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# Radical cyclizations of acylsilanes in the synthesis of (+)-swainsonine and formal synthesis of (−)-epiquinamide

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ABSTRACT

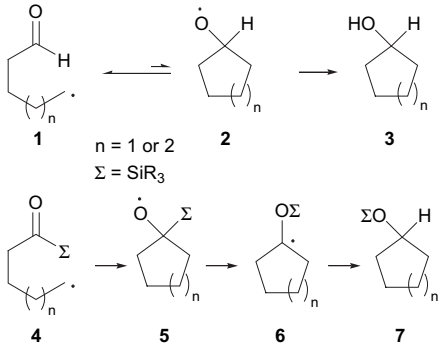
Radical cyclization of acylsilane is an useful synthetic methodology. To demonstrate the versatility of this method using the cyclization as a key step, polyhydroxylated indolizidine (+)-swainsonine was synthesized through two different bond connection approaches to construct the bicyclic skeleton. In the first approach, we used 2,3-isopropylidene-D-ribono-1,4-lactone (**20**) as a chiral building block to form the indolizidine skeleton through a 1,6-cyclization. In the second approach, (*S*)-(+)-5-oxo-2-tetrahydrofurancarboxylic acid (**23**) was used to construct the same ring system through a 1,5-cyclization. Starting from acid **23**, we also synthesized *exo*-1-hydroxyquinolizidin-4-one (**56**), which was a synthetic intermediate in the synthesis of polyhydroxylated quinolizidine (−)-epiquinamide.



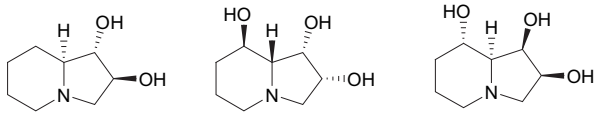
## 1. Introduction

Intramolecular free radical cyclization[1] is an important synthetic methodology for ring formation. Although intramolecular free radical addition to a carbonyl group appears to be an useful method for cyclic alcohol synthesis, this process is reversible and favors the acyclic radical side (Scheme 1).[2] Many methods[3] were developed to trap the cyclized alkoxy radical **2** to drive the reaction toward cyclization. In our previous work, we devised a synthetic equivalent of the formyl cyclization system **1** by replacing the formyl group with an acylsilane group[4,5] as in radical **4**. Cyclization of this radical affords a β-silyl substituted alkoxy radical intermediate **5**. A key radical-Brook rearrangement[6,7] occurs to generate a silyloxy substituted carbon radical **6**. Due to the well-known strong bonding between silicon and oxygen,[8] the cyclization is essentially propelled by this thermodynamic driving force. In the end, a silyl group protected cyclic alcohol **7** can be obtained very efficiently.[9]

Polyhydroxylated alkaloids,[10] such as lentiginosine (**8**) and swainsonine (**9**) (Fig. 1) resemble the structure of carbohydrates. Therapeutic potential of these alkaloids as anticancer and antiviral agents etc. is strongly related to their glycosidase inhibitory activities.[11] Biological activities of these compounds are dependent on




**Scheme 1.**



(+)-lentiginosine (**8**) (−)-swainsonine (**9**) (+)-swainsonine (*ent*-**9**)

**Fig. 1.** Some representative polyhydroxylated indolizidines.

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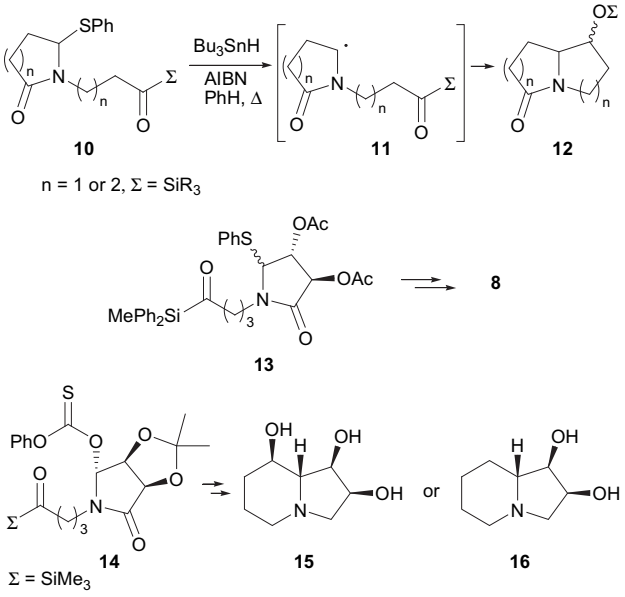
the chiralities of the hydroxyl substituents. Thus while the naturally occurring D-(−)-swainsonine (**9**) is a potent inhibitor of α-D-mannosidases,[12] it has no effect on the α-L-rhamnosidase.[13] On the contrary, the mirror image of **9**, L-(+)- swainsonine (*ent*-**9**), is a potent inhibitor of nariginase (an α-L-rhamnosidase) but with no or low inhibition for D-manosidases.[13] The stereochemical complexity of the structures and their diverse biological activities attracted considerable interest in the synthesis of this class of compounds.[10]

Previously we have demonstrated that the radical chemistry of acylsilane (Scheme 2) could be useful in the construction of silyloxy substituted pyrolizidinones, indolizidinones, and quinolizidinones (**12**).[14] More recently, we successfully employed this method in the synthesis of (+)-lentiginosine (**8**), (+)-1,2-di-*epi*-swainsonine (**15**) and (+)-1,8a-di-*epi*-lentiginosine (**16**).[15] In the present study, we disclose the synthesis of (+)-swainsonine (*ent*-**9**) and some quinolizidinones using this method.



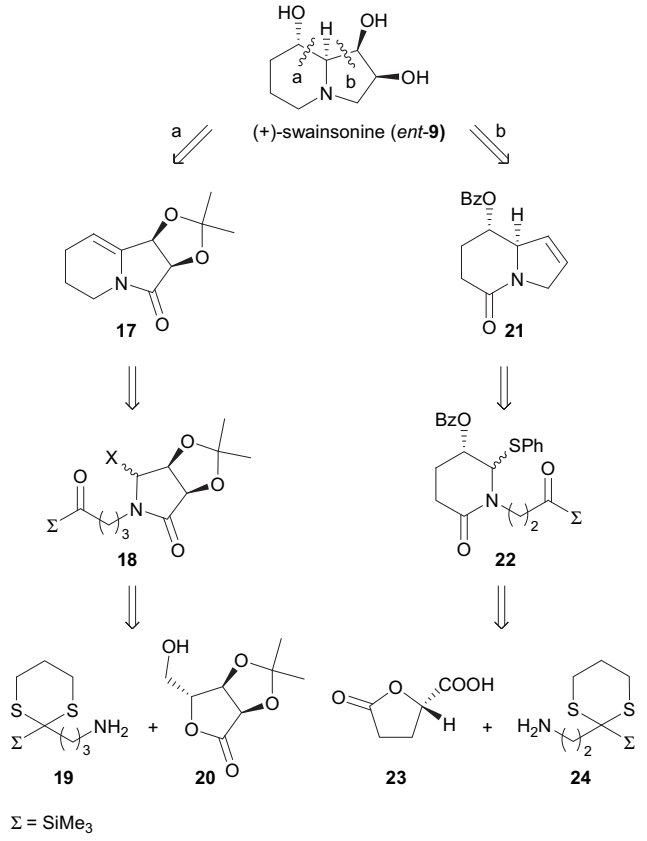

Scheme 2.

## 2. Results and discussion

As shown in Scheme 3, there are two possible routes for the synthesis of (+)-swainsonine using the acylsilane radical cyclization approach. These two routes are differentiated by the manner of ring constructions. In route-a, a six-membered ring is formed through an α-acylamino radical cyclization, and the chiral centers at C(1) and C(2) come from a chiral template **20** derived from D-ribose. In contrast, route-b involves the formation of a five-membered ring with a commercially available carboxylic acid **23** as chiral template.

### 2.1. The first approach of (+)-swainsonine

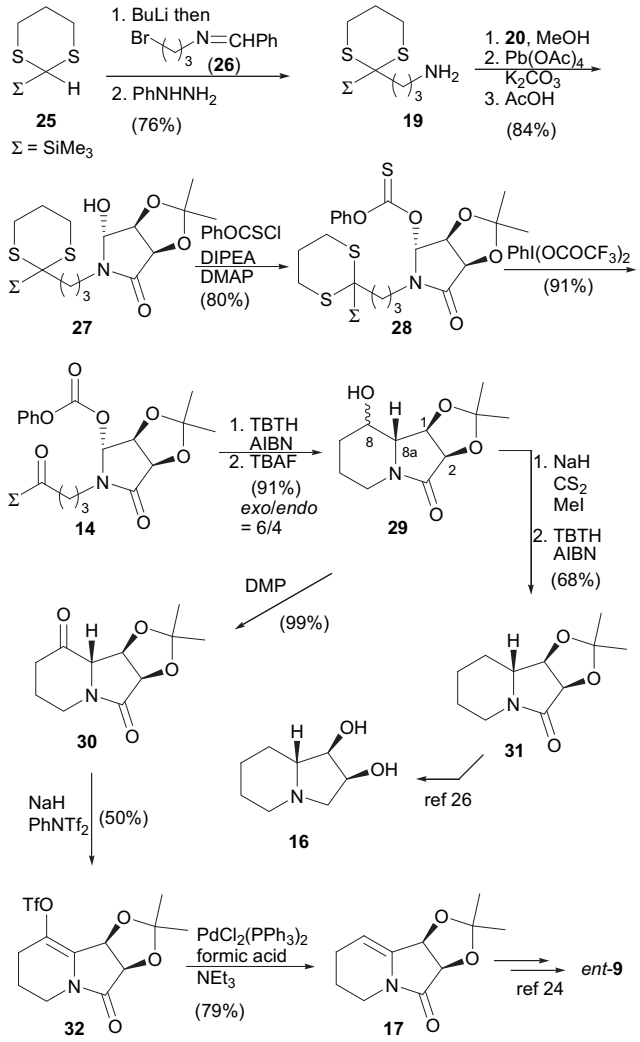
We started from the route-a approach as shown in Scheme 4. 2-Trimethylsilyl-1,3-dithiane (**25**) was alkylated with bromide **26**[16] followed by phenylhydrazine treatment to give amine **19** in 76% yield.[17] This amine reacted with the commercially available 2,3-isopropylidene-D-ribono-1,4-lactone (**20**), and the resulting crude amide diol was cleaved with lead tetraacetate followed by acid promoted cyclization of the intermediate amide aldehyde to afford a single isomer of lactam carbinol **27** in 84% yield over three steps.[18] In the proton NMR spectrum of **27**, the hemiaminal hydrogen (C(4)) appeared as a singlet at $\delta$ 5.10 (in $CDCl_3$). Based on the fact that there is no coupling between C(3) and C(4), we assumed that the two hydrogens adopted a trans relationship in the five-membered ring.




Scheme 3.

