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A conjugate addition/dipolar-cycloaddition cascade sequence for the synthesis of (±)-cylindricine C

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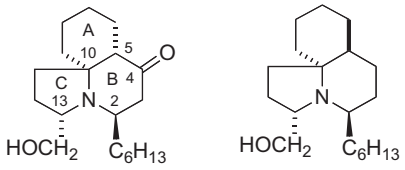
ABSTRACT

An efficient stereocontrolled route to (±)-cylindricine C is described. Reaction of 9-hydroxynon-1-en-5-one oxime with 2,3-bis(phenylsulfonyl)-1,3-butadiene affords a 7-oxa-1-azanorbornane cycloadduct in high yield. The formation of the bicyclic isoxazolidine arises from conjugate addition of the oxime onto the diene to give a transient nitrone that spontaneously undergoes an intramolecular dipolar cycloaddition. The resulting cycloadduct derived from the cascade sequence was converted into (±)-cylindricine C by: (1) a reductive-cyclization to set the BC-ring skeleton, (2) a base-induced cyclization to construct the tricyclic core, and (3) an oxidation-conjugate addition of the *n*-hexyl side chain to complete the synthesis.

1. Introduction

In the early 1990s, a novel family of 2,2-disubstituted piperidine containing alkaloids were isolated by Blackman and co-workers from the ascidian *Clavelina cylindrica* found off the eastern coast of Tasmania.[1] Members of this family possess either the pyrrolo or pyrido[2,1-*j*]quinoline tricyclic framework.[2] Among this class of alkaloids, cylindricine C (**1**) represents an intriguing target.[3] A structurally related alkaloid known as lepadiformine (**2**) was obtained in 1994 from *C. lepadiformis* in the Mediterranean sea and differs only in the cis/trans stereorelationship of the perhydroquinoline ring system and the functionality at C_4 with cylindricine C (**1**) (Fig. 1).[4] These tricyclic marine alkaloids exhibit a broad range of biological activity and consequently have attracted an impressive array of synthetic efforts.[5] Generally, the key synthetic feature of the most common approaches toward cylindricine C have revolved around the establishment of the sterically congested C_{10}-center. The most frequently implemented plan has been the use of a double Michael addition of an amine to deliver a critical bicyclic intermediate in one step from a dienone precursor. This strategy has been independently used by the Molander,[6] Heathcock,[7] and Trost[8] groups. The aza-tricyclic motif present in cylindricine C has also been fabricated by Kibayashi[9] and Hsung[10] by making use of a *N*-acyliminium ion/diene cyclization. Finally, Ciufolini and co-workers employed an oxidative spirocyclization of a phenolic primary amine as the key step in their asymmetric synthesis of (−)-cylindricine C.[11]



1; cylindricine C **2**; lepadiformine

Figure 1. Marine tricyclic alkaloid framework.

The essential element of our plan for the synthesis of cylindricine C (**1**) is based on a *conjugate addition/dipolar-cycloaddition* cascade strategy that we have been involved with for several years and which readily affords 2,2-disubstituted 4-piperidin-ones of type **6**.[12–15] In this cascade sequence, a bicyclic isoxazolidine **5** is first formed by conjugate addition of an oxime with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**3**)[13] to produce a transient nitrone **4** that then undergoes a further intramolecular 1,3-dipolar cycloaddition onto the adjacent vinyl sulfone. Raney-Ni reduction of the 7-oxa-1-azanorbornane cycloadduct **5** results in sequential nitrogen–oxygen bond cleavage followed by a subsequent

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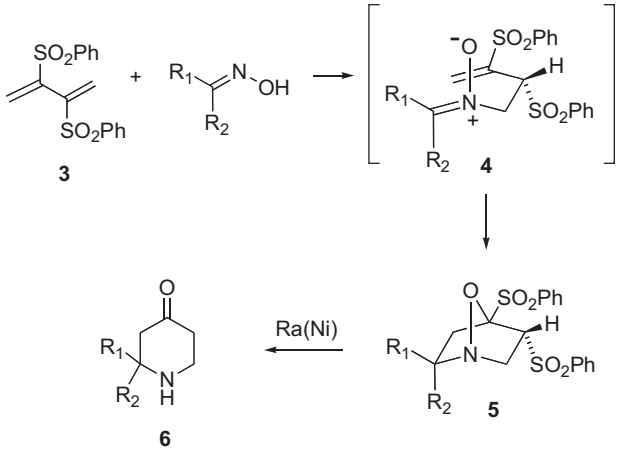
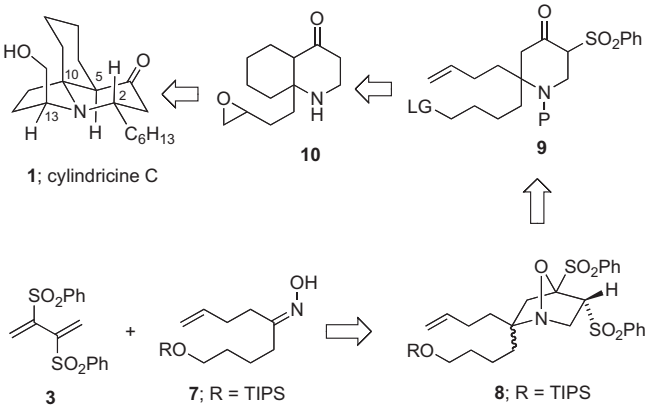
desulfonylation to furnish the 2,2-disubstituted 4-piperidinone (Scheme 1). This reaction sequence proved to be very effective for the synthesis of several alkaloids and related nitrogen-containing heterocyclic compounds.[14,15] Thus, by using this protocol, we have accomplished the total synthesis of yohimbenone[14] as well as 2,7,8-*epi*-perhydrohistrionicotoxin.[15] Since oximes possessing functionalized substituent groups on the side chain are particularly appealing substrates for the cascade sequence, we became interested in making further use of this operation for the synthesis of other alkaloidal skeletons. In this paper we demonstrate that the *conjugate addition/dipolar cycloaddition* based methodology can be used for a total synthesis of (±)-cylindricine C.[12c]



Scheme 1.

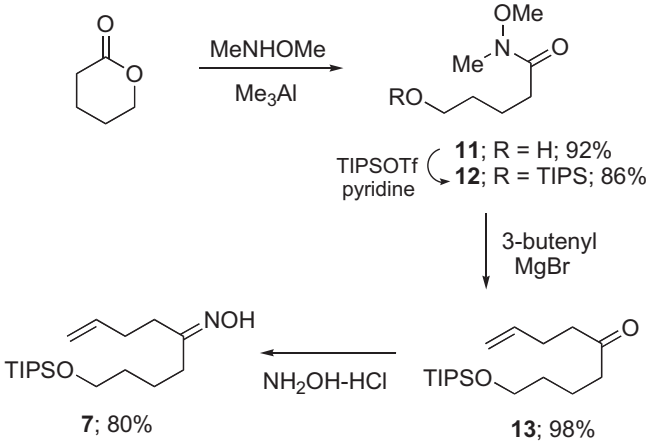
2. Results and discussion

The cylindricine C core was envisioned to evolve from the easily accessible 4-piperidonyl B-ring precursor **9**, which bears two distinguishable tethered groups at the congested C_2 stereogenic center (Scheme 2). 2,3-Bis(phenylsulfonyl)diene **3** and oxime **7** (R=TIPS) were considered as the two building blocks for the construction of cycloadduct **8**. Challenges to overcome in this approach would include the construction of the remaining A- and C-rings around the 4-piperidone periphery. There would also be the need to leverage potential epimerization at the C_5 and C_{13} stereocenters within the azatricyclic core to geometries that would adopt the energetically preferred arrangement relative to the central tetrasubstituted C_{10} carbon prior to the late-stage *n*-hexyl group installation at the C_2 position.



