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AZA-[3 + 3] ANNULATIONS. PART 6. TOTAL SYNTHESES OF PUTATIVE (-)-LEPADIFORMINE AND (-)-CYLINDRICINE C†

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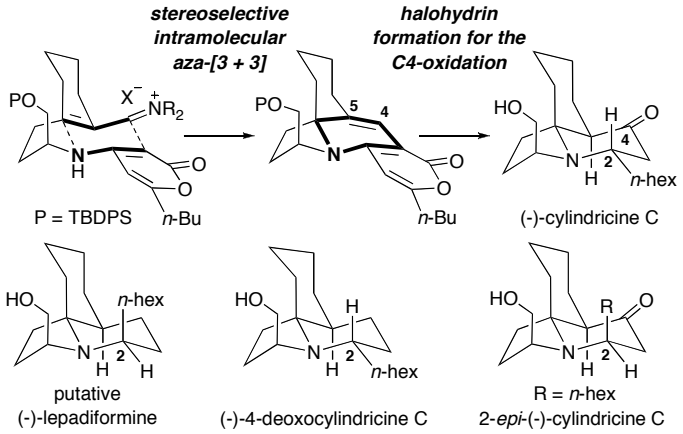
Abstract – Efforts in achieving an enantioselective total synthesis of (-)-cylindricine C along with the syntheses of putative lepadiformine, *epi*-lepadiformines, (-)-4-deoxo-cylindricine C, and (-)-2-*epi*-cylindricine C are described here in details. These syntheses feature a stereoselective intramolecular *aza*-[3 + 3] annulation as a unified strategy, and specifically, the total synthesis of (-)-cylindricine C was accomplished in 22 steps with a 4.5% overall yield from *L*-serine. In addition, we developed an interesting halohydrin formation for the construction of the C4-ketone of cylindricines.



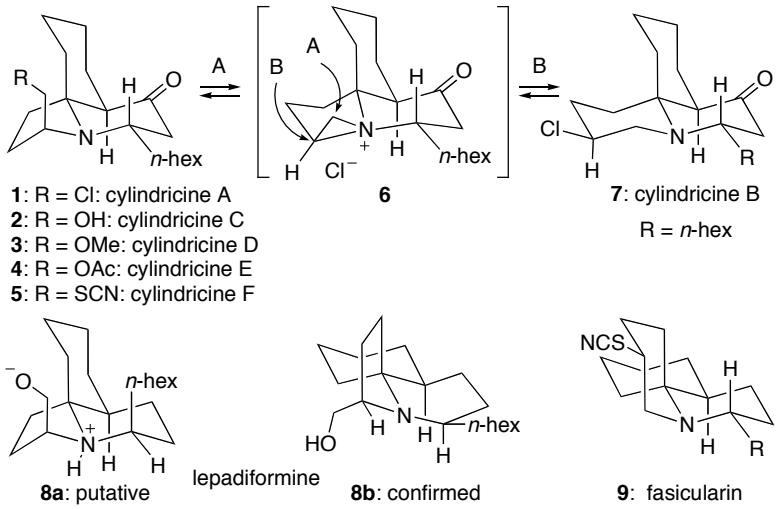
INTRODUCTION

Cylindricines (1-5, 7),[1] lepadiformine (8),[2] and fasicularin (9),[3] isolated from the marine ascidian Clavelina cylindrica, Clavelina lepadiformis,[2] and the Micronesian ascidian Nephteis fasicularis,[3]

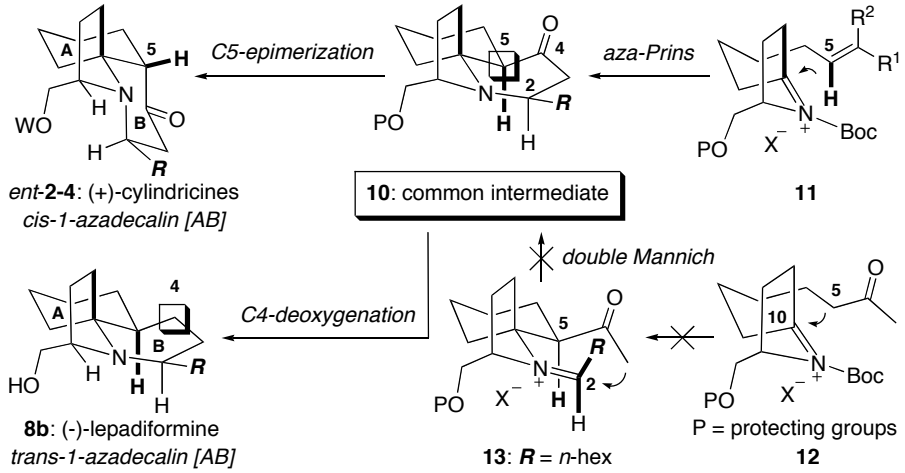
† This paper is dedicated to Professor Steven M. Weinreb, on the special occasion of his 65th birthday, whose illustrious career in developing innovative synthetic methods and ingenious total syntheses of alkaloids has truly been an inspiration to the synthetic community.

respectively, have attracted an immense amount of attention from the synthetic community in the last ten years (**Figure 1**).[4,5] Cylindricine A (**1**) and cylindricine B (**7**) have been shown to exist in an equilibrium mixture [3 : 2] likely through the aziridinium intermediate (**6**).[1a] The correct structure of lepadiformine was established to be (**8b**) independently through impressive earlier efforts from Weinreb,[6] Pearson,[7] and Kibayashi,[8] and not the putative structure in the unusual Zwitter ionic form shown as (**8a**), which attracted Weinreb's attention in the first place. Intriguingly, while lepadiformine (**8b**) shows moderate cytotoxicity toward tumor cell lines *in vitro*,[2] fasicularin (**9**) actually demonstrates substantial cytotoxicity toward Vero cells with an IC_{50} value of 14 μg/mL.[3] This family of alkaloids attracted our attention because of two reasons with one being structurally inspired and the other driven by the need to establish applications of an *aza*-annulation method that we have developed.

Figure 1. Cylindricines, Lepadiformine, and Fasicularin



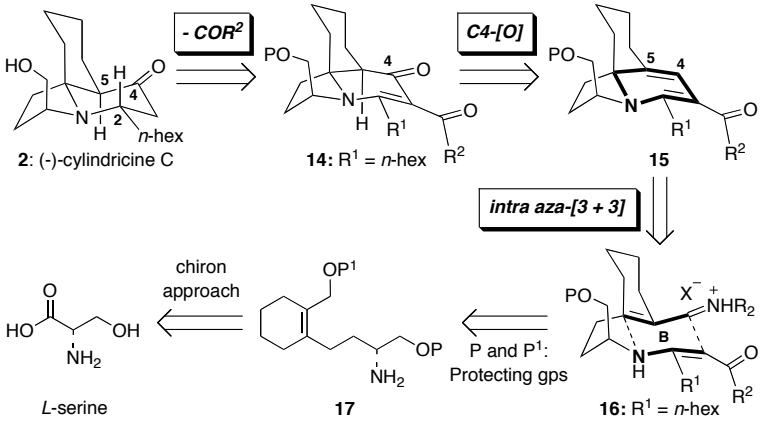
Scheme 1. *Aza*-Prins Approach to (+)-Cylindricines and (-)-Lepadiformine



Abstracting from an impressive array of strategies designed toward ultimate total syntheses of fasicularin,[9] lepadiformine,[11-13] and cylindricines,[12-14] we[15] and Kibayashi[16] were the first ones to recognize and succeed in exploring a unified strategy en route to both (-)-lepadiformine and (+)-cylindricines.

Specifically, as shown in **Scheme 1**, we reported total syntheses of (+)-cylindricines C-E and (-)-lepadiformine through the recognition that the *trans*-fused 1-*aza*-decalinic AB-ring in lepadiformine (**8b**) and *cis*-fused AB-ring in (+)-cylindricines C-E (*ent*-(**2-4**)) could be linked through the C5 epimerization of an appropriate late stage common intermediate such as *aza*-tricycle (**10**). The *aza*-tricycle (**10**) ultimately was derived from an *aza*-Prins type cyclization[17] of **11** inspired by Kibayashi's earlier work[8,10a] and a rare application of Wharton's rearrangement,[18,19] although earlier attempts to access (**10**) from *N*-acyl iminium ion (**12**) felt short[20] via a Robinson-Schöpf's double Mannich strategy.[21,22] This work implies a potential biosynthetic connection between these two classes of natural products.

Scheme 2. *Aza*-[3 + 3] Approach to (-)-Cylindricine C



The second reason that drew us to this family of alkaloids, specifically to cylindricines, was our interest in identifying applications of diastereoselective intramolecular *aza*-[3 + 3] annulations[23-27] employing vinylogous amides (**16**) tethered with vinyl iminium ions (**Scheme 2**). We recently succeeded in an enantioselective total synthesis of (-)-cylindricine C from *L*-serine featuring this *aza*-[3 + 3] annulation strategy.[28] We report here details of this entire synthetic endeavor.

RESULTS AND DISCUSSION

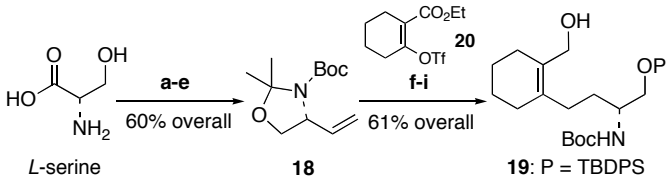
1. Model Studies and Feasibility of the *Aza*-[3 + 3] Annulation.

We commenced our synthetic efforts five years ago in search of an efficient route to the key amino alcohol (**17**) as planned in **Scheme 2**. We attempted several different possible routes before identifying the one employing *L*-serine as the starting chiron. Without belaboring details of the abandoned approaches, the successful route is concisely summarized in **Scheme 3**. The desired Boc-protected amino alcohol (**19**) could be accessed in 8 synthetic steps with a good overall yield from *L*-serine, featuring a Suzuki-Miyaura[29] cross coupling of the hydroborated vinyl oxazoline (**18**)[30] with vinyl triflate (**20**). It is noteworthy that the synthesis of **18** involved the very *Weinreb's amide*.[31]

With amino alcohol (**19**) in hand, we prepared both vinylogous amide (**22**) and amino pyrone (**24**) with former serving as a model and the latter possibly being a real option (see below for more discussions). As

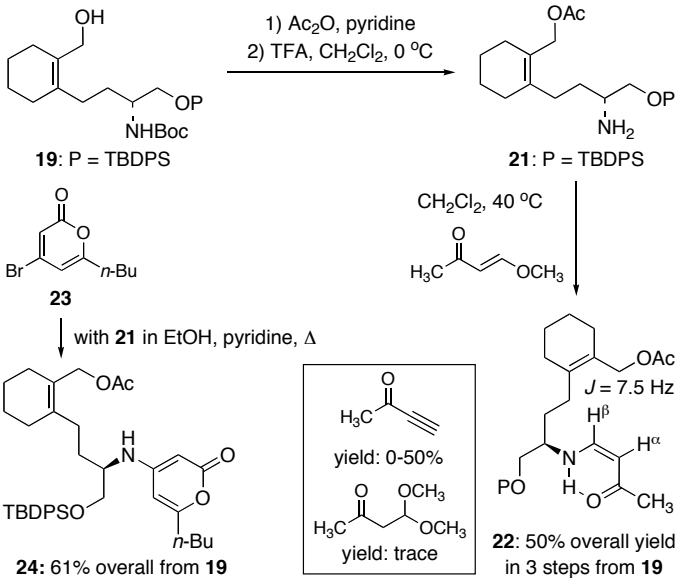
shown in **Scheme 4**, protection of **19** using Ac_2O followed by removal of the BOC group using TFA gave chiral amine (**21**), and treatment of **21** with 4-methoxy-2-buten-2-one in CH_2Cl_2 at 40 °C led to vinylogous amide (**22**) in 50% yield over three steps. Vinylogous amide (**22**) was determined to be *cis* given J = 7.5 Hz for the α and β olefinic protons, and this preference is most likely due to the intramolecular hydrogen bonding shown in **22**.

Scheme 3. Synthesis of the Key Amino Alcohol (**19**)



a. 1.2 equiv Boc_2O, NaOH, dioxane-H_2O, 0 °C - rt. **b.** MeNHOMe-HCl, *N*-methyl morpholine, EDCI, CH_2Cl_2, rt. **c.** 2,2-Dimethoxypropane, BF_3-Et_2O, acetone, 0 °C. **d.** 0.5 equiv LAH, THF, 0 °C, 1 h. **e.** $MePPh_3Br$, KHMDS, THF, -78 °C - rt. **f.** 9-BBN, THF, 0 °C to rt, and then, 5 mol% $PdCl_2$(dppf), 2.0 equiv K_3PO_4, 1.2 equiv of vinyl triflate (**20**), Δ. **g.** PPTS, MeOH, Δ. **h.** TBDPSCl, imidazole, CH_2Cl_2. **i.** Dibal-H, -78 °C, CH_2Cl_2.

Scheme 4. Vinylogous Amide (**22**) and Amino Pyrone (**24**)



Our earlier preparations of **22** had utilized 3-butyn-2-one (see the box) and the reaction was carried out in CH_2Cl_2 or MeOH at either 0 °C or rt. However, the outcome was quite inconsistent with the yield fluctuated between 0-50%. In addition, 4,4-dimethoxy 2-butanone (see the box) was not useful at all in the preparation of **22** in solvents such as CH_2Cl_2 or toluene at rt or 110 °C even when using *p*-TsOH. On the other hand, preparation of amino pyrone (**24**) was much less eventful and could be achieved in 61% overall yield from **19**.

With vinylogous amide (**22**) in hand serving as a quick model study, deacylation was carried out employing K_2CO_3 and MeOH, and a subsequent Ley's TPAP-NMO oxidation[32] of the allyl alcohol

intermediate gave the annulation precursor (**25**) (**Scheme 5**). The ensuing intramolecular *aza*-[3 + 3] annulation of **25** was carried out in the presence of piperidinium acetate at 150 °C in a sealed tube. Although the desired cycloadduct intermediate could be isolated, it was not as stable. Thus, the reaction mixture was hydrogenated to give the desired *aza*-tricycle (**26**) as a single isomer in 41% overall yield.

Scheme 5. Key Intramolecular *Aza*-[3 + 3] Annulations

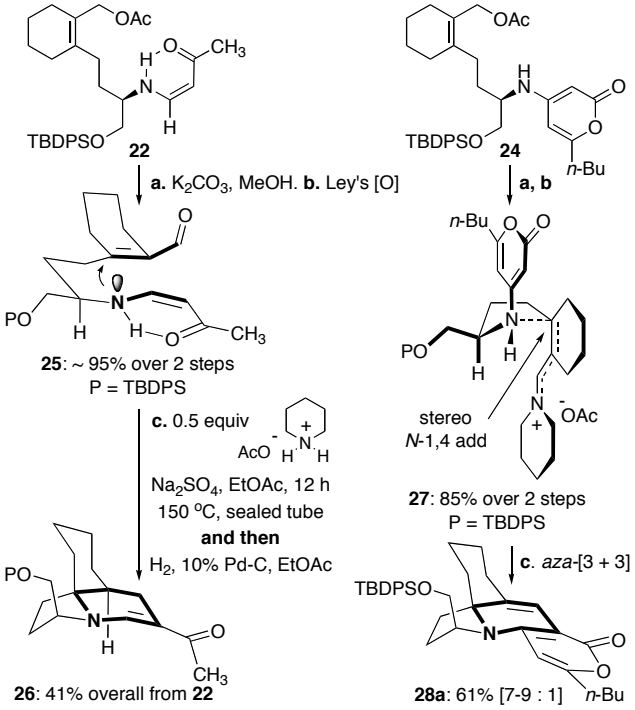
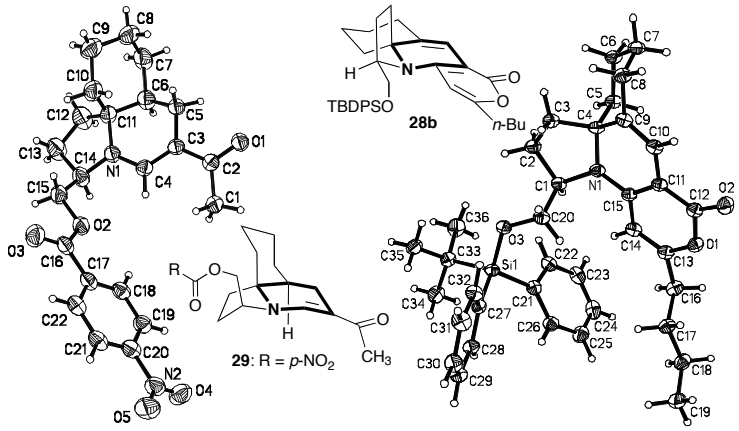


Figure 2. Left: *Para*-Nitro Benzoate (**29**); Right: Minor Isomer (**28b**)

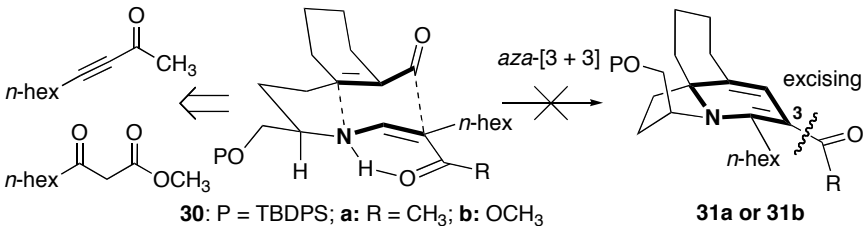


Analogously, an enal (not shown: analogous to **25**) could be accessed from amino pyrone (**24**), and the intramolecular *aza*-[3 + 3] annulation of the iminium salt intermediate (**27**) derived *in situ* from the enal was found to proceed smoothly in toluene in the presence of 0.5 equiv of piperidinium acetate for the vinyl iminium ion formation. After heating at 150 °C for 12 h, the major annulation product was the desired *aza*-tetracycle (**28a**) and it was obtained in 61% yield in addition to a minor isomer (**28b**). The diastereomeric ratio ranged from 7-9 : 1 over several runs. It is noteworthy that *aza*-tetracycle (**28a**) was

much more stable than **26**. The relative stereochemistry of **26** was unambiguously assigned by X-Ray analysis of the *para*-nitrobenzoate derivative (**29**) (**Figure 2**). While the relative stereochemistry of the minor isomer (**28b**) was established via X-Ray structural analysis (**Figure 2**), the major isomer (**28a**) was confirmed stereochemically from an X-Ray structure of an intermediate at a later stage. A rationale for the preferred stereochemical outcome in **28a** could be visualized through the TS-conformational analysis shown for **27** in **Scheme 5**. This analysis is based on our detailed mechanistic studies in organocatalytic asymmetric *aza*-[3 + 3] annulations,[27b] and features a preference that can alleviate gauche interactions between the *N*-substituent and those at the vicinal carbons. With this conformation in places, a stereoselective *N*-1,4-addition would proceed, leading to the observed stereochemical outcome.