Originally we attempted to replace the hydroxyl group with a phenylthio group so that the thio group could be used to generate an α-acylamino radical.[19] However, due to the presence of an acid sensitive isopropylidene protecting group, exchanging the hydroxyl group of **27** with thiophenol under acidic condition was not successful. We therefore took a different approach by converting lactam carbinol **27** to thiocarbonate **28** (80%).[20] Hydrolysis[21] of the dithiane moiety in **28** with iodobenzene bistrifluoroacetate in wet acetonitrile gave acylsilane **14** in 91% yield. Radical cyclization reaction was accomplished by treatment of **14** with tributyltin hydride (TBTH) and catalytic amount of azobisisobutyronitrile (AIBN) in refluxing benzene, and the crude product was directly desilylated in THF with tetrabutylammonium fluoride (TBAF) to give an isomeric mixture of alcohols **29** (isomer ratio=6/4; 91% yield).

Alcohols **29** were oxidized with Dess–Martin periodinane[22] (DMP) to yield ketone **30** (99%) as a single isomer. This indicated that the two isomers of **29** were epimeric at C(8). Although the stereochemical control at C(8) was not satisfactory, the stereocenter at C(8a) was obtained in only one form. Similar to the report of Dener et al.,[23] the α-acylamino radical generated from thicarbonate **14** prefers to attack the acylsilane from the face opposite to the adjacent C–O bond. To confirm the stereochemistry at the ring junction, the alcohol mixture **29** was treated sequentially with sodium hydride, carbon disulfide, and methyl iodide at 0 °C to afford a xanthate mixture. The crude xanthate mixture was then reduced with TBTH in refluxing benzene to give the known indolizidinone **31**[24] in 68% yield. This Barton deoxygenation process[25] therefore identified the C(8a) stereochemistry of alcohols **29**.




Scheme 4.

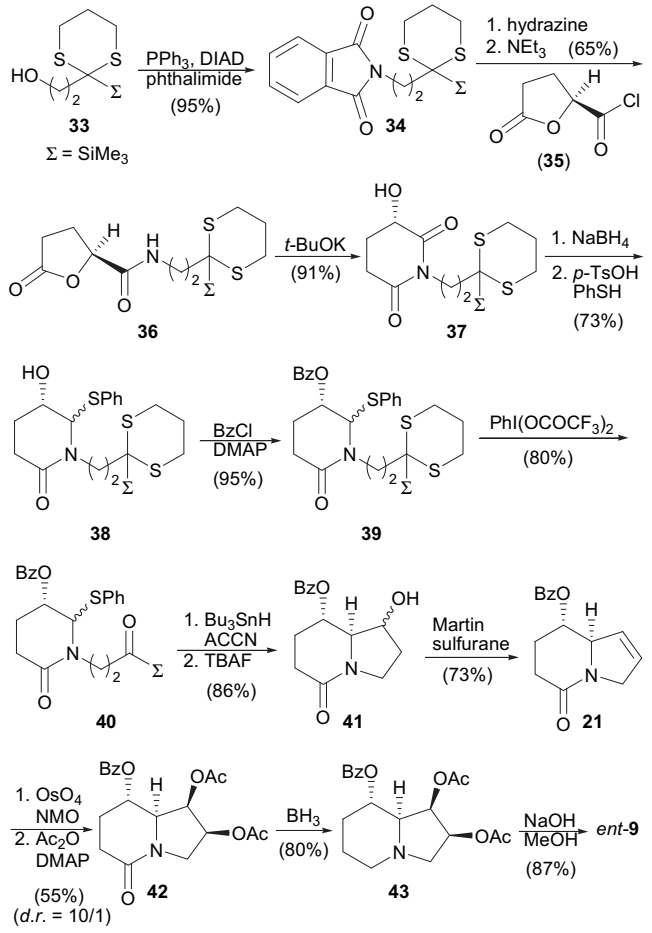
Note that indolizidinone **31** had been converted to (+)-1,8a-di-*epi*-lentiginosine (**16**) by Heitz and Overman.[26]

In the $^1$H NMR spectrum of the major isomer of **29**, the ring junction hydrogen (H(8a)) at $\delta$ 3.16 (in $C_6D_6$) appears as a doublet ($J$=9.6 Hz). The large coupling constant indicates a *trans*-diaxial relationship between H(8) and H(8a) in the pseudo-chair conformation of the piperidine portion of the structure. In contrast, H(8a) of the minor isomer at $\delta$ 3.27 (in $C_6D_6$) appears as a narrow broad singlet indicating a very small coupling with H(8). We therefore assigned the major isomer of **29** as the *exo* isomer. In addition, sodium borohydride reduction of ketone **30** in methanol at −40 °C gave *exo*-**29** (70%) selectively. This is consistent with an axial attack of the hydride to the carbonyl and placed H(8) at the pseudo-axial position.

For the synthesis of (+)-swainsonine (*ent*-**9**), ketone **30** was treated with sodium hydride in the presence of *N*-phenylbis(trifluoromethanesulfonimide) to give selectively enol triflate **32** (50%),[27] which contains a thermodynamically more stable conjugated structure. Removal of the triflate moiety by using bis(triphenylphosphine)palladium(II) dichloride, triethylamine, and formic acid[28] afforded the key olefin intermediate **17** (79%). This material was subsequently converted to *ent*-**9** as previously described in the literature.[24] Up to this point, we have achieved a formal synthesis of (+)-swainsonine.

## 2.2. The second approach of (+)-swainsonine

To further demonstrate the potential synthetic utility of our methodology led us to pursue the total synthesis of (+)-swainsonine (*ent*-**9**) in the synthetic pathway b. As shown in Scheme 5, Mitsunobu coupling[29] of alcohol **33**[30] with phthalimide afforded imide **34** in 95% yield. Imide **34** was deprotected by hydrazine to produce the crude amine **24**.[31] This amine was then reacted with acid chloride **35**, prepared from acid **23** by mixing with oxalyl chloride, to provide lactone **36** (65%). Rearrangement of lactone **36** to glutarimide **37** was achieved via potassium *tert*-butoxide treatment at low temperature in 91% yield.[32]




Scheme 5.

Sodium borohydride reduction of glutarimide **37** selectively reduced the more reactive carbonyl group.[33] Stirring the crude carbinol with thiophenol under acidic condition provided sulfide **38** in 73% yield over two steps. This sulfide appeared to be a pair of diastereomers (2.8/1) epimeric at the newly constructed chiral center. In order to inhibit the generation of acyliminium ion during the dithiane hydrolysis process, we converted the hydroxyl group to a benzoate as an electron-withdrawing group by Wolfe's condition[34] and obtained benzoate **39** in 95% yield. Hydrolysis[21] of the dithiane moiety of **39** under the condition stated above gave acylsilane **40** (80%) successfully without touching the phenylthio group.

Radical cyclization reaction of **40** proceeded with TBTH and catalytic amount of 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) in refluxing toluene to produce the crude silyl ethers that was desilylated to afford alcohols **41** in 86% yield over two steps. As discussed above, at this stage we assumed that the ring junction stereochemistry was constructed very selectively, and H(8a) was

*syn* to the adjacent benzoyloxy group. The chiral center at C(1) was not well-controlled and gave us a pair of epimers. Due to the difficulty in distinguishing *exo*/*endo* isomers of **41** from spectroscopic data, we did not further explore the *exo*/*endo* ratio in detail. Dehydration of the alcohol mixture **41** by Martin sulfurane[35] gave a 73% yield of olefin **21** and a trace amount of the regioisomer. This result confirmed the above assumption that **41** was an epimeric mixture at C(1).

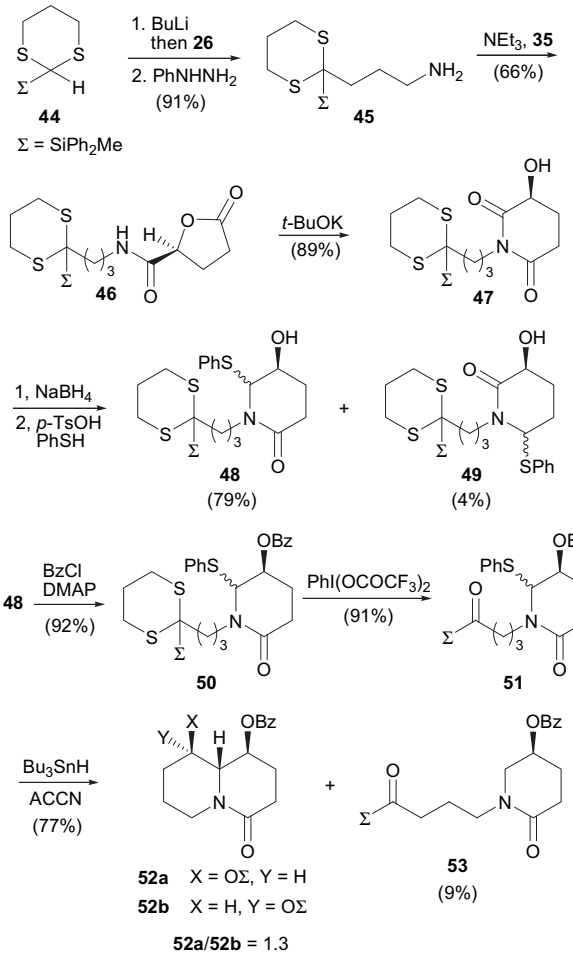
Dihydroxylation of **21** was accomplished by catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide (NMO),[36,37a] and the resulting crude diol was acetylated to give ester **42** (55%). Ester **42** is a mixture of two diastereomers (10/1) presumably derived from the attack of osmium tetroxide from the two faces of the double bond. Acetylation is necessary for the ease of purification. Unfortunately, the two isomers of **42** could not be separated by column chromatography. However, we found that reducing the lactam carbonyl group allowed us to separate the resulting isomers. Thus, borane reduction of **42** followed by chromatographic purification afforded the major ester **43** in 80% yield. The synthesis of (+)-swainsonine (*ent*-**9**) was achieved by removal of the ester groups of **43** by sodium hydroxide treatment in methanol in 87% yield. The spectroscopic data for synthetic *ent*-**9** were the same as the literature data.[24] This also helped us to determine the stereochemistry of the major isomer at the dihydroxylation step. The stereoselectivity is consistent with literature precedents.[37]

### 2.3. Formal synthesis of (−)-epiquinamide

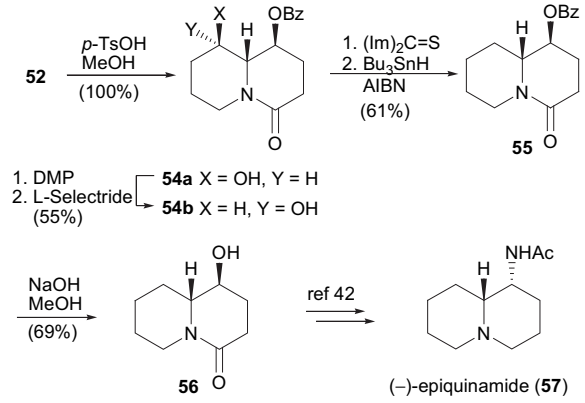
In addition to polyhydroxylated indolizidines, quinolizidines can also be synthesized this way. As shown in Scheme 6, 2-methyldiphenylsilyl-1,3-dithiane (**44**)[4] was alkylated with bromide **26**[16] followed by phenylhydrazine deprotection to afford amine **45** in 91% yield.[17] Amine **45** was treated with acid chloride **35** prepared as above to afford amide **46** in 66% yield. Rearrangement of **46** using potassium *tert*-butoxide provided imide **47** (89%).[32] Reducing the carbonyl group of **47** followed by exchanging the newly formed hydroxyl group with thiophenol gave sulfides **48** and **49** in 79% and 4% yield, respectively. The regioselectivity of reduction is lower than the succinimide system mentioned above. The sulfides obtained are mixtures of two epimers.

