Published in final edited form as:

J Org Chem. 2013 December 6; 78(23): . doi:10.1021/jo402178r.

Synthesis of the Spiroiminal Moiety and Approaches to the Synthesis of Marineosins A and B

Xiao-Chuan Cai and Barry B. Snider

Department of Chemistry, MS 015, Brandeis University, Waltham, Massachusetts 02454-9110, United States

Barry B. Snider: snider@brandeis.edu

Abstract

A short and efficient synthesis of model spiroiminales that have the same stereochemistry but different conformations than marineosins A and B was carried out in 6-7 steps from 6-methyltetrahydropyran-2-one. These spiroiminales were also prepared biomimetically by reduction of an enol ether. A more highly substituted spiroiminal with the same stereochemistry and conformation as marineosin A was prepared in 11 steps from 6-methyl-4-propyl-3-phenyltetrahydropyran-2-one. A macrocyclic pyrrole lactone was prepared stereospecifically in 10 steps. A five step sequence converted the lactone to a late hemi-iminal intermediate that has resisted the methylation and spiroiminal formation that would lead to marineosin A.

Introduction

In 2008 Fenical and co-workers isolated the cytotoxic spiroiminales marineosins A (**1**) and B (**2**) from a marine-derived *Streptomyces*-related actinomycete (see Scheme 1).¹ The structures were determined by analysis of the NMR spectra with the stereochemistry assigned by interpretation of the NOESY spectra. Marineosins A and B differ in stereochemistry at both C-7 and C-8. MMX calculations and examinations of models suggest that the marineosin isomers at the spiroiminal center (C-8) are much less stable than the two isolated isomers because of steric interactions between the methoxy group and the adjacent pyrrole in the macrocycle. The major isomer marineosin A (**1**) inhibited human colon carcinoma HCT-116 with an IC₅₀ of 0.5 μM and testing in the NCI 60 cell line panel showed considerable selectivity against melanoma and leukemia cell lines. In contrast, marineosin B (**2**) showed considerably weaker cytotoxicity against human colon carcinoma HCT-116 with an IC₅₀ of 46 μM.

Marineosins A (**1**) and B (**2**) are novel members of the prodigiosin family of bacterial pigments that appear to be derived from an undecylprodiginine (undecylprodigiosin).² There are many examples of both spiroaminals and iminals, but the spiro-tetrahydropyran-dihydropyrrole (spiroiminal) moiety of the marineosins appears to be unprecedented. Fenical proposed that the biosynthesis of marineosins A and B involves an inverse electron demand intramolecular Diels-Alder reaction with a side chain enone as the diene to give a dihydropyran that undergoes a four-electron reduction to give the marineosins.¹ Lindsley³ and Haran⁴ established that this Diels-Alder reaction could not be achieved in the laboratory suggesting that it is not the biosynthetic route.

Correspondence to: Barry B. Snider, snider@brandeis.edu.

Supporting Information Available: Copies of ¹H, ¹³C, and 2D NOESY NMR spectral data. Crystallographic data for compound **47b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Reynolds and Salem sequenced the gene cluster responsible for the biosynthesis of marineosins A and B in *Streptomyces* CNQ-617.⁵ The enzyme MarG, a RedG homolog from the *mar* gene cluster, oxidizes hydroxyundecylprodigiosine **3** at the asterisked carbon. Subsequent macrocyclization and spiroiminal formation affords dehydromarineosin A (**4**). The enzyme MarA, a putative dehydrogenase/reductase, catalyzes the reduction of **4** to afford marineosin A (**1**).

In 2010, we communicated the synthesis of spiroiminal models **18–21**.⁶ Shi recently reported a very different approach to spiroiminals **18b–21b**⁷ and Lindsley prepared analogous spiroiminals lacking the methyl group.⁸ Lindsley also reported the synthesis of the functionalized macrocyclic pyrrole core of marineosin A.⁹

We report here the full details of our spiroiminal model studies, including those with a fully substituted tetrahydropyran ring with the marineosin A stereochemistry and conformation. We also describe an approach to marineosin A that leads to a fully functionalized macrocyclic core lacking the spiroiminal ring. Our synthetic plan is shown in retrosynthetic form in Scheme 2. The synthesis of **1** and **2** will be completed by acid-catalyzed spiroiminal formation of methoxy iminal **5** and pyrrole deprotection. Hydrogenolysis of isoxazoline **6** over Raney nickel should give a hemi-iminal that will be methylated to give **5**. Addition of a vinyl anion to lactone **7** and protection of the alcohol will give a vinyl ketone that will react with a protected pyrrole nitrile oxide to give isoxazoline **6**, most likely as a mixture of diastereomers that will both be elaborated to both marineosins A or B. Ring-closing metathesis of diene **8** and hydrogenation will construct the macrocycle of **7**. Conjugate addition of an allyl group to **9** should occur by axial attack from the face opposite the methyl group. Equilibration should give the desired stereoisomer of **8** with equatorial allyl and hexenylpyrrole groups. Pyrrole lactone **9** will be prepared by a Suzuki coupling of pyrrole boronic acid **10** and iodolactone **11**.

Results and Discussion

We started with a model study to prepare phenyl spiroiminals **18a–21a** for two reasons (see Scheme 3). The unprecedented spiroiminal moiety is the most intriguing, but also most challenging, moiety of the marineosins (**1** and **2**). The phenyl group is more stable than the pyrrole group,¹⁰ and will allow us to first address the spiroiminal moiety without worrying about the instability of the pyrrole.

Treatment of readily available model lactone **12** with vinylmagnesium bromide afforded the known hydroxy ketone **13a** in 85% yield (see Scheme 3).¹¹ Benzaldehyde oxime was treated with NCS at room temperature to provide the chloro oxime, which was cooled to $-78\text{ }^{\circ}\text{C}$ and treated with Et_3N to generate benzonitrile *N*-oxide, which was treated with enone **13a** to provide the hemiketal form of the isoxazoline in 75% yield as a 1:1 mixture of two diastereomers (see eq 1). Torsell reported in 1983 that hydrogenolysis of the isoxazolinyl methyl ketone analogous to **14a** gave a hemi-iminal.¹² Vinyl ketone **13a** exists preferentially in the open form because conjugation energy ($\sim 3\text{ kcal/mol}$) is lost on cyclization to the hemiketal. However, once the isoxazoline is formed, the hemiketal dominates ($>95\%$) in the equilibrium between the hemiketal and the corresponding saturated hydroxy ketone. Therefore it is not surprising that hydrogenolysis of the isoxazoline hemiketal formed from **13a** over Raney nickel to reduce the isoxazoline failed to form a hemi-iminal by cyclization of the imine to the ketone. A variety of other reduction approaches were also unsuccessful.¹³

To prevent hemiketal formation we protected the hydroxy group of **13a** with TESCl, Et₃N, and DMAP to give **13b** in 96% yield. Reaction of benzaldehyde oxime, NCS, and Et₃N at 25 °C generated benzonitrile *N*-oxide which was cooled to –78 °C and treated with **13b** to give the [3 + 2]-cycloadduct isoxazoline ketone **14a** in 78% yield as a 1:1 mixture of diastereomers. As expected, treatment of isoxazoline ketone **14a** with Raney Ni 2800 and H₂ in MeOH afforded the desired hemi-iminal **15a** as a mixture of diastereomers. Unfortunately, attempted deprotection of the silyl ether under a variety of acidic conditions resulted in decomposition, rather than formation of the desired hydroxy spiroiminal. Hemi-iminal **15a** even decomposed in CDCl₃ (containing adventitious HCl) in 10 h. We therefore treated **15a** with sodium hydride and methyl iodide to afford methyl ether iminal **16a** in 58% yield from **14a**.

The conversion of **16a** to spiroiminals **18a–21a** was explored under a variety of acidic conditions (see Scheme 4). Treatment of **16a** with 2% TFA in chloroform or PPTS in MeOH resulted in decomposition. Treatment of **16a** with HF•Pyr and pyridine in THF gave the desired spiroiminals **18a–21a** in only 15% yield and the undesired methoxypyrrole **17a** in ~50% yield. Finally, we found that treatment of **16a** with 2 M HCl in 1:1 THF/ CH₃CN afforded three of the four desired spiroiminal diastereomers **18a** (46%), **19a** (13%) and **21a** (12%) and only 8% of the undesired methoxypyrrole **17a**. Over a 2–3 week period in CDCl₃ (containing adventitious HCl), solutions of either pure **19a** or **21a** equilibrated to an identical 3:1 mixture of **19a** and **21a**. Therefore, these two spiroiminals differ only at the iminal center C-5 and have the identical relative stereochemistry at C-4 and C-7. Under the same conditions, the major isomer **18a** equilibrated to give a 19:1 mixture of **18a** and **20a**. Therefore, these two compounds also differ only at the iminal center C-5. Attempts to accelerate the equilibration of **18a–21a** by addition of 2% TFA to CDCl₃ resulted in the formation of methoxypyrrole **17a**.

The structure of **21a** was established by an NOE between the CHOMe proton H-4 and the CHMe proton H-7 as shown in Scheme 4. In the other three isomers these two protons are too far apart for an NOE to be observed. The structure of **19a** follows from the structure of **21a** because these compounds differ only in the stereochemistry at the spiroiminal center. The structure of **19a** was confirmed by NOEs between the CHOMe proton H-4 and the adjacent tetrahydropyran methylene group as shown in Scheme 4. The CHMe proton H-7 in **18a** (δ 4.41) and **19a** (δ 4.45) is deshielded by the axial nitrogen and absorbs much further downfield than the CHMe proton H-7 in **20a** (δ 3.78) and **21a** (δ 3.79) with an axial carbon.¹⁴ The major isomer **18a** has no NOEs as expected between the protons on the tetrahydropyran ring and those on the dihydropyrrole ring.

The presence of the imine double bond makes the formation of spiroiminals from **16a** quite different from that of spiroketals and spiroaminals.¹⁵ Desilylation should occur easily to give the alcohol. Protonation of the resulting alcohol on the iminal methoxy group and loss of MeOH would give a stabilized allylic type cation C⁺-N=C that could cyclize to form the spiroiminal, but the nitrogen lone pair can't stabilize the cation by resonance because the five-membered ring precludes a linear cumulene C=N⁺=C. Formation and equilibration of the spiroiminals could also occur by initial isomerization of the imine to an enamine or by protonation on the imine nitrogen and ring opening of the dihydropyrrole ring to give an oxycarbenium ion.

Having developed a sequence to make phenyl-substituted spiroiminals **18a–21a**, we turned our attention to making pyrrole-substituted spiroiminals **18b–21b**, which have the same spiroiminal moieties as marineosins A and B (**1** and **2**). Treatment of **13b** with 2-pyrrolecarboxaldehyde oxime in THF with NCS and Et₃N in THF at –78 °C provided isoxazoline **14b** in 62% yield. Hydrogenolysis of **14b** over Raney nickel provided hemi-iminal **15b**, but selective methylation of the hydroxyl groups without methylation of the pyrrole could not be achieved. The *N*-Me dimethyl ether **16d** was obtained in 41% yield from **14b** with NaH and MeI. Other methylation conditions were investigated unsuccessfully. Treatment of *N*-Me dimethyl ether **16d** with 2 M HCl afforded *N*-Me pyrrole spiroiminals **18d**, **19d**, and **21d** in 65% yield as a mixture of three diastereomers whose structures were assigned by analogy to **18a**, **19a**, and **21a**.

We therefore needed to protect the pyrrole *N*-H to prevent *N*-methylation. Oxidation of *N*-Boc-2-pyrrolecarboxaldehyde oxime with PhI(OAc)₂¹⁶ generated *N*-Boc-2-pyrrole-2-carbonitrile *N*-oxide, which added to enone **13b** to produce the desired isoxazoline **14**, Ar = *N*-Boc-pyrrol-2-yl, in 55% yield. However, treatment of the *N*-Boc pyrrole isoxazoline with Raney Ni and hydrogen not only cleaved the N-O bond of the isoxazoline but also hydrogenated the *N*-Boc pyrrole. The strong electron-withdrawing group on the pyrrole nitrogen reduces the aromaticity of the pyrrole ring making the pyrrole susceptible to hydrogenation.¹⁷

A SEM-protected pyrrole should be compatible with the hydrogenation step.^{18,19} *N*-SEM-pyrrole-2-carboxaldehyde¹⁸ was easily converted to the oxime with hydroxylamine hydrochloride and sodium acetate in aqueous MeOH. However, the oxidation conditions (NCS or iodobenzene diacetate) that were successful with other oximes gave **14c** in <30% yield. Fortunately, reaction of *N*-SEM-pyrrole-2-carboxaldehyde oxime with 5% aqueous NaOCl²⁰ in CH₂Cl₂ at 25 °C generated the nitrile *N*-oxide that reacted with enone **13b** to give isoxazoline **14c** in 73% yield. Hydrogenolysis over Raney Ni and methylation both now proceeded uneventfully to give **16c** in 42% yield from **14c**. Treatment of **16c** with 2 M aqueous hydrochloric acid in 1:3 THF/CH₃CN hydrolyzed the triethylsilyl ether and effected loss of methanol and cyclization to give SEM-protected spiroiminal **18c** (34%), an inseparable 3:2 equilibrium mixture of SEM-protected spiroiminals **19c** and **21c** (34%), and <2% of methoxypyrrole **17c**. The ¹H and ¹³C NMR spectra of these spiroiminals in the aliphatic region spiroiminals are virtually identical to those of **18a–21a** and their stereochemistry was assigned accordingly.

The initial model study was completed by deprotection of **18c** with TBAF and molecular sieves in THF at 60 °C for 3 hours to provide spiroiminal **18b** in 54% yield (see Scheme 5). Similarly, deprotection of the 3:2 mixture of **19c** and **21c** afforded a 7:3 mixture of **19b** and **21b** in 56% yield. The stereochemistry was again assigned from the NMR spectra, which are very similar to those of **18a–21a**.

Salem and Reynolds's biosynthetic studies established that the last step of the biosynthesis of marineosin A (**1**) is the reduction of the enol ether of **4** to give **1**.⁵ We wanted to explore this approach for the preparation of model spiroiminals **18–21**. Berner and co-workers reported that oxidation of 3-methoxypyrrole **22** with MnO₂ in acetone afforded **23** in 73% yield (see Scheme 6).²¹ We thought that the analogous oxidation of 3-methoxypyrrole **17a** would give **24** and **25**, with the oxidized intermediate trapped intramolecularly by the hydroxy group in the side chain rather than intermolecularly by water. 3-Methoxy-5-phenylpyrrole **17a** was a minor byproduct (8%) in the cyclization of **16a** to **18a–21a** with HCl in THF/CH₃CN, but was formed in ~50% yield on treatment of **16a** with HF•pyr and pyr. Further optimization led to the formation of **17a** in 65% yield by treatment of **16a** with HF in THF. As expected, treatment of **17a** with MnO₂ in acetone gave a mixture of easily

separated spiroiminals **24** (14%) and **25** (35%), whose stereochemistry was assigned by hydrogenation to **18a–21a**.

Hydrogenation of the major isomer **25** over Pd/C afforded a mixture of over-reduced spiroaminal diastereomers in ~70% yield in which both the imine and enol ether double bonds had been hydrogenated. Hydrogenation of **25** over Raney Ni gave a mixture of the previously prepared spiroiminals **20a** (15%), and **21a** (15%) in addition to 3-methoxy-5-phenylpyrrole **17a** (45%) resulting from hydrogenolysis. The best results were obtained by hydrogenation of **25** over 5% Pd/BaSO₄, which afforded the desired spiroiminals **20a** (40%) and **21a** (20%) and only 10% of 3-methoxypyrrole **17a**. Similarly, hydrogenation of the minor isomer **24** over 5% Pd/BaSO₄ provided **18a** (35%), **19a** (26%) and **17a** (10%). We were pleased to find that spiroimino **20a**, which has the same stereochemistry as marineosin A (**1**) was obtained in 40% yield by hydrogenation of **25**. This isomer was formed in trace amounts by the HCl-catalyzed spiroimino formation from **16a** and was formed in only ~5% yield during the equilibration of **18a** in CDCl₃ over two weeks.

3-Methoxy-5-phenylpyrrole **17a** was obtained in 65% yield by treating **16a** with HF in THF. Unfortunately treatment of *N*-SEM-pyrrole dimethyl ether **16c** with HF•Pyr or HF in THF and a variety of other acidic conditions gave a complex mixture rather than the desired 2,2'-bi-1*H*-pyrrole **17c** so this approach can't be used to prepare **18c–21c**.²²

Marineosin A (**1**) and model spiroimino **20a** have the same stereochemistry but very different conformations. As expected **20a** adopts the conformation with an equatorial nitrogen and methyl group, whereas the macrocyclic ring of **1** locks the conformation of the tetrahydropyran ring so that both the nitrogen and methyl groups are axial. We therefore next turned to the preparation of a more highly substituted model lactone that would lead to a spiroimino with the same conformation as marineosin A.