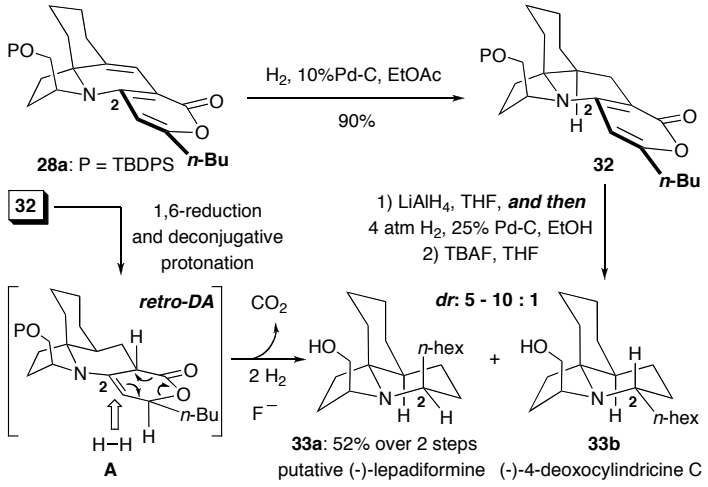
These initial studies firmly established the *aza*-[3 + 3] annulation as a viable approach to the *aza*-tricyclic frame of the cylindricine alkaloids. However, despite the success with vinylogous amide (**22**) as a model, we encountered difficulties in succeeding *aza*-[3 + 3] annulations employing more elaborate vinylogous amides (**30a**) and (**30b**), and failed to obtain the respective *aza*-tricycles (**31a**) and (**31b**) (**Scheme 6**). While **31a** poses a significant challenge in excising of the acetyl group at C3, **31b** would have been an ideal advanced intermediate given the relative ease in removing a methoxy carbonyl group at C3.

Scheme 6. Failed *Aza*-[3 + 3] Annulations.



With these failures, we elected to carry on the total synthesis using *aza*-tetracycle (**28a**) derived from amino pyrone (**24**). In employing **28a**, the outcome could still be disastrous given the pending obstacle in ring-opening of the 2-pyrone moiety, although the required *n*-hexyl group at C2 is embedded in the 2-pyrone (see bolded portion or **28a** in **Scheme 7**). However, we do possess one precedent in such a ring-opening[26d] that gave us sufficient assurance to pursue this synthetic route.

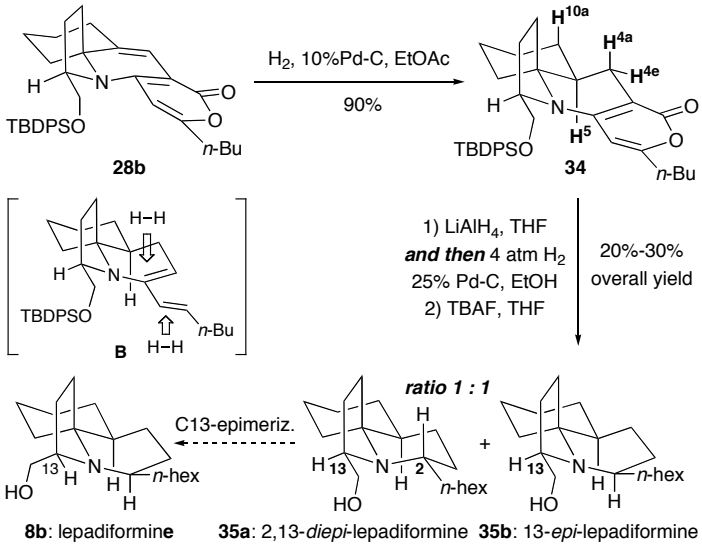
Scheme 7. Reductive Ring-Opening of 2-Pyrone



To demonstrate this possibility, *aza*-tetracycle (**28a**) was hydrogenated to give **32** as a single diastereomer in 90% yield, and to reductively open the 2-pyrone ring in (**32**), a unique sequence using LAH followed by 4 atm H_2 was employed (**Scheme 6**).[26d] The reaction sequence led to the putative (-)-lepadiformine (**33a**) (or: (-)-4-deoxo-2-*epi*-cyclindricine C), which matched the spectroscopic data reported by Weinreb,[6b] along with a minor isomer (**33b**) ((-)-4-deoxocyclindricine) in 52% overall yield after desilylation using TBAF. The isomeric ratio of **33a** : **33b** varied in the range of 5-10:1 over several runs. The two isomers were painstakingly separated via HPLC, leading to a minute quantity of the minor isomer (**33b**), and thus, (-)-4-deoxocyclindricine (**33b**) was not fully characterized.

While we do not know the details of this unique transformation, pyrone **A**, derived from an initial 1,6-hydride reduction followed by deconjugative protonation, is likely a key intermediate that could go on and lose CO_2 via a retro-Diels-Alder cycloaddition. The ensuing hydrogenation of the resulting amino diene intermediate (not shown) should be favored from the bottom face (see the hollow arrow) to provide a possible explanation for the stereochemical outcome at C2.

Scheme 8. Attempted Synthesis of (-)-Lepadiformine



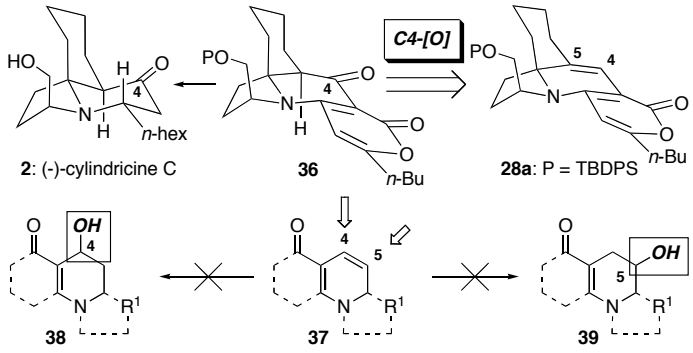
Encouraged by this facile reductive ring-opening of the 2-pyrone motif, we attempted to synthesize (-)-lepadiformine (**8b**) from the minor isomer (**28b**). However, after hydrogenation of **28b**, reductive ring-opening employing (**34**)[33] only gave an inseparable mixture of *epi*-lepadiformines (**35a**) (2,13-*diepi*) and (**35b**) (13-*epi*) in low yields over several trials (**Scheme 8**). A diastereomeric ratio of 1 : 1 suggests that after the retro Diels-Alder step to extrude CO_2, both faces of the resulting amino diene intermediate **B** (see the bracket and hollow arrows) were comparably susceptible to hydrogenation. No attempts were made to separate the two isomers on HPLC. Therefore, we abandoned our attempt to synthesize (-)-lepadiformine (**8b**) through a potential C13-epimerization sequence. This thwarted our hope in achieving another total synthesis of (-)-lepadiformine through the same strategy or advanced intermediate used for cylindricines.[15]

2. Halohydrin Formation for Installing the C4 Ketone.

Success of the key intramolecular *aza*-[3 + 3] annulation reaction provided us with an opportunity to complete the total synthesis of (-)-cylindricine C. The remaining goal was to install the desired ketone functionality at C4 using *aza*-tetracycle (**28a**). However, as shown in **Scheme 9**, transforming the C4-5 *endo*-cyclic olefin of **28a** into the C4-oxo group in **36** proved to be challenging. In fact, direct transformations of the endo-cyclic olefin in any *aza*-annulation products (see **37**) into products (**38**) and (**39**) containing the desired oxidation state at C4 and C5, respectively, were difficult employing various protocols as shown. These difficulties prompted us to explore alternative methods to functionalize the C4 and C5 positions of *aza*-[3 + 3] annulation products.

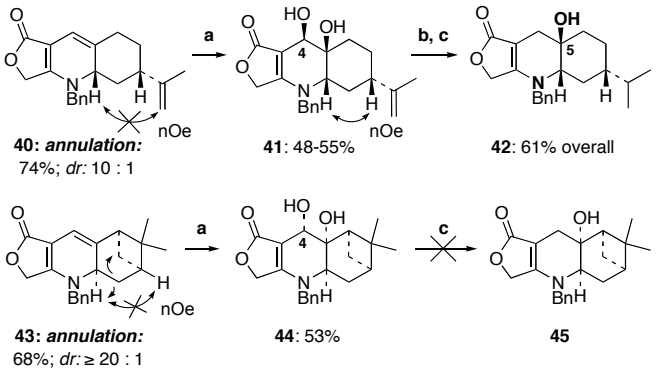
We were able to quickly establish a stepwise sequence suitable for installing a hydroxyl group at the C5 position. As shown in **Scheme 10**, we prepared *aza*-tricycle (**40**) in 74% yield via a stereoselective (*dr:* 10 : 1 - assigned via NOE) *aza*-[3 + 3] annulation of tetronamide with (*S*)-(-)-perillaldehyde (see the experimental section). A subsequent dihydroxylation of **40** gave diol (**41**) as a single isomer. The C4-OH group in **41** could be selectively removed under reductive conditions[34] employing Et_3SiH and TFA to give **42** in 61% yield after an initial hydrogenation of the terminal olefin in **41**. On the other hand, while *aza*-tricycle (**43**), derived from (*R*)-(-)-myrtenal (see the experimental section), could be readily dihydroxylated to give **44**, selective removal of the C4-OH group proved to be problematic. This is likely due to competing Wagner-Meerwein rearrangement under the cationic conditions. Nevertheless, the two-step sequence illustrated here should find utility for systems that call for the C5-OH group.

Scheme 9. Problems in Installing the C4 Ketone



DMDO; Oxone™; *m*-CPBA, MMPP [magnesium monoperoxyphthalate]; aq $KMnO_4$; 9-BBN or BH_3-Me_2S/H_2O_2/HaOH; $Hg(OAc)_2$/$NaBH_4$; NBS/DMSO.

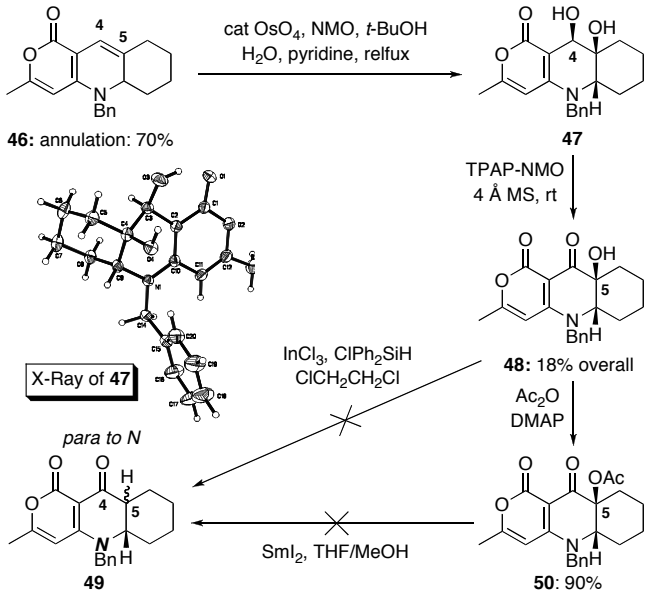
Scheme 10. A Suitable Sequence for the C5-Oxidation



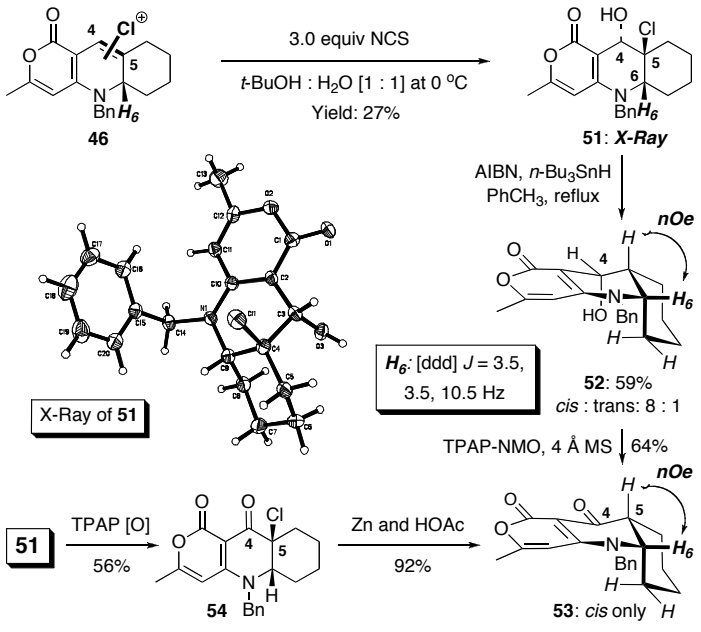
a. i) OsO_4, pyridine, CH_2Cl_2, rt, 4 h; **ii)** mannitol, 10% aq KOH, rt, 12 h.
b. 1 atm H_2, Pd-C, EtOAc, rt. **c.** Et_3SiH, TFA, CH_2Cl_2, -15 ºC, 48 h.

We then turned our attention to installing the C4-OH group and elected to utilize *aza*-tricycle (**46**), for it represents a better model system for (-)-cylindricine C. We again dihydroxylated **46** and obtained diol (**47**) as a single isomer with its relative stereochemistry assigned via a single-crystal X-Ray structure (**Scheme 11**). Oxidation of **47** led to hydroxy ketone (**48**), thereby allowing us to examine reductive removal of the C5-OH group. However, the removal of the C5-OH group was not successful using Ph_2ClSiH as a hydride source in the presence of a catalytic amount of $InCl_3$ for promoting the radical process.[35] A second attempt involved acetoxy ketone (**50**), but we were unable to remove the C5-OAc group using SmI_2.[36]

Scheme 11. Failed Attempts for the C5-Oxidation



Scheme 12. Chlorohydrin Formation of *Aza*-Tricycle (**46**)

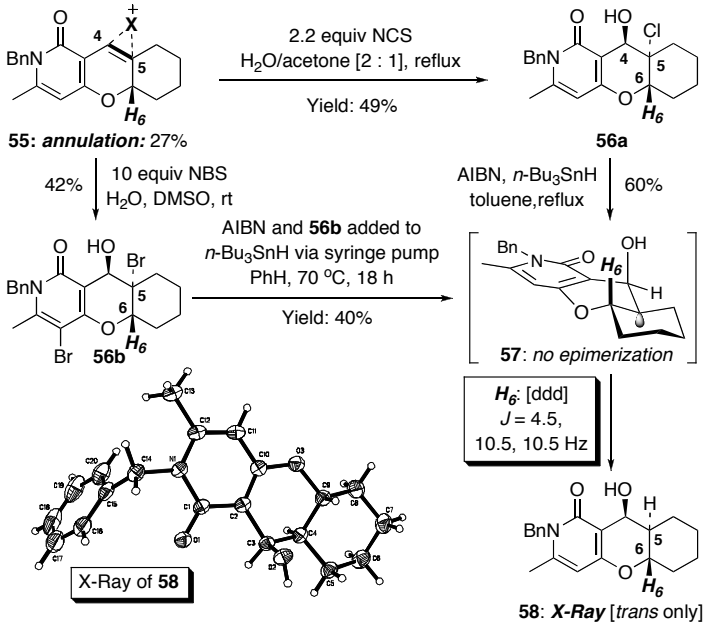


These failures prompted us to explore another strategy involving halohydrin formation. As shown in **Scheme 12**, treatment of *aza*-tricycle (**46**) with NCS (*N*-chloro-succinimide) in *t*-BuOH and H_2O (1 : 1)

led to chlorohydrin (**51**), although the yield was only 27%. The relative *anti* stereochemistry of **51**, and more critically, the regiochemistry (C4-OH and C5-Cl) were unambiguously confirmed via X-Ray structural analysis. While the chlorohydrin formation seemed to be a trivial reaction, the starting material appeared to decompose readily under these conditions, and if an insufficient amount of H_2O was added, the addition of succinimide to C4 was observed. Efforts were exerted to optimize the chlorohydrin formation but only led to a best yield of 30%.