Benzoylation[34] of sulfides **48** (92%) followed by hydrolysis[21] of the dithiane moiety afforded acylsilane **51** (91%). Radical cyclization of **51** with TBTH and ACCN in refluxing toluene provided quinolizidinones **52** (**52a**/**52b**=1.3/1) and uncyclized reduction product **53** in 77% and 9% yield, respectively. Surprisingly, TBAF desilylation of **52** caused partial transferring of the benzoyl group to the hydroxyl group. Thus, instead we treated **52** with methanol in the presence of TsOH (Scheme 7) and successfully removed the silyl group to yield alcohols **54** (100%) without any acyl migration. Although we were not able to separate the two epimers in **54**, the major isomer could be identified as **54a** by comparing with the literature data.[38] The other isomer **54b** could be obtained in 55% yield by treating the alcohol mixture through DMP oxidation[22] and L-Selectride reduction in sequence. The bulky reducing agent selectively donates hydride from the equatorial face of the 3-azacyclohexanone structure to produce **54b**. In contrast, Marquart et. al.[38] already demonstrated that reduction of the same ketone substrate using sodium borohydride gave **54a** as the sole product.

Again, a very high stereoselectivity at the ring junction was obtained during the radical cyclization step, and the stereochemical course is the same as the above mentioned cases. Although the stereoselectivity at C(9) is low, the chirality at C(9) can be attenuated through an oxidation–reduction sequence. In this system, switching the silyl group to a trimethylsilyl group showed a lower cyclization yield (68%) accompanied by a higher reduction yield




**Scheme 6.**




**Scheme 7.**

(20%).[39] As we have reported previously,[40] phenyl groups on silicon facilitates the radical cyclization reaction. This effect is particularly helpful in this quinolizidinone system.

Barton deoxygenation process[25] of **54** as mentioned above afforded benzoate **55** (61%). Removal of the ester group under basic condition provided a known alcohol **56** (69%).[41] Note that alcohol **56** was a synthetic intermediate in the synthesis of (−)-epiquinamide (**57**),[41] whose enantiomer is a natural product isolated recently from an Ecuadorian frog *Epipedobates tricolor*.[42–45]

## 3. Conclusion

We have demonstrated a versatile synthetic method in the synthesis of polyhydroxylated indolizidines and quinolizidines via α-acylamino radical cyclizations with acylsilanes. The key radical cyclization step constructed the fused bicyclic structure with good efficiency and stereo-control at the ring junction position. This methodology can easily adopt existing chiral building blocks and is quite versatile in the way of bond constructions. The flexibility was exemplified in the two approaches for the synthesis of (+)-swainsonine (*ent*-**9**). Similarly, a formal synthesis of quinolizidine (−)-epiquinamide (**57**) was also accomplished. In addition, several synthetic intermediates obtained along the way in the synthesis exhibit the potential to be converted to other polyhydroxylated indolizidines and quinolizidines. This work successfully extended the synthetic utility of acylsilanes both in the synthesis of structurally complex acylsilanes and their applications.

## 4. Experimental section

### 4.1. General

Melting points are uncorrected. $^1$H NMR spectra were recorded at 400 MHz; $^{13}$C NMR spectra were recorded at 100 MHz. Choroform ($\delta$=7.24 ppm) was used as internal standard in $^1$H NMR spectra, whereas $CDCl_3$ ($\delta$=77.0 ppm) was used as internal standard in $^{13}$C NMR spectra. When benzene-$d_6$ was used as NMR solvent, benzene, and benzene-$d_6$ was used as internal standard for $^1$H ($\delta$=7.16 ppm) and $^{13}$C NMR ($\delta$=128.4 ppm) spectra, respectively. Benzene and THF were distilled from sodium benzophenone ketyl under $N_2$. Triethylamine, diisopropylethylamine, dichloromethane, *N*,*N*-dimethylformamide, and toluene were dried with $CaH_2$ and distilled. The solvent used for cyclization reactions was deoxygenated by passing a gentle stream of argon through for 0.5 h before use. All reactions were performed under a blanket of $N_2$ or Ar.

### 4.2. 2-(3-Aminopropyl)-2-trimethylsilyl-1,3-dithiane (19)

To a solution of **25** (8.70 g, 45.2 mmol) in THF (45 mL) cooled in a dry ice-acetone bath was added over 25 min a 1.6 N BuLi solution in hexane (29 mL, 47 mmol). The resulting solution was stirred at the same temperature for another 30 min followed by the addition of a solution of **26** (10.2 g, 44.9 mmol) in THF (45 mL) over 30 min. The resulting mixture was slowly warmed up to rt and then stirred overnight. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give a liquid residue. The liquid was dissolved in EtOH (67 mL) followed by the addition of phenylhydrazine (4.50 mL, 45.4 mmol) and then stirred at rt for 3.5 h. The resulting mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (MeOH/concd $NH_3$, 9:1) to give 8.54 g (76%) of **19** as a pale yellow liquid: IR (neat) 3370 (br) cm$^{-1}$; $^1$H NMR ($C_6D_6$, 400 MHz) $\delta$ 0.33 (s, 9H, TMS), 1.13 (br s, 2H, $NH_2$), 1.40–1.45 (m, 1H), 1.58–1.78 (m, 3H), 2.06 (dt, *J*=14.6, 3.2 Hz, 2H, equatorial–$SCH_2$), 2.23–2.30 (m, 2H), 2.53 (t, *J*=6.6 Hz, 2H, $NCH_2$), 2.73 (td, *J*=14.6, 3.2 Hz, 2H, axial–$SCH_2$); $^{13}$C NMR ($C_6D_6$, 100 MHz) $\delta$ −1.6 ($CH_3$), 24.0 ($CH_2$), 26.0 ($CH_2$), 32.4 ($CH_2$), 35.7 ($CH_2$), 39.6 (C), 43.3 ($CH_2$); HRMS (EI) calcd for $C_{10}H_{23}NS_2Si$ 249.1041, found 249.1042.

### 4.3. (−)-(3*R*,4*S*,5*R*)-5-Hydroxy-3,4-(isopropylidenedioxy)-1-[3-(2-trimethylsilyl-1,3-dithian-2-yl)propyl]pyrrolidin-2-one (27)

To a solution of **19** (3.06 g, 16.3 mmol) in MeOH (40 mL) was added **20** (5.07 g, 20.4 mmol), and the resulting solution was stirred at rt overnight and then concentrated to give a liquid. The liquid was dissolved in $CH_3CN$ (100 mL), cooled in an ice-water bath followed by the addition of $K_2CO_3$ (2.47 g, 17.9 mmol) and $Pb(OAc)_4$ (7.94 g, 17.9 mmol) sequentially. The resulting mixture was stirred at the same temperature for 30 min and then at rt for another 30 min. The reaction mixture was filtered and concentrated to give a liquid residue. The residue was dissolved in $CH_2Cl_2$ (100 mL) followed by the addition of AcOH (0.7 mL), stirred at rt for 13 h and then concentrated to give a solid. The solid was chromatographed on silica gel (hexane/EtOAc, 7:3) to yield 5.53 g (84%) of **27** as a white solid: $[\alpha]_D^{19}$ −4.0 (*c* 2.3, $CHCl_3$); mp 77–78 °C; IR ($CH_2Cl_2$) 3350 (br), 1693 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.16 (s, 9H, TMS), 1.35 (s, 3H), 1.40 (s, 3H), 1.65–1.96 (m, 3H), 1.97–2.06 (m, 1H), 2.10–2.22 (m, 2H), 2.41 (dt, *J*=14.2, 3.6 Hz, 2H, equatorial–$SCH_2$), 2.93–3.04 (m, 2H, axial–$SCH_2$), 3.21 (dt, *J*=13.8, 6.8 Hz, 1H, $NCH_2$), 3.52 (dt, *J*=13.8, 6.8 Hz, 1H, $NCH_2$), 4.52 (d, *J*=5.4 Hz, 1H, C(4)H), 4.81 (d, *J*=5.4 Hz, 1H, C(3)H), 5.10 (s, 1H, NCHO); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −1.9 ($CH_3$), 23.7 ($CH_2$), 25.3 ($CH_2$), 25.5 ($CH_2$), 26.0 ($CH_3$), 27.4 ($CH_3$), 34.7 ($CH_2$), 38.4 (C), 40.5 ($CH_2$), 76.9 (CH), 79.5 (CH), 84.5 (CH), 112.9 (C), 171.4 (C); HRMS (EI) calcd for $C_{17}H_{31}NO_4S_2Si$ 405.1458, found 405.1462.

### 4.4. (−)-(3*R*,4*S*,5*R*)-3,4-(Isopropylidenedioxy)-5-(phenoxythiocarbonyloxy)-1-[3-(2-trimethylsilyl-1,3-dithian-2-yl)propyl]pyrrolidin-2-one (28)

To a solution of **27** (437 mg, 1.08 mmol), diisopropylethylamine (0.26 mL, 1.6 mmol) and DMAP (12 mg, 0.11 mmol) in $CH_2Cl_2$ (10 mL) at rt was added slowly *O*-phenyl chlorothioformate (0.18 mL, 1.3 mmol). The resulting mixture was stirred at the same temperature for 2 h, concentrated and chromatographed on silica gel (hexane/EtOAc, 7:3) to give 464 mg (80%) of **28** as a colorless liquid: $[\alpha]_D^{20}$ −14.4 (*c* 2.2, $CHCl_3$); IR ($CH_2Cl_2$) 1716 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.17 (s, 9H, TMS), 1.38 (s, 3H), 1.44 (s, 3H), 1.68–1.94 (m, 3H), 1.96–2.05 (m, 1H), 2.13–2.24 (m, 2H), 2.40 (br d, *J*=14.0 Hz, 2H, equatorial–$SCH_2$), 2.93–3.04 (m, 2H, axial–$SCH_2$), 3.10–3.20 (m, 1H, $NCH_2$), 3.75 (dt, *J*=13.8, 7.6 Hz, 1H, $NCH_2$), 4.83 (d, *J*=6.0 Hz, 1H, C(4)H), 4.89 (d, *J*=6.0 Hz, 1H, C(3)H), 5.12 (s, 1H, NCHO), 7.13 (d, *J*=8.0 Hz, 2H), 7.25 (t, *J*=8.0 Hz, 1H), 7.37 (t, *J*=8.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −2.1 ($CH_3$), 23.5 ($CH_2$), 24.9 ($CH_2$), 25.1 ($CH_2$), 26.0 ($CH_3$), 27.3 ($CH_3$), 34.3 ($CH_2$), 38.3 (C), 41.1 ($CH_2$), 67.3 (CH), 76.9 (CH), 79.5 (CH), 112.9 (C),120.5 (CH), 126.1 (CH), 129.1 (CH), 149.9 (C), 166.1 (C), 170.4 (C); HRMS (EI) calcd for $C_{24}H_{35}NO_5S_3Si$ 541.1441, found 541.1440.

