*S*)-**16** on hand, it was then submitted to the aza-Achmatowicz protocol, thereby providing a formal chiral synthesis of azimic acid (**5**), deoxocassine (**9**), cassine (**8**), and spicigerine (**7**).

In conclusion, we have developed a useful and efficient protocol for the preparation of several hydroxylated piperidine alkaloids. The approach involves a flexible combination of an aza-Achmatowicz oxidative rearrangement, dihydropyridone reduction, and a subsequent stereoselective allylsilane addition to a *N*-sulfonyliminium ion. Catalytic reduction of the olefinic π-bond followed by conversion of the ester group to the corresponding Weinreb amide provided an extremely useful intermediate which was utilized for the eventual synthesis of azimic acid, deoxocassine, cassine, and spicigerine. These synthetic studies have allowed us to further define the scope of the aza-Achmatowicz reaction and to optimize the introduction of various substituents at the 6-position of the *Cassia* and *Prosopis* alkaloid frameworks. The facile preparation of (*S*)-*N*-tosylamidofuran **16** and its conversion to the chiral Achmatowicz oxidation product **18** demonstrates the promise of using this method for the efficient asymmetric synthesis of other members of the piperidinol class of alkaloids.

Experimental Section

6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (17). A 0.39 g (1.1 mmol) sample of furyl sulfonamide **16**,[35] 4 mL of CH_2Cl_2, and *m*CPBA (0.39 g, 2.3 mmol) were placed in a round-bottom flask, and the mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (15 mL), and 15 mL of ether was added. The solution was extracted with ether. The layers were separated, and the organic layer was dried ($MgSO_4$). Concentration under reduced pressure and purification by silica gel chromatog-

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raphy gave 0.27 g (0.96 mmol, 85%) of the labile hemiaminal as a clear oil: IR (thin film) 1686, 1597, 1449, 1332, 1165, 1110, and 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, $J = 7.2$ Hz, 3H), 2.38 (s, 3H), 3.82 (brs, 1H), 4.36 (q, 1H, $J = 7.2$ Hz), 5.90 (dd, 1H, $J = 4.8$ and 1.2 Hz), 5.96 (dd, 1H, $J = 10.0$ and 1.2 Hz), 6.86 (dd, 1H, $J = 10.4$ and 4.8 Hz), 7.25 (d, 2H, $J = 8.4$ Hz), and 7.62 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.1, 57.0, 73.3, 126.2, 126.7, 130.0, 136.5, 143.5, 144.3, and 195.3.

A 1.0 g (3.5 mmol) sample of the above 6-hydroxy-2*H*-pyridin-3-one was dissolved in 20 mL of CH_2Cl_2, and trimethyl orthoformate (777 μL, 7.1 mmol) and $BF_3{\cdot}OEt_2$ (45 μL, 0.36 mmol) were added to the solution. The solution was stirred for 3 h at 0 °C and quenched with a saturated aqueous $NaHCO_3$ solution (25 mL), and 40 mL of ether was added. The solution was extracted with ether. The layers were separated, and the organic layer was dried ($MgSO_4$). Concentration under reduced pressure and purification by silica gel chromatography gave 0.89 g (3.0 mmol, 85%) of **17** as a white solid: mp 113−115 °C; IR (thin film) 1692, 1597, 1453, 1340, 1168, 1080, and 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, 3H, $J = 7.6$ Hz), 2.38 (s, 3H), 3.57 (s, 3H), 4.30 (q, 1H, $J = 7.6$ Hz), 5.58 (dd, 1H, $J = 4.8$ and 0.8 Hz), 5.82 (dd, 1H, $J = 10.4$ and 0.8 Hz), 6.82 (dd, 1H, $J = 10.4$ and 4.8 Hz), 7.24 (dd, 2H, $J = 8.0$ and 1.2 Hz), and 7.56 (dd, 2H, $J = 8.0$ and 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.5, 56.0, 57.2, 80.7, 126.6, 126.8, 130.0, 136.1, 142.5, 144.1, and 195.5. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.81; N, 4.75. Found: C, 56.81; H, 5.69; N, 4.70.

6-Ethoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (18). A procedure similar to that described above was used to prepare 18 (95%): mp 94−96 °C; IR (thin film) 2981, 1690, 1357, 1335, 1169, 1072, 1012, 815, and 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, $J = 7.2$ Hz), 1.58 (d, 2H, $J = 7.6$ Hz), 2.38 (s, 3H), 3.71 (dq, 1H, $J = 14.0$ and 7.2 Hz), 4.02 (dq, 1H, $J = 14.0$ and 7.2 Hz), 4.30 (q, 1H, $J = 7.2$ Hz), 5.68 (d, 1H, $J = 4.8$ Hz), 5.82 (d, 1H, $J = 10.4$ Hz), 6.82 (dd, 1H, $J = 4.8$ and 4.8 Hz), 7.24 (d, 2H, $J = 8.4$ Hz), and 7.56 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 21.1, 21.7, 57.4, 64.2, 79.4, 126.7, 127.0, 130.2, 136.4, 143.1, 144.3, and 195.8. Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.17; H, 6.17; N, 4.44.

6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridin-3-ol (20). To a solution of 4.7 g (12.5 mmol) of cerium trichloride heptahydrate in 100 mL of MeOH was added 3.7 g (12.5 mmol) of *N*-tosylaminal **17**. The solution was chilled to −40 °C, and 0.5 g (14 mmol) of $NaBH_4$ was added. The solution was stirred for 10 min at −40 °C and was then quenched with a saturated $NaHCO_3$ solution. The solution was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give 2.2 g (60% yield) of the title compound **20** as a colorless oil: IR (thin film) 2939, 1332, and 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, 3H, $J = 6.8$ Hz), 1.68 (d, 1H, $J = 7.6$ Hz), 2.42 (s, 3H), 3.49 (s, 3H), 3.87 (m, 1H), 4.03 (dq, 1H, $J = 7.2$ and 7.2 Hz), 5.37 (m, 1H), 5.62 (ddd, 1H, $J = 10.8$, 3.2, and 1.6 Hz), 5.81 (ddd, 1H, $J = 10.4$, 3.6, and 2.4 Hz), 7.28 (d, 2H, $J = 8.0$ Hz), and 7.69 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 21.7, 49.8, 56.3, 65.5, 80.9, 125.3, 127.2, 129.9, 130.7, 138.1, and 143.9; HRMS calcd for $C_{14}H_{19}NSO_4$ 297.1035, found 297.1033.