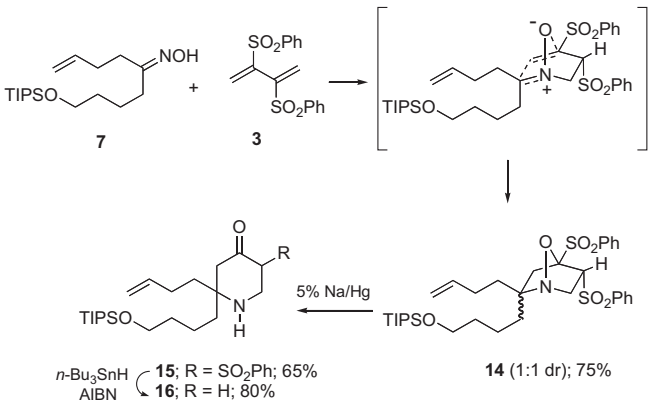
Scheme 2.

The required oxime **7** for the planned cascade was prepared by treating δ-valerolactone with Me_3Al and *N*,*O*-dimethylhydroxylamine hydrochloride so as to install the Weinreb amide **11**. The hydroxyl group present in **11** was silylated with TIPS triflate to give **12** prior to treatment with 3-butenylmagnesium bromide. The resulting ketone **13** was then converted to the corresponding oxime **7** by condensation with hydroxylamine hydrochloride (Scheme 3). This four-step sequence proceeded in 62% overall yield from δ-valerolactone and could be used to produce gram quantities of oxime **7** without the need for chromatographic purification.



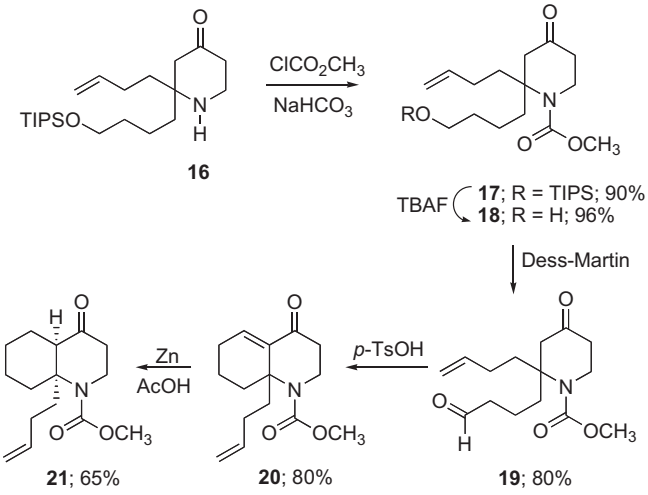
Scheme 3.

Heating a sample of oxime **7** and bis(phenylsulfonyl)diene **3** in $CHCl_3$ at 90 °C in a sealed tube for 12 h afforded the expected cycloadduct **14** as a 1:1-mixture of diastereomers in 75% yield. N,O-reduction of the aza-oxanorbornane adduct could be readily accomplished by using 5% Na/Hg in a 2:1-mixture of THF/ethanol mixture, which furnished 4-piperidinone **15** (65%). Removal of the remaining phenylsulfonyl group in **15** was carried out using the radical reduction conditions developed by Smith and Hale[16] to give the desired 2,2-disubstituted piperidinone **16** in 80% yield (Scheme 4). With piperidinone **16** in hand, our next task was to install the A-ring and then epoxidize the tethered π-bond in order to induce a 5-*exo trig* cyclization so as to generate the core azadecalin ring system of cylindricine C. We chose to accomplish this goal by first converting **16** to aldehyde **19** and then subjecting it to acidic conditions in order to induce an intramolecular aldol condensation to produce enone **20**.[17] Reaction of **16** with methyl chloroformate gave the corresponding carbamate **17** in 90% yield. Removal of the



Scheme 4.

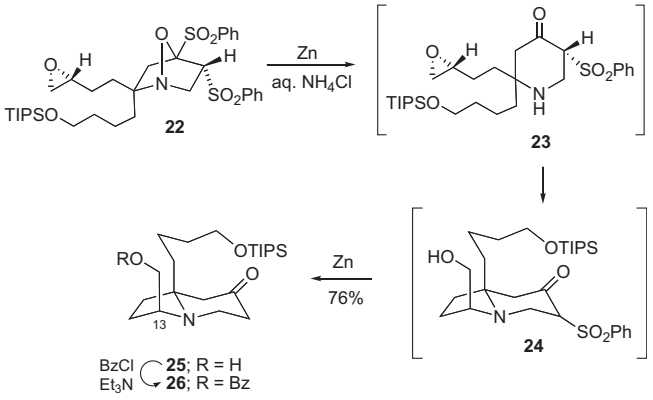
silyl group in **17** with TBAF afforded alcohol **18** (95%) that could be readily oxidized using Dess–Martin periodinane to furnish aldehyde **19** (80%). Next, the intramolecular aldol condensation-dehydration of **19** was easily achieved using *p*-toluenesulfonic acid in benzene at 50 °C resulting in a 80% yield of the target bicyclic enone **20** (Scheme 5). Heating enone **20** in the presence of zinc dust and acetic acid gave the *cis*-fused azadecalone **21** as the exclusive product and whose spectral properties were identical with those reported by Heathcock.[7] The *cis*-fusion selectivity can be attributed to the protonation step, which occurs from the least hindered face of the bicyclic system under the reducing conditions.[18] Preliminary attempts were made to epoxidize both **16** and **21** using a variety of oxidants (i.e., H_2O_2, *m*CPBA, trifluoroperacetic acid, and vanadium oxidants). However, on all occasions we failed to produce the desired epoxides, typically resulting in a return of starting material with a 30–40% loss to decomposition. Our efforts to remove the carbamate group from **21** also proved to be extremely difficult, as the exceedingly hindered nitrogen atom was surprisingly challenging to deprotect. Thus, carbamate **21** was treated exhaustively under basic hydrolysis conditions, acidic removal conditions, and nucleophilic cleavage conditions such as the use of LiI/collidine or mercaptan anion/HMPA. All attempts to remove the protecting carbamate group failed, resulting in recovery of the starting material.



Scheme 5.