Both the second model study and the marineosin A synthesis start with (±)-parasorbic acid (**26**),²³ but enantiomerically pure **26** can be easily prepared once the sequence is worked out (see Scheme 7).²⁴ Parasorbic acid (**26**) was treated with iodine and pyridine to afford iodolactone **11** in 74% yield. Suzuki coupling of iodolactone **11** with phenylboronic acid and 10 mol% Pd(PPh₃)₄ afforded phenyl lactone **27** in 47% yield. The yield was increased to 85% by using Buchwald's Pd(OAc)₂, SPhos and *n*-butanol conditions.²⁵

All attempts to achieve 1,4-addition of an allylcuprate to **27** were unsuccessful as had previously been noted for a related unsaturated lactone by Waldmann and co-workers.²⁶ Trauner and co-workers reported that treatment of a variety of enones with allyltributyltin and Tf₂O afforded the corresponding vinyl triflates that can be used for intramolecular Heck reactions.²⁷ Unsaturated lactone **27** reacted similarly with allyltributyltin, di-*t*-butyl peroxide and Tf₂O to afford the vinyl triflate in 78% yield, which underwent Stille coupling with tributylvinyltin and Pd(PPh₃)₄ to afford **30** in 83% yield. Cycloaddition of **30** with *N*-SEM-pyrrolecarboxaldehyde oxime and NaOCl occurred selectively as desired on the vinyl group of **30** in 58% yield. However, we were not able to hydrolyze the dihydropyran enol ether to give the required hydroxy ketone precursor for the Raney nickel hydrogenation step.

Fortunately, treatment of unsaturated lactone **27** with allylmagnesium bromide, ZnBr₂, and TMSCl as described by Waldmann afforded a 1:3 to 1:1 mixture of the desired conjugate addition products **28a** and **29a** in 63–72% yield. We expected that conjugate addition of the allyl group would occur by axial attack from the face opposite the methyl group. Treatment of the mixture with DMAP in CDCl₃ provided a 6:1 equilibrium mixture favoring the desired trans isomer **28a**. The equilibration of **28a** and **29a** establishes that they differ only in the stereochemistry at the phenyl substituted carbon. The vicinal coupling constants

between the methine hydrogens establish that the phenyl and allyl groups are trans in **28a** ($J = 9.8$ Hz) and cis in **29a** ($J = 5.6$ Hz). The stereochemistry of **28a** was confirmed by a strong NOE between the CHPh proton at δ 3.46 and CHMe at δ 4.66–4.56, which indicates that these two protons are mast protons in the expected boat conformer²⁸ of **28a**. The allyl double bond is needed for the ring-closing metathesis in the synthesis, but not for the model study, so the 6:1 mixture of **28a** and **29a** was hydrogenated over Raney nickel to afford a 6:1 mixture of trisubstituted lactones **28b** and **29b**.

Attempted addition of vinylmagnesium bromide to the 6:1 mixture of **28b** and **29b** resulted in enolization and the formation of a 1:1 mixture of **28b** and **29b** on acidification. The phenyl group makes the α -proton more acidic than those of lactone **12** and hinders the approach of the nucleophile to the carbonyl group. Addition of CeCl_3 to the Grignard reagent helped, but the desired hydroxy vinyl ketone analogous to **13a** was obtained in only 17% yield along with ~70% recovered **28b** and **29b**. Fortunately, treatment of the 6:1 mixture of lactones **28b** and **29b** with *i*-PrMgCl and *N,O*-dimethylhydroxylamine•HCl²⁹ afforded Weinreb amides **31a** (78%) and the diastereomer **31b** (13%), which were easily separated. Reaction of **31a** with TESCl, Et_3N , and DMAP gave TES ether **32** in 85% yield, which was treated with vinylmagnesium bromide to give protected vinyl ketone **33** in 72% yield.

The sequence developed to elaborate **13b** to **18c–21c** worked efficiently to convert **33** to **36** and **37** (see Scheme 8). Cycloaddition of **33** with *N*-SEM-pyrrole oxime and NaOCl afforded a difficultly separable 7:1 mixture of **34** and **35** in 61% yield, whose stereochemistry was assigned from the stereochemistry of the final model spiroiminals **36** and **37**. Hydrogenolysis of the isoxazoline over Raney nickel, methylation with NaH and MeI, and HCl-catalyzed hydrolysis of the silyl ether and cyclization afforded the spiroiminals **36** (33% from **34**) and **37** (15% from a 1:1 mixture of **34** and **35**).

The stereochemistry of **36** and **37** was assigned by analysis of the ^1H NMR spectral data. The CHPh proton H-10 absorbs as a doublet at δ 2.84 ($J = 10.9$ Hz) in **36** and at δ 3.01 ($J = 11.6$ Hz) in **37** thereby establishing that both the phenyl and propyl groups are equatorial in both **36** and **37**. The axial methyl groups are deshielded by the 1,3-diaxial nitrogen and absorb at δ 1.47 in **36** and δ 1.57 in **37**. These shifts are similar to that of the axial methyl group in marineosin A (**1**) at δ 1.51 and very different from those of the equatorial methyl groups of **18c**, **19c** and **21c** at δ 1.13, 1.21 and 1.21, respectively and the methyl group of marineosin B (**2**) at δ 1.20. A large NOE between the axial CHPr proton H-9 and the axial methyl group confirmed this stereochemical assignment. The stereochemistry of the methoxy group was established by NOEs between the CHPh proton H-10 and the CHOMe proton H-7 in **36** and between the CHPh methine proton H-10 and the methoxy group in **37** as shown in Scheme 8.

The single stereocenter in **13b** is too far from the vinyl ketone to affect the cycloaddition so that **14** was obtained as a 1:1 mixture of isomers. We were very encouraged by the observation that the two additional stereocenters in vinyl ketone **33** are close enough to the double bond to influence the stereochemistry of the cycloaddition leading to 7:1 selectivity favoring the isomer with the marineosin A stereochemistry. Furthermore spiroiminal **36** with a fully substituted tetrahydropyran ring adopts the same conformation as marineosin A, whereas model **20**, which has the same stereochemistry as **36**, adopts the other chair conformation with an equatorial nitrogen and methyl group. Minor spiroiminal **37** has the same stereochemistry as marineosin B (**2**) at the methoxy-substituted carbon, but the opposite stereochemistry at the spiroiminal carbon.

Having developed a practical route to **36** with the marineosin A stereochemistry and conformation, we turned our attention to preparing lactone **7** with the macrocyclic pyrrole tether. *N*-(Ts)-pyrrole-2-carboxaldehyde (**38**) was treated with 4-pentenylmagnesium bromide, NMO/TPAP, and then NaBH₄ under Muchowski's conditions^{3,30} to generate 2-(5-hexenyl)pyrrole (**39**)³¹ in 47% overall yield (see Scheme 9). Protection of **39** with (Boc)₂O, Et₃N, and DMAP afforded *N*-Boc-pyrrole **40** in 74% yield. Boronic acid **41** was prepared using Fürstner's procedure for 4-pentenyl-*N*-Boc-pyrroleboronic acid.³¹ Deprotonation at the 5-position with lithium 2,2,6,6-tetramethylpiperidide followed by trapping of the resulting carbanion with trimethyl borate gave the unstable boronic acid **41** in about 60% yield. Great care was required during the workup. The organic phases from the extraction were slowly concentrated at room temperature until a solid started to precipitate. The mixture was then cooled to 0 °C and was filtered. Trituration of the solid with cold ether afforded **41** as a yellowish solid that was used immediately for the Suzuki coupling. To our delight, treatment of iodolactone **11** and boronic acid **41** with Pd(PPh₃)₄, Na₂CO₃, and LiCl in aqueous 1,2-dimethoxyethane at 80 °C afforded pyrrolyl lactone **42** in 55% yield.

We were unable to remove the Boc protecting group at this point, so we treated unsaturated lactone **42** with allylmagnesium bromide, ZnBr₂, and TMSCl. To our surprise, we obtained an inseparable 5:4 mixture of the undesired *cis* isomer **43** and ketene acylal **44** resulting from Boc migration in 56% yield. The CH-pyrrole proton of **43** absorbs as a doublet at δ 4.73 (J = 4.9 Hz) analogously to that of **29a**, δ 3.94 (J = 5.6 Hz). There is no CH-pyrrole proton in **44**, but LCMS analysis indicates that it has the same molecular weight as **43**, suggesting that a precedented Boc migration occurred.³² Apparently, the enolate generated by conjugate addition of the allyl group undergoes kinetically controlled protonation from the face opposite the allyl group to give *cis* isomer **43** and Boc migration to give **44**. Fortunately, treatment of the 5:4 mixture of **43** and **44** with TMSOTf and 2,6-lutidine^{32a} removed the Boc groups from both compounds and epimerized the α position to afford a 19:1 mixture of the desired deprotected *trans* isomer **45** and the deprotected *cis* isomer in 91% yield. The CH-pyrrole proton of **45** absorbs as a doublet at δ 3.57 (J = 6.7 Hz) and shows a strong NOE to the CHMe proton establishing that lactone **45** also adopts a boat conformation. The coupling constant is smaller than those of the CHPh proton (J = 9.8 Hz) in **28a** and the CH-*N*-SEM-pyrrole proton (J = 9.2 Hz) in the protected analogue of **45** that leads to **47a**. This suggests that hydrogen bonding between the lactone carbonyl group and the pyrrole nitrogen perturbs the lactone conformation in **45**.

Treatment of a 10⁻⁴ molar solution of **45** with 15 mol% Grubbs II catalyst in CH₂Cl₂ at reflux for 12 hours gave **46** as a *cis/trans* mixture of isomers in 18% yield. The yield of **46** was increased to 41% by using more catalyst (2 $\times$ 15 mol%) and prolonging the reaction time to 16 h. Although this yield was not satisfactory, it provided sufficient material for further elaboration. Hydrogenation of **46** over Raney nickel reduced the double bond to afford **47b** as a single compound in 90% yield. The ¹H NMR spectrum of **47b** shows the expected shielding of protons on the seven carbon methylene bridge by the pyrrole ring to δ 0.83 (m, 1) and δ 0.39 (m, 1) similar to that observed in marineosins A at δ 0.69 (m, 1) and δ 0.52 (m, 1). The large coupling constant for the CH-pyrrole proton at δ 3.47 (J = 12.1 Hz) indicates that the macrocycle is *trans* fused to the lactone. The structure of **47b** was confirmed by X-ray crystal structure determination, which indicates that the lactone adopts the boat conformation as shown in Figure 1.

N-H pyrrole lactone **47b** was converted to *N*-H pyrrole isoxazoline **51b** by the sequence developed to prepare isoxazolines **34** and **35** (see Scheme 10). Treatment of **47b** with *i*-PrMgCl and *N,O*-dimethylhydroxylamine•HCl afforded Weinreb amide **48b** in 86% yield, which was protected to give triethylsilyl ether **49b** in 77% yield. To our surprise,

considerable reduction to the aldehyde occurred on treatment of Weinreb amide **49b** with vinylmagnesium bromide. This problem has been previously noted, especially as the Grignard reagent ages.^{33,34} Fortunately, addition of a solution of vinylolithium³⁴ freshly prepared from vinyl bromide and *n*-BuLi to **49b** afforded enone **50b** in 70% yield.

The cycloaddition of **50b** with *N*-SEM-pyrrole-2-carboxaldehyde oxime and NaOCl gave isoxazoline **51b** in ~67% yield as a mixture of stereoisomers although the reaction was not as clean as those with enones **13b** and **33**. Hydrogenolysis of **51b** over Raney nickel provided a crude mixture in ~67% yield that appeared to contain hemi-iminals **52b** based on the similarity of the ¹H NMR spectrum to those of **15** and the crude hydrogenation product from **34**.

We were concerned that it might not be possible to methylate the two hydroxy groups of **52b** without *N*-methylation of the pyrrole. However, to our disappointment, *O*-methylation of **52b**, with or without concomitant *N*-methylation could not be accomplished. The use of NaH and MeI, which was successful in all the model studies, afforded a complex mixture. Other bases (KOH or KO^tBu) and methylating reagents (Me₂SO₄) were also successful with **15a** as was acid-catalyzed methylation with CH₂N₂ or TMSCHN₂. Unfortunately, all of these conditions failed to methylate hemi-iminal **52b**. Hemi-iminals are unstable and may decompose if the methylation doesn't occur rapidly. Apparently the hydroxy groups of **52b** are more hindered than those of the model hemi-iminals so that only decomposition occurs on attempted methylation.

We attempted to form the spiroiminal prior to methylation, but **52b** decomposed on treatment with 2 M HCl or Dowex 50 WX ion exchange resin. Hemi-iminal **52b** decomposed after 10 h in CDCl₃ indicating that it is very acid sensitive.

We had previously prepared macrocyclic *N*-SEM pyrrole lactone **47a**.^{13, 35} The four step sequence leading to isoxazoline **51a** proceeded uneventfully, but all attempts to hydrogenolyze the isoxazoline and to form hemi-iminal **52a** failed completely. We hypothesized that the protecting group on the pyrrole in the tether prevented formation of the hemi-iminal. We couldn't deprotect **47a** to give **47b**, so we developed the route to **47b** described in detail above. We can form hemi-iminal **52b** lacking the pyrrole protecting group, but the sequence fails one step later at the methylation stage.

In conclusion we have developed a short and efficient synthesis of model spiroiminals **18a–21a** (six steps) and **18b–21b** (seven steps) that have the same stereochemistry but different conformations than marineosins A and B. Phenyl substituted spiroiminals **18a–21a** were also prepared biomimetically by reduction of an enol ether. More highly substituted spiroiminal **36** with the same stereochemistry and conformation as marineosin A was prepared in 11 steps. Macrocyclic pyrrole lactone **47b** was prepared stereospecifically in 10 steps. A five step sequence converted the lactone to a late hemi-iminal intermediate **52b** that has resisted the methylation and spiroiminal formation that would lead to marineosin A.

Experimental Section

General Experimental Methods

Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The phrase "concentrated" refers to removal of solvents by means of a rotary evaporator attached to a diaphragm pump (15–60 Torr) followed by removal of residual solvents at < 1 Torr with a vacuum pump. Flash chromatography was performed on silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F-254 pre-coated glass plates (0.25 mm). TLC Plates were

analyzed by short wave UV illumination, or by dipping in vanillin stain (27 g of vanillin in 380 mL of EtOH, 50 mL of water and 20 mL of concentrated sulfuric acid) and heating on a hot plate. THF and ether were dried and purified by distillation from sodium/benzophenone. Et₃N was distilled from CaH₂. ¹H and ¹³C NMR spectra were obtained on a 400 MHz spectrometer in CDCl₃ with CHCl₃ as an internal standard (δ 7.26, CDCl₃ at δ 77.00) unless otherwise indicated. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). IR spectra were acquired on an FT-IR spectrometer and are reported in wave numbers (cm⁻¹). High resolution mass spectra were obtained using the following ionization techniques: chemical ionization (CI), electron impact (EI), electrospray ionization analyzed by quadrupole time of flight (QTof).

Benzaldehyde Oxime

A solution of benzaldehyde (530 mg, 5.0 mmol) in 20 mL of EtOH was treated with a mixture of NaOH (300 mg, 7.50 mmol) and NH₂OH•HCl (783 mg, 11.4 mmol) in 10 mL of H₂O. The reaction mixture was stirred at 25 °C for 6 h, concentrated to remove EtOH, diluted with CH₂Cl₂, washed with brine, and dried (Na₂SO₄). Flash chromatography on silica gel (8:1 hexanes/EtOAc) gave 482 mg (84%) of the oxime as a brown solid with data identical to those previously reported.⁴¹

1-[[2-(Trimethylsilyl)ethoxy]methyl]-1*H*-pyrrole-2-carboxaldehyde was prepared by the literature procedure.¹⁸ A solution of pyrrole-2-carboxaldehyde (245 mg, 2.57 mmol) in anhydrous THF (2 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 124 mg, 3.09 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and SEMCl (0.50 mL, 2.83 mmol) was added by syringe over 3 min. The reaction was warmed to 25 °C and stirred for 2 h. The mixture was quenched with saturated aqueous NH₄Cl (3 mL). The aqueous layer was extracted with EtOAc and the combined organic layers were dried (Na₂SO₄) and concentrated. Flash chromatography on silica gel (8:1 hexanes/EtOAc) gave 538 mg (93%) of *N*-SEM-pyrrole-2-carboxaldehyde as a pale yellow gum: ¹H NMR 9.58 (s, 1), 7.15-7.13 (m, 1), 6.96 (dd, 1, *J* = 1.5, 3), 6.30 (dd, 1, *J* = 3, 4), 5.70 (s, 2), 3.54 (t, 2, *J* = 8.1), 0.89 (t, 2, *J* = 8.1), -0.04 (s, 9); ¹³C NMR 179.3, 131.6, 130.8, 125.0, 110.2, 76.2, 65.8, 17.5, -1.7 (3 C); IR (neat) 1671.