With chlorohydrin (**51**) in hand, we were able to remove the C5-Cl group under radical conditions using AIBN and *n*-Bu_3SnH in refluxing toluene to give alcohol (**52**). Subsequent Ley's TPAP and NMO oxidation[32] of **52** afforded ketone (**53**) with the desired C4-oxo group, thereby establishing a possible route to (-)-cylindricine C. Determinations of the relative stereochemistry in both **52** and **53** relied on NOE experiments as well as the coupling constants of the key proton H6. These assignments collectively suggest that there was no epimerization at C5 during the radical dehalogenation. In addition, another possibility involved first oxidizing chlorohydrin (**51**) to chloro ketone (**54**), and unlike the reaction involving acetoxy ketone (**50**), we were able to reductively remove the C5-Cl group in **54** employing Zn and HOAc to give ketone (**53**) in high yield, thereby implying that there was again no epimerization at C5.

Scheme 13. Halohydrin Formation of *Oxa*-Tricycle (**56**)



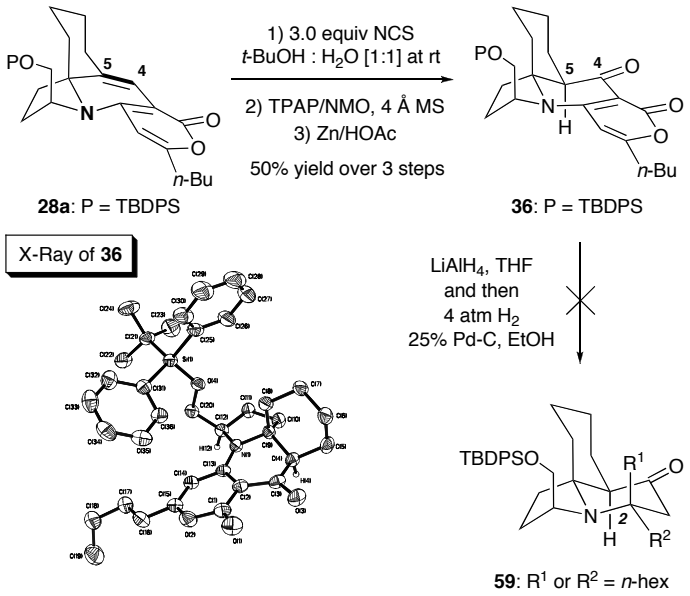
We also pursued halohydrin formation of the *oxa*-[3 + 3] annulation product (**55**) (**Scheme 13**) and found that not only the yield was better in leading to chlorohydrin (**56a**), but we were also able to prepare bromohydrin (**56b**) employing NBS (*N*-bromosuccinimide). In contrast, it was a complete disaster when treating *aza*-tricycle (**46**) with NBS, although **56b** is really a di-brominated product. Reductive removal of the C5-Cl in **56a** and C5-Br (and the bromo group on the 2-pyridone ring) in **56b**[37] afforded the crystalline alcohol (**58**) in good yields. The single-crystal X-Ray structure of **58** revealed that the C5-6 ring junction is not *cis* as in **51** and **52** but *trans*. Based on the intuitive notion that halohydrin formation leads to *anti* relative stereochemistry, this stereochemical outcome implies that there was no

epimerization during the radical dehalogenation, and more intriguingly, that halonium formation of C4-5 olefin of **55** had occurred at the face *anti* to the proton H6 unlike that of **46** shown in **Scheme 12**. We are not certain at this point the origin of these contrasts.

3. Completion of the Total Syntheses.

With this halohydrin protocol in hand, we were poised to complete our total synthesis. As shown in **Scheme 14**, while the bromohydrin formation with NBS was again unsuccessful, leading a mixture dibromo compounds, we were able to isolate the desired chlorohydrin (not shown) as a single diastereomer in much better yield than we had anticipated (76% yield). After TPAP-NMO-oxidation[32] followed by a reductive removal of the tertiary C5-Cl group using Zn and HOAc, the desired ketone (**36**) was isolated in 50% yield overall as a single diastereomer. A single-crystal X-Ray structure of **36** removed any doubts in its stereochemical assignments.

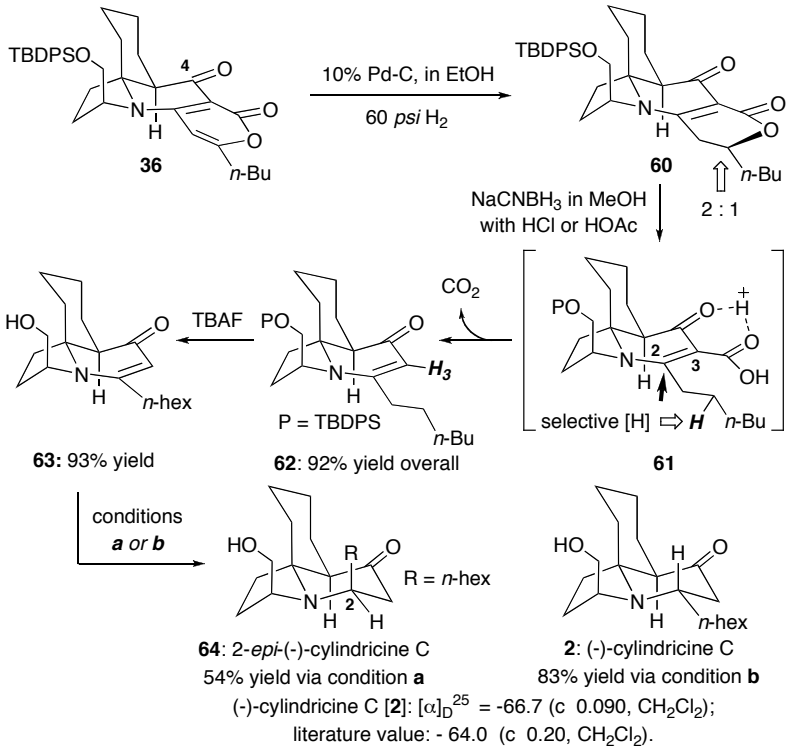
Scheme 14. Application of the Chlorohydrin Formation



We were then very disappointed to find out that the reductive ring-opening of the 2-pyrone in **36** was completely unsuccessful and again forced to explore other options. Without belaboring with details, we ultimately found a much more reliable stepwise sequence as shown in **Scheme 15**. Hydrogenation of **36** with 60 *psi* H_2 gave dihydropyrone (**60**) as a 2 : 1 isomeric mixture. An ensuing $NaCNBH_3$ reduction was carried out in the presence of HCl (or HOAc) to give dihydro-4-pyridone (**62**) in 92% overall yield, and a subsequent desilylation gave alcohol (**63**) in 93% yield. The deprotection was carried out earlier than anticipated because we could not do anything with **62** in completing the total synthesis.

A decarboxylation had likely occurred through intermediate (**61**) after a selective reduction (see the hollow arrow) of the lactone in **60** in a simple S_N2 manner. There was a slight confusion initially as to if the decarboxylation had indeed occurred. Attempted thermal "decarboxylation" of **62** led to no change in the proton NMR. For reasons unknown, the proton H3 evidently was broadened in $CDCl_3$, and thus, appeared to be missing but it showed up at 5.50 ppm in toluene-d_8. Over reduction did occur at C2 (solid arrow in **61**) when the reaction time was prolonged.

Scheme 15. Completion of a Total Synthesis of (-)-Cylindricine C



To complete our total synthesis, a Stork-Crabtree directed hydrogenation[38,39] of dihydro-4-pyridone (**63**) (condition ***a*** in **Scheme 15**) led to (-)-2-*epi*-cylindricine C (**64**)[40] in 54% yield along with recovered **63** in 35% yield. On the other hand, inspired by Ciufolini's work,[13b] a remote hydroxyl-directed reduction using $Na(OAc)BH_3$[13b] gave (-)-cylindricine (**2**) in 83% yield (condition ***b***). While (-)-2-*epi*-cylindricine C (**64**) spectroscopically matched those reported by Weinreb[6b] and Ciufolini,[13b] (-)-cylindricine (**2**) matched Molander's report.[13a]

CONCLUSION

We have described here our detailed efforts in achieving an enantioselective total synthesis of (-)-cylindricine C along with the syntheses of putative lepadiformine, *epi*-lepadiformines, (-)-4-deoxo-cylindricine C, and (-)-2-*epi*-cylindricine C. Our work features applications of a stereoselective intramolecular *aza*-[3 + 3] annulation strategy with an overall yield of 4.5% in 22 steps from *L*-serine specifically for the synthesis of (-)-cylindricine C, and we also developed an interesting halohydrin formation for the construction of the C4-carbonyl group.

EXPERIMENTAL

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separation were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VI-400, and VI-500 spectrometers using $CDCl_3$ (except where noted) with

TMS or residual $CHCl_3$ in the solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Midac M2000 FTIR, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain. Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or an IonSpec HiRes-MALDI FT-Mass Spectrometer. High-resolution mass spectral analyses were performed at University of Wisconsin and University of Minnesota Mass Spectrometry Laboratories. X-Ray analyses were performed at the X-Ray facility in University of Minnesota.

Chiral Amine (21). To a solution of vinyl oxazoline (**18**) (6.81 g, 30.0 mmol) in anhyd THF (60 mL) was added 9-BBN (0.5 *M* in THF: 72.0 mL, 36.0 mmol, 1.2 equiv) carefully dropwise at 0 ˚C. After the reaction mixture was allowed to warm up to rt and stirred for an additional 2 h, to the resulting terminal borane solution were added 3 *M* aq K_3PO_4 (20.0 mL, 60.0 mmol, 2.0 equiv), a solution of vinyl triflate (**20**) in THF (10.9 g dissolved in 35 mL THF, 36.1 mmol, 1.2 equiv), and $PdCl_2$(dppf)-CH_2Cl_2 (1.22 g, 1.50 mmol, 0.05 equiv) sequentially. The resulting red reaction mixture was refluxed for 12 h at which time the TLC analysis indicated the disappearance of the starting material. The reaction mixture was diluted by ether and washed with sat aq $NaHCO_3$ and sat aq NaCl. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude residue. The palladium catalyst was removed via a quick filtration through a short silica gel column and the resulting Suzuki-Miyaura coupled product was carried over to the next step.

To a solution of the above Suzuki-Miyaura coupled product in MeOH (80 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (3.76 g, 15.0 mmol, 0.5 equiv) at rt and the reaction was refluxed for 10 h. The solvent was removed under reduced pressure, and the crude oil was dissolved in the ether and washed with sat aq $NaHCO_3$ and sat aq NaCl. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude residue that was purified by silica gel flash column chromatography (gradient eluent: 10% – 60% EtOAc in hexanes) to provide the Boc-protected amino alcohol as colorless oil (7.67 g, 22.5 mmol) in 75% yield over two steps. R_f = 0.32 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 43.0 (*c* 0.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.45 (s, 9H), 1.56 - 1.63 (m, 5H), 1.66 (ddd, 1H, *J* = 9.5, 7.0, 7.0 Hz), 2.09 - 2.33 (m, 5H), 2.48 (ddd, 1H, *J* = 9.5, 9.5, 9.5 Hz), 3.15 (brs, 1H), 3.55 - 3.66 (m, 2H), 3.71 - 3.78 (m, 1H), 4.17 (q, 2H, *J* = 7.0 Hz), 5.10 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.2, 22.3, 26.2, 28.4, 30.1, 31.9, 32.0, 52.6, 60.1, 64.9, 79.2, 124.3, 150.8, 156.4, 168.6; IR (neat) cm^{-1} 3400brs, 2977s, 2932s, 2865s, 1701s, 1675s, 1513s, 1391s, 1367s, 1232s, 1170s, 1082s, 1043s; mass spectrum (FAB): m/e (% relative intensity) 342 (21) M^++H, 286 (11), 242 (100), 222 (31); m/e calcd for $C_{18}H_{31}NO_5$+H 342.2280, found 342.2279.

To a solution of the above Boc-protected amino alcohol (9.50 g, 27.8 mmol) in anhydrous CH_2Cl_2 (90 mL) were added imidazole (3.78 g, 55.6 mmol, 2.0 equiv) and TBDPSCl (10.8 mL, 41.7 mmol, 1.5 equiv) sequentially at 0 ˚C. The resulting mixture was allowed to warm up to rt and stirred for an

additional 2 h. After complete conversion of the starting material to the silyl ether as indicated by TLC analysis, the reaction mixture was diluted with ether and washed with sat aq NaCl. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude residue that was subjected to the DIBAL-H reduction without further purification.

To a solution of the above silyl ether in anhyd CH_2Cl_2 (150 mL) was added DIBAL-H (1.0 *M* in hexanes, 111.2 mL, 111.2 mmol, 4.0 equiv) dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 1 h before being warmed up to 0 ºC and stirred for an additional 1 h. When TLC analysis indicated complete conversion of the ester to the corresponding alcohol, 1 *M* aq HCl was added slowly and carefully to quench the reaction. The resulting mixture was diluted with ether and washed with sat aq NaCl. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude residue that was purified by silica gel flash column chromatography (gradient eluent: 0% – 30% EtOAc in hexanes) to afford the pure allylic alcohol (**19**) as colorless oil (12.0 g, 22.4 mmol) in 81% yield over two steps. **19**: R_f = 0.61 [30% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 14.2 (*c* 0.64, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.45 (s, 9H), 1.48 - 2.30 (m, 12H), 3.55 - 3.66 (m, 3H), 3.91 (d, 1H, *J* = 13.0 Hz), 4.13 (d, 1H, *J* = 13.0 Hz), 4.65 (d, 1H, *J* = 7.5 Hz), 7.37 - 7.45 (m, 6H), 7.63 - 7.66 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 23.0, 23.1, 26.9, 27.6, 28.5, 29.1, 29.4, 30.3, 51.5, 62.2, 66.3, 79.4, 127.8, 129.8, 131.8, 132.7, 133.4, 135.6, 156.2; IR (neat) cm^{-1} 3400brs, 2930m, 2858m, 1688s, 1365m, 1171m, 1113s; mass spectrum (FAB): m/e (% relative intensity) 538 (7) M^++H, 438 (17), 436 (19), 421 (34), 420 (100), 342 (13), 199 (23), 197 (18), 137 (23), 135 (54), 119 (55); m/e calcd for $C_{32}H_{47}NO_4Si$+H 538.3353, found 538.3352.

To a solution of allylic alcohol (**19**) (6.00 g, 11.2 mmol) in pyridine (20 mL) was added acetic anhydride (5.3 mL, 56.0 mmol, 5.0 equiv) dropwise at 0 ˚C. The reaction mixture was allowed to warm up to rt and stirred overnight. The mixture was diluted with ether and washed with sat aq $NaHCO_3$ and sat aq NaCl. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude residue that was subjected to the next step without further purification.

To a solution of the above acetate in CH_2Cl_2 (10 mL) was added TFA (10.0 mL, 130.0 mmol, 11.6 equiv) dropwise at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 1 h before it was neutralized with sat aq $NaHCO_3$ being added slowly and carefully, and the resulting mixture was extracted with CH_2Cl_2 (5 x equal volume). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude residue, which was used for the next step without further purification. The free amine (**21**) was obtained as light yellow oil in quantitative yield. A sample for characterization was obtained by silica gel flash column chromatography (gradient eluent: 10% – 100% EtOAc in hexanes). **21**: R_f = 0.15 [100% EtOAc]; $[\alpha]_D^{20}$ = 2.10 (*c* 6.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.51 - 1.61 (m, 6H), 1.88 - 2.01 (m, 8H), 2.30 - 2.36 (m, 1H), 3.12 - 3.18 (m, 1H), 3.67 (dd, 1H, *J* = 11.0 , 8.0 Hz), 3.71 (dd, 1H, *J* = 11.0 , 4.0 Hz), 4.41 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 7.37 (s, 1H), 7.38 - 7.47 (m, 6H), 7.64 - 7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 20.9, 22.6, 22.7, 26.8, 27.7, 29.1, 29.2, 29.4, 53.6, 64.7, 64.9, 126.5, 127.9, 128.4, 130.1, 132.6, 132.7, 135.5, 135.6, 136.1, 171.9; IR (neat) cm^{-1}

2932brs, 1735s, 1696s, 1428s, 1237s, 1114s; mass spectrum (FAB): m/e (% relative intensity) 480 (100) M^++H, 420 (15), 197 (18), 135 (45), 91 (22), 79 (16); m/e calcd for $C_{29}H_{41}NO_3Si$+H 480.2934, found 480.2933.