3-(*tert*-Butyldimethyl-silanyloxy)-6-methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (22). To a solution of 0.7 g (2.3 mmol) of **20** in 25 mL of CH_2Cl_2 was added 0.3 g (4.6 mmol) of imidazole and a catalytic amount of 4-(dimethylamino)-pyridine followed by 0.4 g (2.8 mmol) of *tert*-butyldimethylchlorosilane. The resulting solution was stirred at room temperature for 30 min. Water was added, and the solution was extracted with ether and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography to give 0.82 g (86% yield) of the title compound **22** as a colorless oil: IR (thin film) 2935, 1469, 1382, 1159, and 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.12 (d, 6H, $J = 5.6$ Hz), 0.80 (s, 9H), 1.17 (d, 3H, $J = 7.2$ Hz), 2.42 (s, 3H), 3.49 (s, 3H), 3.69 (m, 1H), 3.84 (dq, 1H, $J = 6.8$ and 6.8 Hz), 5.36 (m, 1H), 5.50 (dd, 1H, $J = 10.8$ and 1.6 Hz), 5.72 (ddd, 1H, $J = 10.0$, 7.2, and 7.2 Hz), 7.29 (d, 2H, $J = 8.4$ Hz), and 7.70 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.01, −4.85, 13.2, 18.2, 21.7, 25.8, 50.3, 56.1, 65.6, 80.9, 124.2, 127.3, 129.9, 132.0, 138.5, and 143.8; HRMS calcd for $C_{20}H_{33}NSiSO_4$ 411.1899, found 411.1903.

3-(*tert*-Butyldimethyl-silanyloxy)-6-ethoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (23). To a solution of 6-ethoxy-2*H*-pyridin-3-one **18** (0.78 g, 2.5 mmol) at −50 °C in MeOH (30 mL) was added $CeCl_3{\cdot}7H_2O$ (0.95 g, 2.5 mmol) followed by the portionwise addition of $NaBH_4$ (0.1 g, 2.5 mmol) over a 20 min period. The reaction mixture was stirred at −40 to −50 °C for an additional 30 min and was then diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography gave 0.64 g of **21** as a clear oil which was immediately used in the next step. The oil was taken up in CH_2Cl_2 (20 mL) and cooled to 0 °C, and then TBSCl (0.37 g, 2.4 mmol) was added, followed by imidazole (0.28 g, 4.0 mmol) and a catalytic amount of DMAP. The solution was stirred from 0 °C to 25 °C over 16 h, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated to an oil which was purified by silica gel chromatography to provide 0.7 g (66%) of **23** as a clear oil: IR (thin film) 2929, 2853, 1470, 1393, 1343, 1171, 1114, 1076, 987, 885, and 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.15 (d, 6H, $J = 6.0$ Hz), 0.78 (s, 9H), 1.19 (m, 6H), 2.40 (s, 3H), 3.64 (m, 2H), 3.85 (m, 2H), 5.47 (m, 2H), 5.71 (m, 1H), 7.27 (d, 2H, $J = 8.0$ Hz), and 7.68 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, −4.9, 13.3, 15.3, 18.2, 21.6, 25.8, 50.3, 63.8, 65.5, 79.5, 124.7, 127.3, 129.9, 131.8, 138.5, and 143.7; HRMS calcd for $[(C_{21}H_{35}NO_4SSi) + H^+]$ 426.2056, found 426.2129.

5-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentanoic Acid Methyl Ester (26). To a solution of 0.7 g of TBS ether **22** or **23** (1.7 mmol) in 20 mL of CH_2Cl_2 at −78°C was added 0.6 g (2.9 mmol) of methyl-3-(trimethylsilyl)-4-pentenonate (**24**) followed by 4 drops of $BF_3{\cdot}OEt_2$. The reaction was stirred at −78° for 7 h and was then quenched with a saturated sodium bicarbonate solution. After warming to room temperature, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude unsaturated ester **25** was dissolved in 20 mL of methanol, and a catalytic amount of platinum(IV) oxide was added. The flask was purged with hydrogen gas three times before being allowed to stir under a hydrogen balloon for 17 h. The solution was filtered through a pad of Celite, concentrated under reduced pressure, and subjected to flash silica gel chromatography to give 0.72 g (87%) of **26** as a white solid: mp 75−76 °C; IR (thin film) 2950, 1739, 1463, 1339, and 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.08 (d, 6H, $J = 3.6$ Hz), 0.80 (s, 9H), 1.22 (d, 3H, $J = 7.2$ Hz), 1.50 (m, 10H), 2.32 (t, 2H, $J = 7.2$ Hz), 2.41 (s, 3H), 3.19 (m, 1H), 3.67 (s, 3H), 3.96 (m, 3H), 7.28 (d, 2H, $J = 7.4$ Hz), and 7.69 (d, 2H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 14.9, 18.1, 21.6, 23.6, 24.9, 25.9, 26.9, 27.5, 34.1, 34.9, 51.7, 51.9, 53.1, 69.4, 126.9, 129.8, 139.1, 143.1, and 174.3. Anal. Calcd for $C_{25}H_{43}NO_5SSi$: C, 60.32; H, 8.71; N, 2.81. Found: C, 60.21; H, 8.58; N, 2.81.

5-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentan-1-ol (27). To a solution of 0.13 g (0.26 mmol) of piperidino ester **26** at 0 °C was slowly added 0.3 mL of a solution of lithium aluminum hydride (1M in THF). After the addition was complete, the reaction was quenched by the careful addition of $Na_2SO_4{\cdot}10H_2O$. After stirring for 30 min at room

temperature, $MgSO_4$ was added and the solution was filtered. The solution was concentrated under reduced pressure, and the crude product was subjected to flash silica gel chromatography to give 0.12 g (97%) of the title compound **27** as a clear oil: IR (thin film) 3418, 2855, 1462, and 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.08 (d, 6H, J = 3.6 Hz), 0.82 (s, 9H), 1.23 (d, 3H, J = 7.2 Hz), 1.30−1.80 (m, 13H), 2.43 (s, 3H), 3.19 (m, 1H), 3.66 (dt, 2H, J = 2.8, and 6.8 Hz), 3.98 (m, 2H), 7.28 (d, 2H, J = 8.0 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 14.9, 18.2, 21.7, 23.6, 25.6, 25.9, 27.0, 27.5, 32.8, 35.2, 51.9, 53.1, 63.0, 69.4, 126.9, 129.8, 139.1, and 143.0; HRMS calcd for $C_{24}H_{43}NSiSO_4$ 469.2682, found 469.2675.

