An Intramolecular Nitrone−Olefin Dipolar Cycloaddition-Based Approach to Total Synthesis of the Cylindricine and Lepadiformine Marine Alkaloids

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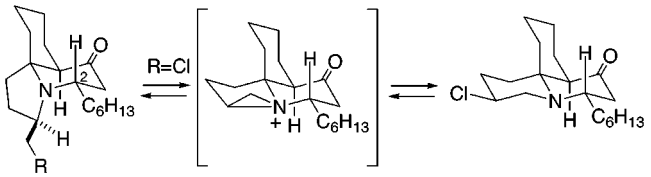
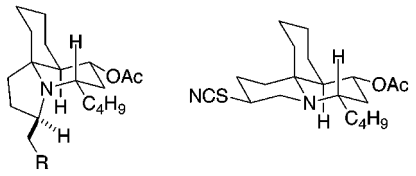
A synthetic route to the cylindricine skeleton as well as to the reported structure of the marine alkaloid lepadiformine has been achieved using an intramolecular nitrone/1,3-diene dipolar cycloaddition as the key step. The synthesis began with sequential alkylations of acetone oxime to afford key intermediate oxime **30**, which contains all of the carbons necessary to form the tricyclic skeleton of the alkaloids. Nitrone **40**, available from oxime **30** by standard transformations, underwent an intramolecular 1,3-dipolar cycloaddition to provide isoxazolidine **43**. Related 1,3-dipolar cycloadditions were also explored on two additional nitrone−olefin substrates **41** and **42**, which were prepared in a manner similar to that of **40**. The tricyclic alkaloid core **52** was formed stereoselectively by a tandem oxidation−Michael addition of amino alcohol **49** derived from isoxazolidine **43**. Cleavage of the *O*-phenyl ether of **52** provided 2-*epi*-cylindricine C (**53**). Several unsuccessful attempts were made to convert **52** to cylindricine C by epimerization at C2. Tricyclic ketone **52** was deoxygenated to give amine **59**, whose structure and relative stereochemistry were confirmed by single-crystal X-ray analysis of its picrate salt. Removal of the *O*-phenyl protecting group from **59** provided tricyclic amino alcohol **60** having the putative structure of lepadiformine, but whose NMR data did not correspond to those of the natural product.

In the early 1990s, Blackman and co-workers described the isolation of a series of structurally related alkaloids from the marine ascidian *Clavelina cylindrica*, collected at sites off the coast of Tasmania.[1] The most abundant of these alkaloids are cylindricines A (**1**) and B (**7**), whose structures were firmly established by X-ray crystallography of the corresponding picrates. Interestingly,



1 R=Cl cylindricine A
2 R=OH cylindricine C
3 R=OMe cylindricine D
4 R=OAc cylindricine E
5 R=SCN cylindricine F

these two compounds exist as a 3:2 equilibrium mixture, presumably interconverting through the aziridinium intermediate **6**.[1a] Subsequent investigations led to the isolation of some minor compounds having the cylindricine A pyrroloquinoline framework and stereochemistry, but differing in the functionality at C14. Examples of these alkaloids include cylindricines C (**2**), D (**3**), E (**4**), and F (**5**). In addition, a few alkaloids were found which possess a butyl chain at C2 rather than the hexyl group (e.g. cylindricines H (**8**) and I (**9**)). Similarly, compounds in the cylindricine B (pyridoquinoline) series exist which also have a butyl appendage (e.g. cylindricine J (**10**)). It might be noted that the X-ray crystal structure and NMR data, as well as molecular mechanics calculations,[1c] indicate that these molecules prefer to exist in the conformations shown.



8 R=SCN cylindricine H
9 R=NCS cylindricine I
10 cylindricine J

In 1994, Biard et al. reported the isolation of lepadiformine from the tunicate *Clavelina lepadiformis* Muller collected in the Mediterranean near Tunisia.[2] It was found that this material has moderate in vitro cytotoxic activity against various tumor cell lines. On the basis of spectroscopic data, the structure of lepadiformine was formulated as the zwitterionic pyrroloquinoline **11**, related to the cylindricine A series. Thus, lepadiformine is epimeric at C2 and lacks the C4 oxygen of the cylindricines. Also, NMR NOESY data suggested that lepadiformine has conformation **11a**, rather than the flip form **11b**.[2] However, we have performed molecular mechanics

† Author to be contacted about the X-ray crystal structure determination.