Vinylogous Amide (22). To a solution of the free amine (**21**) (1.34 g, 2.80 mmol) in MeOH (15 mL) was added but-3-yn-2-one (0.34 mL, 4.38 mmol, 1.5 equiv) dropwise at 0 ºC. The reaction mixture was stirred overnight, and after which, the TLC analysis indicated complete conversion of the starting material to the product. The solvent was removed under reduced pressure and the resulting crude product was purified by silica gel flash chromatography (gradient eluent: 0% – 30% EtOAc in hexanes) to afford the pure vinylogous amide (**22**) as light yellow oil (770.0 mg, 1.41 mmol) in 50% yield from **19**. **22**: R_f = 0.68 [30% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 5.10 (*c* 4.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.46 - 1.55 (m, 1H), 1.55 - 1.61 (m, 4H), 1.66 (dddd, 1H, *J* = 14.0, 10.0, 7.0, 4.0 Hz), 1.94 - 2.10 (m, 5H), 2.03 (s, 3H), 2.07 (s, 3H), 2.12 - 2.19 (m, 1H), 3.03 - 3.11 (m, 1H), 3.51 (dd, 1H, *J* = 10.0, 7.0 Hz), 3.60 (dd, 1H, *J* = 10.0, 5.0 Hz), 4.50 (ABq, 2H, *J* = 12.0 Hz), 4.99 (d, 1H, *J* = 7.5 Hz), 6.66 (dd, 1H, *J* = 13.0, 7.5Hz), 7.36 - 7.45 (m, 6H), 7.60 - 7.65 (m, 4H), 9.76 (dd, 1H, *J* = 13.0, 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 20.8, 22.6, 26.7, 26.8, 27.7, 28.8, 29.4, 29.5, 30.2, 60.7, 64.1, 67.0, 93.7, 126.5, 127.7, 129.7, 132.8, 132.9, 135.5, 136.1, 151.9, 170.6, 196.7; IR (neat) cm^{-1} 3071m, 3048m, 3013m, 2930s, 2857s, 1736s, 1640s, 1575s, 1473s, 1428s, 1380s, 1234s, 1112s, 1021s, 962s, 740s, 703s, 614s; mass spectrum (FAB): m/e (% relative intensity) 548 (98) M^++H, 488 (80), 278 (18), 246 (11), 218 (16), 197 (57), 135 (100); m/e calcd for $C_{33}H_{45}NO_4Si$+H 548.3196, found 548.3194.

Bromo-Pyrone (23). The commercial 4-hydroxy-6-methyl-2-pyrone (6.30 g, 50.0 mmol) was dissolved in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (100 mL) at rt, and the resulting solution was heated up to 90 ˚C for 1 h. The solvent was then removed under reduced pressure and the residue was dissolved in the anhyd THF (120 mL). To this THF solution was added *n*-BuLi (2.5 *M* in hexanes, 50.0 mL, 125.0 mmol, 2.5 equiv) dropwise at -78 ˚C. After the resulting mixture was stirred for 1 h at -78 ˚C, 1-iodopropane (14.7 mL, 150.0 mmol, 3.0 equiv) was added dropwise at -78 ˚C. The reaction mixture was allowed to warm up to rt and stirred overnight. Subsequently, 6 *N* aq HCl was added to quench the reaction and the solvent was removed under reduced pressure. The residue was dissolved in sat aq NaCl and extracted with EtOAc (3 x equal volume). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude residue that was purified by silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) to afford 4-hydroxy-6-butyl-2-pyrone as orange solid.
To a solution of 4-hydroxy-6-butyl-2-pyrone prepared above in DMF (100 mL) was added PBr_3 (19.0 mL, 200.0 mmol, 4.0 equiv) dropwise at 0 ˚C and the resulting mixture was heated up to 90 ˚C overnight. The reaction mixture was dumped to sat aq NaCl and extracted with EtOAc (5 x equal volume). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was purified by silica gel flash column chromatography (gradient eluent: 0% – 20% EtOAc in hexanes) to provide 4-bromo-6-butyl-2-pyrone (**23**) as light yellow oil (2.89 g, 12.5 mmol) in

25% yield over 2 steps. **23**: R_f = 0.76 [10% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.5 Hz), 1.31 (sextet, 2H, *J* = 7.5 Hz), 1.58 (quintet, 2H, *J* = 7.5 Hz), 2.42 (t, 2H, *J* = 7.5 Hz), 6.13 (dd, 1H, *J* = 1.5, 0.9 Hz), 6.38 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 21.9, 28.5, 33.1, 107.5, 114.6, 141.0, 160.5, 165.7; IR (neat) cm^{-1} 2958m, 2931m, 1740s, 1618s, 1545s, 1198m, 835m, 816m; mass spectrum (FAB): m/e (% relative intensity) 233 (32) M^++H, 231 (32), 170 (100), 153 (50); m/e calcd for $C_9H_{11}BrO_2$+H 231.0021, found 231.0012.

Amino-Pyrone (24). To a solution of the free amine (**21**) (1.00 g, 2.09 mmol) in EtOH (8 mL) were added 4-bromo-6-butyl-2-pyrone (**23**) (966.0 mg, 4.18 mmol, 2.0 equiv) and pyridine (0.34 mL, 4.18 mmol, 2.0 equiv) sequentially at rt. The resulting mixture was refluxed for 48 h. TLC indicated complete consumption of the starting material and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (gradient eluent: 0% – 70% EtOAc in hexanes) to afford the pure 4-amino-2-pyrone (**24**) as yellow oil (802.0 mg, 1.27 mmol) in 61% yield from **19**. **24**: R_f = 0.39 [66% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 6.56 (*c* 3.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.06 (s, 9H), 1.36 (sextet, 2H, *J* = 7.5 Hz), 1.48 (dddd, 1H, *J* = 18.5, 10.5, 8.0, 4.5 Hz), 1.55 - 1.64 (m, 6H), 1.82 - 1.89 (m, 1H), 1.92 - 2.02 (m, 4H), 2.02 (s, 3H), 2.04 - 2.12 (m, 1H), 2.24 (ddd, 1H, *J* = 13.0, 11.0, 5.0 Hz), 2.37 (t, 2H, *J* = 7.5 Hz), 3.31 - 3.37 (m, 1H), 3.60 (dd, 1H, *J* = 10.5, 4.0 Hz), 3.69 (dd, 1H, *J* = 10.5, 4.5 Hz), 4.28 (d, 1H, *J* = 12.0 Hz), 4.79 (d, 1H, *J* = 12.0 Hz), 4.86 (s, 1H), 4.88 (brs, 1H), 5.41 (s, 1H), 7.35 - 7.46 (m, 6H), 7.59 - 7.63 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 19.1, 20.9, 22.0, 22.5, 22.6, 26.7, 27.6, 28.6, 29.3, 29.5, 30.1, 33.3, 53.4, 64.1, 80.1, 98.7, 126.2, 127.6, 127.7, 129.7, 129.8, 132.7, 132.8, 135.3, 136.4, 157.5, 164.0, 165.2, 171.0; IR (neat) cm^{-1} 3255s, 3094m, 3089m, 2956s, 2931s, 2857s, 1736s, 1673s, 1548s, 1462s, 1235s, 1112s, 824m, 796m, 740m, 702s; mass spectrum (FAB): m/e (% relative intensity) 630 (60) M^++H, 570 (76), 197 (39), 135 (100), 93 (32); m/e calcd for $C_{38}H_{51}NO_5Si$+H 630.3615, found 630.3617.

***Aza*-Tricycle (26).** To a solution of vinylogous amide (**22**) (136.7 mg, 0.25 mmol) in MeOH (5 mL) and H_2O (2 mL) was added K_2CO_3 powder (173.5 mg, 1.25 mmol, 5.0 equiv) at 0 ºC. After stirred for 1 h at rt the reaction mixture was dumped to sat aq NaCl and extracted 3 times with equal volume of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4fand concentrated under reduced pressure to afford the crude allylic alcohol that was subjected to the next step without further purification.

To a solution of the above free allylic alcohol in anhydrous CH_2Cl_2 (2 mL) were added 4Å molecular sieves (100 mg), NMO (41.8 mg, 0.36 mmol, 1.4 equiv), and TPAP (4.5 mg, 0.0125 mmol, 0.05 equiv) sequentially at room temperature. The resulting dark-colored mixture was stirred for 1 h and TLC analysis indicated the disappearance of the starting material. The mixture was filtered through a pad of silica gel by 50% EtOAc in hexanes to remove the molecular sieves and the metal catalyst. Removing the solvent under reduced pressure afforded the crude enal (**25**), which was carried over to the intramolecular *aza*-[3 + 3] annulation without further purification.

To a solution of the enal (**25**) in anhyd EtOAc (4 mL) in the 25 mL sealed tube were added anhydrous Na_2SO_4 (500.0 mg, 3.52 mmol, 14.0 equiv) and piperidinium acetate (18.1 mg, 0.125 mmol, 0.5 equiv) sequentially at rt. The resulting mixture was heated up to 150 ºC (oil bath temperature) for 12 h and the TLC analysis indicated the disappearance of the starting material. The reaction mixture was filtered through a pad of Celite™ to remove Na_2SO_4 and the filtrate was concentrated under reduced pressure to remove the solvent. The crude *aza*-[3 + 3] annulation product was subjected to the following hydrogenation reaction without further purification.

To a solution of the crude *aza*-[3 + 3] annulation product in EtOAc (2 mL) was added 10% palladium on activated carbon (26.0 mg, 0.025 mmol, 0.1 equiv) at rt. The flask was filled up with 1 atm H_2 and the resulting mixture was stirred for 4 h. The reaction mixture was filtered through a pad of Celite™ to remove the palladium catalyst and concentrated in *vacuo* to provide the crude product which was purified by silica gel flash chromatography (gradient eluent: 0% – 60% EtOAc in hexanes) to afford the pure tricyclic product (**26**) as light yellow oil (50.0 mg, 0.102 mmol) in 41% yield over four steps from **22**. **26**: R_f = 0.35 [60% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 121.2 (*c* 1.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.26 - 1.76 (m, 11H), 2.00 (dddd, 1H, *J* = 12.5, 8.0, 8.0, 1.0 Hz), 2.07 (s, 3H), 2.29 (dd, 1H, *J* = 12.5, 7.5 Hz), 2.36 (dd, 1H, *J* = 16.5, 12.0 Hz), 2.43 (dd, 1H, *J* = 16.5, 5.0 Hz), 3.58 (dd, 1H, *J* = 11.5, 8.0 Hz), 3.74 (dd, 1H, *J* = 11.5, 3.5 Hz), 3.72 - 3.78 (m, 1H), 7.37 - 7.47 (m, 6H), 7.62 (s, 1H), 7.64 - 7.67 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 19.6, 22.0, 23.5, 23.8, 24.8, 26.7, 27.7, 30.3, 34.3, 37.5, 63.0, 64.2, 68.2, 127.8, 127.9, 129.9, 132.8, 132.9, 135.6, 145.5, 192.9; IR (neat) cm^{-1} 3055w, 2930s, 2858s, 1584s, 1428m, 1389s, 1113s, 702s; mass spectrum (FAB): m/e (% relative intensity) 488 (100) M^++H, 307 (23), 219 (14), 218 (65), 154 (94), 107 (20), 77 (22); m/e calcd for $C_{31}H_{41}NO_2Si$+H 488.2985, found 488.2976.

***Para*-Nitrobenzoate Ester (29).** To a solution of the above tricyclic compound (**26**) (50.0 mg, 0.102 mmol) in THF (2 mL) was added TBAF (1.0 *M* in THF, 0.20 mL, 0.20 mmol, 2.0 equiv) slowly at 0 ºC. The resulting mixture was allowed to warm up to rt and stirred for an additional 2 h. TLC analysis indicated complete conversion of the silyl ether to the free primary alcohol. The reaction mixture was poured into the sat aq NaCl and extracted 3 times with equal volume of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afforded the crude alcohol, which was purified via a quick filtration through a small silica gel column to remove the fluoro-silicon byproduct from the deprotection.

To a solution of the above free primary alcohol in CH_2Cl_2 (2 mL) were added *p*-nitrobenzoyl chloride (28.4 mg, 0.153 mmol, 1.5 equiv), the pyridine (1 drop), and DMAP (2.5 mg, 0.0204 mmol, 0.2 equiv) sequentially at 0 ºC. The resulting mixture was allowed to warm up to rt and stirred overnight. TLC analysis indicated complete consumption of the free primary alcohol and the reaction mixture was poured into to sat aq NaCl and extracted 3 times with equal volume of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude benzoate, which was

purified by silica gel flash chromatography (gradient eluent: 0% – 40% EtOAc in hexanes) to afford the pure para-nitrobenzoate (**29**) as orange waxy solid (30.0 mg, 0.075 mmol) in 74% yield over two steps. **29**: R_f = 0.41 [80% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 94.8 (*c* 1.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 - 1.78 (m, 10H), 1.86 (dddd, 1H, *J* = 12.5, 12.5, 9.0, 7.5 Hz), 2.10 (s, 3H), 2.21 (dddd, 1H, *J* = 15.5, 8.0, 8.0, 1.5 Hz), 2.31 - 2.43 (m, 3H), 3.97 (dddd, 1H, *J* = 9.0, 7.0, 7.0, 4.5 Hz), 4.35 (dd, 1H, *J* = 11.5, 7.0, Hz), 4.58 (dd, 1H, *J* = 11.5, 4.5 Hz), 7.53 (s, 1H), 8.22 (d, 2H, *J* = 6.5 Hz), 8.32 (d, 2H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 22.1, 23.9, 25.6, 27.6, 29.6, 30.7, 34.4, 37.5, 60.0, 64.3, 68.3, 109.1, 123.6, 130.6, 134.7, 143.6, 150.6, 164.1, 193.2; IR (neat) cm^{-1} 2926s, 2857s, 1727s, 1584s, 1528s, 1345s, 1269s, 1180m, 1102s, 1015m, 753m, 720s; mass spectrum (FAB): m/e (% relative intensity) 399 (1) M^++H, 307 (34), 289 (15), 154 (100), 136 (64), 107 (16), 65 (8); m/e calcd for $C_{22}H_{26}N_2O_5$+H 399.1920, found 399.1915.

‡Crystallographic data for **29**: [C_{22} H_{26} N_2 O_5], *M* = 398.45, monoclinic, $P2_1/n$, *a* = 13.722(4) Å, α = 90°, *b* = 8.222(3) Å, β = 102.732(6)°, *c* = 17.994(6) Å, γ = 90°, V = 1980(1) Å^3, *T* =173(2) K, *Z* = 4, μ = 0.095 mm^{-1}, 3498 [*R*(int) = 0.0262], Final *R* indices [$I>2\sigma(I)$] , *R*1 = 0.0559, *wR*2 = 0.1634, *R* indices (all data), *R*1 = 0.0638, *wR*2 = 0.1716.

Enal (27). To a solution of the 4-amino-2-pyrone (**24**) (636.0 mg, 1.01 mmol) in MeOH (10 mL) and H_2O (2 mL) was added K_2CO_3 powder (487.0 mg, 3.53 mmol, 3.5 equiv) at 0 °C. After stirred for 1 h at rt, the reaction mixture was poured into sat aq NaCl and extracted with CH_2Cl_2 (3 x equal volume). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude allylic alcohol that was subjected to the next step without further purification.

To a solution of the above free allylic alcohol in anhyd CH_2Cl_2 (8 mL) were added 4Å molecular sieves (500 mg), NMO (186.0 mg, 1.59 mmol, 1.6 equiv), and TPAP (18.5 mg, 0.052 mmol, 0.05 equiv) sequentially at rt. The resulting dark-colored mixture was stirred for 1 h and TLC analysis indicated the disappearance of the starting material. The reaction mixture was filtered through a pad of silica gel eluted with 50% EtOAc in hexanes to remove the molecular sieves and the metal catalyst. Removing of the solvent under reduced pressure afforded the crude product, which was purified by silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) to provide the pure enal (**27**) as yellow oil (504.0 mg, 0.86 mmol) in 85% yield over two steps. **27**: R_f = 0.52 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = -11.1 (*c* 5.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.5 Hz), 1.07 (s, 9H), 1.35 (sextet, 2H, *J* = 7.5 Hz), 1.56 - 1.63 (m, 6H), 1.70 (dddd, 1H, *J* = 5.0, 7.5, 11.0, 14.0 Hz), 1.91 (dddd, 1H, *J* = 14.0, 11.5, 6.0, 6.0 Hz), 2.16 - 2.22 (m, 4H), 2.36 (t, 2H, *J* = 8.0 Hz), 2.46 (ddd, 1H, *J* = 13.0, 13.0, 5.5 Hz), 2.57 (ddd, 1H, *J* = 13.0, 13.0, 5.0 Hz), 3.36 - 3.42 (m, 1H), 3.70 (dd, 1H, *J* = 10.5, 4.0 Hz), 3.74 (dd, 1H, *J* = 10.5, 4.5 Hz), 4.87 (brs, 1H), 4.87 (d, 1H, *J* = 2.0 Hz), 5.34 (s, 1H), 7.36 - 7.47 (m, 6H), 7.58 - 7.62 (m, 4H), 10.00 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 19.1, 21.5, 22.0, 22.3, 26.7, 28.6, 31.2, 31.9, 33.3, 53.6, 64.4, 80.1, 98.8, 127.6, 127.7, 129.8, 129.9, 132.7, 132.8, 133.7, 135.3, 157.7, 158.9, 164.0, 165.3, 190.6; IR (neat) cm^{-1} 3262m, 3096m, 2956m, 2930m, 1671s, 1548s, 1113s, 824m, 796m,

739m, 702s; mass spectrum (FAB): m/e (% relative intensity) 586 (100) M^++H, 307 (17), 197 (12), 154 (65), 77 (17), 57 (13); m/e calcd for $C_{36}H_{47}NO_4Si$+H 586.3353, found 586.3303.