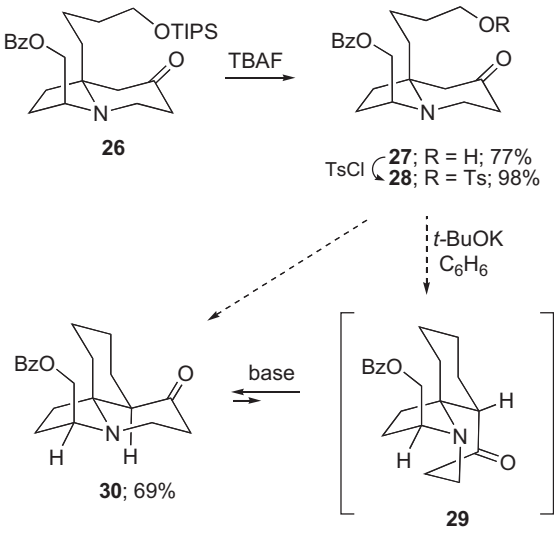
Because of the failure in both the epoxidation and deprotection steps using piperidinone **21**, we looked to an alternate method for generating the required pyrido[2,1-*j*]quinoline tricyclic framework of cylindricine C. In a series of papers, Stack and co-workers showed that terminal olefins can be rapidly and efficiently epoxidized using manganese phenanthroline with commercially available peracetic acid in CH_3CN at room temperature.[19] Using the Stack conditions, we found that the alkenyl group present in cycloadduct **14** could be successfully epoxidized producing epoxide **22** as a single diastereomer in 26% isolated yield.[20] Epoxidation of **14** proceeded with high *exo*- selectivity, and this is probably a result of different steric interactions in the transition state with the Mn^{II} complex for the two different diastereomers. In addition, complexation of the manganese catalyst with the N–O bond of the aza-oxanorbornane might also help to direct the facial selectivity of the epoxidation reaction.

Having synthesized the desired mono-substituted epoxide **22**, we were in a position to examine the planned reductive cyclization reaction. After extensive experimentation using a variety of reducing agents, it was found that treating a sample of **22** with excess zinc dust in an aqueous ammonium chloride/THF mixture[21] at 70 °C resulted in clean N–O bond reduction and this was followed by the spontaneous ejection of phenylsulfenic acid to furnish 4-piperidinone **23** as a transient intermediate. Attack of the basic nitrogen atom of the 4-piperidinone onto the epoxide ring proceeded rapidly and established the indolizidine ring system.[22] This was followed by a further reduction of the remaining phenylsulfonyl group in **24** to give **25** in 76% overall yield as a 9:1-mixture of diastereomers (Scheme 6). The major isomer coincides with the hydroxymethylene geometry at the C_{13} position of the cylindricine C motif. Esterification of alcohol **25** with benzoyl chloride gave the corresponding ester **26** and this allowed for the ready separation of the two diastereomers by column chromatography.



Scheme 6.

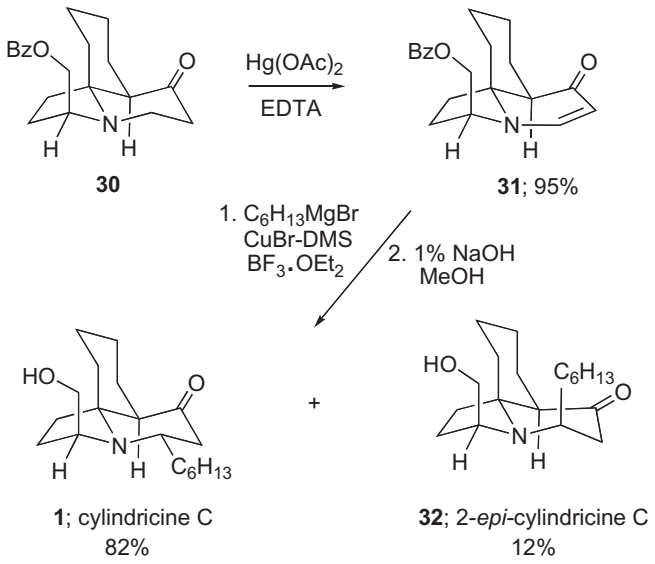
The next challenge was to fashion the core azadecalin ring system **30** by means of an intramolecular enolate alkylation reaction.[23] With this in mind, the desilylation of **26** was first carried out using TBAF and this was followed by tosylation of the resulting primary alcohol **27** to give the expected tosylate **28** in 76% overall yield. Eventually, we determined the most effective method for the formation of the desired tricyclic azadecalin involved treating tosylate **28** with 2 equiv of *t*-BuOK in benzene followed by an aqueous workup, which afforded **30** in 69% yield (Scheme 7). We



Scheme 7.

were pleased to find that the reaction had proceeded with excellent stereoselectivity. This positive result can be explained by assuming that the cyclization reaction proceeds directly to **30** or else occurs by first forming *trans*-1-azadecalin **29**, which then readily epimerizes to the thermodynamically more stable isomer **30**[4,9b,10] possessing the stereochemistry required for the structure of cylindricine C.[24]

To complete the total synthesis of (±)-cylindricine C (**1**), oxidation of **30** to the corresponding 2*H*-piperidonyl enone had to be affected in order to introduce the *n*-hexyl side chain. A variety of standard oxidizing agents such as IBX, CAN, and $PhSeCl/NaIO_4$ were examined but all failed to produce the dihydropyridinone required for the subsequent conjugate addition step. We did have some limited success with the oxidation of **30** when Polonovski conditions were utilized (i.e., *m*CPBA, trifluoroacetic anhydride, and Et_3N in CH_2Cl_2) but the yield of **31** was never greater than 35%. The earlier success of mercuric acetate oxidation of piperidines by Leonard and co-workers[25] led us to test the utility of this oxidizing agent with lactam **30**. We were pleased to find that when a sample of **30** was treated with $Hg(OAc)_2$ in the presence of EDTA,[26] dihydropyridinone **31** was obtained in 95% yield. The next challenge was the conjugate addition of *n*-hexyl cuprate to the vinylogous amide structure **31**. Comins and co-workers had previously demonstrated that the use of a Grignard reagent in the presence of $BF_3 \cdot OEt_2$ and $CuBr \cdot Me_2S$ provides for stereoselective attack of the incoming alkyl group onto *N*-acyl vinylogous amides.[27] Indeed, we found that the organocopper addition could be successfully carried out using *n*-hexylmagnesium bromide under the Comins conditions. The stereochemistry of the *n*-hexyl side chain addition was controlled by the tricyclic topography of **31**, which facilitates a pseudo-equatorial approach of the organometallic reagent. Thus, conjugate addition of the *n*-hexyl cuprate reagent to **31** followed by alkaline saponification[28] furnished a 7:1-mixture of (±)-cylindricine C (**1**) and (±)-2-*epi*-cylindricine C (**32**) in 94% yield (Scheme 8).



Scheme 8.