(1) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645. (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355. (c) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955.

(2) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691.

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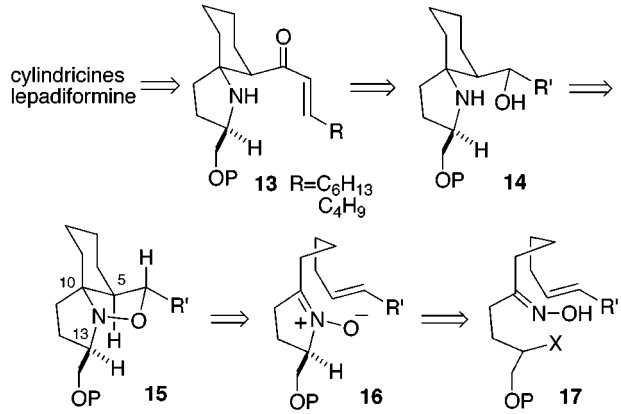
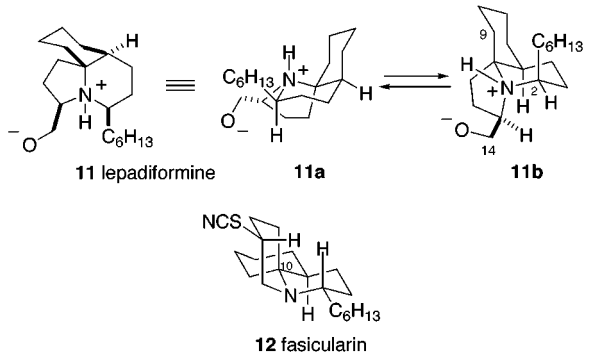
Scheme 1



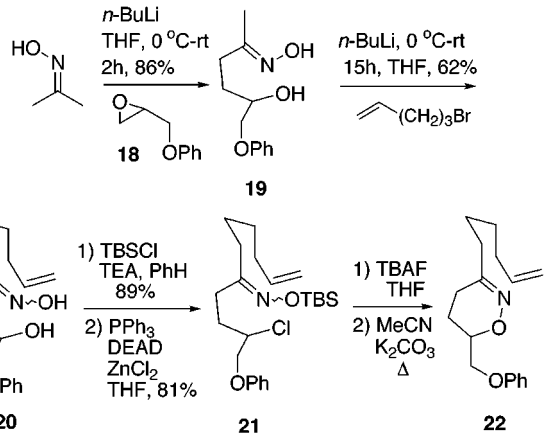
calculations which indicate that conformer **11b** is ~2.6 kcal/mol more stable than **11a**.[3] More recently, a group at SmithKline Beecham reported the structure of the alkaloid fasicularin (**12**), isolated from the ascidian *Neptheis fasicularis*.[4] Compound **12** is closely related structurally to the cylindricine B group of alkaloids but is epimeric at C10 and lacks the C4 oxygenation. Fasicularin has activity against a DNA repair deficient strain of yeast and is also cytotoxic.



In view of the unique structures of these marine metabolites, along with their interesting biological activity, we have recently been involved in a program leading to a stereoselective total synthesis of the pyrroloquinoline subgroup of the alkaloids.[5] While this work was in progress, Snider and Liu described the first total syntheses of cylindricines A, D, and E.[6] Moreover, Pearson and co-workers have recently described some interesting synthetic studies aimed at lepadiformine involving an azaallyl anion cycloaddition strategy.[7]

Our original retrosynthetic approach to these alkaloids is briefly outlined in Scheme 1. The intent was to utilize the methodology of Grigg to convert an oxime substrate

Scheme 2



such as **17** via N-alkylation to a cyclic nitrone **16**.[8] We anticipated that a subsequent intramolecular cyclization of nitrone−olefin **16** would produce spirocyclic isoxazolidine **15** having the requisite cylindricine/lepadiformine stereochemistry at C5, 10, and 13 (cylindricine numbering[1]) (vide infra).[9,10] Cleavage of the N−O bond in **15** should provide amino alcohol **14**, which would then be processed to the various alkaloids, perhaps via an enone like **13**, depending on the nature of R′.