***Aza*-[3 + 3] Annulation Product (28a): The Major Isomer.** To a solution of the above enal (**27**) (504.0 mg, 0.86 mmol) in anhyd EtOAc (8 mL) and toluene (4 mL) in the 50-mL sealed tube were added anhyd Na_2SO_4 (1.00 g, 7.0 mmol, 8.2 equiv) and piperidinium acetate (62.3 mg, 0.43 mmol, 0.5 equiv) sequentially at rt. The resulting mixture was sealed and heated up to 150 ˚C (oil bath temperature) for 12 h and the TLC indicated complete consumption of the starting material. The reaction mixture was filter through a pad of Celite™ to remove Na_2SO_4 and concentrated under reduced pressure to remove the excess solvent. The crude product was purified by silica gel flash column chromatography (gradient eluent: 0% – 30% EtOAc in hexanes) to afford the pure major annulation product (**28a**) as bright yellow oil (296.6 mg, 0.52 mmol) along with the minor annulation product (**28b**) as bright yellow foam (39.1 mg, 0.069 mmol) in 68% combined yield. While the yield is consistently between 60% to 70% range, the diastereomeric ratio over various runs could be as high as 9 : 1. **28a**: R_f = 0.25 [10% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 175.1 (*c* 2.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.5 Hz), 1.07 (s, 9H), 1.28 (sextet, 2H, *J* = 7.5 Hz), 1.42 - 1.62 (m, 6H), 1.65 - 1.72 (m, 2H), 1.78 -1.83 (m, 1H), 1.87 (ddd, 1H, *J* = 11.0, 11.0, 11.0 Hz), 2.01 - 2.09 (m, 2H), 2.17 - 2.26 (m, 3H), 2.48 (dd, 1H, *J* = 13.0, 8.0 Hz), 3.57 (dd, 1H, *J* = 11.0, 7.0 Hz), 3.73 (dd, 1H, *J* = 11.0, 7.0 Hz), 4.00 (dddd, 1H, *J* = 8.0, 7.0, 7.0, 7.0 Hz), 5.82 (s, 1H), 6.12 (s, 1H), 7.38 - 7.48 (m, 6H), 7.65 - 7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 19.2, 22.3, 23.3, 24.5, 26.9, 29.2, 33.6, 34.1, 34.2, 38.9, 62.4, 69.0, 69.3, 92.0, 96.6, 111.2, 127.8, 127.9, 129.9, 130.0, 132.8, 132.9, 134.7, 135.5, 135.6, 152.0, 162.4, 164.0; IR (neat) cm^{-1} 3072w, 3050w, 2962s, 2930s, 2858m, 1695s, 1531s, 1456s, 1262s, 1088s, 799s, 702s; mass spectrum (FAB): m/e (% relative intensity) 568 (76) M^++H, 307 (57), 197 (15), 136 (100), 107 (35), 57 (18); m/e calcd for $C_{36}H_{45}NO_3Si$+H 568.3247, found 568.3233.

The Minor Isomer (**28b**): R_f= 0.30 [10% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 544.3 (*c* 1.31, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 3H, *J* = 7.5 Hz), 1.03 (s, 9H), 1.21 (sextet, 2H, *J* = 7.5 Hz), 1.39 - 1.46 (m, 3H), 1.50 (ddddd, 1H, *J* = 12.5, 12.5, 12.5, 5.0, 5.0 Hz), 1.61 (ddddd, 1H, *J* = 13.5, 13.5, 13.5, 4.0, 4.0 Hz), 1.72 - 1.78 (m, 1H), 1.88 (ddd, 2H, *J* = 13.0, 13.0, 4.0 Hz), 2.06 (ddd, 1H, *J* = 12.5, 12.5, 4.5 Hz), 2.24 - 2.29 (m, 1H), 2.36 (ddd, 1H, *J* = 11.5, 11.5, 7.0 Hz), 3.59 (dd, 1H, *J* = 10.5, 6.5 Hz), 3.68 (dd, 1H, *J* = 10.5, 3.0 Hz), 3.87 (ddd, 1H, *J* = 6.5, 6.5, 3.0 Hz), 5.26 (s, 1H), 6.14 (s, 1H), 7.34 - 7.47 (m, 6H), 7.57 - 7.59 (m, 2H), 7.64 - 7.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 19.2, 22.1, 24.5, 25.5, 26.8, 29.1, 30.7, 31.0, 33.4, 33.9, 37.1, 59.3, 64.0, 69.4, 96.1, 97.6, 111.9, 127.8, 129.8, 129.9, 132.6, 133.3, 135.4, 135.5, 139.7, 150.6, 162.3, 163.7; IR (neat) cm^{-1} 3072w, 3050w, 2958s, 2930s, 2858s, 1688s, 1528s, 1464s, 1113s, 850m, 823m, 741m, 703s; mass spectrum (FAB): m/e (% relative intensity) 568 (100) M^++H, 298 (5), 197 (23), 135 (42), 91 (12), 53 (43); m/e calcd for $C_{36}H_{45}NO_3Si$+H 568.3247, found 568.3244.

‡Crystallographic data for **28b**: [C_{36} H_{45} N O_3 Si], *M* = 567.82, triclinic, P1, *a* = 8.4361(10) Å, α =

87.479(5)°, *b* = 12.9522(13) Å, β = 82.149(4)°, *c* = 15.2727(19) Å, γ = 72.171(5)°, V = 1573.7(3) Å^3, *T* =100(2) K, *Z* = 2, μ = 0.040 mm^{-1}, 7174 [*R*(int) = 0.0653], Final *R* indices [$I>2\sigma(I)$] , *R*1 = 0.0437, *wR*2 = 0.1157, *R* indices (all data), *R*1 = 0.0601, *wR*2 = 0.1229.

Hydrogenated *Aza*-Tetracycle (32). To a solution of the major isomer (**28a**) (253.9 mg, 0.45 mmol) in EtOAc (8 mL) was added 10% Pd on activated carbon (46.8 mg, 0.045 mmol, 0.1 equiv) at rt. The flask was flushed and charged with 1 atm of H_2 and the resulting mixture was stirred for 4 h. The reaction mixture was filtered through a pad of Celite™ to remove the palladium catalyst and concentrated under reduced pressure to provide the crude product, which was purified by silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) to afford the pure *aza*-tetracyclic compound (**32**) (230.2 mg, 0.40 mmol) in 90% yield as colorless oil. **32**: R_f = 0.40 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 60.5 (*c* 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 8.0 Hz), 1.06 (s, 9H), 1.25 - 1.35 (m, 4H), 1.40 - 1.54 (m, 6H), 1.60 - 1.75 (m, 4H), 1.95 - 2.02 (m, 1H), 2.10 - 2.25 (m, 4H), 2.38 (dd, 1H, *J* = 17.0, 5.0 Hz), 2.56 (dd, 1H, *J* = 17.0, 12.5 Hz), 3.54 (dd, 1H, *J* = 10.0, 7.5 Hz), 3.76 (dd, 1H, *J* = 10.0, 6.0 Hz), 3.94 (dddd, 1H, *J* = 7.5, 7.5, 6.0, 6.0 Hz), 5.55 (s, 1H), 7.37 - 7.47 (m, 6H), 7.64 - 7.67 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 19.2, 19.4, 22.2, 22.4, 23.8, 26.4, 26.8, 28.0, 29.2, 31.9, 33.8, 34.5, 36.1, 61.0, 64.7, 67.0, 89.9, 96.3, 127.8, 129.9, 130.0, 132.9, 133.2, 135.5, 135.6, 151.2, 162.5, 164.4; IR (neat) cm^{-1} 2932s, 2858s, 1689s, 1648s, 1544s, 1458s, 1112s, 823m, 802m, 742m, 703s; mass spectrum (FAB): m/e (% relative intensity) 570 (100) M^++H, 512 (8), 300 (66), 197 (17), 135 (35), 91 (8); m/e calcd for $C_{36}H_{47}NO_3Si$+H 570.3404, found 570.3370.

Putative Lepadiformine (33a) and 4-Deoxocylindricine C (33b). To a solution of tetracyclic compound (**32**) (43.1 mg, 0.076 mmol) in anhyd THF (1 mL) was added LAH (1.0 *M* in THF, 0.38 mL, 0.38 mmol, 5.0 equiv) dropwise at -78 ºC. The resulting mixture was stirred at -78 ºC for 1 h then allowed to warm up to 0 ºC and stirred for an additional 3 h. TLC analysis indicated complete consumption of the starting material and the reaction mixture was quenched by absolute EtOH (3 mL) slowly and then was carefully transferred to a vial for the following hydrogenation. To the reaction mixture in the vial was added palladium on activated carbon (20.0 mg, 0.019 mmol, 0.25 equiv). The reaction vessel was charged with 60 *psi* H_2 and stirred at rt for 24 h. The resulting mixture was filtered through a pad of Celite™ to remove the palladium catalyst and inorganic salt and concentrated under reduced pressure to afford the crude product that was purified by silica gel flash chromatography (gradient eluent: 0% - 10% EtOAc in hexanes) to provide a 10 : 1 mixture (28.3 mg, 0.053 mmol) in 70% yield.

To a solution of the above mixture (10.2 mg, 0.019 mmol) in THF (0.5 mL) was added TBAF (1.0 *M* in THF, 0.040 mL, 0.040 mmol, 2.0 equiv) at 0 ºC. The resulting mixture was allowed to warm up to rt and stirred for an additional 2 h. The reaction mixture was dumped to saturated NaCl and extracted 5 times with equal volume of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure afforded the crude product which was purified by silica gel flash column chromatography (gradient eluent: 0:3:100 - 5:10:90 NEt_3 : EtOAc : Hexanes) to provide an inseparable

10:1 mixture as light yellow oil (4.1 mg, 0.014 mmol) in 74% yield. The mixture was further purified by HPLC (3:10:90 NEt_3: EtOAc: hexanes) to afford the pure major isomer (**33a**) and the minor isomer (**33b**).

The major isomer (**33a**): R_f = 0.30 [10:10:90 NEt_3:MeOH:EtOAc]; $[\alpha]_D^{20}$ = -10.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.5 Hz), 1.20 - 1.72 (m, 22H), 1.80 (dddd, 1H, *J* = 13.0, 13.0, 5.5, 4.0 Hz), 1.88 - 2.02 (m, 2H), 2.05 - 2.12 (m, 2H), 2.64 (ddd, 1H, *J* = 6.5, 6.5, 6.5 Hz), 3.13 (ddd, 1H, *J* = 10.0, 3.5, 3.5 Hz), 3.22 (brs, 1H), 3.26 (d, 1H, *J* = 10.0 Hz), 3.48 (dd, 1H, *J* = 10.0, 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.0, 21.8, 22.7, 25.1, 26.1, 28.1, 29.5, 30.3, 31.9, 35.8, 37.1, 54.2, 63.2, 63.5, 64.2; IR (neat) cm^{-1} 3440brs, 2922s, 2854s, 1457m, 1260m, 1097s, 1022s; mass spectrum (FAB): m/e (% relative intensity) 294 (94) M^++H, 276 (60), 262 (100), 154 (17), 136 (20), 91 (25), 69 (62), 55 (66); m/e calcd for $C_{19}H_{35}NO$+H 294.2797, found 294.2808. **The minor isomer** (**33b**): R_f= 0.30 [10:10:90 NEt_3: MeOH: EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.5 Hz), 1.30 - 2.20 (m, 27H), 2.84 - 2.90 (m, 1H), 3.30 (d, 1H, *J* = 10.0 Hz), 3.35 (d, 1H, *J* = 10.5 Hz), 3.41 (dd, 1H, *J* = 3.5, 10.0 Hz); mass spectrum (APCI): m/e (% relative intensity) 293 (5) M^++H, 101 (37). Note: There was not enough material to fully characterize (**33b**).

COMPARISON TABLES FOR PUTATIVE LEPADIFORMINE:

^{13}C NMR

δ, ppm (Weinreb)	δ, ppm (observed)	Δ δ
14.1	14.1	0.0
21.0	21.0	0.0
21.7	21.8	0.1
22.7	22.7	0.0
25.1	25.1	0.0
26.1	26.1	0.0
28.1	28.1	0.0
29.5	29.5	0.0
30.2	30.3	0.1
31.9	31.9	0.0
35.8	35.8	0.0
37.1	37.1	0.0
54.2	54.2	0.0
63.1	63.2	0.1
63.5	63.5	0.0
64.1	64.2	0.1

^{1}H NMR

δ, ppm (Weinreb)	δ, ppm (observed)	Δ δ
0.88 (3H)	0.88 (3H)	0.0
1.17 – 2.12 (27H)	1.20 – 1.72 (22H)	
	1.80 (1H)	
	1.88 – 2.02 (2H)	
	2.05 – 2.12 (2H)	
2.65 (1H)	2.64 (1H)	0.1
3.13 (1H)	3.13 (1H)	0.0
	3.22 (1H, OH)	
3.27 (1H)	3.26 (1H)	0.1
3.48 (1H)	3.48 (1H)	0.0

Hydrogenated *Aza*-Tetracycle (34). To a solution of the minor isomer (**28b**) (60.0 mg, 0.11 mmol) in MeOH (2 mL) was added 10% Pd on activated carbon (5.5 mg, 0.053 mmol) at rt. The flask was filled up

with 1 atm of H_2 and the resulting mixture was stirred for 24 h. The reaction mixture was filtered through a pad of Celite™ to remove the palladium catalyst and concentrated under reduced pressure to provide the compound (**34**) in 91% yield (54.7 mg, 0.096 mmol) as colorless oil. **34**: R_f = 0.48 [20% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 21.4 (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.5 Hz), 1.04 (s, 9H), 1.20 - 1.27 (m, 3H), 1.37 - 1.51 (m, 6H), 1.57 - 1.68 (m, 6H), 2.13 (ddd, 1H, *J* = 20.0, 12.5, 6.5 Hz), 2.18 (dd, 2H, *J* = 14.0, 7.5 Hz), 2.29 (dd, 1H, *J* = 12.5, 6.0 Hz), 2.33 (dd, 1H, *J* = 17.5, 6.5 Hz), 2.57 (dd, 1H, *J* = 17.5, 12.0 Hz), 3.41 (dd, 1H, *J* = 10.5, 7.5 Hz), 3.63 (dd, 1H, *J* = 10.5, 3.5 Hz), 3.96 (ddd, 1H, *J* = 17.5, 7.5, 3.5 Hz), 5.37 (s, 1H), 7.35 - 7.47 (m, 6H), 7.60 (dd, 2H, *J* = 8.0, 1.5 Hz), 7.65 (dd, 2H, *J* = 8.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 18.8, 19.3, 22.2, 22.5, 24.0, 25.4, 26.9, 27.4, 28.3, 29.3, 32.6, 33.8, 37.1, 59.0, 64.1, 91.2, 96.9, 127.90, 127.92, 130.0, 130.1, 132.9, 133.4, 135.5, 135.6, 150.5, 162.5, 164.6 (one carbon missing due to overlap); IR (neat) cm^{-1} 3008w, 2985s, 2898s, 1692s, 1650s, 1190s; mass spectrum (APCI): m/e (% relative intensity) 570 (100) M^++H, 532 (40), 478 (80), 293 (35); m/e calcd for $C_{36}H_{47}NO_3Si$+H 570.3404, found 570.3407.

***Epi*-Lepadiformine (35a) and (35b).** To a solution of tetracyclic compound (**34**) (58.0 mg, 0.101 mmol) in anhydrous THF (2 mL) was added LAH (1.0 *M* in THF, 0.51 mL, 0.51 mmol, 5.0 equiv) dropwise at -78 ºC. The resulting mixture was warmed up to rt and stirred for an additional 12 h before it was quenched with absolute EtOH (10 mL). To the reaction mixture in the vial was added palladium on activated carbon (20.0 mg, 0.019 mmol), and the reaction vessel was charged with 60 *psi* H_2 and stirred rt for 24 h. The resulting mixture was filtered through a pad of Celite™ to remove the palladium catalyst and the inorganic salt, and the filtrate was concentrated under reduced pressure to afford the crude product, which was purified by a quick silica gel flash column chromatography (gradient eluent: 0% – 20% EtOAc in hexanes) to 12.0 mg of recovered starting material and 1 : 1 mixture of TBDPS protected *epi*-lepadiformines (11.1 mg, 0.021 mmol) in 21% yield (or 28 % BRSM) in addition to recovered starting material (12.0 mg).

To a solution of the above mixture (11.1 mg, 0.021 mmol) in THF (1 mL) was added TBAF (1.0 *M* in THF, 0.042 mL, 0.042 mmol, 2.0 equiv) at 0 ºC. The resulting mixture was allowed to warm up to rt and stirred overnight, and after which, it was reaction poured into sat aq NaCl and extracted 5 times with equal volume of CH_2Cl_2. The combined organic extracts were dired over Na_2SO_4 and concentrated under reduced pressure to afforded the crude product that was purified by silica gel flash column chromatography (gradient eluent: 20% – 80% EtOAc in hexanes) to provide an inseparable 1 : 1 mixture of **35a** and **35b** (3.1 mg, 0.011 mmol) in 52% yield as light yellow oil. **35a** and **35b**: R_f = 0.13 [80 % EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.715 (t, 3H, *J* = 6.5 Hz), 0.721 (t, 3H, *J* = 6.5 Hz), 1.04 - 1.34 (m, 26H), 1.43 - 1.73 (m, 22H), 1.88 – 1.97 (m, 6H), 2.48 (brs, 2H), 2.59 - 2.64 (m, 2H), 3.03 (td, 2H, *J* = 10.0, 1.5 Hz), 3.16 (dd, 2H, *J* = 9.5, 9.0 Hz), 3.49 (dd, 2H, *J* = 10.5, 3.0 Hz); carbon-13 NMR was not taken for the mixture. IR (neat) cm^{-1} 3354brs, 2929s, 2861s, 1465m, 1276s, 1074s; mass spectrum (APCI): m/e (% relative intensity) 294 (100) M^++H, 276 (80), 242 (15); m/e calcd for

$C_{19}H_{35}NO$+H 294.2797, found 294.2789.