6-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanenitrile (28). To a solution of 0.26 g (0.6 mmol) of alcohol **27** in 5.5 mL of CH_2Cl_2 was added methanesulfonyl chloride (0.09 g, 0.8 mmol). The solution was cooled to 0 °C, and 0.09 g of triethylamine was added dropwise. After warming to room temperature over 30 min, the reaction was quenched by the addition of water. The solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in 2 mL of DMF, and 0.05 g of sodium cyanide was added. The reaction mixture was heated at 50 °C for 15 h. After cooling to room temperature, water was added, and the mixture was extracted with ether. The ether extracts were washed three time with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.18 g (68%) of the title compound **28** as a clear oil: IR (thin film) 2943, 2242, 1592, 1150, and 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.08 (d, 6H, J = 3.6 Hz), 0.82 (s, 9H), 1.24 (d, 3H, J = 7.2 Hz), 1.30−1.74 (m, 12H), 2.36 (t, 2H, J = 7.2 Hz), 2.43 (s, 3H), 3.17 (m, 1H), 3.96 (m, 1H), 7.29 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 14.9, 17.3, 18.1, 21.7, 23.6, 25.5, 25.9, 26.4, 27.6, 28.6, 35.0, 51.8, 53.2, 69.3, 120.0, 126.9, 129.8, 139.0, and 143.1; HRMS calcd for $C_{25}H_{42}N_2SiSO_3$ 478.2685, found 478.2677.

6-[5-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanoic Acid (29). To a solution of 0.09 g (0.19 mmol) of nitrile **28** in 2 mL of methanol was added 2 mL of a 50% NaOH solution. The mixture was heated at reflux for 3 h and cooled to room temperature. The solution was extracted once with ether, and then the aqueous portion was acidified to pH 2 using a 6 N HCl solution. The acidified solution was extracted with $CHCl_3$, and the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product contained 0.06 g (89%) of the title compound **29** as a clear oil: IR (thin film) 3453, 2934, 2871, 1705, 1328, and 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, 4H, J = 7.2 Hz), 1.35−1.64 (m, 13H), 2.36 (t, 2H, J = 7.6 Hz), 2.42 (s, 3H), 3.37 (m, 1H), 3.94 (q, 1H, J = 6.8 Hz), 4.17 (dq, 1H, J = 6.8 and 6.8 Hz), 7.28 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.7, 23.0, 24.7, 27.1, 27.3, 29.0, 34.1, 35.0, 51.9, 52.4, 69.1, 126.9, 129.9, 138.9, 143.2, and 179.2; HRMS calcd for $C_{19}H_{29}NSO_5$ 383.1766, found 383.1772.

(±)-Azimic Acid (5). To a solution of 0.02 g (0.044 mmol) of carboxylic acid **29** in 0.6 mL of THF at −78 °C was condensed 3 mL of NH_3 using a dry ice condenser. To this solution was added lithium chips which resulted in the formation of a deep blue color. The mixture was allowed to stir at −78 °C for 30 min, and then 0.5 mL of isoprene was added to quench the reaction. The solution was warmed to room temperature, and water was added to the resulting residue. The solution was brought to pH 7 by the addition of 6 N HCl, and the solvent was subsequently removed under reduced pressure. Methanol was added to precipitate any inorganic salts, and the resulting solution was filtered and concentrated under reduced pressure to give 0.007 g (70%) of (±)-azimic acid (**5**) as a white solid: mp 217−218 °C (lit.[15d] 214−215 °C); IR (thin film) 3344, 1633, and 1551 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.33 (d, 2H, J = 6.8 Hz), 1.22−1.81 (m, 11H), 1.96 (m, 1H), 2.17 (t, 2H, J = 7.4 Hz), 3.03 (bs, 1H), 3.21 (q, 1H, J = 6.4 Hz), and 3.83 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.4, 24.0, 26.1, 27.3, 30.4, 31.4, 35.0, 39.0, 57.6, 58.7, 66.3, and 182.9; FAB HRMS calcd for [($C_{12}H_{23}NO_3$) + H^+] 230.1756, found 230.1759.

5-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentanoic Acid Methoxymethylamide (19). To a solution of 0.3 g (0.6 mmol) of piperidino ester **26** in THF (1.2 mL) was added methoxymethylamine hydrochloride. The resulting slurry was chilled to approximately −20 °C, and *iso*-propylmagnesium chloride (0.9 mL of a 2 M solution in THF (1.8 mmol)) was added. The solution was stirred at this temperature for 20 min and was then quenched by addition of a saturated ammonium chloride solution. The reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.27 g (85% yield) of the title compound **19** as a white solid: mp 77−78 °C; IR (thin film) 2947, 2848, 1663, 1461, 1161, and 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.10 (d, 6H, J = 3.6 Hz), 0.79 (s, 9H), 1.21 (d, 3H, J = 7.2 Hz), 1.29−1.73 (m, 10H), 2.40 (s, 3H), 2.43 (m, 2H), 3.16 (m, 4H), 3.67 (s, 3H), 3.95 (m, 2H), 7.26 (d, 2H, J = 8.0 Hz), and 7.67 (d, 2H, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, 14.8, 18.0, 21.6, 23.5, 24.6, 25.8, 27.2, 27.4, 31.9, 32.2, 35.0, 51.9, 53.1, 61.4, 69.3, 126.8, 129.7, 139.0, 143.0, and 174.7; HRMS calcd for $C_{26}H_{46}N_2SiSO_5$ 526.2897, found 526.2889.