Our approach to a nitrone precursor such as **17** began with acetone oxime, which was converted to its dianion and alkylated with commercially available epoxide **18** to afford hydroxy oxime **19** (Scheme 2).[11] Oxime **19**, which is presumably initially *Z*,[11,12] was found to be a mixture of *E*/*Z* isomers after an aqueous workup, and upon further purification by chromatography on silica gel equilibrated completely to the *E* isomer. The *E* oxime **19** was then again metalated and alkylated with 5-bromo-1-pentene to afford oxime **20**. The oxime functionality in compound **20** was first O-silylated, and the secondary hydroxyl group was converted to the corresponding chloride **21** via Mitsunobu methodology.[13] Unfortunately, all attempts to cyclize **21** to a nitrone led to the 1,2-oxazine **22** as the only characterizable product. Although the expectation was that chloro oxime **21** would exist as an equilibrating *E*/*Z* mixture,[14] these results show that cyclization onto oxygen leading to the oxazine **22** is apparently more favorable than closure onto nitrogen, which would provide the desired nitrone. In a similar vein, it has previously been observed by Tiecco and co-workers[14] that electrophile-promoted closure of alkenyl oximes to 1,2-oxazines and/or five-membered nitrones is not dependent upon starting oxime geometry. However, in the cases they examined, the cyclic nitrone was usually the preferred product.

(3) Although at first glance it would seem that **11b**, having an axial hexyl group, should be unfavorable, there is a destabilizing 1,3-diaxial interaction between C9 and C14 in **11a** which leads to the former conformation being preferred. We thank Professor R. L. Funk for assistance in performing these calculations with PC Model.

(4) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363.

(5) For a preliminary account of portions of this work, see: Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686.

(6) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630.

(7) (a) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369. (b) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688.

(8) (a) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1388. (b) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1537.

(9) For a brief review of intramolecular nitrone−olefin cycloadditions, see: Wade, P. A. Intramolecular 1,3-Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 1111.

(10) For some intramolecular nitrone−olefin spirocyclizations, see: Tufariello, J. J.; Trybulski, E. J. *J. Org. Chem.* **1974**, *39*, 3378. Gossinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96.

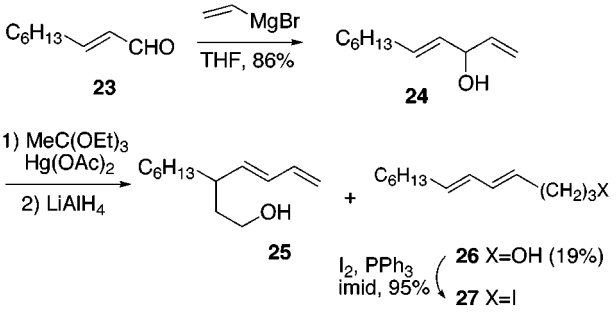
(11) (a) Jung, M. E.; Blair, P. A.; Lowe, J. A. *Tetrahedron Lett.* **1976**, 1439. (b) Kofron, W. G.; Yeh, M.-K. *J. Org. Chem.* **1976**, *41*, 439.

(12) For NMR determination of oxime geometry, see: Bunnell, C. A.; Fuchs, P. L. *J. Org. Chem.* **1977**, *42*, 2614.

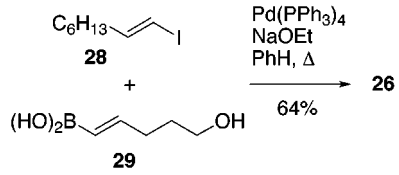
(13) Rollin, P. *Synth. Commun.* **1986**, *16*, 611.

(14) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1989.