Cycloadduct (40). To a flame-dried flask were added commercial (–)-perilaldehyde (0.6 mL, 4.2 mmol, pre-filtered through silica gel) and anhydrous EtOAc (6 mL). The solution was cooled to –10 °C, and piperidine (0.42 mL, 4.2 mmol) and then acetic anhydride (0.41 mL, 4.2 mmol) were added dropwise via syringe. Reaction mixture was sealed under nitrogen and heated at 85 °C for 1 h. The resulting iminium salt solution was transferred via a cannula to a suspension of a *N*-benzyl tetronamide (0.40 g, 2.1 mmol) in anhydrous toluene (8 mL) in a flame-dried sealed tube. The reaction mixture was sealed under nitrogen and heated at 130 °C in a sand bath for 72 h. Reaction progress was monitored using TLC analysis. After vinylogous amide was consumed, the reaction mixture was concentrated under reduced pressure, and crude NMR indicated presence of two diastereomeric cycloadducts with ratio 10 : 1. Purification via silica gel flash column chromatography (gradient eluent: 0% – 63% EtOAc in hexanes) gave **40** (major isomer, 0.50 g) in 74% yield as yellow oil. Minor isomer was not isolated. 40: R_f = 0.37 [EtOAc : hexanes = 5 : 4]; $[\alpha]_D^{20}$ = - 265.4 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (qd, 1H, *J* = 12.0, 5.0 Hz), 1.69 (s, 3 H), 1.82 (m, 3 H), 2.07 (m, 2H), 2.39 (dt, 1H, *J* = 13.8, 3.8 Hz), 4.22 (d, 1H, *J* = 16.5 Hz), 4.32 (m, 1H), 4.42 (d, 1H, *J* = 16.5 Hz), 4.59 (d, 2H, *J* = 3.9 Hz), 4.66 (m, 1H), 4.71 (t, 1H, *J* = 1.5 Hz), 5.88 (s, 1H), 7.26 (d, 2H, *J* = 6.0 Hz), 7.39 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 33.0, 34.1, 37.8, 44.7, 51.2, 62.9, 65.2, 92.6, 109.7, 109.8, 126.9, 128.5, 129.5, 130.9, 134.6, 148.4, 164.1, 171.5; IR (neat) cm^{-1} 3061m, 2934s, 1728m, 1605s, 1267m; mass spectrum (APCI): m/e (% relative intensity) 322 (100) M^+ + H, 320 (10), 230 (18), 101 (13), 87 (5); *m/e* calcd for $C_{21}H_{23}NO_2Na$ (M^+ + Na) 344.1626, found 344.1605.

Cycloadduct (43). According to the procedure described above commercial (–)-myrtenal (0.48 mL, 4.2 mmol, pre-filtered through silica gel) and *N*-benzyl tetronamide (0.40 g, 2.10 mmol) afforded cycloadduct (**43**) (major isomer, 0.46 g) in 68% yield as yellow oil. Minor isomer was not isolated. **43**: R_f = 0.42 [EtOAc : hexanes = 5 : 4]; $[\alpha]_D^{20}$ = - 211.20 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.898 (s, 3.0 H), 1.24 (s, 3 H), 1.45 (d, 1H, *J* = 10.0 Hz), 1.99 (dd, 1H, *J* = 12.0, 9.0 Hz), 2.05 (dd, 1H, *J* = 10.5, 5 Hz), 2.19 (m, 2H), 2.52 (t, 1H, *J* = 5.5 Hz), 4.31 (s, 2H), 4.64 (d, 1H, *J* = 16 Hz), 4.74 (d, 1H, *J* = 16 Hz), 4.81 (td, 1H, *J* = 8.5, 2Hz), 5.80 (d, 1H, *J* = 2.5 Hz), 7.26 (d, 2H, *J* = 7.5 Hz), 7.33 (t, 1H, *J* = 7.5 Hz), 7.38 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 22.9, 25.6, 31.0, 40.5, 42.1, 49.9, 50.7, 53.6, 65.5, 95.9, 110.8, 127.2, 128.4, 129.4, 132.7, 134.2, 165.5, 171.7; IR (neat) cm^{-1} 3056m, 2937s, 2305w, 1740s, 1649s, 1266s; mass spectrum (APCI): m/e (% relative intensity) 322 (100) M^+ + H, 320 (40), 234 (10), 230 (35), 101 (10), 87 (20); *m/e* calcd for $C_{21}H_{23}NO_2Na$ (M^+ + Na) 344.1626, found 344.1617.

Diol (41). To a stirred solution of **40** (0.275 g, 0.86 mmol) and pyridine (0.27 mL, 3.42 mmol) in CH_2Cl_2 (10 mL) at -10 ºC was added a solution of OsO_4 (0.24 g, 0.94 mmol) in CH_2Cl_2 (2 mL). The solution was warmed to rt and stirred for 4 h, then concentrated to a black solid (to remove pyridine). The residue was dissolved in CH_2Cl_2 (20 mL) and a solution of mannitol (0.78 g, 4.28 mmol) in 10% aq KOH (8 mL) was added and the resulting mixture was stirred vigorously overnight. The organic layer was then

separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (gradient eluent: 0% – 75% EtOAc in hexanes) gave diol (**41**) (0.16 g) in 55% yield) as white foam. **41**: R_f = 0.14 [60% EtOAc in hexanes]; $[\alpha]_D^{20}$ = – 107.6 (*c* 0.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (q, 1H, *J* = 12.5 Hz), 1.34 (td, 1H, *J* = 12.5, 2.0 Hz), 1.45 (td, 1H, *J* = 13.5, 4.0 Hz), 1.62 (s, 3H), 1.64 - 1.70 (m, 1H), 1.83 (d, 1H, *J* = 12.5 Hz), 1.96 (tt, 1H, *J* = 12.5, 2.0 Hz), 2.24 (tt, 1H, *J* = 13.5, 3.0 Hz), 3.08 (s, 1H), 3.29 (dd, 1H, *J* = 12.5, 4.0 Hz), 3.60 (s, 1H), 4.28 (d, 1H, *J* = 16.5 Hz), 4.35 (d, 1H, *J* = 16.5 Hz), 4.44 (d, 1H, *J* = 15.5 Hz), 4.59 (d, 1H, *J* = 15.5 Hz), 4.66 (s, 1H), 4.73 (s, 2H), 7.23 – 7.27 (m, 2H), 7.30 – 7.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 28.2, 32.2, 33.9, 43.9, 52.4, 61.0, 65.5, 65.7, 69.4, 90.3, 109.9, 127.0, 128.4, 129.3, 135.5, 148.0, 162.4, 174.5; IR (film) cm^{-1} 3502brs, 3113m, 2970s, 1731s, 1618s, 1265s; mass spectrum (APCI): m/e (% relative intensity) 338 (100) M^+-H_2O, 320 (80), 230 (30); *m/e* calcd for $C_{21}H_{25}NO_4Na$ (M^+ + Na) 378.1676, found 378.1662.

Diol (44). To a stirred solution of **43** (0.092 g, 0.29 mmol) and pyridine (0.10 mL, 1.20 mmol) in CH_2Cl_2 (5 mL) at -10 ºC was added a solution of OsO_4 (0.080 g, 0.32 mmol) in CH_2Cl_2 (1 mL). The solution was warmed to rt and stirred for 4 h, then concentrated to a black solid (to remove pyridine). The residue was dissolved in CH_2Cl_2 (10 mL) and a solution of mannitol (0.26 g, 1.40 mmol) in 10% aq KOH (4 mL) was added and stirred vigorously overnight. The organic layer was then separated and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (gradient eluent: 0% – 60% EtOAc in hexanes) gave diol (**43**) (0.054 g) in 53% yield as yellow oil. **43**: R_f = 0.28 [60% EtOAc in hexanes]; $[\alpha]_D^{20}$ = – 12.2 (*c* 0.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 3H), 1.22 (s, 3H), 1.58 (dd, 1H, *J* = 11.5, 1.5 Hz), 1.61 (d, 1H, *J* = 10.5 Hz), 1.92 (q, 1H, *J* = 5.5 Hz), 2.10-2.16 (m, 1H), 2.23 (t, 1H, *J* = 5.5 Hz), 2.29 (ddd, 1H, *J* = 15.0, 10.0, 5.0 Hz), 3.85 (s, 1H), 3.89 (t, 1H, *J* = 10.0 Hz), 4.06 (brs, 1H), 4.28 (d, 1H, *J* = 17.0 Hz), 4.39 (d, 1H, *J* = 17.0 Hz), 4.52 (d, 1H, *J* = 15.5 Hz), 4.66 (d, 1H, *J* = 15.5 Hz), 4.71 (s, 1H), 7.18 (d, 2H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 7.32 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 23.9, 27.3, 29.7, 39.3, 39.7, 50.1, 51.0, 59.7, 62.7, 65.8, 75.9, 89.9, 126.4, 128.4, 129.5, 135.0, 163.0, 174.7; IR (neat) cm^{-1} 3488brs, 3009w, 2982s, 2875m, 1735s, 1624s; mass spectrum (APCI): m/e (% relative intensity) 338 (65) M^+-H_2O, 320 (100), 230 (25), 102 (15); *m/e* calcd for $C_{21}H_{25}NO_4Na$ (M^+ + Na) 378.1676, found 378.1681.

Alcohol (42). Diol (**41**) (0.062 g, 0.17 mmol) was dissolved in 5 mL of MeOH, and 10% Pd/C (0.010 g) was added. The flask was fitted with a hydrogen balloon and allowed to stir at room temperature overnight. Filtration of catalyst and removal of solvent gave the desired hydrogenated product, which was used in the next step without further purification.

To a flame dried flask under N_2 was added hydrogenated diol prepared above (0. 52 g, 0.15 mmol) and dry CH_2Cl_2 (5 mL). The solution was cooled to -15 ºC and Et_3SiH (0.73 mL, 4.60 mmol) and trifluoroacetic acid (TFA) (0.13 mL, 1.75 mmol) were added dropwise. The solution was kept for 24 h at

-10 ºC (in the freezer), then diluted with CH_2Cl_2 (2 mL) and quenched with sat aq $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (gradient eluent: 0% – 63% EtOAc in hexanes) gave alcohol (**42**) (0.36 g, 61% yield over 2 steps) as white foam. **42**: R_f = 0.13 [60% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 20.7 (*c* 1.66, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, 3H, *J* = 6.5 Hz), 0.84 (d, 3H, *J* = 6.5 Hz), 0.96 (q, 1H, *J* = 12.5 Hz), 1.12 – 1.19 (m, 2H), 1.46 (ddd, 1H, *J* = 13.0, 12.5, 6.5 Hz), 1.61 – 1.69 (m, 2H), 1.79 (dd, 2H, *J* = 13.0, 2.5 Hz), 1.98 (dd, 1H, *J* = 12.5, 2.5 Hz), 2.10 (d, 1H, *J* = 16.5 Hz), 2.20 (brs, 1H), 2.63 (d, 1H, *J* = 16.5 Hz), 3.06 (ddd, 1H, *J* = 12.5, 4.0, 2.0 Hz), 4.31 (d, 1H, *J* = 16.5 Hz), 4.39 (d, 1H, *J* = 16.5 Hz), 4.59 (d, 1H, *J* = 15.0), 4.67 (d, 1H, *J* = 15.0), 7.31 – 7.38 (m, 3H), 7.40 (t, 2H, *J* = 7.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 20.0, 26.4, 26.5, 32.0, 32.4, 37.8, 43.3, 52.9, 65.7, 66.3, 69.2, 88.2, 127.4, 128.4, 129.3, 136.2, 162.3, 174.8; IR (film) cm^{-1} 3487brs, 3023m, 2989s, 1729s, 1618s, 1260s; mass spectrum (APCI): m/e (% relative intensity) 342 (100) M^++H, 326 (60), 252 (35), 216 (90); *m/e* calcd for $C_{21}H_{27}NO_3Na$ (M^+ + Na) 364.1889, found 364.1879.

Model *Aza*-Tricycle (46). To a suspension of 4-*N*-benzyl amino-6-methyl-2-pyrone (1.26 g, 5.85 mmol) in toluene (130 mL) were added oven-dried Na_2SO_4 (3 g) and 1-cyclohexene-1-carboxaldehyde (643.5 mg, 5.85 mmol) that was freshly filtered through silica gel. The mixture was stirred for 10 min at rt before piperidinium trifluoroacetate (2.73 g, 13.70 mmol) was cannulated in as a solution in toluene (20 mL). The reaction flask was sealed and the mixture was heated to 160 ˚C for 48 h before it was cooled to rt and filtered to remove any solids. The mixture was partitioned with 1 *N* aq NaOH and extracted three times with EtOAc. The resulting organic solution was washed with sat aq NaCl, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 30% – 50% EtOAc in hexanes) afforded the model *aza*-tricycle (**46**) (1.26 g) in 70% yield as yellow foam. **46**: R_f = 0.19 [50% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 - 1.44 (m, 2H), 1.68 (ddd, 1H, *J* = 12.0, 12.0, 3.0 Hz), 1.73 - 1.91 (m, 4H), 2.06 (s, 3H), 2.39 (dd, 1H, *J* = 3.5, 15.5 Hz), 4.20 (dd, 1H, *J* = 3.5, 11.5 Hz) 4.38 (d, 1H, *J* = 17.5 Hz), 4.58 (d, 1H, 17.5 Hz), 5.53 (s, 1H), 6.24 (s, 1H), 7.15 - 7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 25.6, 28.0, 34.5, 35.0, 51.8, 64.3, 95.4, 112.1, 125.8, 127.4, 128.9, 131.6, 136.5, 152.1, 160.7; IR (film) cm^{-1} 1681s, 1533m, 1498m, 1451m; mass spectrum (APCI): m/e (% relative intensity) 308 (100) M^+ + H, 306 (5); m/e calcd for $C_{20}H_{21}NO_2K^+$ 346.1209, found 346.1204.

Diol (47). To a solution of **46** (0.356 g, 1.16 mmol) in *t*-BuOH (15 mL) and H_2O (4.5 mL) were added pyridine (0.020 mL, 0.29 mmol) and NMO (0.143 g, 1.22 mmol), and OsO_4 (~ 15.0 mg, 0.058 mmol) very carefully. The mixture was heated to reflux for 29 h, at which point it was cooled to rt. The mixture was carefully quenched with sodium bisulfite, and run through a pad of silica gel and celite. The filtrate was partitioned between H_2O and EtOAc, and the aqueous phase extracted two times with EtOAc. The combined organic layers were washed with 1 *N* aq HCl and sat aq NaCl. The organic layer was dried with

Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% – 60% EtOAc in CH_2Cl_2) gave the desired diol (**47**) (0.120 g) in 30% yield as beige oil. **47**: R_f = 0.46 [50% EtOAc in CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31-1.53 (m, 4H), 1.70 (d, 1H, *J* = 14.0 Hz), 1.78 (d, 1H, 11.5 Hz), 1.90 (d, 1H, 12.5 Hz), 2.09 (s, 3H), 2.37 (d, 1H, *J* = 11.5 Hz), 3.26 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.34 (s, 1H), 4.48 (d, 1H, *J* = 18.0 Hz), 4.62 (d, 1H, 18.0 Hz), 4.92 (s, 1H), 5.62 (s, 1H), 5.71 (s, 1H), 7.15-7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 22.6, 24.4, 27.9, 34.4, 52.4, 61.6, 65.5, 68.5, 90.1, 96.0, 125.9, 127.5, 128.9, 136.2, 152.1, 160.9, 165.4 (two carbons missing due to overlap); IR (neat) cm^{-1} 3415brs, 1669s, 1544m, 1502m, 1452m; mass spectrum (APCI): m/e (% relative intensity) 342 (5) M^+ + H, 324 (100), 298 (20); m/e calcd for $C_{20}H_{23}NO_4K^+$ 380.1264, found 380.1256.

‡Crystallographic data for **47**: [C_{20} H_{23} N O_4], *M* = 341.39, orthorhombic, *P*bca, *a* = 8.5483(2) Å, α = 90°, *b* = 12.1475(3) Å, β = 90°, *c* = 33.4688(8) Å, γ = 90°, V = 3475.42(14) Å^3, *T* =173(2) K, *Z* = 8, μ = 0.091 mm^{-1}, 3074 [*R*(int) = 0.0276], Final *R* indices [$I>2\sigma(I)$], *R*1 = 0.0424, *wR*2 = 0.1020, *R* indices (all data), *R*1 = 0.0511, *wR*2 = 0.1070.