3. Conclusion

In summary, the total synthesis of (±)-cylindricine C (**1**) starting from 9-hydroxynon-1-en-5-one oxime (**7**) and bis(phenylsulfonyl)diene **3** has been accomplished. The resulting cycloadduct **14** derived from the cascade cycloaddition was converted into cylindricine C by: (1) a reductive-cyclization to set the BC-ring skeleton, (2) a base-induced cyclization to construct the tricyclic core, and (3) an oxidation-conjugate addition of the *n*-hexyl side chain. The applicability of the new methodology to other alkaloidal targets is currently under study and further results will be reported in due course.

4. Experimental

4.1. General

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise.

*4.1.1. 9-Triisopropylsilanyloxy-non-1-en-5-one oxime (**7**).* To a stirred solution containing 2.2 g (22.5 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in dry CH_2Cl_2 (5 mL) at 0 °C was added dropwise 11.2 mL (22.5 mmol, 2.0 M in hexane) of $AlMe_3$. The mixture was stirred for 20 min at 0 °C and 1.4 mL (1.5 mmol) of D-valerolactone was added dropwise. After stirring at 0 °C for 20 min, the mixture was diluted with 25 mL of $CHCl_3$ and then 3 mL of a 0.1 N HCl solution was added dropwise at 0 °C. The mixture was stirred for 1 h, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give 2.2 g (92%) of 5-hydroxy-*N*,*O*-dimethylpentanohydroxamic acid (**11**) as a white solid;[29] mp 61–63 °C; IR (CH_2Cl_2) 3440, 1640, 1072, and 1003 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.72 (m, 2H), 2.46 (br s, 2H), 3.17 (s, 1H), 3.63 (t, 2H, J=6.6 Hz), and 3.67 (s, 3H).

To a stirred solution containing 0.9 g (5.5 mmol) of the above alcohol **11** and 1.4 mL (12 mmol) of 2,6-lutidine in 10 mL of dry CH_2Cl_2 at 0 °C was added 1.7 mL (6 mmol) of triisopropylsilyltrifluoromethanesulfonate. The mixture was allowed to warm to rt, stirred for 24 h, and was then quenched with 1 mL of a 0.005 N HCl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 1.5 g (86%) of 5-triisopropylsilanyloxy-*N*,*O*-dimethylpentanohydroxamic acid (**12**) as a pale oil; IR (neat) 1674, 1463, 1415, 1383, 1105, 999, 883, and 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03–1.06 (m, 21H), 1.58 (m, 2H), 1.70 (m, 2H), 2.44 (br s, 2H), 3.16 (s, 3H), 3.66 (s, 3H), and 3.69 (t, 2H, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 21.4, 31.9, 32.9, 61.4, 63.3, and 97.9; HRMS calcd for $[C_{16}H_{35}NO_3Si+H^+]$: 318.2464. Found 318.2460.

To a solution containing 3.4 g (10.6 mmol) of the above hydroxamic acid **12** in 10 mL of THF at 0 °C was added dropwise 20 mL (20.2 mmol, 1.0 M in THF) of a solution of 3-butenylmagnesium bromide. The mixture was stirred for 1 h at 0 °C and was allowed to warm to rt and was further stirred for an additional 1 h. At the end of this time the solution was quenched with 3 mL of a 0.1 N HCl solution and was then diluted with ether. The organic layer was separated and the aqueous layer was further extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3.3 g (98%) of the corresponding ketone **13** as a pale yellow oil; IR (neat) 1716, 1674, 1463, 1105, 996, 882, and 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02–1.20 (m, 21H), 2.29 (dd, 2H, J=13.8 and 6.6 Hz), 2.42 (t, 2H, J=7.2 Hz), 2.47 (t, 2H, J=7.2 Hz), 3.66 (t, 2H, J=6.3 Hz), 4.94 (d, 1H, J=10.2 Hz), 4.99 (d, 1H, J=17.1 Hz), and 5.77

(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 20.6, 28.0, 32.6, 41.9, 42.9, 63.3, 115.4, 137.4, and 210.5; HRMS calcd for [$C_{18}H_{36}O_2Si+H^+$]: 313.2563. Found 313.2559.

To a stirred solution containing 1.0 g (1.5 mmol) of hydroxylamine hydrochloride and 2.4 g (3.0 mmol) of sodium acetate in 50 mL of water was added the above ketone **13** (1.0 g, 5 mmol). The mixture was heated at reflux for 8 h, cooled to rt and extracted with CH_2Cl_2. The organic extracts were washed with a saturated solution of $NaHCO_3$, NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.9 g (80%) of oxime **7** as a 1:1-mixture of the *syn* and *anti* diastereomers; IR (neat) 1642, 1461, 1106, 996, and 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.15 (m, 21H), 1.57 (m, 4H), 2.20 (t, 1H, J=7.4 Hz), 2.27 (m, 3H), 2.36 (t, 1H, J=7.7 Hz), 2.42 (t, 1H, J=7.7 Hz), 3.68 (m, 2H), 4.97 (br d, 1H, J=10 Hz), 5.04 (br d, 1H, J=18 Hz), 5.81 (m, 1H), and 8.87 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 22.2, 22.8, 27.1, 27.5, 29.8, 30.5, 32.7, 33.2, 33.5, 34.3, 63.1, 63.2, 115.2, 115.4, 137.7, 137.9, and 161.2; HRMS calcd for [$C_{18}H_{37}NO_2Si+H^+$]: 328.2672. Found: 328.2667.

*4.1.2. 2-(3-Butenyl)-2-(4-tri-isopropylsilanyloxybutyl)-4,5-bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**14**).* A solution containing 2.5 g (7.2 mmol) of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**3**)[13] and 1.5 g (6 mmol) of oxime **7** in 100 mL of $CHCl_3$ was placed in a Pyrex tube equipped with a stir bar. The tube was sealed and the mixture was heated at 90 °C for 12 h in a sandbath. The mixture was cooled and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (15% EtOAc in hexane) to give 3.5 g (75%) of a 1:1-diastereomeric mixture of cycloadduct **14** as a pale yellow oil: IR (neat) 2942, 2864, 1447, 1331, 1153, 1100, 720, 686, and 614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–1.10 (m, 42H), 1.91 (m, 6H), 1.92 (m, 8H), 2.99 (d, 2H, J=12.8 Hz), 3.53 (m, 1H), 3.63 (t, 4H, J=12.4 Hz), 3.70 (m, 1H), 3.95 (dd, 2H, J=12.8 and 5.6 Hz), 4.32 (ddd, 2H, J=10.8, 5.2 and 2.2 Hz), 4.80 (br d, 2H, J=10 Hz), 5.02 (br d, 2H, J=16.4 Hz), 5.52 (m, 1H), 5.82 (m, 1H), 7.50 (t, 4H, J=7.6 Hz), 7.78–7.60 (m, 12H), and 7.97 (d, 4H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 20.0, 21.2, 27.8, 29.1, 30.4, 30.9, 33.4, 33.5, 37.2, 37.8, 53.3, 62.9, 63.2, 66.7, 75.0, 114.6, 115.5, 129.1, 129.5, 130.5, 134.5, 134.7, 134.9, 137.7, 138.1, and 139.4; Anal. Calcd for $C_{34}H_{51}NO_6S_2Si$: C, 61.69; H, 7.77; N, 2.12; S, 9.69. Found: C, 61.89; H, 7.51; N, 2.21; S, 9.54.