### 4.5. General procedure for dithiane hydrolysis using iodobenzene bistrifluoroacetate: (−)-(3*R*,4*S*,5*R*)-3,4-(isopropylidenedioxy)-5-(phenoxythiocarbonyloxy)-1-[4-oxo-4-(trimethylsilyl)butyl]pyrrolidin-2-one (14)

To a mixture of **28** (570 mg, 1.05 mmol), $NaHCO_3$ (352 mg, 4.19 mmol), water (2.6 mL), and $CH_3CN$ (10.5 mL) was added iodobenzene bistrifluoroacetate (837 mg, 1.95 mmol) in one portion. The resulting mixture was stirred at rt for 23 min and then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 65:35) to give 434 mg (91%) of **14** as a yellow oil: $[\alpha]_D^{24}$ −25.9 (*c* 2.3, $CHCl_3$); IR ($CH_2Cl_2$) 1718, 1645 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.17 (s, 9H, TMS), 1.37 (s, 3H), 1.43 (s, 3H), 1.64–1.78 (m, 1H), 1.82–1.97 (m, 1H), 2.56–2.72 (m, 2H, $COCH_2$), 3.11 (ddd, *J*=13.4, 8.0, 4.6 Hz, 1H, $NCH_2$), 3.62 (dt, *J*=13.4, 8.0 Hz, 1H, $NCH_2$), 4.74 (d, *J*=6.0 Hz, 1H, C(4)H), 4.87 (d, *J*=6.0 Hz, 1H, C(3)H), 5.06 (s, 1H, NCHO), 7.13 (d, *J*=8.0 Hz, 2H), 7.23 (t, *J*=8.0 Hz, 1H), 7.36 (t, *J*=8.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −3.0 ($CH_3$), 19.1 ($CH_2$), 25.9 ($CH_3$), 27.3 ($CH_3$), 40.3 ($CH_2$), 44.8 ($CH_2$), 67.5 (CH), 77.0 (CH), 79.8 (CH), 113.1 (C),120.9 (CH), 126.5

(CH), 129.4 (CH), 150.4 (C), 166.7 (C), 171.0 (C), 245.7 (C); HRMS (ESI) calcd for $C_{17}H_{31}NO_4S_2Si$ $(M+Na)^+$ 474.1383, found 474.1382.

### 4.6. (1*R*,2*R*,8*R*/*S*,8a*R*)-8-Hydroxy-1,2-(isopropylidenedioxy)-1,5,6,7,8,8a-hexahydro-2*H*-indolizin-3-one (29)

To a refluxing solution of **14** (1.29 g, 2.85 mmol) in toluene (14.5 mL) was added over 6 h using a syringe pump a solution of TBTH (1.20 mL, 4.46 mmol) and AIBN (70 mg, 0.43 mmol) in toluene (14.5 mL). The resulting mixture was stirred at the same temperature for 1.3 h and then concentrated in vacuo because the reaction was not complete, the above procedure was repeated using 0.80 mL (2.97 mmol) of TBTH and 70 mg (0.43 mmol) of AIBN with an addition time of 2 h. The reaction mixture was stirred at the same temperature for another 2 h and then concentrated and chromatographed on silica gel (EtOAc/MeOH, 95:5) to give 589 mg (91%) of **29** (*exo*/*endo*=6:4) as a pale yellow oil: IR ($CHCl_3$) 3388 (br), 1697 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 400 MHz) $\delta$ 0.83 (br d, $J$=15.2 Hz, 0.4H), 0.87–1.07 (m, 2H), 1.27 (s, 1.8H), 1.28 (s, 1.2H), 1.42–1.54 (m overlapped with two s at 1.44 and 1.46, 3.6H), 1.61–1.71 (m, 1H), 1.99 (td, $J$=12.8, 3.2 Hz, 0.6H, $NCH_2$ of *exo* isomer), 2.14 (td, $J$=12.8, 4.0 Hz, 0.4H, $NCH_2$ of *endo* isomer), 2.61–2.71 (m, 1.2H), 3.16 (d, $J$=9.6 Hz, 0.6H, NCH of *exo* isomer), 3.25 (br s, 0.4H, OH), 3.27 (br s, 0.4H, NCH of *endo* isomer), 3.54 (br s, 0.4H, C(8)H of *endo* isomer), 3.96 (dd, $J$=12.8, 4.0 Hz, 0.6H, $NCH_2$ of *exo* isomer), 4.08 (dd, $J$=12.8, 4.8 Hz, 0.4H, $NCH_2$ of *endo* isomer), 4.45 (d, $J$=6.6 Hz, 0.6H, C(1)H of *exo* isomer), 4.56 (d, $J$=6.6 Hz, 0.6H, C(2)H of *exo* isomer), 4.60 (d, $J$=6.6 Hz, 0.4H, C(1)H of *endo* isomer), 4.85 (d, $J$=6.2 Hz, 0.4H, C(2)H of *endo* isomer); HRMS (ESI) calcd for $C_{11}H_{18}NO_4$ $(M+H)^+$ 228.1236, found 228.1231.

Pure *exo*-**29** (8*R*-isomer) was obtained by reduction of 50 mg (0.22 mmol) of **30** by $NaBH_4$ (50.4 mg, 1.32 mmol, added over three portions) in MeOH cooled in a dry ice-$CH_3CN$ bath in a period of 30 min. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc) to give 35 mg (70%) of *exo*-**29** as a white solid: $[\alpha]_D^{20}$ −72.9 (*c* 3.0, $CHCl_3$); mp 146–148 °C; IR (neat) 3390 (br), 1682 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.38 (s, 3H), 1.41–1.52 (m overlapped with s at 1.45, 4H), 1.66–1.90 (m, 3H), 2.16 (br d, $J$=9.6 Hz, 1H), 2.63 (td, $J$=12.8, 3.6 Hz, 1H, $NCH_2$), 3.13–3.27 (m, 2H), 4.10 (br d, $J$=12.8 Hz, 1H, $NCH_2$), 4.62 (d, $J$=6.6 Hz, 1H), 4.71 (d, $J$=6.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 23.8 ($CH_2$), 25.3 ($CH_3$), 26.7 ($CH_3$), 33.6 ($CH_2$), 39.6 ($CH_2$), 67.6 (CH), 69.6 (CH), 74.6 (CH), 77.5 (CH), 112.6 (C), 168.7 (C); HRMS (ESI) calcd for $C_{11}H_{18}NO_4$ $(M+H)^+$ 228.1236, found 228.1231.

### 4.7. (−)-(1*R*,2*R*,8a*R*)-1,2-(Isopropylidenedioxy)-1,5,6,7,8,8a-hexahydro-2*H*-indolizin-3-one (31)[26]

To a solution of **29** (78 mg, 0.34 mmol) in THF (3.4 mL) cooled in an ice-water bath was added a 60% NaH dispersion (15 mg, 0.38 mmol) in one portion. The reaction mixture was stirred at the same temperature for 10 min and then at rt for 30 min. The resulting mixture was cooled in an ice-water bath followed by slow addition of $CS_2$ (31 μL, 0.51 mmol). The reaction mixture was stirred at the same temperature for 1 h followed by the addition of MeI (32 μL, 0.51 mmol). The resulting mixture was stirred at rt for 2 h and then poured into water and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$) and concentrated to give an oil residue. The residue was stirred with tributyltin hydride (0.20 mL, 0.74 mmol) and AIBN (11 mg, 0.07 mol) in refluxing benzene (3.4 mL) for 2 h. The resulting solution was concentrated and chromatographed on silica gel (hexane/EtOAc, 2:8) to give 49 mg (68%) of **31** as a white solid: $[\alpha]_D^{21}$ −35.6 (*c* 3.1, $CHCl_3$); mp 106–107 °C [lit.[26] $[\alpha]_D$ −95 (*c* 1.0, $CHCl_3$); mp 107–108 °C]. The NMR-spectroscopic analysis is consistent with literature data.[26]

### 4.8. (−)-(1*R*,2*R*,8a*S*)-1,2-(Isopropylidenedioxy)-1,6,7,8a-tetrahydro-3,8(2*H*,5*H*)-indolizindione (30)

To a solution of **29** (132 mg, 0.581 mmol) in $CH_2Cl_2$ (6 mL) was added a 0.5 M Dess–Martin periodinane solution in $CH_2Cl_2$ (1.8 mL, 0.90 mmol). The reaction mixture was stirred at rt for 2 5 h and then poured into a saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$. The organic layer was washed with a saturated $Na_2S_2O_3$ solution, dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc) to give 130 mg (99%) of **30** as a pale yellow oil: $[\alpha]_D^{20}$ −60.6 (*c* 9.9, $CHCl_3$); IR ($CH_2Cl_2$) 1708 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.34 (s, 3H), 1.41 (s, 3H), 1. 84–1.96 (m, 1H), 2.03–2.14 (m, 1H), 2.45–2.60 (m, 2H, $COCH_2$), 3.17 (ddd, $J$=13.2, 9.2, 4.4 Hz, 1H, $NCH_2$), 4.03 (d, $J$=1.2 Hz, 1H, NCH), 4.11 (dt, $J$=13.2, 5.2 Hz, 1H, $NCH_2$), 4.54 (d, $J$=6.4 Hz 1H, C(2)H), 5.04 (dd, $J$=6.4, 1.2 Hz, 1H, C(1)H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 24.3 ($CH_2$), 25.3 ($CH_3$), 26.9 ($CH_3$), 39.1 ($CH_2$), 39.4 ($CH_2$), 68.7 (CH), 72.3 (CH), 77.1 (CH), 112.8 (C), 168.0 (C), 201.7 (C); HRMS (ESI) calcd for $C_{11}H_{15}NNaO_4$ $(M+Na)^+$ 248.0899, found 248.0891.

### 4.9. (+)-(1*R*,2*R*)-1,2-(Isopropylidenedioxy)-8-(trifluoromethanesulfonyloxy)-1,5,6,7-tetrahydro-2*H*-indolizin-3-one (32)

To a mixture of a 60% NaH dispersion (12.5 mg, 0.313 mmol) in THF (2 mL) cooled in an ice-water bath was added a solution of **30** (59 mg, 0.26 mmol) and *N*-phenylbis(trifluoromethanesulfonimide) (186 mg, 0.52 mmol) in THF (1 mL). The resulting mixture was stirred at rt for 3 h and then poured into water and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 6:4) to give 46.4 mg (50%) of **32** as a white solid: $[\alpha]_D^{24}$ +88.7 (*c* 2.3, $CHCl_3$); mp 102–104 °C; IR ($CHCl_3$) 1742, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.41 (s, 3H), 1.43 (s, 3H), 1.89–2.05 (m, 2H), 2.48–2.63 (m, 2H, C(7)H), 3.45 (ddd, $J$=13.2, 8.4, 4.4 Hz, 1H, $NCH_2$), 3.61 (ddd, $J$=13.2, 6.4, 4.4 Hz, 1H, $NCH_2$), 4.71 (d, $J$=6.4 Hz, 1H, C(1)H), 5.28 (d, $J$=6.4 Hz, 1H, C(2)H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 20.2 ($CH_2$), 25.3 ($CH_2$), 25.7 ($CH_3$), 26.8 ($CH_3$), 38.2 ($CH_2$), 70.7 (CH), 76.2 (CH), 114.4 (C), 118.2 (quartet, $J_{C-F}$=317.0 Hz), 129.5 (C), 132.4 (C), 169.0 (C); HRMS (EI) calcd for $C_{12}H_{14}F_3NO_6S$ 357.0488, found 357.0481.