1-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodec-11-en-5-one (30). To a solution of 0.1 g (0.6 mmol) of 1-iodo-6-heptene in 0.5 mL of heptane at −78 °C was added 1.6 mL of a 1.4 M solution of *tert*-butyllithium in pentane. The mixture was stirred for 5 min, and then a solution of 0.17 g (0.3 mmol) of Weinreb's amide **19** was added slowly. After warming to 0 °C over 30 min, the reaction was quenched by the addition of a saturated NH_4Cl solution. The mixture was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.1 g (56%) of the title compound **30** as a colorless oil: IR (thin film) 2932, 2857, 1712, 1337, and 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.12 (d, 6H, J = 4.0 Hz), 0.77 (s, 9H), 1.18 (d, 3H, J = 7.2 Hz), 1.23−1.72 (m, 16H), 2.00 (q, 2H, J = 6.8 Hz), 2.36 (t, 2H, J = 7.6 Hz), 2.38 (m, 5H), 3.14 (m, 1H), 3.92 (m, 2H), 4.92 (m, 2H), 5.75 (m, 1H), 7.24 (d, 2H, J = 8.0 Hz), and 7.65 (d, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 14.2, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 25.9, 27.0, 27.5, 28.8, 28.9, 33.8, 35.1, 42.8, 42.9, 51.9, 53.1, 69.4, 114.5, 126.9, 129.8, 139.1, 143.0, and 211.6; HRMS calcd for $C_{31}H_{53}NSiSO_4$ 563.3464, found 563.3472.

3-(*tert*-Butyldimethyl-silanyloxy)-6-dodec-11-enyl-2-methyl-1-(toluene-4-sulfonyl)-piperidine (31). To a solution of 0.1 g (0.18 mmol) of ketone **30** in 1.5 mL of absolute ethanol was added 0.037 g (0.19 mmol) of *p*-toluenesulfonylhydrazide. The solution was stirred for 15 h at room temperature and then was concentrated under reduced pressure. To the residue was added 1.5 mL of CH_2Cl_2, and the resulting solution was cooled to 0 °C. To this solution was added 0.35 mL (0.34 mmol) of diisobutylaluminum hydride solution (1 M in hexane). The solution was warmed to room temperature over 30 min and was quenched with a 3.0 M solution of NaOH. The solution was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.04 g (40% yield) of the title compound **31** as a colorless oil: IR (thin film) 2852, 1640, 1598, and 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.07 (d, 6H, J = 4.0 Hz), 0.82 (s, 9H), 1.22 (d, 3H, J = 7.6 Hz), 1.27−1.72 (m, 22H), 2.04 (q, 2H, J = 7.6 Hz), 2.42 (s, 3H), 3.23 (m, 1H), 3.98 (m, 2H), 4.96 (m, 2H), 5.82 (m, 1H), 7.28 (d, 2H, J = 8.0 Hz), and 7.70 (d, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 14.2, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 25.9, 26.5, 27.0, 27.5, 28.8, 28.9, 33.8, 35.1, 52.0, 53.1, 69.4, 114.3, 126.9, 129.8, 139.2, 139.5, and 142.9; HRMS calcd for $C_{31}H_{55}NSiSO_3$ 549.3672, found 549.3661.

6-Dodecyl-2-methyl-1-(toluene-4-sulfonyl)-piperidin-3-ol. To a solution of 0.03 g (0.06 mmol) of alkene **31** in 0.1 mL of methanol was added a catalytic amount of platinum(IV) oxide. After purging the reaction vessel three times with hydrogen gas, the mixture was stirred for 1 h under a hydrogen balloon. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude reaction mixture was taken up in 0.6 mL of THF, and a solution of tetrabutylammonium fluoride (66 μL of a 1 M solution in THF) was added at 0 °C. After warming to room temperature over 30 min, water was added and the reaction mixture was extracted with ether. The ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was subjected to preparative thin-layer chromatography to give 0.024 g (92%) of the title compound as a clear oil: IR (thin film) 3444, 2923, 2852, and 1460 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz), 1.25−1.66 (m, 30H), 2.42 (s, 3H), 3.40 (m, 1H), 3.95 (q, 1H, J = 6.6 Hz), 4.18 (dq, 1H, J = 6.6 and 6.6 Hz), 7.28 (d, 2H, J = 9.0 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 14.7, 21.7, 22.9, 23.2, 27.3, 27.7, 29.6, 29.7, 29.8, 29.9, 32.1, 35.3, 52.1, 52.4, 69.2, 126.9, 129.9, 139.1, and 143.1; HRMS calcd for $C_{25}H_{43}NSO_4$ 453.2913, found 453.2924.

(±)-Deoxocassine (9). To a solution of 0.05 g of the above alcohol in 0.5 mL of THF at −78 °C was condensed 2 mL of NH_3 using a dry ice condenser. To this mixture was added lithium chips (approximately 2 mg), and the solution immediately turned a deep blue color. The reaction mixture was allowed to stir at −78 °C for 30 min, and then 0.5 mL of isoprene was added to quench the reaction. The mixture was warmed to room temperature, and water was added followed by a drop of 50% NaOH solution and $CHCl_3$. After extracting the aqueous layer with additional $CHCl_3$, the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 0.03 g (100%) of (±)-deoxocassine (**9**): IR (thin film) 3394, 2916, 2848, and 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz), 1.15, (d, 3H, J = 6.8 Hz), 1.22−1.36 (m, 22H), 1.46 (m, 2H), 1.90 (m, 2H), 2.50 (m, 2H), 2.72 (qd, 1H, J = 6.8 and 1.2 Hz), and 3.52 (d, 1H, J = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 18.9, 22.9, 26.0, 26.4, 29.6, 29.8, 29.9, 30.0, 32.1, 32.3, 37.2, 56.0, 57.5, and 68.3; FAB HRMS calcd for [($C_{18}H_{37}NO$) + H^+] 284.2953, found 284.2941.