Scheme 3



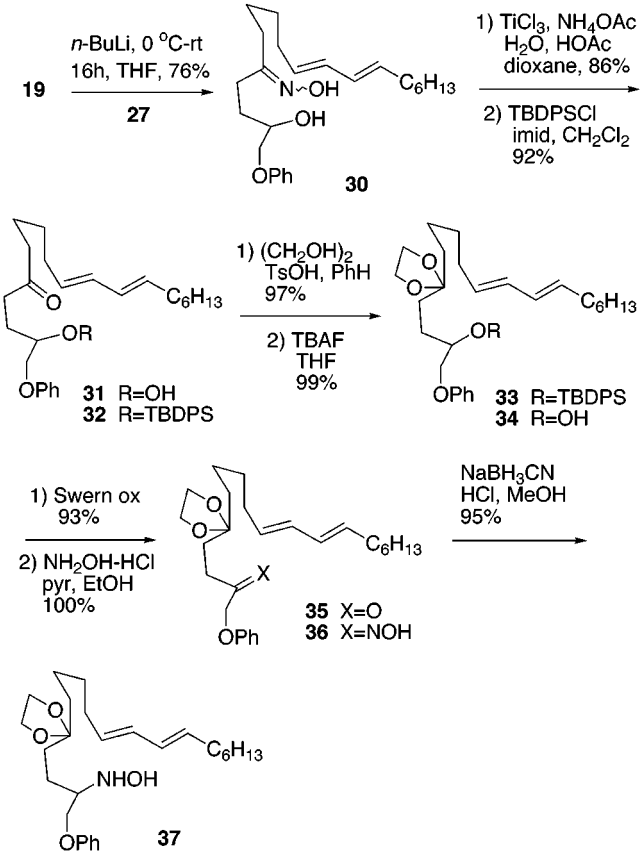
Scheme 4



In view of these disappointing results, we decided to approach synthesis of the cyclic nitrone system **16** via a more reliable strategy involving closure of a keto hydroxylamine. At the same time, we have investigated some systems which differ in the R′ moiety shown in the structures in Scheme 1 (vide infra). It appeared to us that the most convergent and efficient route would utilize a system containing all of the carbon atoms needed for the alkaloids (cf. **13**), and therefore a high priority was to investigate the cycloaddition of a nitrone like **16** containing a 1,3-diene as the dipolarophile.[15]

The required diene subunit was first prepared by the sequence shown in Scheme 3. Unsaturated aldehyde **23** was converted to dienol **24**, which underwent a Johnson ortho ester Claisen rearrangement to afford a mixture of regioisomeric diene esters.[16] This mixture was reduced with lithium aluminum hydride to afford a chromatographically separable 1:1.3 mixture of diene alcohols **25** and **26**. Although the isolated yield of the desired *E*,*E*-dienol **26** was only 19% for the two steps from intermediate **24**, the simplicity of the procedure allowed for preparation of reasonable amounts of this material. This alcohol could then be converted to iodide **27** in high yield. A more efficient alternative procedure was subsequently developed for preparation of the necessary dienol (Scheme 4). Thus, Pd-catalyzed coupling of the known hydroxy vinylboronic acid **29**[17] with the *E*-vinyl iodide **28**[18] using the Suzuki−Miyaura methodology[19,20] afforded **26** in good yield.

Scheme 5



To continue the synthesis, oxime alcohol **19** was converted to the trianion and alkylated with iodo diene **27** to yield **30** (Scheme 5). Cleavage of the oxime functionality of **30** to the corresponding ketone **31** with $TiCl_3$[21] and silylation of the alcohol afforded **32**. The carbonyl group in **32** was ketalized, giving **33**, which was desilylated to alcohol **34**. Swern oxidation of **34** to ketone **35**, followed by oxime formation provided **36**. Finally, reduction of oxime **36** with sodium cyanoborohydride[22] afforded hydroxylamine **37**. The yields in this sequence of reactions were uniformly high.