### 4.10. (+)-(1*R*,2*R*)-1,2-(Isopropylidenedioxy)-1,5,6,7-tetrahydro-2*H*-indolizin-3-one (17)

A mixture of **32** (26 mg, 0.070 mmol), bis(triphenylphosphine) palladium(II) dichloride (5.5 mg, 0.0078 mmol), $Et_3N$ (30 μL, 0.22 mmol), and formic acid (6.0 μL, 0.16 mmol) in DMF (0.7 mL) was heated at 60 °C for 22 h and then directly concentrated in vacuo and chromatographed on silica gel (hexane/EtOAc, 4:6) to give 12 mg (79%) of **17** as a yellow solid: $[\alpha]_D^{21}$ +79.9 (*c* 1.4, $CHCl_3$); mp 57–59 °C. The spectroscopic data is identical to that reported for the racemic mixture.[24]

### 4.11. *N*-[2-(2-Trimethylsilyl-1,3-dithian-2-yl)ethyl] phthalimide (34)

To a solution of **33** (2.36 g, 10.0 mol), phthalimide (1.47 g, 10.0 mmol), and triphenylphosphine (2.88 g, 11.0 mmol) in THF (40 mL) cooled in an ice-water bath was added over 15 min a solution of diisopropyl azodicarboxylate (2.2 mL, 11 mmol) in THF (10 mL). The reaction mixture was stirred at rt for 3 h and then concentrated and chromatographed on silica gel (hexane/EtOAc, 85:15) to give 3.46 g (95%) of **34** as a white solid: mp 138–139 °C; IR ($CHCl_3$) 1772, 1712 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.30 (s, 9H, TMS), 1.91 (dtt, $J$=14.0, 12.4, 3.2 Hz, 1H), 2.08 (br d, $J$=14.0 Hz, 1H), 2.43–2.56 (m, 4H), 3.17 (ddd, $J$=15.0, 13.2, 2.8 Hz, 2H, axial–$SCH_2$),

3.80–3.88 (m, 2H, $NCH_2$), 7.66–7.75 (m, 2H), 7.78–7.87 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ −2.6 ($CH_3$), 23.2 ($CH_2$), 25.0 ($CH_2$), 34.4 ($CH_2$), 36.5 ($CH_2$), 36.7 (C), 123.0 (CH), 132.0 (C), 133.8 (CH), 168.0 (C); HRMS (EI) calcd for $C_{17}H_{23}NO_2S_2Si$ 365.0939, found 365.0951.

### 4.12. (−)-(*S*)-*N*-[2-(2-Trimethylsilyl-1,3-dithian-2-yl)ethyl]-tetrahydro-5-oxo-2-furancarboxamide (36)

To a solution of **34** (1.09 g, 2.98 mmol) in dry THF (6 mL) was added a 1.5 M MeOH solution of hydrazine (6 mL). The resulting mixture was stirred at 55 °C for 4 h and then poured into water and extracted with $Et_2O$. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give a crude amine as a pale yellow oil. To another solution of **23** (412 mg, 3.17 mmol) and one drop of DMF in $CH_2Cl_2$ (8 mL) cooled in an ice-water bath was added slowly oxalyl chloride (0.32 mL, 3.73 mmol). The resulting mixture was stirred at rt for 2 h and then directly concentrated to give a liquid residue. This liquid was dissolved in THF (5 mL), cooled in a dry ice-acetone bath followed by the addition of $Et_3N$ (0.60 mL, 4.3 mmol) and a solution of the crude amine prepared above in THF (1 mL). The resulting mixture was stirred at rt overnight and then poured into water and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 3:7) to give 675 mg (65%) of **36** as a yellow solid: $[\alpha]_D^{21}$ −10.9 (*c* 2.9, $CHCl_3$); mp 128–129 °C; IR ($CH_2Cl_2$) 3434, 1789, 1710, 1678 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.22 (s, 9H, TMS), 1.82–1.98 (m, 1H), 2.01–2.12 (m, 1H), 2.33–2.55 (m overlapped with dt at 2.49, *J*=14.4, 4.0 Hz, 5H), 2.56–2.65 (m overlapped with t at 2.57, *J*=8.0 Hz, 3H), 3.04 (br t, *J*=14.4 Hz, 2H, axial–$SCH_2$), 3.38–3.56 (m, 2H, $NCH_2$), 4.85 (t, *J*=7.6 Hz, 1H, CHO), 6.84 (br s, 1H, NH); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ −2.1 ($CH_3$), 23.8 ($CH_2$), 25.1 ($CH_2$), 26.1 ($CH_2$), 27.9 ($CH_2$), 36.4 ($CH_2$), 37.0 (C), 38.3 ($CH_2$), 77.4 (CH), 168.5 (C), 175.0 (C); HRMS (EI) calcd for $C_{14}H_{25}NO_3S_2Si$ 347.1045, found 347.1052.

### 4.13. (−)-(*S*)-3-Hydroxy-1-[2-(2-trimethylsilyl-1,3-dithian-2-yl)ethyl]-2,6-piperidindione (37)

To a solution of **36** (631 mg, 1.82 mmol) in THF (5.5 mL) cooled in a dry ice-acetone bath was added potassium *tert*-butoxide (203 mg, 1.82 mmol) in one portion. The resulting mixture was warmed up to −40 °C over a period of 1.5 h and then quenched by the addition of a saturated $NH_4Cl$ solution (10 mL). The resulting mixture was poured into a mixture of brine and water (1:1) and extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 4:6) to give 576 mg (91%) of **37** as a pale yellow solid: $[\alpha]_D^{21}$ −23.4 (*c* 5.1, $CHCl_3$); mp 110–111 °C; IR ($CH_2Cl_2$) 3521 (br), 1729, 1677 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.24 (s, 9H, TMS), 1.80–1.97 (m, 2H), 1.99–2.08 (m, 1H), 2.26–2.40 (m, 3H), 2.43 (dt, *J*=14.0, 5.2 Hz, 2H, equatorial–$SCH_2$), 2.63 (ddd, *J*=18.2, 13.4, 5.2 Hz, 1H), 2.88 (ddd, *J*=18.2, 4.6, 2.4 Hz, 1H), 3.07–3.18 (m, 2H, axial–$SCH_2$), 3.80–3.98 (m, 2H, $NCH_2$), 4.21 (dd, *J*=12.6, 5.4 Hz, 1H, CHO); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ −2.3 ($CH_3$), 23.5 ($CH_2$), 25.3 ($CH_2$), 25.7 ($CH_2$), 31.1 ($CH_2$), 33.6 ($CH_2$), 37.0 ($CH_2$), 39.6 ($CH_2$), 68.3 (CH), 170.3 (C), 174.3 (C); HRMS (EI) calcd for $C_{14}H_{25}NO_3S_2Si$ 347.1045, found 347.1049.

### 4.14. (6*R*/*S*,5*S*)-5-Hydroxy-1-[2-(2-trimethylsilyl-1,3-dithian-2-yl)ethyl]-6-(phenylsulfenyl)piperidin-2-one (38)

To a solution of **37** (612 mg, 1.76 mmol) in 30 mL of a mixture of MeOH/THF (7:1) cooled in a dry ice-$CCl_4$ bath was added $NaBH_4$ (333 mg, 8.8 mmol) in two portions separated by a period of 12 min. The resulting mixture was stirred at the same temperature for 10 min and then quenched by the addition of a saturated $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and concentrated to give a solid residue. This solid was dissolved in a mixture of $CH_2Cl_2$ (1 mL) and thiophenol (1 mL) followed by the addition of *p*-toluenesulfonic acid monohydrate (33 mg, 0.17 mmol). The reaction mixture was stirred at rt overnight and then poured into a 15% NaOH solution and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 4:6) to give 570 mg (73%) of **38** as a pale yellow oil: IR ($CHCl_3$) 3372 (br), 1646 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.07 (s, 2.7H, TMS of the minor isomer), 0.21 (s, 6.3H, TMS of the major isomer), 1.71–1.97 (m, 2.7H), 1.98–2.06 (m, 1H), 2.14–2.26 (m, 1.4H), 2.28–2.79 (m overlapped with br t at 2.74, *J*=12.0 Hz, 6.6H), 3.01 (br t, *J*=13.4 Hz, 1H, axial–$SCH_2$), 3.07–3.22 (m overlapped with td at 3.13, *J*=12.8, 4.4 Hz, 1H), 3.42 (td, *J*=12.4, 8.0 Hz, 0.3H), 3.92 (td, *J*=12.4, 4.8 Hz, 0.3H), 4.00 (td, *J*=12.8, 4.8 Hz, 0.7H), 4.11–4.20 (m, 1H), 4.58 (br s, 0.3H, NCHS of the minor isomer), 4.77–4.81 (m, 0.7H, NCHS of the major isomer), 7.25–7.33 (m, 3H), 7.43–7.50 (m, 0.6H), 7.54 (d, *J*=5.6 Hz, 1.4H); HRMS (EI) calcd for $C_{20}H_{31}NO_2S_3Si$ 441.1286, found 441.1291.

### 4.15. (6*R*/*S*,5*S*)-5-Benzoyloxy-1-[2-(2-trimethylsilyl-1,3-dithian-2-yl)ethyl]-6-(phenylsulfenyl)piperidin-2-one (39)

To a solution of **3** (570 mg, 1.29 mmol), DMAP (158 mg, 1.29 mmol) and $Et_3N$ (2 mL) in $CH_2Cl_2$ (10 mL) was added slowly benzoyl chloride (0.2 mL, 1.74 mmol). The reaction mixture was stirred at rt for 2 h and then partitioned between water and $CH_2Cl_2$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 7:3) to give 672 mg (95%) of **39** as a colorless oil: IR ($CH_2Cl_2$) 1720, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.15 (s, 3.6H, TMS of the minor isomer), 0.19 (s, 5.4H, TMS of the major isomer), 1.72–1.93 (m, 1.4H), 1.95–2.06 (m, 0.6H), 2.08–2.34 (m, 2H), 2.34–2.83 (m, 7H), 2.98 (br t, *J*=12.4 Hz, 0.6H, equatorial–$SCH_2$ of the major isomer), 3.14 (br t, *J*=12.4 Hz, 0.6H, equatorial–$SCH_2$ of the major isomer), 3.20–3.39 (m, 0.8H, equatorial–$SCH_2$ of the minor isomer), 3.90–4.03 (m, 1H, $NCH_2$), 4.89 (br s, 0.4H, NCHS of the minor isomer), 5.18–5.25 (m, 0.6H, NCHS of the major isomer), 5.34–5.44 (m, 0.6H, CHOBz of the major isomer), 5.48 (br s, 0.4H, CHOBz of the minor isomer), 6.98–7.10 (m, 2H), 7.28–7.45 (m, 4.4H), 7.46–7.62 (m, 1.6H), 7.83 (d, *J*=6.8 Hz, 1.2H), 7.95 (d, *J*=6.8 Hz, 0.8H); HRMS (EI) calcd for $C_{27}H_{35}NO_3S_3Si$ 545.1543, found 545.1545.