*4.1.3. 2-(3-Butenyl)-2-(4-tri-isopropylsilanyloxybutyl)-5-phenylsulfonyl-4-piperidone (**15**).* A solution containing 2.0 g (3 mmol) of cycloadduct **14** and 2.1 g (15.2 mmol) of sodium phosphate in a 2:1-THF/EtOH mixture (21 mL total volume) at 0 °C was charged with 3.5 g (7.6 mmol) of 5% Na/Hg in two portions. The mixture was stirred at this temperature for 5 h and was then filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to give 1.0 g (65%) of a 1:1-diastereomeric mixture of piperidone **15** as a pale yellow oil; IR (neat) 1711, 1642, 1463, 1104, 883, and 629 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.12 (m, 21H), 1.30–1.62 (m, 8H), 1.95–2.03 (m, 3H), 2.43 (d, 1H, J=13.6 Hz), 2.77 (dd, 1H, J=13.6 and 2.8 Hz), 3.30–3.35 (m, 1H), 3.65–3.67 (m, 2H), 3.71 (t, 1H, J=6 Hz), 3.85 (dd, 1H, J=4.0 and 1.3 Hz), 3.89 (dd, 1H, J=4.0 and 1.6 Hz), 4.95–5.10 (m, 2H), 5.85–5.95 (m, 1H), 7.57 (t, 2H, J=7.6 Hz), 7.60–7.68 (t, 1H, J=7.2 Hz), and 7.84 (d, 2H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 18.3, 19.3, 19.4, 27.3, 27.5, 33.4, 33.5, 33.7, 34.6, 38.6, 39.4, 42.1, 52.5, 52.6, 60.5, 63.1, 72.3, 114.9, 115.2, 128.6, 128.7, 129.6, 134.6, 137.8, 138.1, 138.3, 200.9, and 201.0; HRMS calcd for [$C_{28}H_{47}NO_4SSi+H^+$]: 522.3073. Found: 522.3064.

*4.1.4. 2-(3-Butenyl)-2-(4-tri-isopropylsilanyloxybutyl)-4-piperidone (**16**).* To a solution containing 1.0 g (1.9 mmol) of the above phenylsulfonyl substituted piperidone **15** and 2.1 mL (7.7 mmol) of tri-*n*-butyltin hydride in 50 mL of toluene at reflux was added 0.2 g (1.3 mmol) of AIBN followed by the addition of a further 0.1 g (0.8 mmol) of AIBN after heating for 5 min. The mixture was further heated at reflux for an additional 2 h and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel to give 0.5 g (80%) of piperidone **16** as a pale yellow oil; IR (neat) 1709, 1640, 1381, 1070, 883, and 658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 1H, J=6.4 Hz), 0.94–1.07 (m, 21H), 1.22–1.63 (m, 6H), 1.98 (m, 2H), 2.24 (s, 2H), 2.31 (t, 2H, J=6.0 Hz), 3.10 (t, 2H, J=6.0 Hz), 3.65 (t, 2H, J=6.4 Hz), 4.92 (br d, 1H, J=10 Hz), 4.99 (br d, 1H, J=16.8 Hz), and 5.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 19.3, 27.5, 33.5, 35.9, 36.8, 40.8, 42.6, 52.9, 59.2, 63.1, 114.9, 138.4, and 210.2; HRMS calcd for [$C_{22}H_{43}NO_2Si+H^+$]: 382.3141. Found: 382.3137.

*4.1.5. 2-(3-Butenyl)-2-(4-tri-isopropylsilanyloxybutyl)-4-piperidone-1-carboxylic acid methyl ester (**17**).* To a solution containing 0.3 g (0.8 mmol) of piperidone **16** and 0.1 g (1.6 mmol) of $NaHCO_3$ in CH_3CN (8 mL) at 0 °C was slowly added methyl chloroformate (0.09 mL, 1.2 mmol). The mixture was allowed to warm to rt and was stirred overnight. A saturated aqueous ammonium chloride solution (10 mL) was added and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography to give 0.3 g (90%) of carbamate **17** as a colorless oil; IR (neat) 1727, 1697, 1381, 1102, 883, and 658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.08 (m, 21H), 1.27 (m, 2H), 1.45–1.72 (m, 4H), 1.96 (dd, 2H, J=16.1 and 7.0 Hz), 2.14 (m, 2H), 2.43 (t, 2H, J=6.0 Hz), 2.59 (d, 1H, J=15.6 Hz), 2.64 (d, 1H, J=15.6 Hz), 3.64 (t, 2H, J=6.4 Hz), 3.68 (s, 3H), 3.89 (m, 2H), 4.92 (br d, 1H, J=10 Hz), 4.98 (br d, 1H, J=17.2 Hz), and 5.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 20.4, 28.5, 33.4, 38.9, 39.5, 39.7, 41.3, 48.7, 52.6, 61.4, 63.3, 115.1, 138.1, 155.7, and 210.2; HRMS calcd for [$C_{24}H_{45}NO_4Si+H^+$]: 440.3190. Found: 440.3188.

*4.1.6. 2-(3-Butenyl)-2-(4-hydroxybutyl)-4-piperidone-1-carboxylic acid methyl ester (**18**).* To a solution containing 0.1 g (0.3 mmol) of carbamate **17** in 5 mL of dry THF at 0 °C was added 2 g of 4 Å molecular sieves and 0.3 mL (0.3 mmol) of tetrabutylammonium fluoride. The mixture was allowed to warm to room temperature, stirred for 4 h, and then filtered through a pad of Celite. The solution was diluted with 10 mL of water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography to give 0.08 g (95%) of alcohol **18** as a colorless oil; IR (neat) 1727, 1692, 1384, 1229, 998, 914, and 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 2H), 1.59 (m, 4H), 1.98 (m, 2H), 2.16 (m, 3H), 2.44 (t, 2H, J=6.4 Hz), 2.60 (d, 1H, J=15.6 Hz), 2.65 (d, 1H, J=15.6 Hz), 3.62 (t, 2H, J=6.8 Hz), 3.69 (s, 3H), 3.90 (m, 2H), 4.93 (br d, 1H, J=10.4 Hz), 4.99 (m, 1H, J=17 Hz), and 5.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 28.5, 32.7, 38.8, 39.1, 39.6, 41.4, 48.6, 53.0, 61.4, 62.5, 115.2, 138.0, 155.8, and 210.1; HRMS calcd for [$C_{15}H_{25}NO_4+H^+$]: 284.1856. Found: 284.1856.