1-[[2-(Trimethylsilyl)ethoxy]methyl]-1*H*-pyrrole-2-carboxaldehyde Oxime—A solution of *N*-SEM-pyrrole-2-carboxaldehyde (538 mg, 2.39 mmol) in 11 mL of 10:1 MeOH/H₂O was treated with NH₂OH•HCl (183 mg, 2.63 mmol) and NaOAc (295 mg, 3.59 mmol). The resulting mixture was stirred at 25 °C for 2.5 h, concentrated to remove MeOH, diluted with CH₂Cl₂, washed with brine, dried (Na₂SO₄), and concentrated. Flash chromatography on silica gel (8:1 hexanes/EtOAc) gave 482 mg (84%) of the oxime as a brown gum: ¹H NMR 8.92 (s, 1, OH), 8.20 (s, 1), 6.87-6.85 (m, 1), 6.52 (dd, 1, *J* = 1.2, 2.5), 6.19 (dd, 1, *J* = 3, 4), 5.46 (s, 2), 3.50 (t, 2, *J* = 8.2), 0.91 (t, 2, *J* = 8.2), -0.03 (s, 9); ¹³C NMR 142.3, 126.2, 125.2, 115.0, 109.1, 76.9, 65.5, 17.5, -1.6 (3 C); IR (neat) 3376, 1624; HRMS (EI) calcd for C₁₁H₂₀N₂O₂Si (M⁺) 240.1294, found 240.1298.

7-Hydroxy-1-octen-3-one (13a) was prepared by the literature procedure.¹¹ A solution of 6-Methyltetrahydropyran-2-one (**12**) (0.92 g, 8.76 mmol) in anhydrous THF (15 mL) was treated with vinylmagnesium bromide (1 M in THF, 10.51 mL, 10.51 mmol) by syringe over 15 min under nitrogen at -78 °C. The resulting solution was stirred at -78 °C for 4 h. The mixture was quenched with saturated aqueous NH₄Cl, diluted with EtOAc, washed with brine, dried (Na₂SO₄), and concentrated to give 1.11 g of crude **13a**. Flash chromatography on MeOH-deactivated silica gel (4:1 hexanes/EtOAc) gave 1.06 g (85%) of **13a** as a

colorless liquid: ^1H NMR 6.36 (dd, 1, $J = 10.4, 17.4$), 6.24 (d, 1, $J = 17.4$), 5.85 (d, 1, $J = 10.4$), 3.81-3.76 (m, 1), 2.64 (t, 2, $J = 6.7$), 2.37 (s, 1, OH), 1.75-1.65 (m, 2), 1.50-1.43 (m, 2), 1.19 (d, 3, $J = 6.7$); ^{13}C NMR 201.0, 136.3, 128.2, 67.3, 39.2, 38.4, 23.3, 19.8; IR (neat) 3452 (br), 1729.

7-Triethylsilyloxy-1-octen-3-one (13b)—A solution of alcohol **13a** (836 mg, 5.88 mmol) in 15 mL of THF was treated with Et_3N (1.36 mL, 9.41 mmol), DMAP (69 mg, 0.59 mmol), and TESCl (1.58 mL, 9.41 mmol). The mixture was stirred at 25 °C for 3 h. The reaction was then diluted with Et_2O (10 mL) and washed with brine (3×5 mL). The organic layer was dried (MgSO_4) and concentrated to give 1.78 g of crude **13b**. Flash chromatography on silica gel (18:1 hexanes/ EtOAc) gave 1.45 g (96%) of **13b** as a sticky liquid: ^1H NMR 6.34 (dd, 1, $J = 10.6, 17.6$), 6.21 (d, 1, $J = 17.6$), 5.81 (d, 1, $J = 10.6$), 3.82-3.78 (m, 1), 2.59 (t, 2, $J = 6.4$), 1.72-1.58 (m, 2), 1.46-1.39 (m, 2), 1.14 (d, 3, $J = 6.4$), 0.95 (t, 9, $J = 7.6$), 0.58 (q, 6, $J = 7.6$); ^{13}C NMR 200.8, 136.5, 127.9, 68.2, 39.6, 39.1, 23.8, 20.3, 6.9 (3 C), 4.9 (3 C); IR (neat) 1682; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{27}\text{O}_2\text{Si}$ ($\text{M}-\text{H}^+$) 255.1780, found 255.1787.

1-(4,5-Dihydro-3-phenyl-5-isoxazolyl)-5-triethylsilyloxy-1-hexanone (14a)—A solution of *N*-chlorosuccinimide (220 mg, 1.65 mmol) in anhydrous THF (3 mL) was added dropwise by syringe over 20 min to a solution of benzaldehyde oxime (170 mg, 1.40 mmol) in THF (6 mL). The mixture was stirred at 25 °C for 5 h, cooled to -78 °C, and treated with a solution of enone **13b** (300 mg, 1.17 mmol) in THF (2 mL) and then Et_3N (240 μL , 1.65 mmol). The mixture was gradually warmed to 25 °C and stirred for 3 h. The reaction mixture was diluted with EtOAc , washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography on MeOH-deactivated silica gel (12:1 hexanes/ EtOAc) gave 341 mg (78%) of **14a** as a 1:1 mixture of diastereomers as a colorless gum: ^1H NMR 7.67 (d, 2, $J = 6.1$), 7.43-7.39 (m, 3), 5.03 (dd, 1, $J = 6.1, 12.1$), 3.79 (tq, 1, $J = 6.1, 6.1$), 3.64 (dd, 1, $J = 6.1, 16.8$), 3.48 (dd, 1, $J = 12.1, 16.8$), 2.73 (t, 2, $J = 7.3$), 1.73-1.52 (m, 2), 1.50-1.34 (m, 2), 1.12 (d, 3, $J = 5.5$), 0.94 (t, 9, $J = 6.6$), 0.57 (q, 6, $J = 6.6$); ^{13}C NMR 209.5, 156.6, 130.5, 128.8 (2 C), 128.5, 126.8 (2 C), 84.1, 68.1, (38.96, 38.94), (38.82, 38.81), (37.28, 37.25), 23.7, (19.30, 19.27), 6.8 (3 C), 4.9 (3 C); IR (neat) 1721, 1595; HRMS (EI) calcd for $\text{C}_{19}\text{H}_{28}\text{O}_3\text{NSi}$ ($\text{M}^+-\text{CH}_2\text{CH}_3$) 346.1838, found 346.1837.

1-[4,5-Dihydro-3-[1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrol-2-yl]-5-isoxazolyl]-5-triethylsilyloxy-1-hexanone (14c)—A mixture of *N*-SEM-pyrrole-2-carboxaldehyde oxime (440 mg, 1.83 mmol) and enone **13b** (610 mg, 2.28 mmol) in CH_2Cl_2 (15 mL) was treated with bleach (5.25% aqueous NaOCl, 5.15 mL, 271 mg of NaOCl, 3.66 mmol) and Et_3N (40 μL , 0.28 mmol) at 0 °C. The resulting mixture was warmed to 25 °C and stirred for 3 h. The reaction was then diluted with CH_2Cl_2 , washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography on MeOH-deactivated silica gel (12:1 hexanes/ EtOAc) gave 661 mg (73%) of **14c** as a mixture of diastereomers as a pale yellow gum: ^1H NMR 7.00-6.98 (m, 1), 6.46-6.44 (m, 1), 6.23-6.12 (m, 1), 5.67 (d, 1, $J = 10.4$), 5.60 (d, 1, $J = 10.4$), 4.87 (dd, 1, $J = 6.2, 11.3$), 3.79 (tq, 1, $J = 6.1, 6.1$), 3.60 (dd, 1, $J = 6.2, 16.3$), 3.53-3.46 (m, 3), 2.78-2.63 (m, 2), 1.72-1.50 (m, 2), 1.48-1.34 (m, 2), 1.12 (d, 3, $J = 6.1$), 0.94 (t, 9, $J = 7.8$), 0.89 (t, 2, $J = 7.9$), 0.57 (q, 6, $J = 7.8$), -0.04 (s, 9); ^{13}C NMR 209.7, 150.1, 127.5, 121.3, 116.0, 109.3, 82.4, 77.4, 68.1, 65.7, 39.4, 39.0, 38.8, (23.72, 23.70), 19.3, 17.7, 6.9 (3 C), 4.9 (3 C), -1.5 (3 C); IR (neat) 1721, 1598; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{46}\text{O}_4\text{N}_2\text{Si}_2$ (M^+) 494.2996, found 494.2989.

3,4-Dihydro-2,3-dimethoxy-2-(4-triethylsilyloxypentyl)-4-phenyl-2*H*-pyrrole (16a)—A solution of isoxazoline **14a** (178 mg, 0.47 mmol) in 10 mL of MeOH was treated with a wet slurry of Raney nickel 2800 (~50 mg) and the suspension was stirred at 25 °C

under H₂ (1 atm) for 35 min. The mixture was then diluted with EtOAc and filtered. The filtrate was washed with brine (3 × 5 mL), dried (MgSO₄), and concentrated to give 174 mg of crude hydroxy hemi-iminal **15a** as a mixture of four diastereomers that was used for the next step.

A solution of crude **15a** in anhydrous THF (2 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 152 mg, 3.80 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and MeI (237 μL, 3.80 mmol) was then added by syringe over 3 min. The resulting mixture was warmed to 25 °C and stirred for 4 h. The reaction was quenched with saturated aqueous NH₄Cl (3 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to give 163 mg of crude **16a**. Flash chromatography on silica gel (18:1 hexanes/EtOAc) gave 110 mg (58% for two steps) of **16a** as a mixture of four diastereomers as a colorless gum: ¹H NMR (major (75–80%) pair of diastereomers with either cis or trans methoxy groups) 7.87 (d, 2, *J* = 7.3), 7.46–7.39 (m, 3), 3.96–3.91 (m, 1), 3.84–3.75 (m, 1), 3.48 (s, 6), 3.20 (dd, 1, *J* = 7.3, 17.4), 3.02 (dd, 1, *J* = 3.0, 17.4), 1.96–1.82 (m, 1), 1.67–1.35 (m, 5), 1.14 (d, 3, *J* = 6.1), 0.93 (t, 9, *J* = 7.8), 0.58 (q, 6, *J* = 7.8); ¹H NMR (minor (20–25%) pair of diastereomers with either trans or cis methoxy groups) 3.48–3.24 (m, 2 or 3); IR (neat) 2955, 1619, 1449; HRMS (EI) calcd for C₂₃H₃₉O₃NSi (M⁺) 405.2699, found 405.2710.

3,4-Dihydro-2,3-dimethoxy-2-(4-triethylsilyloxypentyl)-4-(1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrol-2-yl)-2*H*-pyrrole (16c)—A solution of isoxazoline **14c** (203 mg, 0.41 mmol) in 12 mL of 5:1 MeOH/H₂O was treated with a wet slurry of Raney nickel 2800 (~50 mg) and the suspension was stirred at 25 °C under H₂ (1 atm) for about 50 min. The mixture was then diluted with EtOAc and filtered. The filtrate was washed with brine (3 × 5 mL), dried (Na₂SO₄), and concentrated to give 191 mg of crude hydroxy hemi-iminal **15c**.

A solution of crude **15c** in THF (2 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 130 mg, 3.24 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and MeI (203 μL, 3.24 mmol) was added dropwise by syringe over 3 min. The resulting mixture was warmed to 25 °C and stirred for 4 h. The reaction was quenched with saturated aqueous NH₄Cl (3 mL) and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), and concentrated to give 151 mg of crude **16c**. Flash chromatography on silica gel (15:1 hexanes/EtOAc) gave 91 mg (42% for two steps) of **16c** (pale yellow gum) as a mixture of four diastereomers in which two predominate: ¹H NMR 7.03–7.01 (m, 1), 6.58–6.56 (m, 1), 6.21–6.19 (m, 1), 5.93 (d, 1, *J* = 10.4), 5.90 (d, 1, *J* = 10.4), 3.80–3.77 (m, 2), 3.54 (t, 2, *J* = 7.9), 3.44 (s, 3), 3.43 (s, 3), 3.12 (dd, 1, *J* = 6.7, 17.1), 2.96 (dd, 1, *J* = 2.4, 17.1), 1.83–1.77 (m, 1), 1.55–1.37 (m, 5), 1.13 (d, 3, *J* = 6.1), 0.94 (t, 9, *J* = 7.8), 0.87 (t, 2, *J* = 7.9), 0.57 (q, 6, *J* = 7.8), –0.05 (s, 9); IR (neat) 2954, 1617; HRMS (EI) calcd for C₂₇H₅₂O₄N₂Si₂ (M⁺) 524.3466, found 524.3475.

3-Methoxy-α-methyl-5-phenyl-1*H*-pyrrole-2-butanol (17a) and (±)-(4*S*,5*R*,7*R*)-, (±)-(4*R*,5*R*,7*R*)-, and (±)-(4*R*,5*S*,7*R*)-4-Methoxy-7-methyl-2-phenyl-6-oxa-1-azaspiro[4.5]dec-1-ene (18a, 19a, and 21a)—A solution of **16a** (101 mg, 243 μmol) in 6 mL of 1:1 CH₃CN/THF was treated with 2 M HCl (2.49 mL, 4.98 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 40 min. Saturated NaHCO₃ (5 mL) was added to bring the pH to 7. The reaction was extracted with EtOAc and the organic layer was washed with brine, dried (Na₂SO₄), and concentrated. Flash chromatography on MeOH-deactivated silica gel (7:1 to 2:1 hexanes/EtOAc) gave 26 mg (41%) of **18a** as a colorless gum, followed by 8.1 mg (13%) of **19a** as a colorless gum, 7.4 mg (12%) of **21a** as a colorless gum, and then 5.2 mg (8%) of **17a** as a pale yellow gum.

The data for **17a**: ^1H NMR (recorded in C_6D_6 because the compound is unstable in CDCl_3) 7.83 (br, 1, NH), 7.30 (d, 2, $J = 7.3$), 7.20 (t, 2, $J = 7.3$), 7.04 (t, 1, $J = 7.3$), 6.30 (d, 1, $J = 2.5$), 3.60 (s, 3), 3.58-3.48 (m, 1), 2.61 (t, 2, $J = 7.4$), 1.69-1.51 (m, 2), 1.38-1.25 (m, 2), 0.92 (d, 3, $J = 6.1$); ^{13}C NMR (C_6D_6) 146.0, 133.9, 129.0 (2 C), 126.9, 125.5, 123.4 (2 C), 117.5, 95.0, 67.8, 58.5, 38.3, 26.3, 24.5, 24.0; IR (neat) 3316, 2934, 1630; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}$ ($\text{M}^+ - 2\text{H}$) 257.1416, found 257.1407. This compound is unstable and oxidizes easily to **24** and **25**.

The data for **18a**: ^1H NMR 7.84 (d, 2, $J = 6.7$), 7.44-7.38 (m, 3), 4.43-4.39 (m, 1, H-7), 3.88 (dd, 1, $J = 7.0$, 7.0, H-4), 3.46 (s, 3), 3.30 (dd, 1, $J = 17.1$, 7.0, H-3), 2.77 (dd, 1, $J = 16.4$, 7.0, H-3), 2.07 (br ddd, 1, $J = 11$, 11, 11, H-9ax), 1.79 (ddd, 1, $J = 11$, 11, 3, H-10ax), 1.77-1.69 (m, 2, H-8eq, H-9eq), 1.51 (br d, 1, $J = 11$, H-10eq), 1.36 (br ddd, 1, $J = 11$, 11, 11, H-8ax), 1.16 (d, 3, $J = 6.1$, H-7 Me); ^{13}C NMR 169.6, 134.8, 130.8, 128.4 (2 C), 127.6 (2 C), 103.8, 87.2, 68.7, 58.2, 39.1, 33.6, 28.7, 22.4, 19.8; IR (neat) 2932, 1615, 1448; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2\text{N}$ (M^+) 259.1572, found 259.1560. A 1D NOESY experiment with irradiation of H-4 at δ 3.88 showed NOEs to OMe at δ 3.46 (OMe) and H-3s at δ 3.30 and 2.77. A 1D NOESY experiment with irradiation of H-7 at δ 4.43-4.39 showed NOEs to H-9ax at δ 2.07, H-8eq at δ 1.77-1.69 and 7-Me at δ 1.16.