### 4.16. (6*R*/*S*,5*S*)-5-Benzoyloxy-1-[3-oxo-3-(trimethylsilyl) propyl]-6-(phenylsulfenyl)piperidin-2-one (40)

According to the general procedure for dithiane hydrolysis, dithiane **39** (649 mg, 1.19 mmol) was hydrolyzed to give 433 mg (80%) of **40** as a yellow liquid: IR ($CH_2Cl_2$) 1721, 1647 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ −0.01 (s, 2.7H, TMS of the minor isomer), 0.20 (s, 6.3H, TMS of the major isomer), 2.05–2.17 (m, 1H), 2.38–2.67 (m, 3H), 2.89–3.17 (m, 2H), 3.41–3.53 (m, 1H, $NCH_2$), 3.78–3.90 (m, 1H, $NCH_2$), 5.28–5.36 (m, 1H, NCHS), 5.41 (br s, 0.3H, CHOBz of the minor isomer), 5.43–5.47 (m, 0.7H, CHOBz of the major isomer), 7.06–7.17 (m, 2H), 7.26–7.41 (m, 3H), 7.46 (d, *J*=8.0 Hz, 1.3H), 7.51 (t, *J*=8.0 Hz, 1H), 7.58 (d, *J*=6.8 Hz, 0.7H), 7.72 (d, *J*=6.8 Hz, 1.4H), 7.90 (d, *J*=6.8 Hz, 0.6H); HRMS (ESI) calcd for $C_{24}H_{29}NNaO_4SSi$ 478.1484, found 478.1498.

### 4.17. (1*R*/*S*,8*S*,8a*R*)-8-Benzoyloxy-1-hydroxy-1,2,3,7,8,8a-hexahydro-6*H*-indolizin-5-one (41)

To a refluxing solution of **40** (67 mg, 0.15 mmol) in toluene (1.5 mL) was added over 6 h using a syringe pump a solution of

tributyltin hydride (60 μL, 0.22 mmol) and ACCN (5 mg, 0.02 mmol) in toluene (1.5 mL). The reaction mixture was heated for another hour at the same temperature and then concentrated to give a yellow liquid. The liquid was dissolved in THF (1.5 mL) followed by the addition of a 1 M THF solution of TBAF (0.22 mL, 0.22 mmol). The reaction mixture was stirred at rt for 35 min and then concentrated and chromatographed on slica gel (EtOAc/MeOH, 95:5) to give 35 mg (86%) of **41** as a colorless oil: IR ($CHCl_3$) 3466 (br), 1717 (C=O), 1635 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.70–1.90 (m, 1H), 1.94–2.08 (m, 1H), 2.10–2.28 (m, 2.4H), 2.42 (ddd, $J$=17.4, 9.6, 6.4 Hz, 1H, $COCH_2$), 2.47–2.63 (m, 1.3H), 3.38–3.63 (m, 3H), 3.65–3.76 (m, 0.3H), 4.14–4.24 (m, 1H), 5.06–5.17 (m, 1H, CHOBz), 7.39–7.49 (m, 2H), 7.53–7.62 (m, 1H), 8.01 (d, $J$=7.2 Hz, 2H); HRMS (ESI) calcd for $C_{15}H_{18}NO_4$ $(M+H)^+$ 276.1236, found 276.1226.

### 4.18. (+)-(8*S*,8a*R*)-8-Benzoyloxy-3,7,8,8a-tetrahydro-6*H*-indolizin-5-one (21)

To a solution of **41** (60 mg, 0.22 mmol) in THF (2.3 mL) cooled in an ice-water bath was added over 20 min a solution of Martin sulfurane (462 mg, 0.68 mmol) in $Et_2O$ (2.3 mL). The resulting solution was stirred at rt overnight and then poured into a mixture of brine and water, and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 2:8) to give 41 mg (73%) of **21** as a pale yellow solid: $[\alpha]_D^{21}$ +71.6 (*c* 5.2, $CHCl_3$); mp 77–78 °C; IR ($CHCl_3$) 1720, 1646, 1617 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.99 (dq, $J$=13.2, 8.2 Hz, 1H), 2.34 (dq, $J$=13.2, 5.8 Hz, 1H), 2.55 (dt, $J$=17.4, 8.0 Hz, 1H, $COCH_2$), 2.67 (ddd, $J$=17.4, 8.0, 5.4 Hz, 1H, $COCH_2$), 4.10 (dd, $J$=17.6, 4.8 Hz, 1H, $NCH_2$), 4.46–4.56 (m, 2H), 4.96 (td, $J$=8.2, 5.8 Hz, 1H, CHOBz), 5.88–5.99 (m, 2H, HC=CH), 7.45 (t, $J$=7.6 Hz, 2H), 7.58 (t, $J$=7.6 Hz, 1H), 8.03 (d, $J$=7.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 27.0 ($CH_2$), 29.8 ($CH_2$), 53.1 ($CH_2$), 66.4 (CH), 72.0 (CH), 126.9 (CH), 127.1 (CH), 128.0 (CH), 129.1 (C), 129.2 (CH), 132.9 (CH), 164.8 (C), 167.7 (C); HRMS (ESI) calcd for $C_{15}H_{16}NO_3$ $(M+H)^+$ 258.1130, found 258.1121.

### 4.19. (1*R*,2*S*,8*S*,8a*S*)-1,2-Diacetoxy-8-benzoyloxy-1,2,3,7,8,8a-hexahydro-6*H*-indolizin-5-one (42)

A solution of **21** (43 mg, 0.17 mmol) and NMO (39 mg, 0.34 mmol) in 1.7 mL of a mixed solvent of acetone/water (1:0.7) was cooled in an ice-water bath. To it was added osmium tetroxide (26.6 mg, 0.105 mmol), and the reaction mixture was stirred at the same temperature for 2 h and then quenched by the addition of $NaHSO_3$ (118 mg). The resulting mixture was diluted with EtOAc, dried ($MgSO_4$), filtered, and concentrated. The resulting residual oil, DMAP (6 mg, 0.05 mmol) and $Et_3N$ (93 μL, 0.67 mmol) were dissolved in $CH_2Cl_2$ (1.5 mL) and then cooled in an ice-water bath. To the solution was added slowly acetic anhydride (47 μL, 0.50 mmol), and the resulting mixture was stirred at rt for 5 h and concentrated to give a liquid. The liquid was chromatographed on silica gel (EtOAc) to afford 34.5 mg (55%) of **42** and its (1*S*,2*R*) isomer (10:1) as a mixture. Major isomer **42**: IR ($CH_2Cl_2$) 1752, 1725, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.94–2.09 (m overlapped with s at 2.02, 4H), 2.11 (s, 3H, $COCH_3$), 2.29–2.35 (m, 1H), 2.49–2.67 (m, 2H, $COCH_2$), 3.57 (dd, $J$=12.0, 8.8 Hz, 1H, C(3)H), 3.85 (dd, $J$=12.0, 8.8 Hz, 1H, C(3)H), 3.94 (dd, $J$=9.0, 3.6 Hz, 1H, C(8a)H), 5.30 (ddd, $J$=10.4, 9.0, 3.4 Hz, 1H, C(8)H), 5.36 (td, $J$=8.8, 3.6 Hz, 1H, C(2)H), 5.44 (t, $J$=3.6 Hz, 1H, C(1)H), 7.43 (t, $J$=7.6 Hz, 2H), 7.57 (t, $J$=7.6 Hz, 1H), 7.95 (d, $J$=7.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 20.5 ($CH_3$), 20.6 ($CH_3$), 26.6 ($CH_2$), 29.3 ($CH_2$), 46.5 ($CH_2$), 62.4 (CH), 66.1 (CH), 69.2 (CH), 70.3 (CH), 128.3 (CH), 129.0 (C), 129.5 (CH), 133.3 (CH), 165.0 (C), 167.8 (C), 169.4 (C), 169.8 (C); HRMS (ESI) calcd for $C_{19}H_{21}NNaO_7$ 398.1216, found 398.1239.

### 4.20. (+)-(1*R*,2*S*,8*S*,8a*S*)-1,2-Diacetoxy-8-benzoyloxy-1,2,3,5,6,7,8,8a-octahydro-indolizine (43)

To a solution of **42** and its isomer (32.5 mg, 0.087 mmol) in THF (1.7 mL) cooled in an ice-water bath was added borane dimethylsulfide complex (42 μL, 0.44 mmol). The resulting solution was stirred at rt overnight and quenched by the addition of EtOH and then concentrated in vacuo. The resulting residue was chromatographed on silica gel (hexane/EtOAc, 1:1) to give 25 mg (80%) of **43** as a colorless oil: $[\alpha]_D^{20}$ +45.1 (*c* 2.5, $CHCl_3$); IR ($CH_2Cl_2$) 1740, 1713 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.34 (qd, $J$=11.2, 4.8 Hz, 1H, C(7)H), 1.73–1.86 (m, 2H), 1.97 (td, $J$=10.8, 3.4 Hz, 1H, C(5)H), 2.01 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.25–2.35 (m, 2H), 2.61 (dd, $J$=10.9, 7.2 Hz, 1H, C(3)H), 3.07 (br d, $J$=10.8 Hz, 1H, C(5)H), 3.15 (dd, $J$=10.9, 1.8 Hz, 1H, C(3)H), 5.21 (ddd, $J$=11.2, 9.6, 4.8 Hz, 1H, C(8)H), 5.26 (td, $J$=7.2, 1.8 Hz, 1H, C(2)H), 5.49 (dd, $J$=7.2, 4.6 Hz, 1H, C(1)H), 7.39 (t, $J$=8.0 Hz, 2H), 7.52 (t, $J$=8.0 Hz, 1H), 7.94 (d, $J$=8.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 20.5 ($CH_3$), 20.8 ($CH_3$), 23.4 ($CH_2$), 30.0 ($CH_2$), 51.9 ($CH_2$), 59.5 ($CH_2$), 68.9 (CH), 69.1 (CH), 70.0 (CH), 70.2 (CH), 128.2 (CH), 129.4 (CH), 129.9 (C), 132.8 (CH), 165.2 (C), 169.7 (C), 170.0 (C); HRMS (FAB) calcd for $C_{19}H_{24}NO_6$ 362.1604, found 362.1600.