Hydroxy Ketone (48). To a solution of diol (**47**) (0.089 g, 0.261 mmol) in CH_2Cl_2 (3 mL) were added 4Å molecular sieves (0.050 g), NMO (0.048 g, 0.418 mmol), and finally, TPAP (0.046 g, 0.130 mmol). The mixture was stirred at rt for 6 h before it was filtered through a pad of celite and silica gel. The crude material was concentrated and loaded onto a silica gel column. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% – 40% EtOAc in CH_2Cl_2) afforded hydroxy ketone (**48**) (0.053 g) in 60% yield as white waxy solid. **48**: R_f = 0.10 [50% EtOAc in CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24-1.34 (m, 2H), 1.40 - 1.48 (m, 2H), 1.61 - 1.71 (m, 3H), 1.92 - 1.95 (m, 1H), 2.14 (s, 3H), 2.47 - 2.49 (m, 1H), 2.75 (s, 1H), 3.53 (dd, 1H, J = 4.5, 11.0 Hz), 4.59 (d, 1H, J = 17.0 Hz), 4.82 (d, 1H, J = 17.0 Hz), 5.70 (s, 1H), 7.33 - 7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 22.1, 23.7, 25.4, 30.8, 32.2, 53.0, 66.1, 95.1, 125.9, 126.1, 128.0, 128.7, 129.1, 130.8, 134.7, 166.2 (two carbons missing due to overlap); IR (film) cm^{-1} 3415brs, 1721s, 1650s, 1545m, 1484m, 1453w; mass spectrum (APCI): m/e (% relative intensity) 340 (100) M^+ + H, 324 (15), 296 (20), 272 (25), 254 (15); m/e calcd for $C_{20}H_{21}NO_4Na^+$ 362.1368, found 362.1367.

Acetate (50). To a solution of **48** (0.012 g, 0.035 mmol) in CH_2Cl_2 (1.0 mL) were added Et_3N (0.50 mL), Ac_2O (0.50 mL) and DMAP (0.0010 g, 0.0080 mmol). The mixture was stirred at rt for 20 h until there was no starting material remained by TLC. The mixture was partitioned between EtOAc and 2 *N* aq HCl, and the aqueous phase was extracted twice with EtOAc. The organic layer was washed with sat aq $NaHCO_3$ and sat aq NaCl, and dried over Na_2SO_4. The drying agent was removed by filtration and the organic filtrate was concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) gave acetate (**50**) (0.012 g) in 90% yield as colorless oil. **50**: R_f = 0.21 [50% EtOAc in CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 - 1.38 (m, 2H), 1.40 - 1.48 (m, 2H), 1.61 - 1.71 (m, 3H), 1.92 - 1.95 (m, 1H), 2.14 (s, 3H), 2.47 - 2.49 (m,

1H), 2.75 (s, 1H), 3.53 (dd, 1H, J = 4.5, 11.0 Hz), 4.59 (d, 1H, J = 17.0 Hz), 4.82 (d, 1H, J = 17.0 Hz), 5.70 (s, 1H), 7.33 - 7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 22.1, 22.5, 24.2, 25.9, 27.3, 53.3, 63.4, 80.7, 91.9, 94.7, 126.4, 128.3, 129.0, 134.7, 158.4, 166.5, 169.6, 170.4, 181.7 (two carbons missing due to overlap); IR (neat) cm^{-1} 1738s, 1650s, 1543m, 1487m, 1236m 1223m; mass spectrum (APCI): m/e (% relative intensity) 382 (100) M^+ + H, 322 (20), 296 (35), 272 (20), 254 (30); m/e calcd for $C_{22}H_{24}NO_5^+$ 382.1654, found 382.1649.

Chlorohydrin (51). To a solution of **46** (0.071 g, 0.231 mmol) in *t*-BuOH (6 mL) and H_2O (2 mL) was added dropwise a solution of NCS (0.093 g, 0.697 mmol) in *t*-BuOH and H_2O (1:1) at 0 ˚C. The mixture was stirred at 0 ˚C for 35 min, and the solution was poured into a solution of sat aq $Na_2S_2O_3$. The mixture was extracted 2 times with EtOAc, washed with 1 *N* aq NaOH and sat aq NaCl, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in CH_2Cl_2) afforded halohydrin (**51**) (0.022 g) in 27% yield as yellow foam. **51**: R_f = 0.24 [50% EtOAc in CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (ddq, 1H, *J* = 3.5, 3.5, 14.0 Hz), 1.56 - 1.65 (m, 1H), 1.75 - 1.87 (m, 2H), 2.04 - 2.18 (m, 5H), 2.26 (ddq, 1H, *J* = 4.5, 4.5, 13.0 Hz), 2.68 (d, 1H, *J* = 13.5 Hz), 3.31 (s, 1H), 3.44 (ddd, 1H, *J* = 2.0, 2.0, 12.0 Hz), 4.57 (d, 1H, *J* = 17.0 Hz), 4.66 (d, 1H, *J* = 17.0 Hz), 4.97 (s, 1H), 5.73 (s, 1H), 7.28 - 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 24.1, 24.3, 27.0, 39.9, 52.8, 67.2, 69.7, 70.9, 92.5, 95.8, 126.4, 127.7, 128.8, 136.1, 150.7, 161.0, 164.5; IR (film) cm^{-1} 3399brs, 1674s, 1542m, 1500w, 1451w; mass spectrum (ESI): m/e (% relative intensity) 398.1 (100) $(M+K)^+$; m/e calcd for $C_{20}H_{22}NO_3ClK^+$ 398.0920, found 398.0917.

‡Crystallographic data for **51**: [C_{40} H_{44} Cl_2 N_2 O_6], *M* = 719.67, monoclinic, $P2_1/c$, *a* = 13.6782(12) Å, α = 90°, *b* = 11.4078(9) Å, β = 106.106(2)°, *c* = 23.234(2) Å, γ = 90°, V = 3483.1(5) Å^3, *T* =173(2) K, *Z* = 4, μ = 0.239 mm^{-1}, 6117 [*R*(int) = 0.0639], Final *R* indices [$I>2\sigma(I)$] , *R*1 = 0.0481, *wR*2 = 0.0837, *R* indices (all data), *R*1 = 0.1128, *wR*2 = 0.1037.

Alcohol (52). To a solution of **51** (0.145 g, 0.403 mmol) in toluene (20 mL) were added AIBN (0.026 g, 0.16 mmol) and *n*-Bu_3SnH (0.55 mL, 2.015 mmol). The mixture was heated to reflux for 3 h, and after which, it was allowed to cool to rt. TLC was ineffective since R_f was the same as the starting material. No starting material remained by LCMS. The solvent was removed under reduced pressure, and the crude residue was purified by flash silica gel column chromatography (gradient eluent: 0% - 50% EtOAc in CH_2Cl_2). After all remaining product was collected, there was still an impurity, so the residue was dissolved in EtOAc, and was washed with 1 *N* aq NaOH, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give alcohol (**52**) (0.077 g) in 59% yield as thick yellow oil. There appeared to be two isomers, *cis*, and *trans* with a ratio of 8 : 1. ***52-cis***: R_f = 0.25 [50% EtOAc in CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 - 2.38 (m, 12H) 3.32 (brs, 1H), 4.42 (d, 1H, *J* = 17.0 Hz), 4.65 (d, 1H, *J* = 17.0 Hz), 4.93 (d, 1H, *J* = 4.5 Hz), 5.72 (s, 1H), 7.12 - 7.44 (m, 5H); IR (neat) cm^{-1} 3427brs, 1675s, 1540m, 1498w, 1451w; mass spectrum (APCI): m/e (% relative intensity) 326 (100) M^+ + H, 308 (45), 254 (15);

m/e calcd for $C_{20}H_{23}NO_3K^+$ 364.1310, found 364.1318; Also ^{1}H NMR (500 MHz, d-toluene) δ 0.60 - 2.40 (m, 12H), 2.93 (ddd, 1H, J = 3.5, 3.5, 10.5), 3.96 (d, 1H, *J* = 17.5 Hz), 4.11 (d, 1H, *J* = 17.5 Hz), 5.03 (d, 1H, *J* = 5.0 Hz), 5.26 (s, 1H), 6.92 -7.24 (m, 5H).

Ketone (53). *From alcohol* (**52**): To a solution of **52** (0.045 g, 0.140 mmol) in CH_2Cl_2 (3 mL) were added 4Å molecular sieves (0.045 g), NMO (0.030 g, 0.224 mmol), and finally, TPAP (0.025 g, 0.070 mmol). The mixture was stirred at rt for 2 h before it was filtered through a pad of celite and silica gel. The crude material was concentrated and the crude residue was purified via silica gel flash column chromatography (gradient eluent: 0% - 50% EtOAc in CH_2Cl_2) to give ketone (**53**) (0.029 g) in 64% yield as white foam.
From chloro ketone (**54**): To a solution of **54** (see below) (0.023g, 0.064 mmol) in HOAc (10 mL) was added zinc powder (0.063 g, 0.964 mmol). The mixture was stirred at rt for 7 h, and after which, there was no starting material remained as indicated by TLC analysis. The mixture was filtered through a pad of Celite™, and the filtrate was rendered basic (*p*H = 10) with 1 *N* aq NaOH. The mixture was partitioned with EtOAc, and was extracted 3 times. The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was recovered as white foam (0.019 g, 0.059 mmol) with no further purification necessary. **53**: R_f = 0.32 [50% EtOAc in CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 - 1.29 (m, 2H), 1.37 - 1.51 (m, 2H), 1.64 - 1.85 (m, 3H), 2.13 (s, 1H), 2.62 (d, 1H, *J* = 13.5 Hz), 2.95 (brs, 1H), 3.55 (ddd, 1H, *J* = 6.0, 6.0, 11.5 Hz), 4.47 (d, 1H, *J* = 17.0 Hz), 4.83 (d, 1H, *J* = 17.0 Hz), 5.69 (s, 1H), 7.20-7.30 (m, 2H), 7.33-7.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 21.1, 23.8, 24.8, 25.2, 44.8, 53.4, 62.0, 93.5, 94.9, 126.0, 128.3, 129.3, 135.3, 158.3, 159.1, 166.3, 188.5 (two carbons missing due to overlap); IR (film) cm^{-1} 3451brs, 1730m, 1648m, 1540m, 1483m; mass spectrum (APCI): m/e (% relative intensity) 324 (100) M^+ + H, 298 (45), 280 (20), 256 (35); m/e calcd for $C_{20}H_{21}NO_3Na^+$ 346.1419, found 346.1409.

Chloro-Ketone (54). To a solution of chlorohydrin (**51**) (0.128 g, 0.356 mmol) in CH_2Cl_2 (15 mL) was added oven-dried powdered 4 Å molecular sieves (0.20 g) at rt, and after 10 min of stirring, *N*-methyl morpholine *N*-Oxide (0.067 g, 0.572 mmol) and TPAP (0.063 g, 0.179 mmol) were added sequentially. The mixture was stirred for 5.5 h at rt before the solids were removed by filtration through celite. The resulting solution was concentrated under reduced pressure the crude residue was purified via silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in CH_2Cl_2) to afford chloro ketone (**54**) (0.072 g) in 56% yield as light yellow foam. **54**: R_f = 0.33 [50% EtOAc in CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (ddq, 1H, *J* = 3.5, 3.5, 13.5,), 1.44 (ddq, 1H, *J* = 3.0, 3.0, 13.0 Hz), 1.55 (dd, 1H, *J* = 4, 13 Hz), 1.58-1.68 (m, 2H), 1.79 (d, 1H, *J* = 13.5 Hz), 1.9 (d, 1H, *J* = 11.0 Hz), 2.17 (s, 3H), 3.05 (d, 1H, *J* = 12.5 Hz), 3.66 (dd, 1H, *J* = 4.5, 12.5 Hz), 4.58 (d, 1H, *J* = 17.0 Hz), 4.80 (d, 1H, *J* = 17.5 Hz), 5.78 (s, 1H), 7.33 - 7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 23.5, 24.6, 26.9, 34.9, 54.6, 67.2, 68.9, 91.6, 95.2, 127.0, 128.4, 129.1, 134.3, 158.4, 158.6, 166.8, 181.3; IR (film) cm^{-1} 3450brs, 1736m, 1646m, 1541m, 1485m; mass spectrum (APCI): m/e (% relative intensity) 358 (50) M^+ + H, 320 (100), 296 (20), 278 (15); m/e calcd for $C_{20}H_{20}NO_3ClNa^+$ 380.1029, found 380.1028.

***Oxa*-Tricycle Model (55).** *Synthesis of N-Benzyl-4-Hydroxy-6-Methyl-2-Pyridone*: To a suspension of 4-hydroxy-6-methyl-2-pyrone (15.0 g, 118.9 mmol) in EtOH (300 mL) was added benzylamine (32.5 mL, 297.4 mmol), and the mixture was heated to reflux for 14 h. The mixture was then cooled to rt, and solvent was removed under reduced pressure. The crude residue was recrystallized from hot EtOAc to give *N*-benzyl-4-hydroxy-6-methyl-2-pyridone (10.8 g) as an off-white solid that was carried to the next step with no further purification.

Aza-[3 + 3] Annulation. To a solution of 1-cyclohexene-1-carboxaldehyde (1.01 g, 9.10 mmol) in toluene (20 mL) in a sealable flask at 0 ˚C was added piperidine (0.90 mL, 9.10 mmol), and after 5 min of stirring under N_2, Ac_2O (0.90 mL, 9.10 mmol) was added. The mixture was heated to 85 ˚C for 1 h. The mixture was then cooled to rt, and the crude 2-pyridone prepared above (1.95 g, 9.10 mmol) was added. The flask was sealed and heated to 150 ˚C for 90 h, and after which, it was cooled to rt and concentrated under reduced pressure. The residue was adsorbed onto dry silica gel and loaded onto a silica gel column for purification (gradient eluent: 25% – 35% EtOAc in hexanes) to give the *oxa*-tricycle model (**55**) (0.734 g, 2.40 mmol) in 27% yield as off-white waxy solid. **55**: R_f = 0.18 [45% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (ddq, 1H, *J* = 3.5, 3.5, 12.5 Hz), 1.47 (ddq, 1H, *J* = 3.5, 3.5, 13.5), 1.70 - 1.81 (m, 2H), 1.85 - 1.93 (m, 1H), 1.96 - 2.08 (m, 1H), 2.10 - .25 (m, 4H), 2.43 - 2.50 (m, 1H), 4.99 (dd, 1H, *J* = 5.0, 11.5 Hz), 5.20 - 5.36 (m, 2H), 5.67 (s, 1H), 6.35 (s, 1H), 7.11 - 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 24.4, 26.7, 33.0, 35.0, 46.6, 78.5, 100.2, 103.5, 110.8, 126.3, 127.0, 128.6, 132.6, 136.9, 144.9, 159.8, 161.4; IR (film) cm^{-1} 3436brs, 1642m, 1567m; mass spectrum (APCI): m/e (% relative intensity) 308 (80) M^+ + H, 219 (100), 139 (20); m/e calcd for $C_{20}H_{21}NO_2K^+$ 346.1209, found 346.1214.

Alcohol (58). *Chlorohydrin Route:* To a solution of **55** (0.093 g, 0.303 mmol) in acetone (6 mL) was added H_2O (3 mL) followed by NCS (0.044 g, 0.333 mmol). The reaction was stirred for 1 h at rt, and was then heated to reflux for 0.5 h. Only starting material was visible by TLC, and thus, an additional NCS was added to the mixture (0.044 g, 0.333 mmol). The mixture was stirred for 48 h at rt. The mixture was poured into sat aq $Na_2S_2O_3$ and the aqueous phase was extracted with EtOAc (2 x 50 mL). The organic layer was washed with 1 *N* aq NaOH and sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% – 40% EtOAc in CH_2Cl_2) gave chlorohydrin (**56a**) (~49% yield) as yellow foam.

To a solution of the above chlorohydrin (**56a**) (0.053 g, 0.147 mmol) in toluene (8 mL) was added AIBN (0.012 g, 0.074 mmol) followed by *n*-Bu_3SnH (0.20 mL). The reaction mixture was heated at reflux for 3.5 h, and then cooled to rt and poured into sat $Na_2S_2O_3$. The mixture was extracted two times with EtOAc, washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) gave alcohol (**58**) (0.029 g) in 60% yield as off-white waxy solid. **58**: R_f = 0.24 [60% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 - 1.51 (m, 3H), 1.56 - 1.90 (m, 5H), 2.20 - 2.29

(m, 4H), 3.06 (s, 1H), 4.00 (ddd, 1H, *J* = 4.5, 10.5, 10.5 Hz), 4.66 (d, 1H, *J* = 4.0 Hz), 5.29 (s, 2H), 5.78 (s, 1H), 7.11 - 7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 24.3, 25.4, 25.5, 31.9, 42.2, 46.6, 61.5, 74.5, 101.1, 108.4, 126.3, 127.3, 128.8, 136.8, 145.8, 161.7, 164.7; IR (film) cm^{-1} 3411brs, 1645m, 1574m, 1436; mass spectrum (APCI): m/e (% relative intensity) 326 (40) M^+ + H, 307 (100); m/e calcd for $C_{20}H_{23}NO_3Na^+$ 348.1576, found 348.1571.