2-(5-Bromopentyl)-2-methyl-[1,3]dithiolane (32). A mixture of BF_3·OEt_2 (0.04 mL) and 1,2-ethanedithiol (0.3 mL, 4.0 mmol) was added to a solution of 7-bromo-2-heptanone (0.5 g, 2.7 mmol) in 12 mL of CH_2Cl_2, and the reaction mixture was stirred for 18 h at room temperature. The resulting solution was then quenched with an aqueous 1 M NaOH solution, and the organic layer was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.65 g (89%) of the title compound **32** as a pale yellow oil: IR (thin film) 2935, 2856, 1445, and 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (m, 4H), 1.75 (s, 3H), 1.90 (m, 4H), 3.33 (m, 4H), and 3.42 (t, 2H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 28.3, 32.5, 32.7, 33.9, 40.0, 45.6, and 66.8; HRMS calcd for [($C_9H_{17}BrS_2$) + H^+] 268.9955, found 269.0028.

1-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-10-(2-methyl-[1,3]dithiolan-2-yl)-decan-5-one. To a solution of the above bromide **32** (0.7 g, 0.27 mmol) in pentane (2.5 mL) and *tert*-butyl methyl ether (1.25 mL) at −78 °C was added *t*-BuLi (0.22 mL, 0.38 mmol, 1.7 M in pentane) over 15 min, and the resulting solution was stirred for an additional 25 min at −78 °C. A 0.1 g (0.19 mmol) sample of Weinreb's amide **19** in ether (1.8 mL) was added over a 15 min period, and the reaction mixture was stirred at −78 °C for 2.2 h before being quenched with an aqueous NH_4Cl solution. The aqueous layer was extracted with ether, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography to give 0.09 g (70%) of the title compound as a clear oil: IR (thin film) 2935, 2857, 1713, 1463, 1338, and 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.10 (d, 6H, J = 4.0 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.49 (m, 16H), 1.74 (s, 3H), 1.92 (m, 2H), 2.41 (m, 7H), 3.17 (m, 1H), 3.32 (m, 4H), 3.95 (m, 2H), 7.28 (d, 2H, J = 8.6 Hz), and 7.68 (d, 2H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 15.0, 18.2, 21.7, 23.6, 23.8, 23.9, 25.9, 27.0, 27.3, 27.5, 29.5, 32.5, 35.1, 40.0, 42.9, 45.8, 51.9, 53.2, 67.0, 69.4, 126.9, 129.8, 139.1, 143.1, and 211.5; HRMS calcd for [($C_{33}H_{57}NO_4S_3Si$) + H^+] 656.3219, found, 656.3298.

3-(*tert*-Butyldimethyl-silanyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dithiolan-2-yl)-decyl]-1-(toluene-4-sulfonyl)piperidine (33). To a solution of the above ketone (0.07 g, 0.1 mmol) in absolute EtOH (1.2 mL) was added *p*-toluenesulfonylhydrazide (0.02 g, 0.11 mmol), and the reaction mixture was stirred at room temperature for 17 h. The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (1.2 mL). The solution was cooled to 0 °C, and DIBAL-H (0.5 mL, 0.5 mmol, 1.0 M in hexane) was slowly added over a 15 min period. The reaction mixture was stirred at 0 °C and then gradually warmed to room temperature over 1 h. The solution was quenched by the dropwise addition of an aqueous 3 M NaOH solution. The mixture was extracted with ether, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.04 g (57%) of the title compound **33** as a clear oil: IR (thin film) 2924, 2848, 1470, 1163, 1107, 999, 881, and 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.08 (d, 6H, J = 4.0 Hz), 0.81 (s, 9H), 1.20 (d, 3H, J = 6.8 Hz), 1.26−1.72 (m, 22H), 1.75 (s, 3H), 1.94 (m, 2H), 2.41 (s, 3H), 3.22 (ddd, 1H, J = 11.2, 6.0, and 4.0 Hz), 3.32 (m, 4H), 3.97 (m, 2H), 7.27 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, −4.6, 14.9, 18.1, 21.7, 23.6, 25.9, 27.4, 27.56, 27.64, 29.7, 29.8, 29.9, 30.0, 32.5, 35.3, 39.9, 46.1, 52.2, 53.1, 67.2, 69.6, 126.9, 129.8, 139.2, and 142.9; HRMS calcd for [($C_{33}H_{59}NO_3S_3Si$) + H^+] 642.3426, found 642.3490.

12-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodecan-2-one. To a solution of dithiolane **33** (0.03 g, 0.04 mmol) in a 2:1 CH_3CN/H_2O mixture (2.1 mL) was added $CaCO_3$ (0.05 g, 0.45 mmol) and MeI (0.5 mL). The solution was heated at 60 °C for 12 h, cooled to room temperature, and diluted with H_2O and brine. The aqueous layer was extracted with ether, and the organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.02 g (100%) of the title compound as a clear oil: IR (thin film) 2937, 2855, 1717, 1463, 1339, 1253, 1163, 838, and 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.09 (d, 6H, J = 3.6 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.44 (m, 22H), 2.13 (s, 3H), 2.39 (m, 5H), 3.20 (ddd, 1H, J = 11.2, 6.0, and 4.2 Hz), 3.96 (m, 2H), 7.27 (d, 2H, J = 8.4 Hz), and 7.69 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, −4.6, 14.9, 18.2, 21.7, 23.6, 24.1, 25.9, 27.4, 27.5, 29.4, 29.6, 29.64, 29.68, 29.7, 30.1, 35.3, 44.0, 52.2, 53.1, 69.6, 127.0, 129.8, 139.2, 143.0, and 209.7; HRMS calcd for [($C_{31}H_{55}NO_4SSi$) + H^+] 566.3621, found 566.3700.

3-(*tert*-Butyldimethyl-silanyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dioxolan-2-yl)-decyl]-1-(toluene-4-sulfonyl)piperidine (34). To a solution of the above ketone (0.02 g, 0.03 mmol) in CH_2Cl_2 (0.5 mL) was added ethylene glycol (0.5 mL) and BF_3·OEt_2 (8 drops), and the resulting solution was stirred at room temperature for 27 h. The reaction mixture was then diluted with 1 M NaOH and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.02 g (93%) of the title compound **34** as a clear oil: IR (thin film) 2929, 2855, 1463, 1339, 1254, 1163, 1107, 1055, 879, 839, and 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.09 (d, 6H, J = 4.0 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.31 (s, 3H), 1.48 (m, 24H), 2.41 (s, 3H), 3.22 (ddd, 1H, J = 10.0, 6.0, and 4.0 Hz), 3.94 (m, 6H), 7.27 (d, 2H, J = 8.4 Hz), and 7.69 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, −4.6, 14.9, 18.2, 21.7, 23.6, 23.9, 24.3, 25.9, 27.4, 27.6, 29.6, 29.7, 29.8, 30.1, 35.3, 39.4,

52.2, 53.1, 64.8, 69.6, 110.4, 127.0, 129.8, 139.2, and 142.9; HRMS calcd for [($C_{33}H_{59}NO_5SSi$) + H^+] 610.3883, found 610.3962.