The data for **19a**: ^1H NMR 7.86 (d, 2, $J = 7.3$), 7.46-7.36 (m, 3), 4.49-4.42 (m, 1, H-7), 3.77 (dd, 1, $J = 6.1$, 4.0, H-4), 3.50 (s, 3), 3.13 (dd, 1, $J = 17.1$, 6.1, H-3), 3.05 (dd, 1, $J = 17.1$, 4.0, H-3), 2.12 (br ddd, 1, $J = 11$, 11, 11, H-9ax), 1.77 (ddd, 1, $J = 11$, 11, 3, H-10ax), 1.76-1.68 (m, 2, H-8eq, H-9eq), 1.48 (br d, 1, $J = 11$, H-10eq), 1.40 (br ddd, 1, $J = 11$, 11, 11, H-8ax), 1.23 (d, 3, $J = 6.7$, H-7 Me); ^{13}C NMR 170.3, 134.8, 130.7, 128.3 (2 C), 127.7 (2 C), 101.7, 85.4, 68.6, 58.8, 39.6, 34.7, 33.3, 22.3, 20.4; IR (neat) 2930, 1616, 1448; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2\text{N}$ (M^+) 259.1572, found 259.1570. A 1D NOESY experiment with irradiation of H-4 at δ 3.77 showed NOEs to OMe at δ 3.50 (OMe), H-3s at δ 3.13 and 3.05, and H-10ax at δ 1.77 and H-10eq at δ 1.48.

The data for **21a**: ^1H NMR 7.90 (d, 2, $J = 7.4$), 7.44-7.36 (m, 3), 4.11 (dd, 1, $J = 6.7$, 3.6, H-4), 3.83-3.76 (m, 1, H-7), 3.40 (s, 3), 3.36 (dd, 1, $J = 17.4$, 6.7, H-3), 2.94 (dd, 1, $J = 17.4$, 3.6, H-3), 2.06-2.01 (m, 1), 1.88-1.75 (m, 3), 1.62 (br d, 1, $J = 11$), 1.46-1.38 (m, 1), 1.23 (d, 3, $J = 6.1$); ^{13}C NMR 171.9, 134.0, 131.1, 128.2 (2 C), 128.1 (2 C), 105.4, 83.8, 69.9, 57.7, 40.1, 32.2, 28.9, 22.3, 20.6; IR (neat) 2930, 1627, 1448; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2\text{N}$ (M^+) 259.1572, found 259.1556. A 1D NOESY experiment with irradiation of H-4 at δ 4.11 showed NOEs to H-7 at δ 3.83-3.76, OMe at δ 3.40, and H-3s at δ 3.36 and 2.94.

Equilibration of 19a and 21a—A solution of **19a** in 0.6 mL of CDCl_3 (containing HCl/DCI from decomposition of CDCl_3) equilibrated to a 3:1 mixture of **19a** and **21a**. The percentage of **19a** in the mixture was determined as a function of time by ^1H NMR spectroscopy: initial, 100%; 7 days, 90%; 14 days, 80%; 20 days, 75%. The spectrum did not change at longer times. A solution of **21a** in 0.6 mL of CDCl_3 (containing HCl/DCI from decomposition of CDCl_3) equilibrated to a 3:1 mixture of **19a** and **21a**. The percentage of **19a** in the mixture was determined as a function of time by ^1H NMR spectroscopy: initial, <2%; 5 days, 25%; 10 days, 60%; 15 days, 75%. The spectrum did not change at longer times.

Equilibration of 18a and 20a—A solution of **18a** in 0.6 mL of CDCl_3 (containing HCl/DCI from decomposition of CDCl_3) was monitored by ^1H NMR for 14 days, at which time a 19:1 mixture of **18a** and **20a** was present. Partial data for **20a** were determined from the mixture: ^1H NMR 7.91 (d, 2, $J = 7.6$), 7.40-7.20 (m, 3), 4.13 (d, 1, $J = 4.9$, H-4), 3.80-3.74

(m, 1, H-7), 3.36 (s, 3, OMe), 3.20 (d, 1, $J = 17.4$, H-3), 2.99 (dd, 1, $J = 17.4$, 4.9, H-3), 1.30 (d, 3, $J = 6.4$).

(±)-(4*S*,5*R*,7*R*)-, (±)-(4*R*,5*R*,7*R*)-, and (±)-(4*R*,5*S*,7*R*)-4-Methoxy-7-methyl-2-(1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrol-2-yl)-6-oxa-1-azaspiro[4.5]dec-1-ene (18c, 19c, and 21c)—A solution of **16c** (78 mg, 149 μmol) in 8 mL of 3:1 CH₃CN/THF was treated with aqueous 2 M HCl (1.49 mL, 2.98 μmol) at 25 °C. The resulting mixture was stirred at 25 °C for 11 h. Saturated NaHCO₃ (3 mL) was added to bring the pH to 7. The reaction was extracted with EtOAc and the organic layer was washed with brine, dried (Na₂SO₄), and concentrated to give 77 mg of a mixture of spiroiminals. Flash chromatography on MeOH-deactivated silica gel (18:1 to 2:1 hexanes/EtOAc) gave 19 mg (34%) of isomer **18c** as a colorless gum followed by 19 mg (34%) of an inseparable 3:2 mixture of isomers **19c** and **21c** as a colorless gum.

The data for **18c**: ¹H NMR 7.02–7.00 (m, 1), 6.57–6.55 (m, 1), 6.21–6.19 (m, 1), 6.01 (d, 1, $J = 10.1$), 5.88 (d, 1, $J = 10.1$), 4.29–4.22 (m, 1, H-7), 3.77 (dd, 1, $J = 6.9$, 6.9, H-4), 3.55 (t, 2, $J = 8.2$), 3.43 (s, 3), 3.23 (dd, 1, $J = 6.9$, 16.3, H-3), 2.76 (dd, 1, $J = 6.9$, 16.3, H-3), 1.98 (br ddd, 1, $J = 11$, 11, 11, H-9ax), 1.76 (ddd, 1, $J = 11$, 11, 3, H-10ax), 1.76–1.64 (m, 2, H-8eq, H-9eq), 1.49 (br d, 1, $J = 11$, H-10eq), 1.34 (br ddd, 1, $J = 11$, 11, 11, H-8ax), 1.13 (d, 3, $J = 6.1$), 0.88 (t, 2, $J = 8.2$), –0.05 (s, 9); ¹³C NMR 162.6, 127.6, 127.5, 116.6, 108.9, 104.3, 86.2, 76.8, 68.6, 65.5, 58.2, 40.5, 33.6, 29.0, 22.4, 20.0, 18.0, –1.5 (3 C); IR (neat) 1610; HRMS (EI) calcd for C₂₀H₃₄O₃N₂Si (M⁺) 378.2339, found 378.2325.

The data for **19c** and **21c**: IR (CDCl₃) 1613; HRMS (EI) calcd for C₂₀H₃₄O₃N₂Si (M⁺) 378.2339, found 378.2350.

NMR data for **19c** were determined from the mixture: ¹H NMR 7.03–7.01 (m, 1), 6.57–6.55 (m, 1), 6.20–6.17 (m, 1), 6.16 (d, 1, $J = 10.1$), 5.74 (d, 1, $J = 10.1$), 4.35–4.29 (m, 1), 3.67 (dd, 1, $J = 6.0$, 4.8), 3.56 (t, 2, $J = 8.5$), 3.47 (s, 3), 3.06 (dd, 1, $J = 17.2$, 6.0), 3.01 (dd, 1, $J = 17.2$, 4.8), 2.06–1.99 (m, 1), 1.78–1.35 (m, 5), 1.21 (d, 3, $J = 6.1$), 0.90–0.85 (m, 2), –0.05 (s, 9); ¹³C NMR 162.9, 127.6, 127.4, 116.7, 108.9, 102.0, 84.3, 68.6, 65.6, 58.6, 40.8, 34.8, 33.4, 22.3, 20.6, 18.0, –1.5 (3 C), (one peak is obscured by the CDCl₃ triplet at δ 77.0).

NMR data for **21c** were determined from the mixture: ¹H NMR 7.01–6.99 (m, 1), 6.57–6.55 (m, 1), 6.38 (d, 1, $J = 10.4$), 6.20–6.17 (m, 1), 5.54 (d, 1, $J = 10.4$), 3.97 (dd, 1, $J = 6.0$, 3.1), 3.81–3.75 (m, 1), 3.51 (t, 2, $J = 8.5$), 3.36 (s, 3), 3.28 (dd, 1, $J = 16.8$, 6.0), 2.86 (dd, 1, $J = 16.8$, 3.1), 2.06–1.99 (m, 1), 1.78–1.35 (m, 5), 1.21 (d, 3, $J = 6.1$), 0.90–0.85 (m, 2), –0.04 (s, 9); ¹³C NMR 164.8, 127.6, 127.4, 117.0, 108.9, 106.2, 82.0, 70.1, 65.6, 57.4, 41.2, 32.2, 29.4, 22.4, 20.5, 17.9, –1.5 (3 C), (one peak is obscured by the CDCl₃ triplet at δ 77.0).

(±)-(4*S*,5*R*,7*R*)-4-Methoxy-7-methyl-2-(1*H*-pyrrol-2-yl)-6-oxa-1-azaspiro[4.5]dec-1-ene (18b)—A mixture of **18c** (19 mg, 50.2 μmol) and molecular sieves (4 Å, 100 mg) in freshly distilled THF (3 mL) was treated with TBAF (1 M in THF, 1.01 mL, 1.01 mmol) dropwise at 50 °C. The resulting mixture was stirred at 60 °C for 3 h. The reaction was cooled, diluted with Et₂O (15 mL), washed with brine (2 × 5 mL) and H₂O (3 × 5 mL). The organic layer was dried (MgSO₄) and concentrated to give 59 mg crude of **18b**. Flash chromatography on MeOH-deactivated silica gel (4:1 hexanes/EtOAc) gave 5.7 mg (54%) of **18b** as a pale yellow gum: ¹H NMR 6.94–6.91 (m, 1), 6.57–6.54 (m, 1), 6.25–6.23 (m, 1), 4.26–4.20 (m, 1), 3.82 (dd, 1, $J = 6.7$, 6.1), 3.43 (s, 3), 3.19 (dd, 1, $J = 16.4$, 6.7), 2.73 (dd, 1, $J = 16.4$, 6.1), 1.97 (br ddd, 1, $J = 11$, 11, 11, H-9ax), 1.81–1.66 (m, 3, H-10ax, H-8eq, H-9eq), 1.54 (br d, 1, $J = 11$, H-10eq), 1.32 (br ddd, 1, $J = 11$, 11, 11, H-8ax), 1.12 (d, 3, $J = 6.1$, H-7 Me), the pyrrole NH was not observed; ¹³C NMR 162.8,

127.7, 122.1, 113.7, 109.8, 103.4, 86.9, 68.5, 58.1, 38.5, 33.4, 28.7, 22.4, 19.7; IR (CDCl₃) 2930, 1607, 1432, 743; HRMS (EI) calcd C₁₄H₂₀N₂O₂ (M⁺) 248.1525, found 248.1532.

(±)-(4*R*,5*R*,7*R*)- and (±)-(4*R*,5*S*,7*R*)-4-Methoxy-7-methyl-2-(1*H*-pyrrol-2-yl)-6-oxa-1-azaspiro[4.5]dec-1-ene (19*b* and 21*b*)—A 3:2 mixture of **19c** and **21c** (19 mg, 50.2 μmol), and molecular sieves (4 Å, 100 mg) in freshly distilled THF (3 mL) was treated with TBAF (1 M in THF, 1.01 mL, 1.01 mmol) dropwise at 50 °C. The resulting mixture was then stirred at 60 °C for 3 h. The reaction was cooled, diluted with Et₂O (15 mL), washed with brine (2 × 5 mL) and H₂O (3 × 5 mL). The organic layer was dried (MgSO₄) and concentrated to give 65 mg crude of **19b** and **21b**. Flash chromatography on MeOH-deactivated silica gel (4:1 to 2:1 hexanes/EtOAc) gave 5.9 mg (56%) of an inseparable 7:3 mixture of **19b** and **21b** as a pale yellow gum: IR (CDCl₃) 2933, 1612, 1434, 744; HRMS (EI) calcd C₁₄H₂₀N₂O₂ (M⁺) 248.1525, found 248.1533.

NMR data for **19b** were determined from the mixture: ¹H NMR 6.94-6.92 (m, 1), 6.56-6.54 (m, 1), 6.25-6.21 (m, 1), 4.31-4.23 (m, 1), 3.70 (dd, 1, *J* = 6.1, 4.3), 3.48 (s, 3), 3.03 (dd, 1, *J* = 16.4, 6.1), 2.97 (dd, 1, *J* = 16.4, 4.3), 2.08-1.98 (m, 1), 1.81-1.32 (m, 5), 1.19 (d, 3, *J* = 6.1), the pyrrole NH was not observed; ¹³C NMR 163.1, (127.8 or 127.1), (122.5 or 122.2), (114.2 or 113.6), (109.9 or 109.8), 100.7, 85.3, 68.4, 58.8, 38.6, 34.3, 33.3, 22.3, 20.3.

NMR data for **21b** were determined from the mixture: ¹H NMR 6.92-6.90 (m, 1), 6.56-6.54 (m, 1), 6.25-6.21 (m, 1), 4.07 (dd, 1, *J* = 6.1, 3.0), 3.81-3.73 (m, 1), 3.38 (s, 3), 3.24 (dd, 1, *J* = 17.0, 6.1), 2.85 (dd, 1, *J* = 17.0, 3.0), 2.08-1.98 (m, 1), 1.81-1.32 (m, 5), 1.21 (d, 3, *J* = 6.1), the pyrrole NH was not observed; ¹³C NMR 164.4, (127.8 or 127.1), (122.5 or 122.2), (114.2 or 113.6), (109.9 or 109.8), 105.0, 83.1, 70.1, 57.5, 39.4, 32.3, 29.1, 22.4, 20.7.

3-Methoxy-α-methyl-5-phenyl-1*H*-pyrrole-2-butanol (17*a*)—A solution of dimethyl ether **16a** (64 mg, 0.25 mmol) in 10 mL of THF was treated with HF (1.35 M in THF, 3.7 mL, prepared by addition of 1 mL of 48% aqueous HF to 15 mL of THF). The mixture was stirred at 0 °C for 1.5 h. The mixture was diluted with EtOAc, washed with NaHCO₃ (25 mL), brine (10 mL), dried (Na₂SO₄), and concentrated. Flash chromatography of the residue on MeOH-deactivated silica gel (3:1 hexanes/EtOAc) gave 26 mg (65%) of **17a** as a pale yellow gum.

(±)-(5*R*,7*R*)- and (±)-(5*S*,7*R*)-4-methoxy-7-methyl-2-phenyl-6-oxa-1-azaspiro[4.5]deca-1,3-diene (24 and 25)—A solution of pyrrole **17a** (260 mg, 1 mmol) in 12 mL of acetone was treated with activated MnO₂ (435 mg, 5 mmol) at 25 °C. The mixture was stirred for 20 min and filtered through a pad of Celite. The filtrate was concentrated to give 247 mg of crude product. Flash chromatography of the residue on silica gel (10:1 to 4:1 hexanes/EtOAc) gave 56 mg (14%) of **24** as a yellow gum followed by 90 mg (35%) of **25** as a yellow gum.

The data for **24**: ¹H NMR 7.91 (d, 2, *J* = 7.1), 7.45-7.39 (m, 3), 5.64 (s, 1), 4.45 (dq, 1, *J* = 3.0, 6.4, 12.8, H-7), 3.89 (s, 3), 2.22 (dddd, 1, *J* = 4.0, 4.0, 12.8, 12.8, 12.8, H-9ax), 1.92 (ddd, 1, *J* = 3.0, 12.8, 12.8, H-10ax), 1.85 (br d, 1, *J* = 12.8, H-9eq), 1.76 (br d, 1, *J* = 12.8, H-8eq), 1.44 (dddd, 1, *J* = 3.0, 12.8, 12.8, 12.8, H-8ax), 1.35 (br d, 1, *J* = 12.8, H-10eq), 1.21 (d, 3, *J* = 6.1); ¹³C NMR 182.0, 171.4, 134.9, 130.6, 128.4 (2 C), 127.5 (2 C), 99.7, 92.9, 70.0, 59.0, 32.6, 31.2, 22.1, 21.2; IR (neat) 2934, 1631; HRMS (QToF) calcd for C₁₆H₂₀NO₂ (MH⁺) 258.1494, found 258.1485.