*4.1.7. 2-(3-Butenyl)-2-(4-oxobutyl)-4-piperidone-1-carboxylic acid methyl ester (**19**).* To a solution containing 0.05 g (0.2 mmol) of alcohol **18** in 2 mL of dry CH_2Cl_2 at 0 °C was added Dess–Martin periodinane reagent (0.09 g, 0.2 mmol) in one portion. The mixture was allowed to warm to rt over 12 h, diluted with ether, and washed with a saturated solution of sodium bisulfite and sodium bicarbonate. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

0.04 g (80%) of aldehyde **19** as a colorless oil; IR (neat) 2954, 1724, 1693, 1382, 1089, and 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49–1.73 (m, 4H), 1.97 (dd, 2H, J=16 and 6.8 Hz), 2.15 (m, 2H), 2.44 (m, 4H), 2.65 (s, 2H), 3.69 (s, 3H), 3.90 (dt, 2H, J=6.2 Hz), 4.93 (br d, 1H, J=10.4 Hz), 4.99 (m, 1H, J=16.8 Hz), 5.73 (m, 1H) and 9.73 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 28.5, 38.6, 38.9, 39.6, 41.4, 43.9, 48.5, 52.7, 61.3, 115.3, 137.8, 155.7, 201.9, and 209.8; HRMS calcd for $[C_{15}H_{23}NO_4+H^+]$: 282.1701. Found: 282.1699.

*4.1.8. 8a-(3-Butenyl)-3,4,6,7,8a-hexahydro-2H-quinolin-4-one-1-carboxylic acid methyl ester (**20**).* To a solution containing 0.05 g (0.2 mmol) of the above aldehyde **19** in 2 mL of benzene was added 0.03 g (0.2 mmol) of *p*-toluenesulfonic acid monohydrate and the mixture was stirred at 50 °C for 8 h. The solution was allowed to cool to rt and was quenched with 15 mL of a saturated $NaHCO_3$ solution. The aqueous phase was extracted with ether and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 0.04 g (80%) of enone **20** as a colorless oil; IR (neat) 1694, 1623, 1386, 1252, 1093, and 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61–1.82 (m, 5H), 1.97 (m, 1H), 2.28 (m, 2H), 2.36 (t, 1H, J=2.4 Hz), 2.41 (t, 1H, J=2.4 Hz), 2.60 (m, 2H), 3.11 (dt, 1H, J=13.6 and 2.4 Hz), 3.70 (s, 3H), 4.35 (br d, 1H, J=12.8 Hz), 4.90 (br d, 1H, J=10.4 Hz), 4.95 (br d, 1H, J=17.2 Hz), 5.70 (m, 1H), and 6.62 (t, 1H, J=4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 24.8, 28.9, 31.1, 38.9, 39.8, 39.9, 52.6, 60.4, 115.1, 138.2, 138.4, 141.6, 157.9, and 193.2; HRMS calcd for $[C_{15}H_{21}NO_3+H^+]$: 264.1594. Found: 264.1595.

*4.1.9. cis-8a-(3-Butenyl)octahydro-4-quinolin-4-one-1-carboxylic acid methyl ester (**21**).* To a solution containing 0.05 g (0.2 mmol) of enone **20** in 4 mL of acetic acid was added 0.2 g of zinc dust and the mixture was stirred overnight at 120 °C. Water was added and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water, an aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 0.03 g (65%) of the *cis*-fused decalone **21** as a colorless oil: IR (CH_2Cl_2) 2940, 2864, 1686, 1448, and 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38–1.57 (m, 6H), 2.05 (m, 3H), 2.15 (m, 1H), 2.36 (m, 1H), 2.45 (m, 2H), 2.58 (m, 1H), 2.89 (br s, 1H), 3.48 (dt, 1H, J=13.6 Hz), 3.70 (s, 3H), 4.40 (ddd, 1H, J=14.2, 5.2, and 3.6 Hz), 4.96 (br d, 1H, J=10.4 Hz), 5.04 (br d, 1H, J=17.2 Hz), and 5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 22.1, 22.2, 28.1, 30.0, 33.0, 35.7, 39.7, 40.8, 49.9, 52.5, 61.6, 115.1, 138.3, and 210.8. The spectral data for this compound is identical to that reported in the literature.[8]

*4.1.10. 4,5-Bis-benzenesulfonyl-2-(2-oxiranylethyl)-2-(4-tri-isopropylsilanyloxybutyl)-7-oxa-1-aza-bicyclo[2.2.1]heptane (**22**).* To a round bottom flask charged with 11.0 g (16.6 mmol) of cycloadduct **14** in 80 mL of MeCN/AcOH (97:3) at −15 °C was slowly added 16.6 mL (0.4 mmol) of a 2.5 M solution of manganese phenanthroline in MeCN/AcOH (97:3). To this mixture was added 5.9 mL (25 mmol) of a 32 wt % solution of aqueous peracetic acid over the course of 20 min. The solution was allowed to stir for 10 min while being warmed to 0 °C. The reaction mixture was then transferred to a separatory funnel and was partitioned between aqueous $NaHCO_3$ and ethyl acetate. The organic layer was washed twice with water, once with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 3.0 g (26%) of the titled compound as a pale yellow oil that consisted primarily of a single diastereomer: IR (CH_2Cl_2) 2943, 2865, 1329, 1153, 1100, and 603 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03–1.06 (m, 21H), 1.20–1.30 (m, 4H), 1.46–1.56 (m, 3H), 1.89 (dq, 1H, J=6.3 and 2.2 Hz), 2.00–2.05 (m, 2H), 2.51 (q, 1H, J=2.4 Hz), 2.78 (dd, 1H, J=5.2 and 3.6 Hz), 2.92–2.97 (m, 1H), 3.10 (d, 1H, J=12.8 Hz), 3.52–3.55 (m, 2H), 3.61–3.69 (m, 2H), 3.97 (dt, 1H, J=12.4 and 4.7 Hz), 4.29–4.37 (m, 1H), 7.52 (t, 2H, J=7.6 Hz), 7.61–7.79 (m, 6H), and 7.97–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 7.8, 13.9, 15.3, 22.4, 23.0, 23.4, 24.0, 29.0, 33.6, 34.3, 42.7, 43.1, 47.5, 47.8, 49.0, 58.8, 62.3, 70.3, 99.9, 124.6, 124.7, 125.1, 125.2, 126.1, 130.1, 130.4, 130.6, and 135.0; HRMS calcd for $[C_{34}H_{51}NO_7S_2Si+H^+]$: 678.2949. Found: 678.2940.