3-(*tert*-Butyldimethyl-silanyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dioxolan-2-yl)decyl]piperidine. To a solution of **34** (0.03 g, 0.04 mmol) in THF (3 mL) at −78 °C was added 5 mg of lithium wire. The flask was fitted with an acetone/dry ice condenser, and 3 mL of NH_3 was added which resulted in a dark blue solution. The reaction mixture was stirred at −78 °C for 30 min, warmed to room temperature, and quenched by the careful dropwise addition of methanol. The solution was diluted with aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.02 g (94%) of the title compound as a clear oil: IR (thin film) 2927, 2854, 1463, 1373, 1252, 1070, 1032, and 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.04 (d, 6H, J = 6.0 Hz), 0.91 (s, 9H), 1.01 (d, 3H, J = 6.8 Hz), 1.30 (s, 3H), 1.44 (m, 22H), 1.81 (m, 2H), 2.49 (brs, 1H), 2.68 (m, 1H), 3.55 (brs, 1H), and 3.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, −4.3, 18.4, 19.5, 23.9, 24.3, 26.0, 26.1, 26.2, 29.8, 29.9, 30.1, 32.7, 37.6, 39.4, 55.6, 56.5, 64.8, 68.4, 77.5, and 110.4; HRMS calcd for [($C_{26}H_{53}NO_3Si$) + H^+] 456.3795, found 456.3863.

(±)-Cassine (8). To a solution of the above acetal (0.02 g, 0.04 mmol) in THF (3.3 mL) was added a 3 N HCl solution (0.33 mL, 1.0 mmol), and the solution was stirred at room temperature for 27 h. The reaction mixture was then quenched with 1 M NaOH (5.0 mL, 5.0 mmol), and the aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over basic alumina to afford 0.007 g (59%) of (±)-cassine (**8**) as a white solid: mp 63−65 °C (lit.[59] mp 59−60 °C); IR (thin film) 3405, 2926, 2852, 1716, 1464, 1363, 1166, and 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 3H, J = 6.8 Hz), 1.39 (m, 20H), 1.90 (m, 2H), 2.13 (s, 3H), 2.41 (t, 2H, J = 7.6 Hz), 2.54 (m, 1H), 2.76 (m, 1H), and 3.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 24.0, 26.0, 26.1, 29.4, 29.60, 29.63, 29.7, 29.8, 30.0, 30.1, 32.2, 37.0, 44.0, 56.0, 57.4, 68.1, and 209.7; HRMS calcd for [($C_{18}H_{35}NO_2$) + H^+] 298.2668, found 298.2740.

1-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)piperidin-2-yl]-10-(2-methyl-[1,3]dioxolan-2-yl)-decan-5-one (36). To a solution of 2-(5-bromopentyl)-2-methyl-1,3-dioxolane (**35**)[45] (0.06 g, 0.27 mmol) in *tert*-butyl methyl ether (1.25 mL) at −78 °C was added *t*-BuLi (0.22 mL, 0.38 mmol, 1.7 M in pentane) over a 15 min period. The reaction mixture was then stirred at −78 °C for 25 min, and a solution of Weinreb's amide **19** (0.1 g, 0.19 mmol) in *tert*-butyl methyl ether (1.8 mL) was added over 15 min. The resulting solution was stirred at −78 °C for 2.5 h and was subsequently quenched with an aqueous NH_4Cl solution and allowed to warm to room temperature. The aqueous layer was extracted with ether, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.07 g (72%) of the title compound **36** as a clear oil: IR (thin film) 2941, 1713, 1464, 1338, 1254, 1107, and 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.10 (d, 6H, J = 3.6 Hz), 0.80 (s, 9H), 1.21 (d, 3H, J = 6.8 Hz), 1.30 (s, 3H), 1.50 (m, 16H), 2.40 (m, 7H), 3.17 (ddd, 1H, J = 10.8, 6.0, and 4.0 Hz), 3.84 (m, 6H), 7.27 (d, 2H, J = 8.4 Hz), and 7.68 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 24.0, 24.1, 25.9, 27.0, 27.5, 29.6, 35.1, 39.2, 42.8, 42.9, 51.9, 53.1, 64.8, 69.4, 110.3, 126.9, 129.8, 139.1, 143.0, and 211.5; HRMS calcd for [($C_{33}H_{57}NO_6SSi$) + H^+] 624.3676, found 624.3763.

To a solution of the above ketone (0.06 g, 0.09 mmol) in absolute EtOH (1.0 mL) was added *p*-toluenesulfonylhydrazide (0.02 g, 0.01 mmol), and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (1.0 mL). The solution was cooled to 0 °C, and DIBAL-H (0.35 mL, 0.35 mmol, 1.0 M in hexane) was added slowly over 10 min. The solution was stirred at 0 °C and then gradually warmed to room temperature over 1 h. The mixture was quenched by the dropwise addition of an aqueous 3 M NaOH solution and was extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.02 g (41%) of compound **34** which was subsequently converted to cassine (**8**) as described above.