The data for **25**: ¹H NMR 7.94 (d, 2, *J* = 7.1), 7.44-7.38 (m, 3), 5.60 (s, 1), 4.43 (dq, 1, *J* = 3.0, 6.4, 12.8, H-7), 3.87 (s, 3), 2.15 (br dd, 1, *J* = 12.8, 12.8, H-10ax), 2.10 (dddd, 1, *J* = 3.0, 3.0, 12.8, 12.8, 12.8, H-9ax), 1.84 (ddd, 1, *J* = 3.0, 3.0, 12.8, H-10eq), 1.72-1.64 (m, 2,

H-8eq, H-9eq), 1.44 (dddd, $J = 3.0, 12.8, 12.8, 12.8$, H-8ax), 1.25 (d, 3, $J = 6.1$); ^{13}C NMR 185.6, 171.5, 134.1, 130.8, 128.3 (2 C), 127.7 (2 C), 98.9, 92.2, 69.0, 58.9, 32.0, 30.6, 22.3, 18.5; IR (neat) 2954, 1616; HRMS (QTof) calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_2$ (MH^+) 258.1494, found 258.1496.

(4*S*,5*R*,7*R*)- and (4*R*,5*R*,7*R*)-rel-4-Methoxy-7-methyl-2-phenyl-6-oxa-1-azaspiro[4.5]dec-1-ene (18a and 19a)—A solution of **24** (13 mg, 0.19 mmol) in 5 mL of MeOH was treated with 5% Pd/BaSO₄ (20 mg) and the suspension was stirred at 25 °C under H₂ (1 atm) for 3 h. The mixture was then diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated to afford 11 mg of crude product. Flash chromatography of the residue on MeOH-deactivated silica gel (5:1 to 2:1 hexanes/EtOAc) gave 5 mg (35%) of **18a** as a colorless gum, followed by 3 mg (26%) of **19a** as a colorless gum, and then 2 mg (15%) **17a** as a pale yellow gum.

(±)-(4*S*,5*S*,7*R*)- and (±)-(4*R*,5*S*,7*R*)-4-Methoxy-7-methyl-2-phenyl-6-oxa-1-azaspiro[4.5]dec-1-ene (20a and 21a)—A solution of **25** (21 mg, 0.19 mmol) in 6 mL of MeOH was treated with 5% Pd on BaSO₄ (20 mg) and the suspension was stirred at 25 °C under H₂ (1 atm) for 3 h. The mixture was then diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated to afford 46 mg crude product. Flash chromatography of the residue on MeOH-deactivated silica gel (5:1 to 2:1 hexanes/EtOAc) gave 4 mg (20%) of **21a** as a colorless gum, followed by 8 mg (40%) of **20a** as a colorless gum, and then 3 mg (15%) **17a** as a pale yellow gum.

3-Iodo-6-methyl-5,6-dihydropyran-2-one (11)—A solution of parascorbic acid (**26**)²³ (740 mg, 6.59 mmol) in 12 mL of 1:1 ether/pyridine was treated with iodine (5.02 g, 19.8 mmol) and the mixture was stirred for 8 h. The reaction was diluted with ether, washed with saturated aqueous Na₂SO₃ (30 mL), saturated aqueous CuSO₄ (3 × 20 mL), and brine (20 mL). The organic layer was dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (6:1 hexanes/ EtOAc) gave 1.19 g (76%) of **11** as a pale yellow solid: mp 61–64 °C; ^1H NMR 7.53 (dd, 1, $J = 3.0, 6.1$), 4.72–4.63 (m, 1), 2.47–2.33 (m, 2), 1.44 (d, 3, $J = 6.1$); ^{13}C NMR 160.4, 153.7, 89.3, 75.1, 35.0, 20.4; HRMS (QTof) calcd for $\text{C}_6\text{H}_8\text{O}_2\text{I}$ (MH^+) 238.9569, found 238.9560. The ^1H NMR and ^{13}C NMR data are identical to those previously reported for the (*R*) enantiomer.⁴²

3-Phenyl-6-methyl-5,6-dihydro-2*H*-pyran-2-one (27)—A sealed tube was filled with iodolactone **26** (480 mg, 2.0 mmol), phenylboronic acid (726 mg, 6.0 mmol), Pd(OAc)₂ (22 mg, 0.1 mmol), SPhos (41 mg, 0.1 mmol) and K₃PO₄ (1.5 g, 7.0 mmol). Degassed *n*-butanol (5 mL) was added and the mixture was stirred at 80 °C for 6 h. The mixture was diluted with EtOAc and filtered. The filtrate was washed with brine (15 mL), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (8:1 hexanes/EtOAc) gave 322 mg (85%) of **27** as a yellow solid: mp 89–90 °C; ^1H NMR 7.45 (d, 2, $J = 7.0$), 7.40–7.30 (m, 3), 6.94 (dd, 1, $J = 3.0, 5.9$), 4.71–4.61 (m, 1), 2.58–2.43 (m, 2), 1.49 (d, 3, $J = 6.3$); ^{13}C NMR 164.5, 140.7, 135.5, 133.1, 128.3 (2 C), 128.2 (3 C), 74.3, 31.8, 20.7; IR (neat) 2976, 1706; HRMS (QTof) calcd for $\text{C}_{12}\text{H}_{13}\text{O}_2$ (MH^+) 189.0916, found 189.0915.

(±)-(2*S*,3*S*,5*S*)-5-Hydroxy-2-phenyl-4-propyl-*N*-methoxy-*N*-methyl-hexanamide (31a)—A solution of ZnBr₂ (430 mg, 1.83 mmol) in 12 mL THF was treated with allylmagnesium bromide (1.1 M in THF, 3.33 mL, 3.66 mmol) at 0 °C under nitrogen. The mixture was stirred for 30 min at 0 °C and cooled to –78 °C. A mixture of unsaturated lactone **27** (115 mg, 0.61 mmol) and TMSCl (0.47 mL, 3.66 mmol) in 4 mL THF was added dropwise. The reaction was stirred at –78 °C for 3 h. Aqueous NH₄Cl solution was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were

washed with brine (15 mL), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (10:1 hexanes/EtOAc) gave 377 mg (72%) of a 1:3 mixture of **28a** and **29a** as a pale yellow gum. A 1:3 mixture of **28a** and **29a** in CDCl₃ was treated with DMAP. The percentage of **28a** in the mixture was determined as a function of time by ¹H NMR spectroscopy: initial, 25%; 3 h, 50%; 6 h, 75%; 12 h, 85%. The spectrum did not change at longer times. A similar reaction on a 6:5 mixture also gave a 6:1 mixture of **28a** and **29a**.

Data of **28a** were determined from a 6:1 mixture of **28a** and **29a**: ¹H NMR 7.36 (t, 2, J = 7.6), 7.29 (t, 1, J = 7.6), 7.19 (d, 2, J = 7.6), 5.72-5.62 (m, 1), 5.09 (d, 1, J = 10.1), 5.03 (d, 1, J = 17.1), 4.66-4.56 (m, 1), 3.46 (d, 1, J = 9.8), 2.34-2.24 (m, 1), 2.16 (ddd, 1, J = 4.8, 4.8, 14.0), 1.93 (ddd, 1, J = 8.4, 8.4, 14.0), 1.90-1.83 (m, 2), 1.43 (d, 3, J = 6.3). A 1D NOESY experiment with irradiation of CHPh at δ 3.46 showed NOEs to the protons at δ 7.19 (ortho phenyl), δ 4.66-4.56 (CHMe), δ 2.34-2.24, and δ 1.93.

Data of **29a** were determined from a 1:3 mixture of **28a** and **29a**: ¹H NMR 7.36-7.24 (m, 3), 7.18 (d, 2, J = 7.6), 5.62-5.50 (m, 1), 5.10-4.98 (m, 2), 4.82-4.73 (m, 1), 3.94 (d, 1, J = 5.6), 2.31-2.22 (m, 1), 2.10-2.02 (m, 2), 1.89-1.80 (m, 1), 1.73 (ddd, 1, J = 3.9, 9.2, 14.0), 1.42 (d, 3, J = 6.1).

A 6:1 mixture of **28a** and **29a** (375 mg, 1.6 mmol) was dissolved in 6 mL MeOH and treated with a wet slurry of Raney Ni (~30 mg). The suspension was stirred at 25 °C under H₂ (1 atm) for 0.5 h and filtered through a pad of Celite. The filtrate was concentrated to give 341 mg (91%) of a 6:1 mixture of **28b** and **29b** that was used without further purification.

Data of **28b** were determined from the mixture: ¹H NMR 7.37-7.16 (m, 5), 4.66-4.58 (m, 1), 3.40 (d, 1, J = 9.4), 2.20-1.90 (m, 1), 1.89(ddd, 1, J = 8.0, 10.0, 14.4), 1.76(ddd, 1, J = 4.0, 4.0, 14.4), 1.42 (d, 3, J = 6.3), 1.40-1.14 (m, 4), 0.81 (t, 3, J = 7.0); IR (neat) 2929, 1735, 1188.

Partial data of **29b** were determined from the mixture: ¹H NMR 7.37-7.16 (m, 5), 4.83-4.62 (m, 1), 3.89 (d, 1, J = 3.9), 2.05 (ddd, 1, J = 4.8, 6.8, 11.6).

A 6:1 mixture of lactones **28b** and **29b** (175 mg, 0.75 mmol) and NH(OMe)Me•HCl (300 mg, 3.05 mmol) in 8 mL THF was treated with *i*-PrMgCl (1.3 M in THF, 6.40 mL) at -20 °C. The reaction was warmed to 0 °C in 30 min and stirred at 0 °C for 2.5 h. Aqueous NH₄Cl solution was added and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (3:1 hexanes/EtOAc) gave 29 mg (13%) of **31b** as a colorless gum, followed by 173 mg (78%) of **31a** as a colorless gum.

Data for **31a**: ¹H NMR 7.34-7.21 (m, 5), 3.91 (1, d, J = 10.5), 3.78-3.68 (m, 1), 3.56 (s, 3), 3.15 (s, 3), 2.86 (s, 1, OH), 2.50-2.41 (m, 1), 1.66 (ddd, 1, J = 5.2, 8.8, 14.0), 1.37 (ddd, 1, J = 4.4, 7.6, 14.0), 1.30-1.18 (m, 1), 1.20 (d, 3, J = 6.2), 1.20-1.02 (m, 2), 0.98-0.88 (m, 1), 0.69 (t, 3, J = 7.2); ¹³C NMR 175.5, 138.7, 128.9 (2 C), 128.4 (2 C), 127.0, 64.5, 61.3, 51.8, 43.5, 36.3, 33.9, 32.4, 23.4, 18.7, 14.2; IR (neat) 2931, 1649; HRMS (QTof) calcd for C₁₇H₂₈NO₃ (MH⁺) 294.2069, found 294.2065.

Data for **31b**: ¹H NMR 7.34 (d, 2, J = 7.2), 7.28 (t, 2, J = 7.2), 7.22 (t, 1, J = 7.2), 4.03 (br d, 1, J = 8.2), 3.60-3.53 (m, 1), 3.53 (s, 3), 3.15 (s, 3), 2.36-2.26 (m, 1), 1.62 (s, 1, OH), 1.42-1.34 (m, 5), 1.32 (ddd, 1, J = 6.8, 6.8, 14.0), 1.21 (ddd, 1, J = 6.0, 6.0, 14.0), 0.97 (d, 3, J = 5.9), 0.91 (t, 3, J = 6.8); IR (neat) 2959, 1642, 1377.

(±)-(2S,3S,5S)-5-Triethylsilyloxy-2-phenyl-4-propyl-N-methoxy-N-methyl-hexanamide (32)—A solution of alcohol **31a** (87 mg, 0.29 mmol) in THF was treated with TESCl (162 μL, 0.43 mmol), Et₃N (181 μL 0.58 mmol) and DMAP (4 mg, 0.03 mmol).

The mixture was stirred at 25 °C for 3 h. The reaction was then diluted with Et₂O (10 mL) and washed with brine. The organic layers were dried (MgSO₄) and concentrated. Flash chromatography of the residue on silica gel (10:1 hexanes/EtOAc) gave 102 mg (85%) of **32** as a colorless gum: ¹H NMR 7.35 (d, 2, *J* = 7.2), 7.28 (t, 2, *J* = 7.2), 7.21 (t, 1, *J* = 7.2), 3.97 (br d, 1, *J* = 9.4), 3.91-3.83 (m, 1), 3.55 (s, 3), 3.12 (s, 3), 2.32-2.22 (m, 1), 1.56 (ddd, 1, *J* = 5.2, 9.2, 13.6), 1.43 (ddd, 1, *J* = 3.4, 8.0, 13.6), 1.28-1.10 (m, 4), 1.18 (d, 3, *J* = 5.9), 0.97 (t, 9, *J* = 8.0), 0.71 (t, 3, *J* = 7.1), 0.61 (q, 6, *J* = 8.0); ¹³C NMR 174.4, 138.5, 129.0 (2 C), 128.2 (2 C), 126.8, 67.2, 61.3, 51.0, 42.0, 37.8, 32.1 (2 C), 23.3, 17.9, 14.4, 6.8 (3 C), 4.8 (3 C); IR (neat) 2956, 1661, 1264; HRMS (QToF) calcd for C₂₃H₄₁NO₃NaSi (MNa⁺) 430.2753, found 430.2756.

(±)-(4*S*,5*S*,7*S*)-4-Phenyl-5-propyl-7-triethylsilyloxy-1-octen-3-one (33)—A

solution of Weinreb amide **32** (81 mg, 0.2 mmol) in 6 mL of THF was treated with vinylmagnesium bromide (0.7 M, 0.43 mL) slowly at 25 °C. The reaction was stirred for 1.5 h and aqueous NH₄Cl (5 mL) solution was added. The mixture was extracted with EtOAc (3 × 10 mL). The organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (10:1 hexanes/EtOAc) gave 53 mg (72%) of **33** as a colorless gum: ¹H NMR 7.32-7.09 (m, 5), 6.34 (dd, 1, *J* = 10.1, 17.3), 6.24 (d, 1, *J* = 17.3), 5.64 (d, 1, *J* = 10.1), 3.94 (d, 1, *J* = 9.4), 3.94-3.86 (m, 1), 2.41-2.31 (m, 1), 1.55 (ddd, 1, *J* = 6.4, 6.4, 13.6), 1.43 (ddd, 1, *J* = 4.4, 6.8, 13.6), 1.30-1.17 (m, 4), 1.17 (d, 3, *J* = 6.3), 0.96 (t, 9, *J* = 8.0), 0.73 (t, 3, *J* = 7.1), 0.61 (q, 6, *J* = 8.0); ¹³C NMR 199.8, 137.2, 136.2, 129.3 (2 C), 128.6 (2 C), 127.9, 127.1, 67.0, 60.3, 41.6, 36.5, 32.4, 23.6, 18.3, 14.4, 6.9 (3 C), 5.0 (3 C); IR (neat) 2955, 1699, 1676; HRMS (QToF) calcd for C₂₃H₃₈O₂NaSi (MNa⁺) 397.2539, found 397.2545.

(±)-(2*S*,3*S*,5*S*)-1-[(*5R*)-4,5-Dihydro-3-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrole-5-isoxazolyl]-2-phenyl-3-propyl-5-triethylsilyloxy-1-hexanone (34) and (±)-(2*S*,3*S*,5*S*)-1-[(*5S*)-4,5-Dihydro-3-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrole-5-isoxazolyl]-2-phenyl-3-propyl-5-triethylsilyloxy-1-hexanone (35)—A

mixture of *N*-SEM-pyrrole-2-carboxaldehyde oxime (122 mg, 0.51 mmol) and enone **33** (96 mg, 0.26 mmol) in CH₂Cl₂ (15 mL) was treated with bleach (5.25% aqueous NaOCl, 1.12 mL, 58 mg of NaOCl, 0.77 mmol) and Et₃N (13 μL, 0.3 mmol) at 0 °C. The resulting mixture was warmed to 25 °C and stirred for 3 h. The reaction was then diluted with CH₂Cl₂, washed with brine, dried (Na₂SO₄), and concentrated. Flash chromatography of the residue on MeOH-deactivated silica gel (18:1 hexanes/EtOAc) gave 30 mg (20%) of pure **34** as a colorless gum, followed by a 4:1 mixture of **34** and **35** (64 mg, 41% yield) as a colorless gum. Further chromatography of this fraction gave a 1:1 mixture of **34** and **35** (24 mg).