We were pleased to find that treatment of hydroxylamino ketal **37** with aqueous HCl led to the desired cyclic nitrone diene **40** which could be isolated in 92% yield (Scheme 6). Initial cyclization experiments involved heating **40** in *o*-dichlorobenzene at 170 °C, which led to formation of the desired isoxazolidine cycloadduct **43**, but in low yield. However, it was eventually found that thermolysis of **40** in DMSO overnight at 195 °C produced adduct **43** in 63% yield. We were also pleased to find that **43** was formed as a single stereoisomer, whose structure was eventually confirmed by X-ray analysis of a subsequent intermediate (vide infra).

We have also briefly investigated cyclizations of some other related alkenyl nitrones which seemed to have some potential as useful intermediates for synthesis of the cylindricines. Thus, using the same methodology outlined in Scheme 5, we prepared hydroxylamine olefins **38** and **39** (for experimental details, see Supporting Information). Compounds **38** and **39** could be converted

(15) An example of an intramolecular nitrone−conjugated diene cycloaddition has been described: Holmes, A. B.; Hughes, A. B.; Smith, A. L.; Williams, S. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1089. Intermolecular 1,3-dipolar cycloaddition reactions of nitrones with conjugated dienes leading to indolizidines and quinolizidines have been reported: (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Tufariello, J. J.; Dyszlewski, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1138 and references cited. Conjugated dipolarophiles also tend to show higher reactivity than nonconjugated ones: Sustmann, R. *Tetrahedron Lett.* **1971**, 2717.

(16) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.

(17) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.

(18) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219.

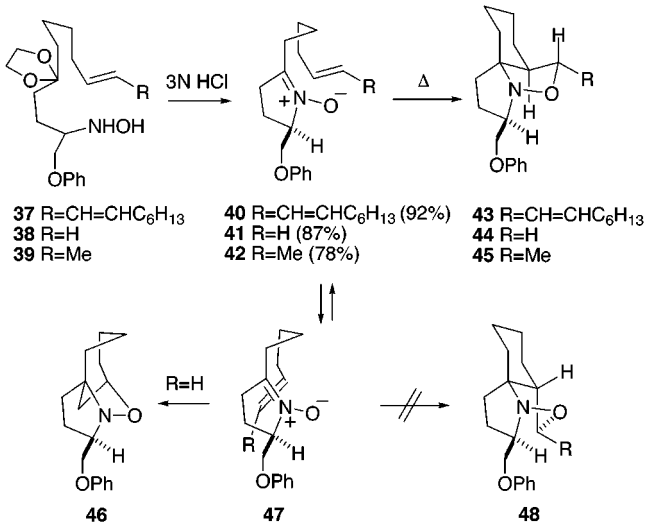
(19) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron* **1983**, *39*, 3271.

(20) We are grateful to Ann Bullion for synthesis of diene alcohol **26** via the Suzuki−Miyaura coupling route.

(21) Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, 195.

(22) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

Scheme 6

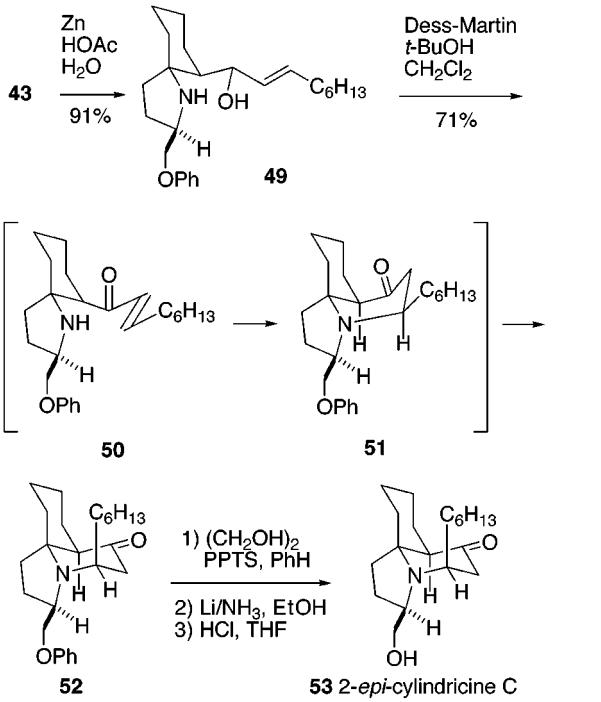


cleanly to cyclic nitrones **41** and **42**, respectively, by mild acid hydrolysis. Interestingly, cyclization of the terminal alkene nitrone **41** occurred in xylene at 150 °C to give a 1:2 mixture of spirocyclic isoxazolidine **44** and the unwanted bridged isomer **46** in 69% total yield.[23a] In the case of the *E*-olefin nitrone **42**, cyclization was extremely sluggish. At best, we were only able to isolate 15% (38% based on recovered nitrone) of a single cycloadduct which has tentatively been assigned spirocyclic structure **45**.