### 4.21. (+)-Swainsonine (ent-9)

To a solution of **43** (21 mg, 0.058 mmol) in MeOH (1 mL) was added NaOH (16 mg, 0.40 mmol). The resulting mixture was stirred at rt for 1 h and then directly chromatographed on Dowex-50W×8 resin (eluted with MeOH followed by aqueous $NH_4OH$) to give *ent*-**9** as a white soild: $[\alpha]_D^{24}$ +80.6 (*c* 0.3, MeOH); mp 138–140 °C [lit.[46] $[\alpha]_D^{25}$ +75 (*c* 0.92, MeOH); mp 142–143 °C]. The NMR-spectroscopic analysis is consistent with literature data.[46]

### 4.22. 2-(3-Aminopropyl)-2-diphenylmethylsilyl-1,3-dithiane (45)

Using the same procedure as the synthesis of amine **19**, dithiane **44** (11.7 g, 36.9 mmol) was alkylated with bromide **26** (8.70 g, 38.5 mmol) to give 12.7 g (91%) of **45** as a pale yellow solid: mp 70–71 °C; IR ($CH_2Cl_2$) 3072, 3047 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 400 MHz) δ0.90 (s, 3H), 1.04 (br s, 2H, $NH_2$), 1.35–1.46 (m, 1H), 1.54–1.65 (m, 3H), 2.04 (ddd, $J$=14.4, 4.8, 3.6 Hz, 2H, equatorial–$SCH_2$), 2.24–2.35 (m overlapped with t at 2.33, $J$=6.8 Hz, 4H), 2.69 (ddd, $J$=14.4, 11.6, 2.8 Hz, 2H, axial–$SCH_2$), 7.16–7.27 (m, 6H), 7.98–8.06 (m, 4H); $^{13}C$ NMR ($C_6D_6$, 100 MHz) $\delta$ −2.0 ($CH_3$), 25.1 ($CH_2$), 26.0 ($CH_2$), 32.4 ($CH_2$), 36.6 ($CH_2$), 40.5 (s), 43.4 ($CH_2$), 128.3 (CH), 130.2 (CH), 135.4 (C), 136.8 (CH); HRMS (EI) calcd for $C_{20}H_{27}NS_2Si$ 373.1349, found 373.1352.

### 4.23. (−)-(*S*)-*N*-[3-(2-Diphenylmethylsilyl-1,3-dithian-2-yl) propyl]-tetrahydro-5-oxo-2-furancarboxamide (46)

To a solution of acid **23** (2.40 g, 18.5 mmol) and a few drops of DMF in $CH_2Cl_2$ (40 mL) cooled in an ice-water bath was added over 15 min oxalyl chloride (1.90 mL, 22.3 mmol). The reaction mixture was stirred at rt overnight and then concentrated to give a liquid. The liquid and $Et_3N$ (3.20 mL, 23.1 mmol) were dissolved in THF (20 mL) and cooled in an ice-water bath. To the solution was added over 40 min a solution of **43** (5.75 g, 23.1 mmol) in THF (25 mL). The resulting mixture was stirred at rt for 3 h and then partitioned between water and $CH_2Cl_2$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexane/EtOAc, 2:8) to give 4.94 g (66%) of **46** as a pale yellow solid: $[\alpha]_D^{23}$ −7.0 (*c* 3.3, $CHCl_3$); mp 42–43 °C; IR ($CH_2Cl_2$) 3430, 1790, 1710, 1679 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.77 (s, 3H), 1.53–1.62 (m, 2H), 1.82–2.02 (m, 2H), 2.12–2.20 (m, 2H), 2.21–2.30 (m, 1H), 2.43 (dt,

$J$=14.0, 4.0 Hz, 2H, equatorial–$SCH_2$), 2.46–2.62 (m, 3H), 2.94 (br t, $J$=14.0 Hz, 2H, axial–$SCH_2$), 3.03–3.20 (m, 2H, $NCH_2$), 4.73 (t, $J$=7.4 Hz, 1H, CHO), 6.16 (br s, 1H, NH), 7.32–7.44 (m, 6H), 7.78 (d, $J$=6.4 Hz, 4H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −3.4 ($CH_3$), 24.4 ($CH_2$), 24.9 ($CH_2$), 26.1 ($CH_2$), 27.6 ($CH_2$), 27.9 ($CH_2$), 35.3 ($CH_2$), 38.8 (C), 39.5 ($CH_2$), 77.2 (CH), 127.3 (CH), 129.4 (CH), 133.5 (C), 135.4 (CH), 168.3 (C), 174.9 (C); HRMS (EI) calcd for $C_{25}H_{31}NO_3S_2Si$ 485.1509, found 485.1511.

### 4.24. (−)-(*S*)-3-Hydroxy-1-[3-(2-diphenylmethylsilyl-1,3-dithian-2-yl)propyl]-2,6-piperidindione (47)

Using the same procedure as the synthesis of imide **37**, lactone amide **46** (2.74 g, 5.63 mmol) was rearranged to give 2.43 g (89%) of **47** as a pale yellow solid: $[\alpha]_D^{23}$ −18.8 ($c$ 1.1, $CHCl_3$); mp 114–115 °C; IR ($CH_2Cl_2$) 3509 (br), 1678 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.78 (s, 3H), 1.60–1.76 (m, 3H), 1.82–2.04 (m, 3H), 2.05–2.16 (m, 2H), 2.19–2.27 (m, 1H), 2.38–2.45 (m overlapped with br d, $J$=14.0 Hz, 3H), 2.74 (ddd, $J$=15.6, 4.4, 2.0 Hz, 1H), 2.99 (br t, $J$=14.0 Hz, 2H, axial–$SCH_2$), 3.59–3.72 (m, 2H, $NCH_2$), 3.97 (dd, $J$=13.0, 5.4 Hz, 1H, CHO), 7.31–7.44 (m, 6H), 7.77 (d, $J$=8.4 Hz, 4H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −3.3 ($CH_3$), 24.3 ($CH_2$), 25.0 ($CH_2$), 25.6 ($CH_2$), 26.2 ($CH_2$), 31.1 ($CH_2$), 35.0 ($CH_2$), 38.8 (C), 40.5 ($CH_2$), 68.1 (CH), 127.2 (CH), 129.3 (CH), 133.5 (C), 135.4 (CH), 170.2 (C), 174.3 (C); HRMS (EI) calcd for $C_{25}H_{31}NO_3S_2Si$ 485.1509, found 485.1513.

### 4.25. (6*R*/*S*,5*S*)-5-Hydroxy-1-[3-(2-diphenylmethylsilyl-1,3-dithian-2-yl)propyl]-6-(phenylsulfenyl)piperidin-2-one (48) and (3*S*,6*R*/*S*)-3-hydroxy-1-[3-(2-diphenylmethylsilyl-1,3-dithian-2-yl)propyl]-6-(phenylsulfenyl)piperidin-2-one (49)

Using the same procedure as the synthesis of sulfide **38**, imide **47** (2.27 g, 4.67 mmol) was reduced and exchanged to give 2.14 g (79%) of **48** as a colorless oil: IR ($CHCl_3$) 3596 (br), 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.67 (s, 1.8H, $SiCH_3$ of the major isomer), 0.74 (s, 1.2H, $SiCH_3$ of the minor isomer), 1.47 (quintet, $J$=7.6 Hz, 1.6H), 1.65–2.01 (m, 4H), 2.02–2.55 (m, 7.4H), 2.82–3.04 (m, 3H), 3.73 (br s, 0.6H), 3.94–4.14 (m, 1.8H), 4.37 (dd, $J$=4.4, 2 Hz, 0.6H, NCHS of the major isomer), 7.24–7.45 (m, 11H), 7.68–7.80 (m, 4H); HRMS (EI) calcd for $C_{31}H_{37}NO_2S_3Si$ 579.1750, found 579.1725. We also isolated 119 mg (4%) of **49** as a colorless oil: IR ($CHCl_3$) 3501 (br), 1647 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.75 (s, 2.1H, $SiCH_3$ of the major isomer), 0.77 (s, 0.9H, $SiCH_3$ of the minor isomer), 1.36–2.23 (m, 11H), 2.36–2.48 (m, 2H, equatorial–$SCH_2$), 2.96 (br t, $J$=11.4 Hz, 2H, axial–$SCH_2$), 2.99–3.17 (m, 1H, $NCH_2$), 3.64 (dd, $J$=10.0, 6.0 Hz, 0.3H, CHO of the minor isomer), 3.81 (dd, $J$=11.4, 6.8 Hz, 0.7H, CHO of the major isomer), 3.89 (dt, $J$=13.6, 6.8 Hz, 0.3H, $NCH_2$ of the minor isomer), 4.01 (dt, $J$=13.6, 6.8 Hz, 0.7H, $NCH_2$ of the major isomer), 4.11 (t, $J$=6.8 Hz, 0.3H, NCHS of the minor isomer), 4.23 (br s, 0.7H, NCHS of the major isomer), 7.25–7.43 (m, 11H), 7.74 (d, $J$=7.6 Hz, 2.8H), 7.78 (d, $J$=7.6 Hz, 1.2H); HRMS (ESI) calcd for $C_{31}H_{37}NNaO_2S_3Si$ $(M+Na)^+$ 602.1653, found 602.1652.

### 4.26. (6*R*/*S*,5*S*)-5-Benzoyloxy-1-[3-(2-diphenylmethylsilyl-1,3-dithian-2-yl)propyl]-6-(phenylsulfenyl)piperidin-2-one (50)

Using the same procedure as the synthesis of benzoate **39**, alcohol **48** (2.10 g, 3.46 mmol) was esterified to give 2.18 g (92%) of **50** as a colorless oil: IR ($CH_2Cl_2$) 1720, 1651 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.52 (s, 1.65H, $SiCH_3$ of the major isomer), 0.76 (s, 1.35H, $SiCH_3$ of the minor isomer), 1.38–1.54 (m, 0.55H), 1.55–2.12 (m, 5.45H), 2.13–2.63 (m, 6H), 2.77–3.03 (m, 3H), 3.86–3.98 (m, 1H), 4.52 (br s, 0.55H, NCHS of the major isomer), 4.82 (br s, 0.45H, NCHS of the minor isomer), 5.11–5.19 (m, 0.45H, CHOBz of the minor isomer), 5.43 (s, 0.55H, CHOBz of the major isomer), 7.12–7.23 (m, 3H), 7.25–7.44 (m, 9H), 7.45–7.50 (m, 1H), 7.55 (t, $J$=7.4 Hz, 1H), 7.65 (d, $J$=6.8 Hz, 2H), 7.74–7.83 (m, 3H), 7.94 (d, $J$=7.2 Hz, 1H). Anal. Calcd for $C_{38}H_{41}NO_3S_3Si$: C, 66.72; H, 6.04; N, 2.05; S, 14.06. Found: C, 66.44; H, 6.20; N, 1.88; S, 13.69.