Data for **34**: ¹H NMR 7.32-7.22 (m, 5), 6.97-6.94 (m, 1), 6.40-6.37 (m, 1), 6.20-6.17 (m, 1), 5.72 (d, 1, *J* = 10.2), 5.49 (d, 1, *J* = 10.2), 4.77 (dd, 1, *J* = 6.7, 11.5), 4.28 (d, 1, *J* = 10.2), 3.81 (tq, 1, *J* = 5.8, 5.8), 3.63 (dd, 1, *J* = 6.7, 16.8), 3.52 (t, 2, *J* = 7.8), 3.23 (dd, 1, *J* = 11.5, 16.8), 2.34-2.25 (m, 1), 1.51 (ddd, 1, *J* = 5.6, 8.4, 14.0), 1.25-1.12 (m, 4), 1.10 (d, 3, *J* = 5.8), 0.98-0.90 (m, 1), 0.93 (t, 9, *J* = 7.8), 0.93 (t, 2, *J* = 7.8), 0.67 (t, 3, *J* = 7.0), 0.55 (q, 6, *J* = 7.8), -0.06 (s, 9); ¹³C NMR 207.2, 150.3, 136.5, 129.5 (2 C), 128.8 (2 C), 127.4, 127.2, 121.4, 115.9, 109.3, 91.5, 81.0, 77.4, 67.2, 65.7, 58.5, 42.0, 37.8, 36.1, 32.2, 23.5, 17.8, 14.5, 6.9 (3 C), 4.9 (3 C), -1.4 (3 C); IR (neat) 2956, 1720, 1358; HRMS (QToF) calcd for C₃₄H₅₇N₂O₄Si₂ (MH⁺) 613.3857, found 613.3860.

Partial data for **35** were obtained from a 1:1 mixture of **34** and **35**: ¹H NMR 7.34-7.12 (m, 5), 6.93-6.92 (m, 1), 6.17-6.15 (m, 1), 6.14-6.12 (m, 1), 5.57 (d, 1, *J* = 10.2), 5.41 (d, 1, *J* = 10.2), 4.86 (dd, 1, *J* = 6.4, 12.0), 4.33 (d, 1, *J* = 10.2), 3.92-3.84 (m, 1), 3.48 (t, 2, *J* = 7.8), 3.40 (dd, 1, *J* = 12.0, 16.8), 3.16 (dd, 1, *J* = 6.4, 16.8), 2.34-2.25 (m, 1), 1.64-1.55 (m, 1), 1.35-1.12 (m, 4), 1.17 (d, 3, *J* = 5.8), 0.90 (t, 9, *J* = 7.8), 0.63 (q, 6, *J* = 7.8), -0.06 (s, 9).

(±)-(4*R*,5*R*,7*S*,9*S*,10*S*)-4-Methoxy-7-methyl-9-propyl-10-phenyl-2-(1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrol-2-yl)-6-oxa-1-azaspiro[4.5]dec-1-ene (36)—A solution of pure isoxazoline **34** (29 mg, 47 μmol) in 6 mL of MeOH was treated with a wet slurry of Raney nickel 2800 (~20 mg) and the suspension was stirred at 25 °C under H₂ (1 atm) for about 30 min. The mixture was then diluted with EtOAc and filtered. The filtrate was washed with brine (3 × 5 mL), dried (Na₂SO₄), and concentrated to give 27 mg of crude hydroxy hemi-iminal.

A solution of crude hydroxy hemi-iminal in THF (1 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 15 mg, 0.37 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and MeI (23 μL, 0.37 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed to 25 °C and stirred for 4 h. The reaction was quenched with saturated aqueous NH₄Cl (3 mL) and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), and concentrated to give 23 mg of crude dimethyl ether. Flash chromatography on silica gel (25:1 hexanes/EtOAc) gave 13 mg (45% for two steps) of a single isomer of the dimethyl ether as a pale yellow gum: ¹H NMR 7.16–7.10 (m, 5), 7.06–7.03 (m, 1), 6.50–6.46 (m, 1), 6.21–6.18 (m, 1), 6.01 (d, 1, *J* = 9.8), 5.77 (d, 1, *J* = 9.8), 3.98 (tq, 1, *J* = 5.9, 5.9), 3.64 (dd, 1, *J* = 3.1, 7.9), 3.50 (t, 2, *J* = 8.2), 3.43 (s, 3), 3.34 (s, 3), 3.03 (d, 1, *J* = 4.3), 2.64 (dd, 1, *J* = 3.1, 17.4), 2.58–2.48 (m, 1), 2.40 (dd, 1, *J* = 7.9, 17.4), 2.15–2.05 (m, 1), 1.46–1.14 (m, 4), 1.19 (d, 3, *J* = 5.9), 0.98 (t, 9, *J* = 7.8), 0.94–0.80 (m, 6), 0.64 (q, 6, *J* = 7.8), –0.03 (s, 9); IR (neat) 2955, 1615.

A solution of the dimethyl ether (13 mg, 21 μmol) in 8 mL of 3:1 CH₃CN/THF was treated with aqueous 2 M HCl (210 μL, 420 nmol) at 25 °C. The resulting mixture was stirred at 25 °C for 20 h. Saturated NaHCO₃ (4 mL) was added to bring the pH to 7. The reaction was extracted with EtOAc and the organic layer was washed with brine, dried (Na₂SO₄), and concentrated to give 12.5 mg of crude **36**. Flash chromatography of the residue on MeOH-deactivated silica gel (6:1 hexanes/EtOAc) gave 7.2 mg (70%) of **36** as a colorless gum: ¹H NMR (CDCl₃) 7.25–7.18 (m, 2), 7.16–7.11 (m, 3), 7.02–6.98 (m, 1), 6.37–6.33 (m, 1), 6.27 (d, 1, *J* = 9.8), 6.15–6.11 (m, 1), 5.71 (d, 1, *J* = 9.8), 4.50–4.41 (m, 1), 3.64–3.53 (m, 3), 3.36 (s, 3), 2.84 (d, 1, *J* = 10.9), 2.66 (dd, 1, *J* = 5.2, 16.2), 2.62–2.51 (m, 1), 2.06 (dd, 1, *J* = 7.0, 16.2), 1.99 (ddd, 1, *J* = 4.0, 4.0, 12.8), 1.73 (ddd, 1, *J* = 5.6, 9.6, 12.8), 1.47 (d, 3, *J* = 6.6), 1.40–1.27 (m, 1), 1.18–1.02 (m, 2), 1.02–0.88 (m, 3), 0.74 (t, 3, *J* = 7.1), 0.00 (s, 9); ¹H NMR (acetone-*d*₆) 7.36–7.30 (m, 2), 7.18–7.10 (m, 4), 6.42–6.38 (m, 1), 6.32 (d, 1, *J* = 9.8), 6.11–6.08 (m, 1), 5.73 (d, 1, *J* = 9.8), 4.40–4.30 (m, 1), 3.66 (t, 2, *J* = 7.1), 3.56 (dd, 1, *J* = 4.2, 7.0), 3.39 (s, 3), 2.90 (d, 1, *J* = 11.3), 2.62–2.51 (m, 1), 2.50 (dd, 1, *J* = 4.2, 16.2), 2.12–2.03 (m, 1), 1.90 (dd, 1, *J* = 7.0, 16.2), 1.73 (ddd, 1, *J* = 4.8, 7.6, 12.8), 1.40 (d, 3, *J* = 6.6), 1.42–1.33 (m, 1), 1.20–1.07 (m, 2), 1.07–0.82 (m, 3), 0.74 (t, 3, *J* = 7.1), 0.00 (s, 9); ¹³C NMR (CDCl₃) 164.3, 140.1, 130.4 (br, 2 C), 127.7 (2 C), 127.3, 127.0, 126.3, 116.9, 108.4, 103.4, 82.1, 77.4, 69.4, 65.7, 58.4, 56.0, 39.6, 36.1, 35.8, 31.8, 23.4, 19.2, 18.1, 14.2, –1.4 (3 C); ¹³C NMR (acetone-*d*₆) 164.8, 141.3, 131.5 (br, 2 C), 129.1 (br, 2 C), 128.6, 128.2, 127.2, 117.9, 109.1, 105.1, 83.2, 78.0, 68.9, 66.0, 58.7, 56.9, 41.5, 37.1, 36.9, 33.3, 23.9, 20.1, 18.7, 14.6, –1.2 (3 C); IR (neat) 2925, 1616, 1084. HRMS (QToF) calcd for C₂₉H₄₅N₂O₃Si (MH⁺) 497.3199, found 497.3192.

A 2D NOESY experiment in CDCl₃ showed NOEs between CHOMe H-4 at δ 3.64–3.53 and both CHPh H-10 at δ 2.84 and the phenyl protons at δ 7.25–7.18 and between CHPr H-9 at δ 2.62–2.51 and 7-Me at δ 1.47.

(±)-(4*S*,5*R*,7*S*,9*S*,10*S*)-4-Methoxy-7-methyl-9-propyl-10-phenyl-2-(1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrol-2-yl)-6-oxa-1-azaspiro[4.5]dec-1-ene (37)—A 1:1 mixture of isoxazolines **34** and **35** (24 mg, 39 μmol) in 5 mL of MeOH was

treated with a wet slurry of Raney nickel 2800 (~20 mg) and the suspension was stirred at 25 °C under H₂ (1 atm) for about 30 min. The mixture was then diluted with EtOAc and filtered. The filtrate was washed with brine (3 × 5 mL), dried (Na₂SO₄), and concentrated to give 22 mg of crude hydroxy hemi-iminals.

A solution of crude hydroxy hemi-iminals in THF (1 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 15 mg, 0.37 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and MeI (23 µL, 0.37 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed to 25 °C and stirred for 4 h. The reaction was quenched with saturated aqueous NH₄Cl (3 mL) and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), and concentrated to give 17 mg of crude mixture of dimethyl ethers. Flash chromatography on silica gel (25:1 hexanes/EtOAc) gave 11 mg (45% for two steps) of a 1:1 mixture of two diastereomeric dimethyl ethers as a colorless gum.

Data for the isomer not obtained from **34** were determined from the mixture: ¹H NMR 7.46-7.41 (d, 2, *J* = 7.0), 7.28-7.19 (m, 3), 7.06-7.03 (m, 1), 6.59-6.56 (m, 1), 6.46 (d, 1, *J* = 9.8), 6.21-6.18 (m, 1), 5.54 (d, 1, *J* = 9.8), 3.85 (tq, 1, *J* = 5.9, 5.9), 3.66 (d, 1, *J* = 3.0, 7.2), 3.61-3.54 (m, 2), 3.36 (s, 3), 3.08 (dd, 1, *J* = 7.2, 17.6), 2.96 (s, 3), 2.82 (dd, 1, *J* = 3.0, 17.6), 2.55 (d, 1, *J* = 4.8), 2.29-2.20 (m, 1), 2.15-2.05 (m, 1), 1.46-1.14 (m, 4), 1.06 (d, 3, *J* = 5.9), 0.92-0.80 (m, 6), 0.87 (t, 9, *J* = 7.8), 0.49 (m, 6, *J* = 7.8), -0.03 (s, 9).

A 1:1 mixture of dimethyl ethers (22 mg, 36 µmol) in 8 mL of 3:1 CH₃CN/THF was treated with aqueous 2 M HCl (360 µL, 720 µmol) at 25 °C. The resulting mixture was stirred at 25 °C for 20 h. Saturated NaHCO₃ (10 mL) was added to bring the pH to 7. The reaction was extracted with EtOAc and the organic layer was washed with brine, dried (Na₂SO₄), and concentrated to give 24 mg of a crude mixture of **36** and **37**. Flash chromatography of the residue on MeOH-deactivated silica gel (10:1 hexanes/EtOAc) gave 5.6 mg (32%) of **37** as a colorless gum, followed by 5.0 mg (29%) of **36** as a colorless gum.

Data for **37**: ¹H NMR (CDCl₃) 7.23 (d, 2, *J* = 7.2), 7.07-7.6.98 (m, 3), 6.98-6.96 (m, 1), 6.19 (d, 1, *J* = 10.0), 6.18-6.15 (m, 1), 6.11-6.08 (m, 1), 5.70 (d, 1, *J* = 10.0), 4.44-4.36 (m, 1), 3.80 (dd, 1, *J* = 8.8, 8.8), 3.66-3.55 (m, 2), 3.42 (s, 3), 3.01 (d, 1, *J* = 11.6), 2.61 (dd, 1, *J* = 8.8, 15.6), 2.47-2.36 (m, 1), 1.96 (ddd, 1, *J* = 4.0, 4.0, 13.6), 1.70 (ddd, 1, *J* = 5.2, 10.0, 13.6), 1.57 (d, 3, *J* = 6.8), 1.38-1.26 (m, 1), 1.11 (dd, 1, *J* = 8.8, 15.6), 1.16-0.88 (m, 5), 0.72 (t, 3, *J* = 7.1), 0.00 (s, 9); ¹H NMR (acetone-*d*₆) 7.32 (d, 2, *J* = 7.2), 7.12-7.09 (m, 1), 7.09-6.92 (m, 3), 6.29-6.23 (m, 3), 6.08-6.04 (m, 1), 5.71 (d, 1, *J* = 10.0), 4.38-4.29 (m, 1), 3.78 (dd, 1, *J* = 8.8, 8.8), 3.66 (t, 2, *J* = 7.1), 3.41 (s, 3), 3.00 (d, 1, *J* = 11.4), 2.69 (dd, 1, *J* = 8.8, 15.6), 2.55-2.45 (m, 1), 1.97 (ddd, 1, *J* = 3.6, 3.6, 13.6), 1.67 (ddd, 1, *J* = 6.4, 10.0, 13.6), 1.56 (d, 3, *J* = 7.1), 1.41-1.28 (m, 1), 1.10 (dd, 1, *J* = 8.8, 15.6), 1.20-0.85 (m, 5), 0.72 (t, 3, *J* = 7.1), 0.00 (s, 9); ¹³C NMR (CDCl₃) 163.0, 140.0, 131.5 (br, 2 C), 127.24, 127.19, 126.7 (2 C), 125.7, 116.8, 108.4, 105.4, 88.3, 69.5, 65.5, 58.3, 52.1, 39.2, 35.7 (2 C), 31.2, 22.9, 19.2, 18.0, 14.1, -1.4 (3 C), one peak is obscured by the CDCl₃ triplet at δ 77.0; ¹³C NMR (acetone-*d*₆) 163.7, 141.3, 132.6 (br, 2 C), 129.1 (br, 2 C), 128.0, 127.5, 126.5, 117.8, 109.0, 106.3, 89.4, 77.9, 69.9, 65.9, 58.5, 53.2, 40.1, 36.8, 36.7, 32.2, 23.5, 20.0, 18.6, 14.6, -1.2 (3 C); IR (neat) 2928, 1619; HRMS (QTof) calcd for C₂₉H₄₅N₂O₃Si (MH⁺) 497.3199, found 497.3199.

A 2D NOESY experiment showed NOEs between the OMe at δ 3.42 and CHPh H-10 at δ 3.01 and the phenyl protons at δ 7.23 and between CHPr H-9 at δ 2.47-2.36 and 7-Me at δ 1.57.

2-(Hex-5-enyl)-1H-pyrrole (39) was prepared by Muchowski's procedure.^{3,30} Magnesium ribbon (400 mg, 16.67 mmol) and a small crystal of iodine (~20 mg) were placed in a 100 mL flask. The flask was flushed with nitrogen and was treated with 30 mL of THF. The suspension of magnesium in THF was slowly treated with 4-bromo-1-pentene (1.64 g, 11.0 mmol) and was heated to reflux gently. The resulting solution was refluxed for 2 h, cooled to 25 °C and cannulated to a solution of 1-(phenylsulfonyl)-2-pyrrolecarboxaldehyde⁴³ (1.95 g, 8.25 mmol) in THF (15 mL) at 0 °C. The mixture was then stirred at 25 °C for 3 h and was quenched with 0.5 M HCl (8 mL). The aqueous layer was extracted with EtOAc and the combined organic layers were dried (Na₂SO₄) and concentrated. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 1.62 g (64%) of α-5-hexen-1-yl-1-(phenylsulfonyl)-1H-pyrrole-2-methanol as a pale yellow gum: ¹H NMR 7.78 (d, 2, *J* = 7.4), 7.62 (t, 1, *J* = 7.4), 7.51 (t, 2, *J* = 7.4), 7.30 (dd, 1, *J* = 1.5, 3.3), 6.32-6.25 (m, 2), 5.79-5.68 (m, 1), 4.98-4.90 (m, 2), 4.81 (t, 1, *J* = 6.0), 2.74 (br s, 1, OH), 2.06-1.92 (m, 2), 1.89-1.73 (m, 2), 1.54-1.42 (m, 1), 1.42-1.31 (m, 1); ¹³C NMR 139.2, 138.4, 138.2, 133.9, 129.4 (2 C), 126.4 (2 C), 123.5, 114.7, 112.4, 111.7, 65.0, 34.4, 33.2, 25.2; IR (neat) 3554, 1364, 1175; HRMS (Qtof) calcd for C₁₆H₁₉NO₃NaS (MNa⁺) 328.0983, found 328.0980.