*4.1.11. 3-Hydroxymethyl-8a-(4-tri-isopropylsilanyloxybutyl)-hexahydroindolizin-7-one (**25**).* To a round bottom flask charged with 2.4 g (3.5 mmol) of epoxide **22** in 220 mL of a saturated NH_4Cl/H_2O/THF (1:1:1) solution was added 11.6 g (177 mmol) of zinc dust. The reaction mixture was vigorously stirred and then heated to 70 °C for 12 h, cooled to rt, and filtered through a pad of Celite. The filtered solid was washed with an aqueous $NaHCO_3$ solution and the filtrate was collected, and extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 1.07 g (68%) of the major diastereomer of **25** as a pale yellow oil: IR (CH_2Cl_2) 3454, 2940, 2864, 1701, 1459, and 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.03–1.05 (m, 21H), 1.34–1.39 (m, 4H), 1.49–1.52 (m, 4H), 1.83–1.91 (m, 2H), 2.04–2.08 (m, 2H), 2.20 (dd, 1H, J=13.6 and 2.1 Hz), 2.34 (d, 1H, J=13.6 Hz), 2.50–2.54 (m, 1H), 3.05–3.10 (m, 1H), 3.21 (ddd, 1H, J=14.4, 6.6, and 1.7 Hz), 3.34 (d, 1H, J=9.0 Hz), 3.44 (dd, 1H, J=10.8 and 1.8 Hz), and 3.64–3.69 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 7.8, 13.9, 15.9, 20.4, 29.1, 31.2, 31.9, 33.1, 38.4, 43.5, 55.7, 58.2, 58.9, 64.8, and 205.8; HRMS calcd for $[C_{22}H_{43}NO_3Si+H^+]$: 398.3046. Found: 398.3085.

The minor diastereomer (9%) could not be fully separated from the major diastereomer but showed characteristic ^1H NMR peaks at δ 1.03–1.05 (m, 21H), 1.34–1.39 (m, 4H), 1.49–1.52 (m, 2H), 1.83–1.91 (m, 2H), 2.04–2.08 (m, 1H), 2.20–2.30 (m, 2H), 2.45–2.58 (m, 2H), 2.62 (t, 1H, J=9.6 Hz), 2.67 (dd, 1H, J=13.6 and 2.1 Hz), 2.83 (dt, 1H, J=9.6 and 3.6 Hz), 2.88–2.96 (m, 1H), 3.05–3.10 (m, 1H), 3.43–3.46 (m, 1H), and 3.64–3.69 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 12.2, 18.2, 21.4, 26.4, 27.5, 33.8, 34.6, 40.3, 52.1, 59.6, 61.5, 63.1, 66.4, and 210.3.

*4.1.12. Benzoic acid 7-oxo-8a-(4-tri-isopropylsilanyloxybutyl)octahydroindolizin-3-yl methyl ester (**26**).* To a round bottom flask charged with 1.0 g (2.4 mmol) of the above alcohol **25** in 24.4 mL of CH_2Cl_2 was added 0.7 mL (4.9 mmol) of Et_3N, 0.4 mL (2.9 mmol) of benzoyl chloride, and a catalytic amount of DMAP, sequentially. The reaction mixture was stirred at rt for 2 h, and was then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was extracted with ether, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 1.2 g (97%) of the titled compound as a pale yellow oil: IR (CH_2Cl_2) 2942, 2856, 1722, 1269, 1108, and 712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03–1.06 (m, 21H), 1.25–1.35 (m, 4H), 1.41–1.55 (m, 4H), 1.76–1.83 (m, 1H), 1.90–1.98 (m, 1H), 2.04–2.10 (m, 1H), 2.12–2.18 (m, 1H), 2.19 (dd, 1H, J=13.6 and 2.1 Hz), 2.33 (d, 1H, J=13.6 Hz), 2.51–2.60 (m, 1H), 3.07–3.15 (m, 1H), 3.41 (ddd, 1H, J=14.4, 6.4, and 1.9 Hz), 3.52–3.56 (m, 1H), 3.59 (t, 2H, J=6.8 Hz), 4.24–4.33 (m, 2H), 7.44 (t, 2H, J=7.6 Hz), 7.56 (t, 1H, J=7.4 Hz), and 8.03 (dd, 2H, J=7.4 and 1.4 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 12.2, 18.2, 20.1, 25.5, 33.5, 34.9, 36.7, 37.3, 44.3, 48.2, 58.5, 63.3, 68.1, 69.2, 128.6, 129.8, 133.2, 166.8, and 210.7; HRMS calcd for $[C_{29}H_{47}NO_4Si+H^+]$: 502.3347. Found: 502.3342.

*4.1.13. Benzoic acid 7-oxo-decahydropyrrolo[2,1-j]quinolin-3-yl methyl ester (**30**).* An oven-dried round bottom flask was charged with 0.96 g (1.92 mmol) of the starting silyl ether **26**, 4 Å molecular sieves and 19 mL of anhydrous THF and the mixture was cooled to 0 °C

under an argon atmosphere. To this mixture was added 2.3 mL (2.3 mmol) of a 1.0 M solution of TBAF in THF over the course of 30 min. The solution was allowed to stir for an additional 1.5 h while being warmed to rt. The reaction mixture was filtered through a pad of Celite and the collected solid was rinsed with ether. The filtrate was then partitioned between ether and aqueous $NaHCO_3$ and the organic layer was extracted, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.51 g (77%) of alcohol **27** as a colorless oil: IR (CH_2Cl_2) 3361, 2918, 1717, 1271, 1146, and 713 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22–1.29 (m, 4H), 1.38–1.54 (m, 4H), 1.78–1.83 (m, 2H), 1.89–1.96 (m, 1H), 2.04–2.06 (m, 1H), 2.10–2.14 (m, 1H), 2.16 (d, 1H, J=7.6 Hz), 2.32 (d, 1H, J=9.2 Hz), 2.50–2.57 (m, 1H), 3.05–3.12 (m, 1H), 3.39 (ddd, 1H, J=9.4, 4.2, and 0.8 Hz), 3.49–3.54 (m, 1H), 4.23 (dd, 1H, J=7.4 and 3.0 Hz), 4.35 (dd, 1H, J=7.4 and 3.8 Hz), 7.4 (t, 2H, J=7.6 Hz), 7.55 (dt, 1H, J=7.4 and 0.4 Hz) and 8.01 (dd, 2H, J=7.4 and 1.4 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.7, 26.0, 33.8, 35.6, 37.4, 37.8, 45.0, 48.9, 59.3, 63.5, 68.5, 69.9, 129.3, 130.4, 131.1, 133.9, 167.4, and 211.5; HRMS calcd for [$C_{20}H_{27}NO_4$+H^+]: 346.2019. Found: 346.2007.

To a round bottom flask charged with 42 mg (0.12 mmol) of alcohol **27** was added 1.2 mL of CH_2Cl_2 and 0.025 mL (0.27 mmol) of pyridine, sequentially. The reaction mixture was cooled to 0 °C prior to the addition of 49 mg (0.26 mmol) of *p*-tosyl chloride. The solution was allowed to stir for 1 h while being warmed to rt. The reaction mixture was then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was extracted with ether, washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica chromatography to give 60 mg (98%) of the reactive tosylate **28** as a pale yellow oil that was taken up in 4 mL of dry benzene and immediately subjected to the following reaction conditions.