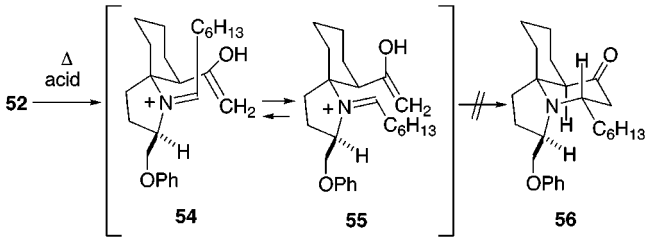
It would appear that these cyclizations can occur via the two conformations shown in **40**−**42** and **47** (the bridging chain must be boatlike for stereoelectronic reasons). In both situations, the olefin resides exclusively on the face of the nitrone opposite to the bulky phenoxymethyl group. When R is large, conformer **47** is probably disfavored relative to **40**−**42** for steric reasons, therefore leading to the spirocyclic series of adducts. The alternative regioisomeric isoxazolidine system **48** was not detected in any case, presumably for stereoelectronic reasons.[23b]

With the desired cycloadduct **43** now in hand, we turned to developing methodology for converting it to one or more of the marine alkaloids of interest. Cleavage of the N−O bond of this isoxazolidine could be effected in high yield with Zn/HOAc to give the amino alcohol **49** (Scheme 7). Oxidation of **49** with the Dess−Martin reagent in the presence of *tert*-butyl alcohol[24] led directly to tricycle **52**, presumably via enone **50**. It might be noted that in the absence of *tert*-butyl alcohol, the Dess−Martin oxidation went poorly.[24] Compound **52** is a single stereoisomer whose configuration and conformation have been assigned as shown on the basis of 2D NMR experiments (NOESY, HMQC, and ^{13}C Inadequate), along with the results of subsequent transformations (vide infra). The formation of the C2 axial epimer shown is not surprising, since for stereoelectronic reasons conjugate addition of the amino group to the enone in **50** must occur through a transition state initially leading to a boat ketone **51**, which ring flips to the observed product **52**. As a further confirmation of structure, ketone **52** was subsequently

Scheme 7



Scheme 8



protected as its ethylene ketal (35% unoptimized), and the phenyl protecting group was removed by Birch reduction, followed by acid hydrolysis (26% unoptimized), to afford 2-*epi*-cylindricine C (**53**).[25] The proton NMR data for this material were similar to, but clearly different from, those of authentic cylindricine C (**2**).[26]

We have also made some attempts to epimerize tricycle **52** at C2 to produce the cylindricine C stereochemistry. It was our hope that **52** could be converted via a retro-Mannich process into iminium ion **54**, which might then equilibrate to isomer **55** (Scheme 8). Mannich reclosure of **55** would afford *O*-phenylcylindricine C (**56**). However, all attempts to promote this interconversion using various acids failed, and in most cases only starting material was recovered.

Another approach to adjusting the C2 stereochemistry is outlined in Scheme 9. It was found that activated MnO_2 oxidation of amino ketone **52** afforded the vinylogous amide **57** (33% unoptimized yield). Unfortunately, reduction of **57** with sodium cyanoborohydride/HCl gave back ketone **52**. Similarly, reduction of **57** using Li/NH_3 rather surprisingly also gave only the original ketone **52**.