A solution of the above alcohol (1.62 g, 5.26 mmol) in CH₂Cl₂ (20 mL) was treated with 4A molecular sieves (2.5 g), *N*-methyldmorpholine-*N*-oxide (1.23 g, 10.52 mmol) and tetrapropylammonium perruthenate (0.19 g, 0.53 mmol) at 0 °C. The reaction was stirred at 25 °C for 4 h and filtered through a pad of Celite. The filtrate was concentrated to afford 2.78 g reaction crude as a black oil. Flash chromatography on silica gel (8:1 hexanes/EtOAc) gave 1.44 g (89%) of 1-(1-(phenylsulfonyl)-1H-pyrrol-2-yl)hex-5-en-1-one as a pale yellow gum: ¹H NMR 7.99 (d, 2, *J* = 7.2), 7.80 (dd, 1, *J* = 3.2, 1.6), 7.59 (t, 1, *J* = 7.2), 7.52 (t, 2, *J* = 7.2), 7.03 (dd, 1, *J* = 3.2, 1.6), 7.34 (t, 1, *J* = 1.6), 5.78-5.66 (m, 1), 5.01-4.92 (m, 2), 2.67 (t, 2, *J* = 7.6), 2.00 (dt, 2, *J* = 7.6, 7.6), 1.69 (tt, 2, *J* = 7.6, 7.6); ¹³C NMR (rotamer) 188.7, 138.9, 137.8, 133.5, 133.4, 130.10 (130.06), 128.7 (2 C), 128.1 (2 C), 123.3, 115.3 (br), 110.4 (110.3), 38.4, 32.9, 23.7; IR (neat) 1672, 1438, 1141; HRMS (Qtof) calcd for C₁₆H₁₈NO₃S (MH⁺) 304.1007, found 304.0999.

A solution of the ketone (1.44 g, 4.75 mmol) in *i*-PrOH (50 mL) was treated with NaBH₄ (1.26 g, 33.3 mmol). The mixture was refluxed for 16 h, cooled to 25 °C, and slowly quenched with water (50 mL) and saturated aqueous NH₄Cl (30 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄) and concentrated to give 1.06 g of crude **39**. Flash chromatography on silica gel (12:1 hexanes/EtOAc) gave 0.65 g (84%) of **39** as a pale colorless gum with data identical to those previously reported.³¹

2-(Hex-5-enyl)-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (40)—A solution of pyrrole **39**³¹ (654 mg, 4.08 mmol) in 8 mL of CH₂Cl₂ was treated with (Boc)₂O (1.24 g, 5.69 mmol), Et₃N (0.82 mL, 5.69 mmol) and DMAP (30 mg, 0.43 mmol). The resulting solution was stirred for 5 h and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 811 mg (74%) of **40** as a colorless gum: ¹H NMR 7.19 (dd, 1 *J* = 1.8, 3.3), 6.08 (t, 1, *J* = 3.3), 5.96 (dd, 1, *J* = 1.8, 3.3), 5.82 (ddt, 1, *J* = 10.2, 17.2, 6.7), 5.01 (ddt, 1, *J* = 1.4, 17.2, 1.4), 4.95 (ddt, 1, *J* = 1.4, 10.2, 1.0), 2.85 (t, 2, *J* = 7.6), 2.10 (dt, 2, *J* = 6.7, 7.6), 1.64 (tt, 2, *J* = 7.6, 7.6), 1.59 (s, 9), 1.48 (tt, 2, *J* = 7.6, 7.6); ¹³C NMR (rotamer) 149.5, 138.9 (138.8), 136.3, 120.8 (120.7), 114.3, 110.8 (110.6), 109.9 (109.7), 83.1, 33.6 (br), 28.7, 28.6, 28.3, 28.0 (3 C); IR (neat) 2935, 1742, 1330; HRMS (EI) calcd for C₁₅H₂₃NO₂ (M⁺) 249.1729, found 249.1733.

3-[5-(Hex-5-enyl)-1-*tert*-butoxycarbonylpyrrol-2-yl]-6-methyl-5,6-dihydro-2H-pyran-2-one (42)—A solution of 2,2,6,6-tetramethylpiperidine (1.37 mL, 8.13 mmol) in 12 mL of THF was treated with *n*-BuLi (1.6 M in THF, 5.08 mL) dropwise at -78 °C under

nitrogen. The solution was stirred for 15 min, warmed to 0 °C for 30 min, and recooled to –78 °C. A solution of pyrrole **40** (1.35 g, 5.40 mmol) in 2 mL of THF was added dropwise and the reaction mixture was stirred at –78 °C for 2 h. Trimethyl borate (6.3 mL, 27.0 mmol) was added at –78 °C and the solution was warmed to 25 °C over 2 h and stirred overnight. Aqueous HCl (0.2 N, 45 mL) was added and the resulted mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (25 mL) and dried (Na₂SO₄). The solution was slowly concentrated until a white solid started to precipitate. 5 mL of dry 1,2-dimethoxyethane was added and the solution was slowly concentrated to 2 mL to remove the remaining EtOAc. The solution was kept at 0 °C and degassed. Boronic acid **41** was unstable and was used immediately after being degassed.

A resealable tube was filled with iodolactone **26** (400 mg, 1.67 mmol), LiCl (214 mg, 5.00 mmol), Na₂CO₃ (1.06 g, 10.0 mmol), and Pd(PPh₃)₄ (155 mg, 0.13 mmol) and was purged with nitrogen. 2 mL of the above 1,2-dimethoxyethane solution of boronic acid **41** was added to the mixture, and then 0.3 mL of degassed H₂O was added to the mixture. The tube was sealed and stirred at 80 °C for 8 h. The mixture was diluted with EtOAc and filtered. The filtrate was washed with brine (15 mL), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (8:1 hexanes/EtOAc) gave 330 mg (55%) of **42** as a yellow gum: ¹H NMR 6.74 (dd, 1, *J* = 3.1, 5.5), 6.06 (d, 1, *J* = 2.7), 5.88 (d, 1, *J* = 2.7), 5.81 (ddd, 1, *J* = 6.6, 10.2, 17.2), 5.00 (br d, 1, *J* = 17.2), 4.94 (br d, 1, *J* = 10.2), 4.76-4.67 (m, 1), 2.85-2.72 (m, 2), 2.48-2.35 (m, 2), 2.08 (m, 2), 1.65-1.40 (m, 4), 1.55 (s, 9), 1.47 (d, 3, *J* = 6.1); ¹³C NMR 164.3, 150.1, 138.8, 137.4, 136.9, 129.3, 128.6, 114.4, 112.6, 109.3, 84.1, 74.2, 33.6, 31.4, 29.3, 28.7, 28.5, 27.9 (3 C), 20.7; IR (neat) 1730 (br), 1367, 1216; HRMS (QToF) calcd for C₂₁H₃₀NO₄ (MH⁺) 360.2175, found 360.2177.

(±)-(3S,4S,6S)-3-[5-(Hex-5-enyl)-1H-pyrrol-2-yl]-4-(2-propen-1-yl)-6-methyl-3,4,5,6-tetrahydro-2H-pyran-2-one (45)—A solution of ZnBr₂ (1.00 g, 4.44 mmol) in 20 mL THF was treated with allylmagnesium bromide (1.7 M in THF, 5.22 mL) at 0 °C under nitrogen. The mixture was stirred for 30 min at 0 °C and cooled down to –78 °C. A mixture of unsaturated lactone **42** (400 mg, 1.11 mmol) and TMSCl (1.13 mL, 4.44 mmol) in 4 mL THF was added dropwise. The reaction was stirred at –78 °C for 3 h. Aqueous NH₄Cl solution was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (10:1 hexanes/EtOAc) gave 249 mg (56%) of a 5:4 mixture of *cis*-addition product **43** and *Boc*-migration product **44** as a pale yellow gum

Partial data of **43** were determined from the mixture: ¹H NMR 6.04–6.02 (m, 1), 5.90–5.86 (m, 1), 5.86–5.72 (m, 1), 5.65–5.52 (m, 1), 5.20–4.82 (m, 4), 4.72 (d, 1, *J* = 4.9), 4.72–4.64 (m, 1), 2.80–2.70 (m, 2), 2.48–2.30 (m, 2), 2.20–1.70 (m, 5), 1.59 (s, 9), 1.62–1.40 (m, 4), 1.39 (d, 3, *J* = 6.1).

Partial data of **44** were determined from the mixture: ¹H NMR 5.98–5.95 (m, 1), 5.90–5.86 (m, 1), 5.86–5.65 (m, 2), 5.20–4.82 (m, 4), 4.60–4.52 (m, 1), 2.80–2.70 (m, 2), 2.48–2.30 (m, 1), 2.20–1.70 (m, 6), 1.59 (s, 9), 1.62–1.40 (m, 4), 1.41 (d, 3, *J* = 6.1).

A solution of the mixture of **43** and **44** (270 mg, 0.67 mmol) in CH₂Cl₂ was treated with 2,6-lutidine (0.43 mL, 4.05 mmol) and TMSOTf (0.6 mL, 2.7 mmol) at 0 °C. The reaction was stirred at 25 °C for 8 h, diluted with CH₂Cl₂, and treated with AcOH (0.5 mL). The mixture was washed with water (10 mL), NaHCO₃ (5 mL), and brine (3 × 10 mL). The organic phase was dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (6:1 hexanes/EtOAc) gave 182 mg (91%) of a 19:1 equilibrium mixture of **45** and the *cis* isomer **45** as a pale yellow gum.

Data of **45** were determined from the mixture: ^1H NMR 8.39 (br s, 1, NH), 5.92 (t, 1, $J = 2.7$), 5.79 (t, 1, $J = 2.7$), 5.86-5.69 (m, 2), 5.11 (d, 1, $J = 10.0$), 5.09 (d, 1, $J = 17.2$), 5.00 (d, 1, $J = 17.2$), 4.94 (d, 1, $J = 10.4$), 4.64-4.58 (m, 1), 3.57 (d, 1, $J = 6.7$), 2.56 (t, 2, $J = 7.6$), 2.44-2.30 (m, 2), 2.17-2.10 (m, 1), 2.07 (dt, 2, $J = 7.0$, 7.0), 1.89 (ddd, 1, $J = 6.4$, 10.0, 14.4), 1.80 (ddd, 1, $J = 3.6$, 3.6, 14.4), 1.62 (tt, 2, $J = 7.6$, 7.6), 1.45 (tt, 2, $J = 7.6$, 7.6), 1.37 (d, 3, $J = 6.4$); ^{13}C NMR 173.1, 138.8, 134.9, 133.4, 124.2, 118.0, 114.5, 106.5, 104.6, 73.7, 43.6, 38.4, 33.6, 33.5, 32.9, 28.9, 28.6, 27.6, 21.3; IR (neat) 3365, 1704; HRMS (QTof) calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_2$ (MH^+) 302.2120, found 302.2114. A 2D NOESY experiment showed NOEs between H-3 at δ 3.57 and H-6 at δ 4.64-4.58.

Partial data for the cis isomer of **45** were determined from the mixture: ^1H NMR 4.09 (d, 1, $J = 6.8$).

(±)-(3S,4aS,15aS)-3-Methyl-3,4,4a,5,6,7,8,9,10,11-decahydro-12,15-epiminocycloundeca[c]pyran-1(15aH)-one (47b)—A solution of diene **45** (40 mg, 0.13 mmol) in 250 mL of degassed CH_2Cl_2 was slowly treated with a solution of Grubbs II catalyst (8 mg, 72 μmol) in 5 mL degassed CH_2Cl_2 at reflux under nitrogen. The solution was stirred at reflux for 8 h, and another solution of Grubbs II catalyst (8 mg, 72 μmol) in 5 mL CH_2Cl_2 was slowly added. The solution was stirred at reflux for another 8 h. The reaction was cooled to 25 °C, and five drops of DMSO were added. The solution was stirred overnight and concentrated. Flash chromatography of the residue on silica gel (6:1 hexanes/EtOAc) gave 16 mg (41%) of **46** as a brown solid, which was used directly for the next step.

A solution of alkene **46** (48 mg, 0.18 mmol, from three runs of the previous reaction) in 5 mL MeOH was treated with a wet slurry of Raney nickel 2800 (~15 mg) and the suspension was stirred at 25 °C under H_2 (1 atm) for 25 min. The mixture was then diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated and filtered again through a pad of silica gel to give 43 mg (90%) of **47b** as a white solid: mp 165 °C (decomposed); ^1H NMR 8.23 (br s, 1, NH), 5.92 (m, 1), 5.77 (m, 1), 4.64-4.54 (m, 1), 3.47 (d, 1, $J = 12.1$), 2.55 (ddd, 1, $J = 4.4$, 4.4, 14.4), 2.44 (ddd, 1, $J = 3.8$, 10.8, 14.4), 2.20-2.09 (m, 1), 2.04 (ddd, 1, $J = 10.0$, 10.0, 14.0), 1.67 (ddd, 1, $J = 4.0$, 4.0, 14.0), 1.64-1.44 (m, 4), 1.39 (d, 3, $J = 6.4$), 1.37-1.02 (m, 5), 0.91-0.72 (m, 2), 0.48-0.35 (m, 1); ^{13}C NMR 175.0, 134.0, 124.4, 110.2, 105.7, 73.1, 45.5, 38.3, 33.1, 32.5, 28.1, 26.8, 25.5, 24.6, 24.2, 24.1, 20.9; IR (neat) 3343, 2924, 1725, 1211; HRMS (QTof) calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_2$ (MH^+) 276.1964, found 276.1969.

(±)-(2S,3S)-3-((S)-2-hydroxy)propyl)-N-methoxy-N-methyl-14-azabicyclo[9.2.1]tetradeca-1(13),11-diene-2-carboxamide (48b)—A mixture of lactone **47b** (43 mg, 0.16 mmol) and $\text{NH}(\text{OMe})\text{Me}\cdot\text{HCl}$ (64 mg, 0.65 mmol) in 8 mL THF was treated with *i*-PrMgCl (1.3 M in THF, 1.37 mL) at -20 °C. The reaction was warmed to 0 °C in 30 min and stirred at 0 °C for 2.5 h. Aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc (3 $\times$ 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue on silica gel (3:1 hexanes/EtOAc) gave 43 mg (86%) of **48b** as a colorless gum: ^1H NMR 8.43 (br s, 1, NH), 5.86 (m, 1), 5.74 (m, 1), 3.91 (d, 1, $J = 11.0$), 3.75 (s, 3), 3.74-3.65 (m, 1), 3.19 (s, 3), 2.72 (br s, 1, OH), 2.65 (ddd, 1, $J = 4.0$, 4.0, 14.4), 2.49 (ddd, 1, $J = 3.2$, 11.2, 14.4), 2.28-2.17 (m, 1), 1.75-1.20 (m, 9), 1.18 (d, 3, $J = 6.1$), 1.18-1.04 (m, 2), 1.04-0.74 (m, 3), 0.47-0.35 (m, 1); ^{13}C NMR 175.5, 133.7, 127.2, 108.5, 105.3, 64.8, 61.6, 46.4, 45.0, 35.1, 32.2, 28.8, 28.2, 27.8, 25.2, 25.0, 24.8, 24.5, 23.3; IR (neat) 2958, 1667; HRMS (QTof) calcd for $\text{C}_{19}\text{H}_{33}\text{N}_2\text{O}_3$ (MH^+) 337.2491, found 337.2485.