An oven-dried round bottom flask equipped with a stir bar and 4 Å molecular sieves was degassed with argon. To this flask was added 2 mL of dry benzene and 0.25 mL (0.25 mmol) of a 1.0 M solution of potassium *tert*-butoxide in THF. The mixture was cooled to 0 °C and 4 mL (0.12 mmol) of a 0.03 M solution of tosylate **28** in benzene was added dropwise over the course of 30 min. After stirring for an additional 30 min, the reaction mixture was warmed to rt and was stirred for an additional 1 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and then partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was extracted with ether and washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 27 mg (69%) of the titled compound **30** as a pale yellow oil: IR (CH_2Cl_2) 2923, 1717, 1459, 1271, and 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.25–1.51 (m, 8H), 1.67 (d, 1H, J=10.4 Hz), 1.74–1.84 (m, 2H), 2.07–2.10 (m, 1H), 2.14–2.18 (m, 2H), 2.23–2.26 (m, 1H), 2.40 (d, 1H, J=4.2 Hz), 2.59 (ddd, 1H, J=13.5, 12.0, and 5.4 Hz), 3.30 (ddd, 1H, J=14.4, 11.7, and 3.5 Hz) 3.38 (ddd, 1H, J=14.4, 6.3, and 3.3 Hz), 3.60 (dt, 1H, J=9.6 and 3.6 Hz), 4.29 (dd, 1H, J=11.4 and 6.0 Hz), 4.30 (dd, 1H, J=11.4 and 5.9 Hz), 7.46 (t, 2H, J=7.6 Hz), 7.57 (dt, 1H, J=7.4 and 1.2 Hz), and 8.03 (dd, 2H, J=7.4 and 1.4 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.8, 22.8, 24.5, 25.6, 35.5, 36.5, 37.5, 44.4, 50.9, 59.0, 68.5, 69.4, 128.6, 129.7, 130.4, 133.2, 166.8, and 211.1; HRMS calcd for [$C_{20}H_{25}NO_3$+H^+]: 328.1907. Found: 328.1901.

*4.1.14. Benzoic acid 7-oxo-2,3,7,7a,8,9,10,11-octahydro-1H-pyrrolo-[2,1-j]quinolin-3-yl methyl ester (**31**).* To a round bottom flask charged with 4.8 mg (14.4 mmol) of the above tricyclic compound **30** dissolved in 1.0 mL of a 2:1-EtOH/H_2O mixture at rt was added 5.8 mg (15.5 mmol) of EDTA and 4.9 mg (15.5 mmol) of mercuric acetate. The mixture was heated at 80 °C for 1.5 h, cooled to rt and the solution was partitioned between aqueous NH_4Cl and CH_2Cl_2. The organic layer was extracted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 4.7 mg (95%) of **31** as a pale yellow oil: IR (CH_2Cl_2) 2926, 2854, 1721, 1633, 1579, 1269, 1211, and 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.25–1.34 (m, 4H), 1.45–1.48 (m, 1H), 1.65–1.71 (m, 1H), 1.76–1.82, (m, 1H), 1.88–1.96 (m, 1H), 2.03–2.07 (m, 1H), 2.27 (p, 1H, J=6.9 Hz), 2.43 (dd, 1H, J=12.3 and 6.9 Hz), 2.50 (br s, 1H), 2.53 (br s, 1H), 4.09 (br t, 1H, J=13.5 Hz), 4.31 (dd, 1H, J=12.0 and 6.0 Hz), 4.55 (dd, 1H, J=12.0 and 4.6 Hz), 4.95 (d, 1H, J=7.2 Hz), 7.22 (d, 1H, J=7.2 Hz), 7.47 (t, 2H, J=7.6 Hz), 7.60 (t, 1H, J=7.4 Hz) and 8.03 (d, 2H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 22.1, 22.9, 24.6, 27.4, 27.8, 30.3, 35.6, 51.1, 60.0, 66.8, 97.6, 129.2, 130.0, 130.2, 134.0, 147.1, 166.7, and 193.6; HRMS calcd for [$C_{20}H_{23}NO_3$+H^+]: 326.1750. Found: 326.1750.

*4.1.15. (±)-Cylindricine C (**1**).* An oven-dried round bottom flask was charged with 11 mg (53 mmol) of copper bromide-dimethyl sulfide and 0.3 mL of dry THF. The flask was degassed with argon and immersed in an ice bath. To the resulting slurry was added dropwise 0.3 mL (18.4 mmol) of a 37.0 M solution of **31** in dry THF over the course of 30 min at 0 °C. The reaction mixture was cooled to −78 °C and 8.2 mL (65 mmol) of $BF_3{\cdot}OEt_2$ was added dropwise over the course of 10 min. To this reaction mixture was added dropwise 28.7 mL (53 mmol) of a 1.86 M solution of *n*-hexylmagnesium bromide in ether over the course of 30 min at −78 °C. The reaction mixture was allowed to stir for an additional 90 min at −78 °C and was then warmed to rt and partitioned between ether and aqueous NH_4Cl. The organic layer was extracted with ether, washed with water, brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica chromatography. The major fraction was immediately added to 5 mL of a 1% NaOH in methanol solution. The mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and 1 N NaOH. The organic layer was extracted with ether, washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 4.1 mg (82%) of (±)-cylindricine C (**1**) as a colorless oil that exhibited spectroscopic data identical to that described in the literature:[10] IR (CH_2Cl_2) 2926, 2854, 1724, 1633, 1462, 1024, and 804 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, J=7.0 Hz), 1.22–1.65 (m, 19H), 1.83 (dd, 1H, J=13.0 and 8.5 Hz), 2.13 (dd, 1H, J=12.5 and 8.0 Hz), 2.23 (dd, 2H, J=13.0 and 3.0 Hz), 2.30 (t, 2H, J=11.4 Hz), 2.88 (br s, 1H), 3.26–3.32 (m, 1H), 3.43 (t, 1H, J=9.3 Hz), and 3.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 14.6, 22.4, 23.1, 23.3, 24.9, 27.7, 29.3, 30.3, 32.2, 35.8, 36.5, 37.0, 43.1, 50.8, 55.9, 57.1, 58.1, 71.3, and 197.0; HRMS calcd for [$C_{19}H_{33}NO_2$+H^+]: 308.2584. Found: 308.2578.

The minor diastereomer (12%) could not be fully separated from the major diastereomer but exhibited spectroscopic data identical to 2-*epi*-(±)-cylindricine C (**32**) as reported in the literature:[10] IR (CH_2Cl_2) 2926, 2854, 1724, 1633, 1462, 1024, and 804 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, J=7.0 Hz), 1.22–1.65 (m, 19H), 2.02–2.07 (m, 2H), 2.17 (dd, 1H, J=16.0 and 6.0 Hz), 2.26 (d, 1H, J=10.5 Hz), 2.52–2.53 (m, 1H), 2.65 (dd, 1H, J=15.3 and 5.7 Hz), 2.86 (br s, 1H), 3.22 (dt, 1H, J=6.6 and 1.8 Hz), 3.26–3.32 (m, 1H), 3.36–3.41 (m, 1H), and 3.52–3.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 14.6, 22.4, 23.1, 23.3, 24.9, 27.7, 29.3, 29.9, 32.3, 35.8, 36.5, 37.0, 43.1, 50.8, 55.9, 57.1, 58.1, 66.9, and 197.0; HRMS calcd for [$C_{19}H_{33}NO_2$+H^+]: 308.2584. Found: 308.2579.

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