‡Crystallographic data for **58**: [C_{20} H_{23} N O_3], *M* = 325.39, monoclinic, $P2_1/c$, *a* = 11.4926(11) Å, α = 90°, *b* = 8.8020(8) Å, β = 97.566(2)°, *c* = 16.9803(16) Å, γ = 90°, V = 1702.7(3) $Å^3$, *T* =173(2) K, *Z* = 4, μ = 0.085 mm^{-1}, 3889 [*R*(int) = 0.0327], Final *R* indices [$I>2\sigma(I)$], *R*1 = 0.0503, *wR*2 = 0.1050, *R* indices (all data), *R*1 = 0.0739, *wR*2 = 0.1147.

Bromohydrin Route: To a solution of **55** (1.09 g, 3.55 mmol) in DMSO (40 mL) was added H_2O (10 mL) followed by NBS (3.44 g, 35.5 mmol). The reaction was stirred for 4 h at rt, and was then partitioned between EtOAc and H_2O. The organic layer was extracted three times with EtOAc, and was washed 4 times with H_2O and once with sat aq NaCl. The combined organic fractions were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (0% – 60% EtOAc in hexanes) gave the partially pure di-bromohydrin (**56b**) in an approximate 42% yield.

To a solution of *n*-Bu_3SnH (3.0 mL, 7.5 mmol) in benzene (6 mL) were added a partially dissolved solution of AIBN (0.10 g, 0.6 mmol) and (**56b**) (0.72 g, 1.5 mmol) in benzene (20 mL) dropwise via a syringe pump over 3 h. The resulting mixture was heated at 70 °C for 12 h before it was cooled and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (gradient eluent: 40% – 50 % EtOAc in hexanes) to give alcohol (**58**) (0.19 g) in 40% yield as an off-white waxy solid along with 0.12 g (20% yield) of the mono-bromo reduction product. Spectral data of **58** matched that of chlorohydrin route mentioned above.

Ketone (36). To a solution of the annulation product (**28a**) (0.12 g, 0.21 mmol) in *t*-BuOH (5 mL) and of H_2O (5 mL) was added NCS (0.085 g, 0.63 mmol) over 10 min in three portions. The mixture was stirred for 1 h at rt before it was poured into a solution of sat aq $Na_2S_2O_3$. The aqueous layer was partitioned with Et_2O, and extracted with Et_2O (3 x equal volume). The combined organic layers were washed with 1 *N* aq NaOH, sat aq NaCl, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified via silica gel flash column chromatography (gradient eluent: 0% – 40% EtOAc in hexanes) to afford the desired chlorohydrin (0.099 g, 0.16 mmol) in 76% yield as light yellow foam. R_f = 0.38 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = 66.0 (*c* 0.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.5 Hz), 1.07 (s, 9H), 1.21 - 1.36 (m, 3H), 1.37 - 1.73 (m, 6H), 1.81 - 2.00 (m, 2H), 2.08 - 2.22 (m, 2H), 2.26 (t, 2H, *J* = 8.0 Hz), 2.4 (q, 2H, *J* = 13.5 Hz), 2.65 (dd, 1H, *J* = 5.0, 14.0 Hz), 3.27 (brs, 1H), 3.63 (dd, 1H, *J* = 7.0, 10.5 Hz), 3.69 (dd, 1H, *J* = 7.0, 10.0 Hz), 4.13 (dq, 1H, *J* = 5.0, 7.5 Hz), 4.91 (s, 1H), 5.74 (s, 1H), 7.34-7.50 (m, 6H), 7.58 - 7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 19.0, 21.9, 22.1, 23.2, 26.3, 26.7, 28.9, 33.8, 34.0, 34.9, 38.0, 62.4, 65.6, 68.7, 72.1, 74.5, 91.9, 97.1, 127.8, 129.9, 130.0, 132.7,

132.8, 135.4, 135.5, 149.9, 164.1, 164.9; IR (film) cm^{-1} 2960s, 2930s, 2364m, 1697s, 1544m, 1428m, 1261m, 1105s; mass spectrum (APCI): m/e (% relative intensity) 620 (80) $M^+ + H$, 602 (100), 584 (20), 558 (10), 474 (35); m/e calcd for $C_{36}H_{46}NO_4ClSiNa^+$ 642.2782, found 642.2744.

To a solution of the above chlorohydrin (0.18 g, 0.29 mmol) in CH_2Cl_2 (25 mL) was added powdered 4 Å molecular sieves (0.40 g) were added. The mixture was stirred for 10 min at rt before NMO (0.138 g, 1.18 mmol) was added followed by TPAP (0.026 g, 0.074 mmol), and the resulting mixture was stirred for 4 h at rt. Subsequently, the mixture was filtered through Celite™ and concentrated under reduced pressure. The crude residue was purified via silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) to give the desired chloro ketone (0.12 g, 0.192 mmol) in 66% yield as off-white foam. R_f = 0.13 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 26.4 (*c* 0.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.5 Hz), 1.06 (s, 9H), 1.21 - 1.35 (m, 4H), 1.38 - 1.66 (m, 6H), 1.88 - 2.08 (m, 3H), 2.17 - 2.30 (m, 2H), 2.39 (p, 1H, *J* = 7.5 Hz), 2.48 (t, 1H, *J* = 10.0 Hz), 2.92 (d, 1H, *J* = 13.0 Hz), 3.67 (dd, 1H, *J* = 7.0, 11.0 Hz), 3.72 (dd, 1H, *J* = 6.5, 11.0 Hz), 4.28 (dd, 1H, *J* = 7.0, 14.5 Hz), 5.69 (s, 1H), 7.38 - 7.50 (m, 6H), 7.60 - 7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 18.9, 22.1, 22.4, 23.0, 26.6, 27.0, 28.4, 31.8, 33.0, 34.2, 34.3, 62.8, 64.6, 70.4, 71.3, 90.1, 96.0, 127.8, 130.0, 130.1, 132.2, 132.3, 135.4, 135.5, 156.9, 158.8, 169.5, 181.7; IR (film) cm^{-1} 2962s, 2932s, 2362m 2342m, 1745s, 1644s, 1525s, 1486s, 1263m, 1106s, 1028s; mass spectrum (ESI): m/e (% relative intensity) 640.3 (100) $(M+Na)^+$; m/e calcd for $C_{36}H_{44}NO_4ClSiNa^+$ 640.2620, found 640.2617.

To a solution of the above chloro ketone (0.36 g, 0.58 mmol) in HOAc (10 mL) was added Zn powder (0.57 g, 8.64 mmol). The resulting heterogeneous mixture was stirred at rt for 2 h until no starting material remained by TLC. The *p*H was made basic (*p*H = 10) with 3 *N* aq NaOH and the mixture extracted with EtOAc (3 x equal volume). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude dechlorinated ketone (**36**) was recovered in a 98% yield (0.33 g, 0.56 mmol) as off-white foam that could be used without further purification. **36**: R_f = 0.08 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 7.8 (*c* 0.63, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.5 Hz), 1.06 (s, 9H), 1.20 - 1.35 (m, 4H), 1.39 -1.56 (m, 4H), 1.63 (brs, 2H), 1.81 (dt, 1H, *J* = 3.5, 13 Hz), 1.88 - 2.00 (m, 1H), 2.02 - 2.12 (m, 1H), 2.12 - 2.29 (m, 4H), 2.44 (brs, 1H), 2.60 (d, 1H, *J* = 13.0 Hz), 3.65 (dd, 1H, *J* = 7.0, 11.0 Hz), 3.77 (dd, 1H, *J* = 6.0, 10.5 Hz), 4.08 - 4.18 (m, 1H), 5.57 (s, 1H), 7.36 - 7.50 (m, 6H), 7.60 - 7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 18.9, 20.4, 22.0, 22.4, 23.1, 26.4, 26.6, 28.5, 30.8, 34.2, 34.4, 49.3, 62.2, 65.1, 66.6, 92.3, 95.7, 127.8, 129.9, 130.0, 132.3, 132.5, 135.3, 135.4, 157.2, 158.6, 169.0, 188.7; IR (film) cm^{-1} 2956s, 2932s, 2860s, 1736s, 1644s, 1524m, 1480m, 1110m; mass spectrum (APCI): m/e (% relative intensity) 584 (5) $M^+ + H$, 538 (20), 422 (30), 364 (100), 360 (80); m/e calcd for $C_{36}H_{46}NO_4Si^+$ 584.3191, found 584.3205.

‡Crystallographic data for (**36**): [C_{36} H_{45} N O_4 Si], *M* = 583.82, orthorhombic, $P2_12_12_1$, *a* = 8.3022(7) Å, α = 90°, *b* = 14.6332(12) Å, β = 90°, *c* = 26.376(2) Å, γ = 90°, V = 3204.4(4) $Å^3$, *T* =173(2) K, *Z* = 4, μ = 0.113 mm^{-1}, 5661 [*R*(int) = 0.0505], Final *R* indices [$I>2\sigma(I)$], *R*1 = 0.0399, *wR*2 = 0.0831, *R* indices (all data), *R*1 = 0.0694, *wR*2 = 0.0971.

Dihydropyrone (60). To a solution of ketone (**36**) (0.040 g, 0.079 mmol) in EtOH (3 mL) was added 10% Pd on activated carbon (0.10 g, 0.094 mmol). The vessel was charged with 60 *psi* of hydrogen and the resulting mixture was stirred for 48 h. The reaction mixture was filtered through a pad of Celite™ to remove the palladium catalyst, and the filtrate was concentrated under reduced pressure to provide the crude product as a 2 : 1 mixture of inseparable diastereomers. A preliminary attempt to purify the crude residue via flash column chromatography partially decomposed the product into an unknown. The crude dihydropyrone (**60**) was, therefore, carried forward without any further purification.

Dihydro-4-pyridone (62). To a solution of dihydropyrone (**60**) (8.00 mg, 0.014 mmol) in MeOH (2 mL) were added 1 *N* aq HCl in Et_2O (0.25 mL, 0.25 mmol) and $NaCNBH_3$ (3.00 mg, 0.048 mmol). The resulting mixture was stirred at rt for 30 min. When there was no starting material remained by TLC analysis, the mixture was concentrated under reduced pressure. The crude residue was partitioned between CH_2Cl_2 and sat aq $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2 x equal volume). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (gradient eluent: 0% – 100% EtOAc in hexanes) to provide dihydro-4-pyridone (**62**) (7.00 mg, 0.013 mmol) in 92% yield as colorless oil. (**62**): R_f = 0.47 [100% EtOAc]; ^{1}H NMR (500 MHz, Toluene-d_8) δ 0.98 (t, 3H, *J* = 7.0 Hz), 1.21 - 1.53 (m, 25H), 1.58 - 1.69 (m, 1H), 1.70 - 1.80 (m, 1H), 1.80 - 1.99 (m, 2H), 2.00 - 2.12 (m, 1H), 2.43 (brs, 1H), 2.81 (d, 1H, *J* = 13.0 Hz), 3.50 (t, 1H, *J* = 9.0 Hz), 3.64 (dd, 1H, *J* = 4.5, 10.0 Hz), 3.80 - 4.00 (m, 1H), 5.50 (s, 1H), 7.26 - 7.34 (m, 6H), 7.72 - 7.80 (m, 4H)**;** ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.0, 21.3, 22.3, 22.8, 23.2, 26.7, 27.1, 28.0, 28.8, 29.5, 30.9, 31.4, 34.0, 38.1, 61.7, 64.4, 77.1, 97.0, 105.4, 127.8, 129.9, 130.0, 132.8, 135.4, 135.5, 171.1; mass spectrum (ESI): m/e (% relative intensity) 544.5 (100) $(M+H)^+$; m/e calcd for $C_{35}H_{50}NO_2Si^+$ 544.3605, found 544.3605.

Alcohol (63). To a solution of dihydro-4-pyridone (**62**) (7.00 mg, 0.013 mmol) in THF (2 mL) was added 1 *M* TBAF in THF (0.50 mL, 0.5 mmol) at 0 °C. The resulting solution was slowly warmed to rt and was stirred for 12 h. The mixture was quenched with sat aq NH_4Cl, and was extracted with EtOAc (3 x equal volume). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (gradient eluent: 0% – 100% EtOAc in hexanes) to give the deprotected alcohol (**63**) (3.70 mg, 0.012 mmol) in 93% yield as clear oil. **63**: R_f = 0.29 [100% EtOAc]; $[\alpha]_D^{20}$ = 175.8 (*c* 0.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.5 Hz), 1.00 - 1.90 (m, 15 H), 1.95 - 2.20 (m, 4H), 2.2 - 2.35 (m, 3H), 2.40 (s, 1H), 2.51 (dd, 1H, *J* = 2.5, 12.5 Hz), 3.58 (t, 1H, *J* = 9.5 Hz), 3.68 (dd, 1H, *J* = 5.5, 10.5 Hz), 3.96 - 4.08 (m, 1H), 4.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.4, 22.3, 22.9, 23.5, 27.3, 28.2, 29.0, 31.3, 31.4, 33.5, 34.4, 47.4, 61.3, 63.9, 66.7; IR (neat) cm^{-1} 3329brm, 2929s, 2854s, 2361s, 2344s, 1599w, 1527w, 1455w 1257w, 1219w, 1067w; mass spectrum (ESI): m/e (% relative intensity) 306.5 (100) $(M+H)^+$; m/e calcd for $C_{19}H_{32}NO_2^+$ 306.2428, found 306.2436.

2-*Epi*-(-)-Cylindricine C (64). To a solution of **63** (3.70 mg, 0.012 mmol) in CH_2Cl_2 was added Crabtree's catalyst (10.0 mg, 0.012 mmol). The mixture was placed under 50 *psi* of H_2 at rt for 48 h. After which, the mixture was filtered through a plug of Celite™ and silica gel while being eluted with EtOAc. The resulting filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) to furnish 2-(-)-*epi*-cylindricine (**64**) (2.00 mg, 0.0060 mmol) in 54% yield as colorless oil along with 35% yield for the recovered starting material (1.30 mg, 0.0040 mmol). **64**: R_f = 0.40 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 12.4 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.5 Hz), 1.18 - 1.86 (m, 19H), 1.98 - 2.08 (m, 2H), 2.17 (dd, 1H, *J* = 6.0, 16.0 Hz), 2.26 (d, 1H, *J* = 10.5 Hz), 2.54 (m, 1H), 2.66 (dd, 1H, *J* = 5.5, 15.5 Hz), 2.82 (m, 1H), 3.22 (m, 1H), 3.28 - 3.35 (m, 1H), 3.36 - 3.41 (m, 1H), 3.56 (dd, 1H, *J* = 4, 10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.3, 22.4, 22.7, 24.1, 26.1, 26.5, 29.1, 29.5, 31.6, 36.5, 36.8, 39.1, 42.6, 50.7, 57.8, 63.5, 64.6, 211.4; IR (neat) cm^{-1} 3398brw, 2925s, 2851s, 2362m, 2341m, 1702m, 1447m; mass spectrum (ESI): m/e (% relative intensity) 308.3 (100) $(M+H)^+$; m/e calcd for $C_{19}H_{34}NO_2^+$ 308.2584, found 308.2577. Tabulation of ^{1}H NMR comparisons has been reported: See ref. 28.

(-)-Cylindricine C (2). To a solution of alcohol (**63**) (1.30 mg, 0.0043 mmol) in $CDCl_3$ (1 mL) were added a catalytic amount of AcOH and $Na(OAc)_3BH$ (1.00 mg, 0.0047 mmol). The mixture was stirred at rt and periodically checked by TLC analysis. Since starting material still remained after 20 h, an additional $Na(OAc)_3BH$ (3.00 mg, 0.0142 mmol) was added to the solution, along with additional $CDCl_3$ (2 mL), and the mixture was heated to reflux for 40 min. When there was no starting material remained by TLC, the mixture was partitioned with sat aq $NaHCO_3$ and $CDCl_3$. The mixture was extracted with $CDCl_3$ (3 x equal volume), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified via silica gel flash column chromatography (gradient eluent: 0% – 50% EtOAc in hexanes) to afford the natural product (-)-cylindricine C (**2**) (1.10 mg, 0.0036 mmol) in 83% yield as light yellow oil. **2**: R_f = 0.42 [50% EtOAc in hexanes]; $[\alpha]_D^{20}$ = - 66.7 (*c* 0.09, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.18 - 1.74 (m, 19H), 1.84 (dd, 1H, *J* = 8.5, 13.0 Hz), 2.13 (dd, 1H, *J* = 8.0, 12.5 Hz), 2.23 (dd, 2H, *J* = 3.0, 13.0 Hz), 2.31 (t, 2H, *J* = 12Hz), 2.90 (brs, 1H), 3.29 (m, 1H), 3.43 (m, 1H), 3.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.9, 22.8, 23.0, 24.5, 27.3, 29.0, 29.5, 31.9, 35.4, 36.1, 36.7, 42.8, 50.5, 55.5, 56.8, 66.6, 70.9, 210.5; IR (neat) cm^{-1} 2959s, 2921s, 2852s, 1707m, 1454m, 1411m, 1260s, 1093s, 1021s, 800s; mass spectrum (APCI): m/e (% relative intensity) 308 (3) M^+ + H, 279 (20), 242 (70), 217 (10), 186 (100); m/e calcd for $C_{19}H_{34}NO_2^+$ 308.2584, found 308.2587. Tabulation of ^{1}H NMR comparisons has been reported: See ref. 28.

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