1-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)piperidin-2-yl]-tridec-12-en-5-one (37). To a solution of 8-bromo-1-octene (0.25 mL, 0.29 g, 1.5 mmol) in *tert*-butyl methyl ether (4.2 mL) at −78 °C was added *t*-BuLi (1.1 mL, 1.9 mmol, 1.7 M in pentane) over 15 min. The reaction mixture was stirred at −78 °C for 25 min, and then a solution of Weinreb's amide **19** (0.5 g, 0.95 mmol) in ether (8.8 mL) was added over 15 min. The resulting solution was stirred at −78 °C for 3 h and then quenched with an aqueous NH_4Cl solution, and the mixture was warmed to room temperature. The aqueous layer was extracted with ether, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to afford 0.33 g (59%) of the title compound **37** as a clear oil: IR (thin film) 2936, 2856, 1713, 1463, 1339, 1163, 1107, 934, 838, and 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.10 (d, 6H, J = 3.6 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 6.8 Hz), 1.50 (m, 18H), 2.03 (m, 2H), 2.39 (m, 7H), 3.17 (ddd, 1H, J = 10.0, 6.0, and 4.0 Hz), 3.95 (m, 2H), 4.89 (bd, 1H, J = 10.0 Hz), 4.98 (dq, 1H, J = 17.2 and 1.6 Hz), 5.79 (ddt, 1H, J = 17.2, 10.0, and 6.8 Hz), 7.27 (d, 2H, J = 8.4 Hz) and 7.68 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, −4.6, 15.0, 18.1, 21.7, 23.6, 23.8, 24.0, 25.9, 27.0, 27.5, 28.9, 29.1, 29.3, 33.9, 35.1, 42.8, 43.0, 51.9, 53.1, 69.4, 114.4, 126.9, 129.8, 139.1, 139.3, 143.0, and 211.6; HRMS calcd for [($C_{32}H_{55}NO_4SSi$) + H^+] 578.3621, found 578.3697.

3-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl-6-tridec-12-enyl-piperidine (38). To a solution of ketone **37** (0.06 g, 0.095 mmol) in absolute EtOH (1.0 mL) was added *p*-toluenesulfonhydrazide (0.02 g, 0.1 mmol), and the reaction mixture was stirred at room temperature for 18.5 h. The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (0.9 mL). The solution was cooled to 0 °C, and DIBAL-H (0.3 mL, 0.34 mmol, 1.0 M in hexane) was slowly added over 15 min. The solution was stirred at 0 °C and was gradually warmed to room temperature over 1 h. The mixture was diluted with CH_2Cl_2, quenched by the dropwise addition of an aqueous 3.0 M NaOH solution, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.04 g (76%) of the title compound **38** as a clear oil: IR (thin film) 2928, 2855, 1463, 1340, 1254, 1164, 1105, 880, 838, 776, and 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.08 (d, 6H, J = 4.0 Hz), 0.82 (s, 9H), 1.22 (d, 3H, J = 7.6 Hz), 1.49 (m, 24H), 2.04 (m, 2H), 2.41 (s, 3H), 3.22 (ddd, 1H, J = 11.2, 6.0, and 4.0 Hz), 3.98 (m, 2H), 4.92 (dt, 1H, J = 10.0 and 1.2 Hz), 4.99 (dt, 1H, J = 16.8 and 1.6 Hz), 5.80 (ddt, 1H, J = 17.2, 10.4, and 6.8 Hz), 7.27 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, −4.6, 14.9, 18.2, 21.1, 21.7, 23.6, 25.9, 26.2, 27.4, 27.6, 29.2, 29.4, 29.7, 29.8, 29.9, 34.0, 35.3, 52.2, 53.1, 69.6, 114.3, 127.0, 129.8, 139.2, 139.5, and 142.9; HRMS calcd for [($C_{32}H_{57}NO_3SSi$) + H^+] 564.3828, found 564.3903.

12-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodecanal (39). To a solution of **38** (0.1 g, 0.17 mmol) in a 2:1 dioxane/H_2O mixture (5.5 mL) was added 2,6-lutidine (0.05 mL, 0.43 mmol), OsO_4 (7 drops, 2.5% in *t*-BuOH), and $NaIO_4$ (0.16 g, 0.75 mmol). After stirring for 3.5 h at room temperature, an aqueous mixture of Na_2SO_3 was added and the aqueous layer was then extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was

(59) Oetting, J.; Holzkamp, J.; Meyer, H. H.; Pahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 477.

purified by silica gel to give 0.09 g (93%) of the title compound **39** as a yellow oil: IR (thin film) 2933, 2854, 1725, 1463, 1338, 1254, 1164, 1107, 879, 838, 776, and 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.10 (d, 6H, J = 3.6 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.48 (m, 24H), 2.42 (m, 5H), 3.21 (ddd, 1H, J = 10.4, 5.6, and 4.0 Hz), 4.00 (m, 2H), 7.27 (d, 2H, J = 8.4 Hz), 7.70 (d, 2H, J = 8.4 Hz), and 9.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.7, 14.9, 18.1, 21.6, 22.3, 23.6, 25.9, 27.4, 27.5, 29.3, 29.5, 29.6, 29.7, 29.9, 35.3, 44.1, 52.2, 53.1, 69.5, 127.0, 129.8, 139.2, 142.9, and 203.2; HRMS calcd for [($C_{31}H_{55}NO_4SSi$) + H^+] 566.3621, found 566.3698.

12-[5-(*tert*-Butyldimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodecanoic Acid (40). To a solution of aldehyde **39** (0.36 g, 0.64 mmol) in *t*-BuOH (4.5 mL) was added resorcinol (0.09 g, 0.83 mmol) followed by an acetate buffer (pH = 3.6, 1.3 mL). To the resulting mixture was added a solution of $NaClO_2$ (0.07 g, 0.8 mmol) in H_2O (5 mL), and the mixture was stirred at room temperature for 6 h. The organic layer was diluted with brine and extracted with ether, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.37 g (99%) of the title compound **40** as a yellow oil: IR (thin film) 2936, 2854, 1709, 1463, 1338, 1254, 1164, 1105, 838, and 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.09 (d, 6 H, J = 3.6 Hz), 0.81 (s, 9H), 1.25 (m, 24H), 1.22 (d, 3H, J = 6.8 Hz), 2.34 (t, 2H, J = 7.6 Hz), 2.41 (s, 3H), 3.22 (ddd, 1H, J = 11.2, 5.6, and 4.0 Hz), 3.97 (m, 2H), 7.27 (d, 2H, J = 8.4 Hz), and 7.69 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 14.9, 18.2, 21.7, 23.6, 24.9, 25.9, 27.4, 27.6, 29.3, 29.4, 29.6, 29.7, 34.2, 35.3, 52.2, 53.1, 69.6, 127.0, 129.8, 139.2, 143.0, and 180.0; HRMS calcd for [($C_{31}H_{55}NO_5SSi$) + H^+] 582.3570, found 582.3643.