### 4.27. (6*R*/*S*,5*S*)-5-Benzoyloxy-1-[4-oxo-4-(diphenylmethylsilyl)butyl]-6-(phenylsulfenyl)piperidin-2-one (51)

According to the general procedure for dithiane hydrolysis, dithiane **50** (1.40 g, 2.05 mmol) was hydrolyzed to give 1.11 g (91%) of **51** as a yellow liquid: IR ($CH_2Cl_2$) 1721, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.69 (s, 0.9H, $SiCH_3$ of the minor isomer), 0.77 (s, 2.1H, $SiCH_3$ of the major isomer), 1.80 (quintet, $J$=7.0 Hz, 2H), 1.99–2.14 (m, 1H), 2.14–2.78 (m, 5H), 3.03 (dt, $J$=13.8, 7.2 Hz, 1H, $NCH_2$), 3.88 (dt, $J$=13.8, 7.2 Hz, 1H, $NCH_2$), 4.84 (s, 0.3H, NCHS of the minor isomer), 5.19–5.21 (m, 0.7H, NCHS of major isomer), 5.30 (dt, $J$=10.8, 4.0 Hz, 0.7H, CHOBz of the major isomer), 5.43 (s, 0.3H, CHOBz of the minor isomer), 7.02–7.11 (m, 2.3H), 7.31–7.46 (m, 10H), 7.48–7.64 (m, 5.7H), 7.76 (d, $J$=7.6 Hz, 1.4H), 7.88 (d, $J$=7.2 Hz, 0.6H); HRMS (ESI) calcd for $C_{35}H_{36}NO_4SSi$ $(M+H)^+$ 594.2134, found 594.2178.

### 4.28. (1*S*,9*R*/*S*,9a*S*)-1-Benzoyloxy-9-diphenylmethylsilyloxy-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizin-4-one (52) and (−)-(*S*)-5-benzoyloxy-1-[4-oxo-4-(diphenylmethylsilyl)butyl] piperidin-2-one (53)

To a refluxing solution of **51** (471 mg, 0.794 mmol) in toluene (7.9 mL) was added over 6 h using a syringe pump a solution of TBTH (0.32 mL, 1.2 mmol) and ACCN (29 mg, 0.12 mmol) in toluene (1.5 mL). The reaction mixture was heated for another hour at the same temperature and then concentrated and chromatographed on silica gel (hexane/EtOAc/$Et_3N$, 40:60:1) to give 297 mg (77%) of **52** (*exo*/*endo*=1.3) as a pale yellow liquid, and 34 mg (9%) of **53** as a colorless liquid. Compound **52**: IR ($CH_2Cl_2$) 1719,1638 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.69 (s, 1.35H, $SiCH_3$ of *endo* isomer), 0.72 (s, 1.65H, $SiCH_3$ of *exo* isomer), 1.31–2.00 (m, 4.9H), 2.08 (br d, $J$=10.4 Hz, 0.55H), 2.23 (dd, $J$=17.6, 5.6 Hz, 0.55H), 2.28–2.61 (m, 3H), 3.39–3.50 (m, 1.55H), 4.17 (br s, 0.45H, C(8)H of *endo* isomer), 4.70 (br d, $J$=12.8 Hz, 0.55H, $NCH_2$ of *exo* isomer), 4.83 (br d, $J$=13.2 Hz, 0.45H, $NCH_2$ of *endo* isomer), 5.18 (dt, $J$=6.8, 3.6 Hz, 0.45H, CHOBz of *endo* isomer), 5.78 (br s, 0.55H, CHOBz of *exo* isomer), 7.29–7.46 (m, 8H), 7.51–7.59 (m, 3H), 7.61 (d, $J$=6.0 Hz, 1.1H), 7.66 (d, $J$=6.0 Hz, 0.9H), 7.96 (d, $J$=7.2 Hz, 0.9H), 8.01 (d, $J$=7.2 Hz, 1.1H); HRMS (FAB) calcd for $C_{29}H_{32}NO_4Si$ $(M+H)^+$ 486.2101, found 486.2096. **53**: $[\alpha]_D^{19}$ −8.2 ($c$ 5.8, $CHCl_3$); IR ($CHCl_3$) 1717, 1636 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.74 (s, 3H, $SiCH_3$), 1.60–1.82 (m, 2H), 1.96–2.15 (m, 2H), 2.36 (dt, $J$=17.2, 5.2 Hz, 1H), 2.55 (ddd, $J$=17.2, 10.4, 6.8 Hz, 1H), 2.60–2.79 (m, 2H), 3.18–3.35 (m, 2H, exocyclic–$NCH_2$), 3.39 (dd, $J$=13.2, 2.6 Hz, 1H, C(6)H), 3.58 (dd, $J$=13.2, 4.0 Hz, 1H, C(6)H), 5.36 (br s, 1H, CHOBz), 7.26–7.46 (m, 9H), 7.54 (d, $J$=6.8 Hz, 4H), 7.96 (d, $J$=7.2 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −5.2 ($CH_3$), 19.2 ($CH_2$), 25.6 ($CH_2$), 27.9 ($CH_2$), 46.3 ($CH_2$), 46.6 ($CH_2$), 51.2 ($CH_2$), 66.7 (CH), 128.0 (CH), 128.3 (CH), 129.4 (CH), 129.9 (CH), 132.1 (C), 132.2 (C), 133.1 (CH), 134.7 (CH), 165.3 (C), 168.3 (C), 242.7 (C); HRMS (ESI) calcd for $C_{29}H_{31}NNaO_4Si$ $(M+Na)^+$ 508.1920, found 508.1928.

### 4.29. (−)-(1*S*,9*R*,9a*R*)-1-Benzoyloxy-9-hydroxy-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizin-4-one (54a) and (−)-(1*S*,9*S*,9a*R*)-1-benzoyloxy-9-hydroxy-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizin-4-one (54b)

A solution of **52** (297 mg, 0.611 mmol) and *p*-toluenesulfonic acid monohydrate (11 mg, 0.058 mmol) in MeOH (6 mL) was stirred

at rt for 1 h and then quenched by the addition of a few drops of $Et_3N$. The reaction mixture was concentrated and chromatographed on silica gel (eluted with EtOAc followed by EtOAc/MeOH, 95:5) to give 177 mg (100%) of a mixture of **54a**/**b** (1.3:1). The presence of **54a** was confirmed by comparison of the $^1H$ NMR data of the mixture with that reported in the literature.[39]

To a solution of **54a**/**b** (135 mg, 0.467 mmol) in $CH_2Cl_2$ (5 mL) at rt was added slowly a 0.5 M solution of Dess–Martin periodinane in $CH_2Cl_2$. The reaction mixture was stirred for another 2 h and then partitioned between saturated $NaHCO_3$ solution and $CH_2Cl_2$. The organic layer was washed with a saturated $Na_2S_2O_3$ solution, dried ($MgSO_4$), and concentrated to give a liquid. The liquid was chromatographed on silica gel (hexane/EtOAc, 2:8) to give 114 mg of a ketone. To a solution of the ketone in THF (1.2 mL) cooled in a dry ice-acetone bath was added a 1 M solution of L-Selectride in THF (0.14 mL, 0.14 mmol). The reaction mixture was stirred at the same temperature for another 40 min, quenched by the addition of brine at low temperature and then slowly warmed up to rt. The resulting mixture was extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc) to give 23 mg (55%) of **54b** as a white solid: $[\alpha]_D^{23}$ −7.7 (*c* 2.5, $CHCl_3$); mp 112–113 °C; IR ($CH_2Cl_2$) 3450 (br), 1714,1632 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.53 (br d, *J*=12.8 Hz, 1H, C(7)H), 1.67 (br t, *J*=13.6 Hz, 1H, C(8)H), 1.77–1.92 (m, 1H, C(7)H), 1.94–2.06 (m, 2H, C(2)H, C(8)H), 2.34–2.68 (m, 5H), 3.45 (d, *J*=4.0 Hz, 1H, NCH), 4.03 (br s, 1H, C(9)H), 4.77 (dt, *J*=13.6, 2.0 Hz, 1H, C(6)H), 5.42 (dt, *J*=7.2, 4.0 Hz, 1H, CHOBz), 7.43 (t, *J*=7.6 Hz, 2H), 7.57 (t, *J*=7.6 Hz, 1H), 8.00 (d, *J*=7.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 19.3 ($CH_2$), 24.9 ($CH_2$), 28.6 ($CH_2$), 32.1 ($CH_2$), 42.9 ($CH_2$), 64.0 (CH), 65.8 (CH), 70.0 (CH), 128.1 (CH), 129.2 (CH), 129.3 (C), 133.0 (CH), 165.5 (C), 168.8 (C); HRMS (ESI) calcd for $C_{16}H_{20}NO_4$ $(M+H)^+$ 290.1392, found 290.1395.

### 4.30. (−)-(1*S*,9a*R*)-1-Benzoyloxy-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizin-4-one (55)

A solution of alcohol mixture **54** (54 mg, 0.18 mmol) and 1,1′-thicarbonyldiimidazole (35 mg, 0.20 mmol) in benzene (2 mL) was refluxed for 2.5 h followed by the addition of another portion of 1,1′-thicarbonyldiimidazole (31 mg, 0.17 mmol). The reaction mixture was stirred at the same temperature for another 2 h and then concentrated and chromatographed on silica gel (EtOAc/MeOH, 95:5) to give 69 mg of a pale yellow liquid. The liquid was heated with TBTH (0.12 mL, 0.46 mmol) and AIBN (4 mg, 0.02 mmol) in toluene (1.7 mL) at 110 °C for 2 h. The resulting solution was concentrated and chromatographed on silica gel (hexane/EtOAc, 15:85) to give 31 mg (61%) of **55** as a colorless oil: $[\alpha]_D^{21}$ −12.3 (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) 1716, 1628 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.15–1.60 (m, 3H), 1.66 (br d, *J*=13.2 Hz, 1H), 1.89 (br t, *J*=13.2 Hz, 2H), 1.99–2.18 (m, 2H), 2.38–2.45 (m, 2H), 2.64 (ddd, *J*=13.6, 10.8, 6.0 Hz, 1H), 3.45 (br d, *J*=12.0 Hz, 1H, NCH), 4.77 (br d, *J*=13.6 Hz, 1H, $NCH_2$), 5.10 (dt, *J*=5.2, 2.6 Hz, 1H, CHOBz), 7.41 (t, *J*=8.0 Hz, 2H), 7.54 (t, *J*=8.0 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 23.5 ($CH_2$), 24.9 ($CH_2$), 25.5 ($CH_2$), 28.1 ($CH_2$), 31.5 ($CH_2$), 43.4 ($CH_2$), 61.4 (CH), 71.3 (CH), 128.0 (CH), 129.1 (CH), 129.2 (C), 132.9 (CH), 165.0 (C), 166.9 (C); HRMS (ESI) calcd for $C_{16}H_{20}NO_3$ $(M+H)^+$ 274.1443, found 274.1431.

### 4.31. (−)-(1*S*,9a*R*)-1-Hydroxy-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizin-4-one (56)[41]

A solution of **55** (24 mg, 0.090 mmol) and NaOH (20 mg, 0.50 mmol) in MeOH (2 mL) was stirred at rt for 15 min and then poured into water and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (EtOAc/MeOH, 9:1) to give 10.2 mg (69%) of **56** as a white solid: $[\alpha]_D^{23}$ −10.3 (*c* 1.1, $CHCl_3$) [lit.[41] $[\alpha]_D^{20}$ −8.5 (c 0.7, $CHCl_3$)]; mp 71–72 °C. The NMR-spectroscopic analysis is consistent with literature data.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## Supplementary data

Additional experimental procedures and compound characterization data of the trimethylsilyl analogs of compounds shown in Scheme 6. $^1H/^{13}C$ NMR spectra of **14**, **17**, **19**, **21**, **27**–**55**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.12.048. These data include MOL files and InChiKeys of the most important compounds described in this article.

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