(±)-(2S,3S)-N-methoxy-N-methyl-3-((S)-2-((triethylsilyl)oxy)propyl)-14-azabicyclo[9.2.1]tetradeca-1(13),11-diene-2-carboxamide (49b)—A solution of

alcohol **48b** (43 mg, 0.16 mmol) in 3 mL of THF was treated with TESC1 (90 μ L, 0.24 mmol), Et₃N (100 μ L, 0.32 mmol) and DMAP (2 mg, 0.02 mmol). The mixture was stirred at 25 °C for 3 h. The reaction was then diluted with Et₂O (10 mL) and washed with brine (10 mL). The organic layer was dried (MgSO₄) and concentrated. Flash chromatography of the residue on silica gel (10:1 hexanes/EtOAc) gave 52 mg (77%) of **49b** as a pale yellow gum: ¹H NMR 8.49 (br s, 1, NH), 5.83 (t, 1, *J* = 2.7), 5.74 (t, 1, *J* = 2.7), 3.88 (tq, 1, *J* = 6.1, 6.1), 3.85 (d, 1, *J* = 11.0), 3.71 (s, 3), 3.17 (s, 3), 2.65 (ddd, 1, *J* = 4.6, 4.6, 14.6), 2.46 (ddd, 1, *J* = 3.7, 11.2, 14.6), 2.10-1.98 (m, 1), 1.79-1.44 (m, 3), 1.46-1.20 (m, 7), 1.18 (d, 3, *J* = 6.1), 1.18-1.02 (m, 2), 0.96 (t, 9, *J* = 8.0), 0.92-0.72 (m, 2), 0.59 (q, 6, *J* = 8.0), 0.45-0.35 (m, 1); ¹³C NMR 174.5, 133.2, 127.4, 108.1, 105.6, 66.7, 61.5, 46.9, 45.8, 35.9, 31.9, 29.1, 28.1, 26.6, 25.9, 25.2, 24.9, 24.6, 23.0, 6.9 (3 C), 4.8 (3 C); IR (neat) 2935, 1679, 1268; HRMS (QToF) calcd for C₂₅H₄₆N₂O₃NaSi (MNa⁺) 473.3175, found 473.3173.

(±)-1-((2*S*,3*S*)-3-((*S*)-2-((triethylsilyl)oxy)propyl)-14-azabicyclo[9.2.1]tetradeca-1(13),11-dien-2-yl)prop-2-en-1-one (50b)—A solution of vinyl bromide (24 μ L, 76 μ mol) in 4 mL of ether was treated with *n*-BuLi (1.6 M in THF, 48 μ L) dropwise at –78 °C. Then the solution was transferred to a solution of Weinreb amide **49b** (17 mg, 38 μ mol) in 2 mL of ether by cannula at 0 °C. The mixture was stirred at 0 °C for 2 h. Aqueous NH₄Cl solution was added and extracted with EtOAc (3 $\times$ 5 mL). The organic solution was washed with brine (5 mL), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (16:1 hexanes/EtOAc) gave 11 mg (70%) of **50b** as a pale yellow gum (containing 5% of bisvinyl tertiary alcohol): ¹H NMR 8.13 (br s, 1, NH), 6.44 (dd, 1, *J* = 10.4, 17.6), 6.22 (d, 1, *J* = 17.6), 5.88 (t, 1, *J* = 2.8), 5.80 (d, 1, *J* = 10.4), 5.75 (t, 1, *J* = 2.8), 3.90 (tq, 1, *J* = 6.1, 6.1), 3.86 (d, 1, *J* = 10.2), 2.63 (ddd, 1, *J* = 4.6, 4.6, 14.6), 2.47 (ddd, 1, *J* = 3.7, 11.2, 14.6), 2.18-2.10 (m, 1), 1.62-1.50 (m, 2), 1.44-1.24 (m, 7), 1.18 (d, 3, *J* = 6.1), 1.18-1.02 (m, 2), 0.96 (t, 9, *J* = 8.0), 0.95-0.70 (m, 2), 0.60 (q, 6, *J* = 8.0), 0.55-0.43 (m, 1); ¹³C NMR 201.2, 136.2, 133.6, 129.0, 125.9, 109.0, 106.2, 66.6, 53.9, 46.3, 35.3, 29.2, 28.0, 26.2, 25.3, 25.2, 25.0, 24.9, 23.1, 6.9 (3 C), 4.9 (3 C); HRMS (QToF) calcd for C₂₅H₄₄NO₂Si (MH⁺) 418.3136, found 418.3142.

X-Ray data collection, solution, and refinement for 47b—All operations were performed on a modern, kappa-geometry X-ray diffractometer equipped with a CCD detector and graphite-monochromated MoK α radiation. All diffractometer manipulations, including data collection, integration, scaling, and absorption corrections were carried out using standard software.⁴⁴ Preliminary cell constants were obtained from three sets of 12 frames. Data collection was carried out at 120K, using a frame time of 30 sec and a detector distance of 60 mm. The optimized strategy used for data collection consisted of three phi and one omega scan sets, with 0.5° steps in phi or omega; completeness was 99.7 %. A total of 2133 frames were collected. Final cell constants were obtained from the xyz centroids of 7440 reflections after integration.

From the systematic absences, the observed metric constants and intensity statistics, space group C2/c was chosen initially; subsequent solution and refinement confirmed the correctness of this choice. The structure was solved using direct methods,⁴⁵ and refined by using full-matrix-least squares methods.⁴⁶ The asymmetric unit contains one complex (*Z* = 8; *Z'* = 1). All ordered non-hydrogen atoms were refined using anisotropic displacement parameters. After location of H atoms on electron-density difference maps, the H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C---H in the range 0.93–0.98 Å and *U*_{iso} (H) in the range 1.2–1.5 times *U*_{eq} of the parent atom), after which the positions were refined with riding constraints.⁴⁷ Minor ring disorder was observed at atom C(10); the two orientations were modeled as C(10) and C(101), and the occupancies were constrained to sum to 1.0. The major component

occupancy (atom C(10), refined using an anisotropic displacement parameters) was 0.922(5); atom C(101) was refined using an isotropic displacement parameter. Atom H(1), attached to N(1) was refined using an isotropic displacement parameter. The final least-squares refinement converged to $R_1 = 0.0434$ ($I > 2\sigma(I)$, 3018 data) and $wR_2 = 0.1117$ (F^2 , 3333 data, 190 parameters). The final CIF is available as supporting material.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of Health (GM-50151) for partial support of this work. We thank Mark W. Bezpalko, Brandeis University, for carrying out the X-ray crystallographic structure determination.

References and Notes

1. Boonlarpradab C, Kauffman CA, Jensen PR, Fenical W. *Org. Lett.* 2008; 10:5508–5508.
2. (a) Fürstner A. *Angew. Chem., Int.* 2003; 42:3582–3603. (b) Williamson NR, Fineran PC, Leeper FJ, Salmond GPC. *Nat. Rev. Microbiol.* 2006; 4:887–899. [PubMed: 17109029] (c) Williamson NR, Fineran PC, Gristwood T, Chawrai SR, Leeper FJ, Salmond GPC. *Future Microbiol.* 2007; 2:605–618. [PubMed: 18041902] (d) Mo S, Sydor PK, Corre C, Alhamadsheh MM, Stanley AE, Haynes SW, Song L, Reynolds KA, Challis GL. *Chem. Biol.* 2008; 15:137–148. [PubMed: 18291318]
3. Aldrich LN, Dawson EW, Lindsley CW. *Org. Lett.* 2010; 12:2231–2234.
4. Ross, DJ.; Harran, P. ORGN 657; 239th ACS National Meeting; March 21–25, 2010; San Francisco, CA.
5. Reynolds, KA. NORM 132; 68th Northwest Regional Meeting of the American Chemical Society; July 21–24, 2013; Corvallis, OR. (b) Salem, SM. Ph.D. Thesis. Portland State University; 2012.
6. For a preliminary communication of a portion of this work, see: Cai X-C, Wu X, Snider BB. *Org. Lett.* 2010; 12:1600–1603. [PubMed: 20218641]
7. Li G, Zhang X, Li Q, Feng P, Shi Y. *Org. Biomol. Chem.* 2013; 11:2936–2938. [PubMed: 23535777]
8. Panarese JD, Konkol LC, Berry CB, Bates BS, Aldrich LN, Lindsley CW. *Tetrahedron Lett.* 2013; 54:2231–2234. [PubMed: 23606772]
9. Aldrich LN, Berry CB, Bates BS, Konkol LC, So M, Lindsley CW. *Eur. J. Org. Chem.* 2013:4215–4218.
10. Cycloadditions with the nitrile *N*-oxide derived from benzaldehyde oxime can be carried out at room temperature, whereas those with the nitrile *N*-oxide of pyrrole-2-carboxaldehyde must be carried out at -78°C Ghabrial SS, Thomsen I, Torrsell KBG. *Acta Chem. Scand. B.* 1987; B41:426–434.
11. Cohen N, Banner BL, Blount JF, Weber G, Tsai M, Saucy G. *J. Org. Chem.* 1974; 39:1824–1833.
12. Andersen SH, Sharma KK, Torrsell KBG. *Tetrahedron.* 1983; 39:2241–2245.
13. For full details Cai X. Ph.D. Thesis. 2013Brandeis University
14. For a similar effect by an axial oxygen in spiroketals, see: Doubský J, Šaman D, Zedník J, Vašíková S, Koutek B. *Tetrahedron Lett.* 2005; 46:7923–7926.
15. For the formation and equilibration of spiroketals, see: Zhou X-T, Lu L, Furkert DP, Wells CE, Carter RG. *Angew. Chem. Int. Ed.* 2006; 45:7622–7626. Taber DF, Joerger J-M. *J. Org. Chem.* 2007; 72:3454–3457. [PubMed: 17397225] Philips ST, Shair MD. *J. Am. Chem. Soc.* 2007; 129:6589–6598. [PubMed: 17469826] Sinibaldi M-E, Canet I. *Eur. J. Org. Chem.* 2008:4391–4399. Wurst JM, Verano AL, Tan DS. *Org. Lett.* 2012; 14:4442–4445. [PubMed: 22924668]
16. (a) Das B, Holla H, Mahender G, Banerjee J, Reddy MR. *Tetrahedron Lett.* 2004; 45:7347–7350. (b) Mendelsohn BA, Lee S, Kim S, Teyssier F, Aulakh VS, Ciufolini MA. *Org. Lett.* 2009; 11:1539–1542. [PubMed: 19254039]
17. Kaiser H-P, Muchowski JM. *J. Org. Chem.* 1984; 49:4203–4209.

18. Muchowski JM, Solas DR. *J. Org. Chem.* 1984; 49:203–205.
19. For a comprehensive review of pyrrole protection and deprotection Jolicoeur B, Chapman EE, Thompson A, Lubell WD. *Tetrahedron*. 2006; 62:11531–11563.
20. Lee GA. *Synthesis*. 1982:508–509.
21. Berner H, Schulz G, Reinshagen H. *Monatsh. Chem.* 1978; 109:137–145.
22. Hydrogenolysis of **14a** over Raney nickel containing boric acid afforded the expected 2-hydroxy-1,4-diketone (65%). Methylation of the hydroxy group with CH₂N₂ (65%), formation of the pyrrole with ammonium acetate (57%), and hydrolysis of the silyl ether with HCl provided **17a**. However, hydrogenolysis of **14c** under these conditions gave a complex mixture rather than the analogous desired 2-hydroxy-1,4-diketone
23. Stevenson R, Weber JV. *J. Nat. Prod.* 1988; 51:1215–1219.
24. Sperry J, Yuen TY, Brimble MA. *Synthesis*. 2009:2561–2569.
25. Billingsley KL, Anderson KW, Buchwald SL. *Angew. Chem. Int. Ed.* 2006; 45:3484–3488.
26. Brohm D, Philippe N, Metzger S, Bhargava A, Müller O, Folker L, Waldmann H. *J. Am. Chem. Soc.* 2002; 124:13171–13178. [PubMed: 12405845]
27. Beaulieu ED, Voss L, Trauner D. *Org. Lett.* 2008; 10:869–872. [PubMed: 18232702]
28. The analogous triphenyl substituted lactone also adopts the boat conformation see: Fuller-Stanley JA, Loehlin JH, Bolin KA, Fairbrother G, Nazaire F. *J. Org. Chem.* 2002; 67:27–31. [PubMed: 11777435]
29. Hartmann E, Oestreich M. *Angew. Chem. Int. Ed.* 2010; 49:6195–6198.
30. Greenhouse R, Ramierz C, Muchowski JM. *J. Org. Chem.* 1985; 50:2961–2964.
31. Fürstner A, Grabowski J, Lehmann CW. *J. Org. Chem.* 1999; 64:8275–8280. [PubMed: 11674748]
32. (a) Xue F, Silverman RB. *Tetrahedron Lett.* 2010; 51:2536–2538. [PubMed: 20414457] (b) Albanese D, Landini D, Penso M, Tagliabue A, Carlini E. *Org. Proc. Res. Dev.* 2010; 14:705–711.
33. For differences in the reactivity of freshly prepared and commercially available vinylMgBr, see: Ushakov DB, Navickas V, Ströbele M, Maichle-Mössmer C, Sasse F, Maier ME. *Org. Lett.* 2011; 13:2090–2093. [PubMed: 21413694] Han X-J, Yao M, Lu C-D. *Org. Lett.* 2012; 14:2906–2909. [PubMed: 22621235]
34. (a) Reich HJ, Holtan RC, Bolm C. *J. Am. Chem. Soc.* 1990; 112:5609–5617. (b) Reich HJ, Olson RE, Clark MC. *J. Am. Chem. Soc.* 1980; 102:1423–1424.
35. Halogen-metal exchange of 2-bromo-*N*-SEM-pyrrole³⁶ with *n*-BuLi and alkylation with 6-iodo-1-hexene³⁷ afforded 2-(5-hexenyl)-*N*-SEM pyrrole in 67% yield. The preparation of 2-pyrroleboronic acids requires an electron withdrawing protecting group on the nitrogen,^{38,39} so we treated the pyrrole with NBS to prepare 5-bromo-2-(5-hexenyl)-*N*-SEM pyrrole in 91% yield. Metal-halide exchange of iodolactone **11** with isopropylmagnesium chloride and treatment with PinBOMe afforded the unstable pinacol boronic ester in 74% yield.⁴⁰ Treatment of the bromopyrrole and lactone pinacol boronic ester with Pd(PPh₃)₄ and K₃PO₄ afforded the compound analogous to **42** with an *N*-SEM, rather than *N*-Boc protecting group in 55% yield. Further elaboration to **47a** was analogous to that described above for **47b**
36. Garg NK, Caspi DD, Stoltz BM. *J. Am. Chem. Soc.* 2004; 126:9552–9553. [PubMed: 15291554]
37. Panarello AP, Khinast JG. *Tetrahedron Lett.* 2003; 44:4095–4098.
38. Billingsley K, Buchwald SL. *J. Am. Chem. Soc.* 2007; 129:3358–3366. [PubMed: 17326639]
39. Primas N, Bouillon A, Rault S. *Tetrahedron*. 2010; 66:8121–8136. and references cited therein.
40. (a) Ashburn BO, Rathbone LK, Camp EH, Carter RG. *Tetrahedron*. 2008; 64:856–865. (b) Knochel P, Dohle W, Gommermann N, Kneisel FF, Kopp F, Korn T, Sapountzis I, Vu VA. *Angew. Chem. Int. Ed.* 2003; 42:4302–4320. and references therein.
41. Jain N, Kumar A, Chauhan SMS. *Tetrahedron Lett.* 2005; 46:2599–2602.
42. Moreau X, Campagne J-M. *J. Org. Chem.* 2003; 68:5346–5350. [PubMed: 12816497]
43. Hinz W, Jones RA, Anderson T. *Synthesis*. 1986:620–623.
44. Apex2, Version 2 User Manual, M86-E01078, Bruker Analytical X-ray Systems. Madison, WI: 2006 Jun.

45. Altomare A, Cascarano G, Giacovazzo G, Guagliardi A, Burla MC, Polidori G, Camalli M. J. Appl. Cryst. 1994; 27:435–436.
46. Betteridge, PW.; Carruthers, JR.; Cooper, RI.; Prout, K.; Watkin, DJ. J. Appl. Cryst. Prout, CK.; Pearce, LJ., editors. Vol. 36. Oxford, UK: CAMERON, Chemical Crystallography Laboratory; 2003. p. 14871996
47. Cooper RI, Thompson AL, Watkin DJ. J. Appl. Cryst. 2010; 43:1100–1107.

Figure 1. Structure of **47b** determined by X-ray crystallography. The tether is disordered with two positions for atom C10; only the major component (92.2%) is shown.

SCHEME 1.
Structures and Biosynthesis of Marineosins A and B

SCHEME 2.
Retrosynthesis of Marineosins A and B

SCHEME 3.
Synthesis of Methoxy Iminal 16

SCHEME 4.
Preparation of Spiroiminals 18–21.

SCHEME 5.
Deprotection of 18c–21c

SCHEME 6.
Biomimetic Synthesis of 18a–21a

SCHEME 7.
 Preparation of Vinyl Ketone 33

SCHEME 8.
Preparation of Marineosin A Model 36

SCHEME 9.
 Synthesis of Macrocyclic Fused Lactone **47b**

SCHEME 10.

Elaboration of 47b to Hemi-iminal 52b