The same carboxylic acid **40** was prepared by the direct oxidation of piperidinyl alkene **38**. To a solution of alkene **38** (0.03 g, 0.05 mmol) in DMF (1.2 mL) was added OsO4 (3 drops, 2.5% in *t*-BuOH), and the reaction mixture was stirred at room temperature for 5 min. Oxone was added in one portion, and the mixture was stirred at room temperature for an additional 35 min and then diluted with EtOAc. The aqueous layer was acidified with 10% HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a clear oil which was purified by silica gel chromatography to give 0.02 g (53%) of **40**.

12-[5-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)piperidin-2-yl] Dodecanoic Acid. To a solution of carboxylic acid **40** (0.37 g, 0.6 mmol) in THF (8 mL) at 0 °C was added TBAF (0.8 mL, 0.76 mmol, 1.0 M in THF), and the mixture was gradually warmed to room temperature over 40 min. The solution was stirred at room temperature for an additional 3 h, over which time an additional 2.0 equiv (1.3 mL) of TBAF was added in portions. The mixture was then diluted with H_2O and brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.23 g (77%) of the title compound as a yellow oil: IR (thin film) 3448, 2927, 2853, 1709, 1458, 1404, 1330, 1166, 1098, 985, 911, 814, 732, and 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (m, 27H), 2.34 (t, 2H, J = 7.2 Hz), 2.40 (s, 3H), 3.38 (ddd, 1H, J = 10.4, 6.0, and 4.4 Hz), 3.93 (q, 1H, J = 6.8 Hz), 4.17 (p, 1H, J = 6.8 Hz), 7.26 (d, 2H, J = 8.4 Hz), and 7.69 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.7, 23.1, 24.9, 27.3, 27.6, 29.2, 29.4, 29.56, 29.65, 29.70, 29.90, 34.2, 35.2, 52.1, 52.4, 69.2, 126.9, 129.9, 139.0, 143.1, and 179.5; HRMS calcd for [($C_{25}H_{41}NO_5S$) + H^+] 468.2705, found 468.2779.

(±)-Spicigerine (7). To a solution containing 0.04 g **(**0.08 mmol) of the above compound in THF (3 mL) at −78 °C was added 5 mg of lithium wire. The flask was fitted with an acetone/dry ice condenser, and 3 mL of ammonia was added which gave rise to a dark blue solution. The mixture was stirred at −78 °C for 0.5 h, allowed to warm to room temperature, and quenched by the careful dropwise addition of methanol. The solution was diluted with an aqueous NH_4Cl solution and extracted with EtOAc. The aqueous layer was acidified to pH = 2 with 6 N HCl and extracted with EtOAc. The aqueous layer was further extracted with a 3:1 mixture of $CHCl_3$/*i*-PrOH. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 0.02 g (64%) of (±)-spicigerine (**7**) as a white solid requiring no further purification: mp 168−169 °C; IR (thin film) 3416, 2914, 2848, 1726, 1460, 1408, 1173, 1102, and 1010 cm^{-1}; ^1H NMR (400 MHz, CD3OD) δ 1.61 (m, 27H), 2.26 (t, 2H, J = 8.0 Hz), 3.05 (brs, 1H), 3.22 (m, 1H), and 3.82 (m, 1H); ^{13}C NMR (100 MHz, CD3OD) δ 16.1, 23.7, 26.2, 26.5, 30.4, 30.5, 30.6, 30.7, 30.8, 30.9, 31.1, 34.9, 35.1, 57.6, 58.8, 66.0, and 177.9; HRMS calcd for [($C_{18}H_{35}NO_3$) + H^+] 314.2617, found 314.2685.

(*S,E*)-*N*-(1-Furan-2-yl-ethyl)toluene *p*-Sulfinamide (41). A mixture of (*S*)-(+)-*p*-toluenesulfinamide[57] (0.03 g, 0.19 mmol), 2-acetylfuran (0.02 g, 0.19 mmol), and $Ti(OEt)_4$ (0.3 mL, 1.5 mmol) in $CHCl_3$ (4 mL) was heated at reflux for 41 h. The reaction mixture was then cooled to 0 °C. H_2O was added, and the resulting suspension was filtered over Celite. The filtrate was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.03 g (69%) of the title compound **41** as a yellow solid: mp 65−67 °C; IR (thin film) 3129, 2925, 2243, 1581, 1479, 1397, 1307, 1168, 1099, 1066, 1029, 907, 813, and 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.66 (s, 3H), 6.48 (s, 1H), 7.09 (d, 1H, J = 3.6 Hz), 7.29 (d, 2H, J = 8.0 Hz), 7.53 (s, 1H) and 7.69 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.6, 112. 7, 115.9, 125.3, 130.0, 142.0, 143.4, 146.4, 152.5, and 164.2.

***(S)*-*N*-(1-Furan-2-yl-ethyl)toluene *p*-Sulfonamide ((*S*)-16).** To a −78 °C solution of the above sulfinimine **41** (0.08 g, 0.33 mmol) in 4.7 mL of THF was added $LiAlH(O^tBu)_3$ (0.11 g, 0.43 mmol) in 2.5 mL of THF over a 15 min period. The mixture was stirred at −78 °C for 2 h and then warmed and stirred between −50 and −55 °C for 20 h. The solution was quenched with a saturated aqueous NH_4Cl solution, warmed to room temperature, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a 1:1 inseparable mixture of **41** and **42**, which was used immediately in the next step. A solution of the crude mixture in 5 mL of CH_2Cl_2 was added to a solution of *m*CPBA in 5 mL of CH_2Cl_2 at −30 °C. The mixture was stirred and allowed to warm to 0 °C over 1.5 h. A saturated aqueous $NaHCO_3$ solution was added, and the aqueous layer was extracted with CH_2Cl_2. The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting clear oil was purified by silica gel chromatography to give 0.03 g (35%) of the title compound: $[\alpha]_D$ −63.5 (*c* 1.0, EtOH) 0.58

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Supporting Information Available: ^1H and ^{13}C NMR data of various key compounds lacking CHN analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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