At this point we turned to removing the carbonyl group of intermediate ketone **52** to access the proposed lepadi-

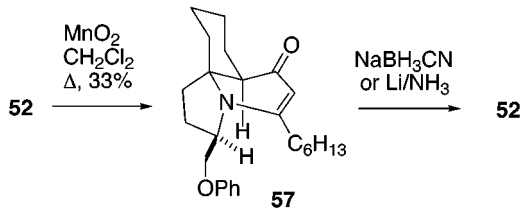
(23) (a) For formation of both fused and bridged isoxazolidines in a related system, see: LeBel, N. A.; Lajiness, T. A. *Tetrahedron Lett.* **1966**, 2173. (b) Cf. LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759.

(24) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

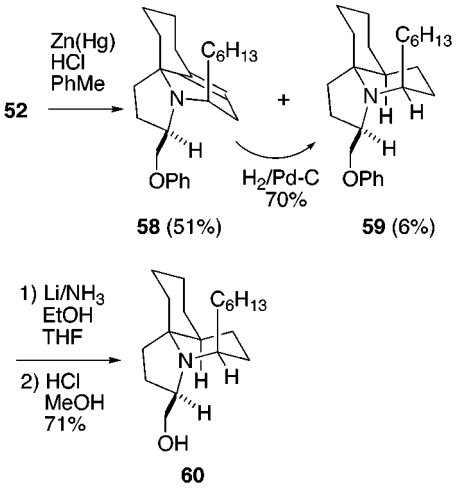
(25) Aryl protection for alcohols has not been widely used. Cf. Marshall, J. A.; Partridge, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 1090. In this case a *p*-chlorophenyl ether protecting group was used for oxygen.

(26) We are grateful to Professors Barry Snider and A. J. Blackman for copies of the NMR spectra of several of the cylindricines including cylindricine C.

Scheme 9



Scheme 10



formine structure **11**. All attempts to deoxygenate **52** by a Wolff−Kishner reduction,[27] or by reduction of the tosylhydrazone,[28] failed. In addition, we were unable to convert ketone **52** to the corresponding thioketal. Alternatively, Clemmensen reduction[29] of **52** did provide some of the deoxygenated tricyclic amine **59** (6%), but the primary product of this reaction was the trisubstituted olefin **58** (51%) (Scheme 10). Although alkenes have previously been observed as minor byproducts in Clemmensen reductions of ketones, the fact that compound **58** was the major product is quite surprising.[29,30] It was possible, however, to stereoselectively hydrogenate olefin **58** to produce the desired intermediate **59**. To firmly establish the structure and stereochemistry of **59**, a single-crystal X-ray analysis was performed on its picrate salt. An ORTEP plot of this structure is depicted in Figure 1. Interestingly, tricycle **59** has the conformation as is shown in **11b**, which was predicted by molecular modeling for lepadiformine (vide supra).[3]

Finally, the phenyl protecting group in **59** was removed by a dissolving metal reduction, followed by acid hydrolysis, providing tricyclic amino alcohol **60**. Although **60** has the structure proposed for lepadiformine (cf. **11**), direct comparison of the proton and carbon NMR spectra of this material with those of the natural alkaloid kindly supplied by Professor Biard[31] clearly showed that the two compounds were in fact different. Moreover, there is no indication that our synthetic tricycle **60** exists in the unusual zwitterionic form proposed for lepadiformine. It

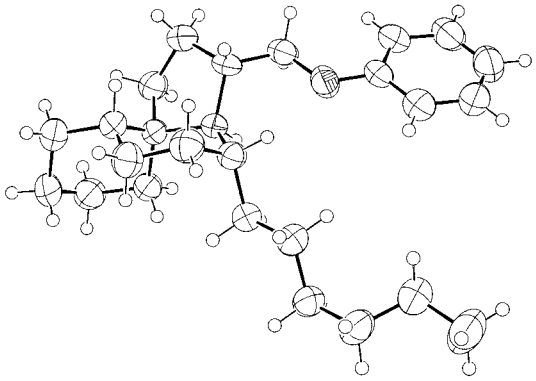


Figure 1. ORTEP plot of the picrate of tricycle **59** (anion omitted for clarity).

appears, therefore, that the structure of lepadiformine is not as originally formulated and requires revision. It might also be added that Pearson and Ren[7b,32] have recently synthesized the three other possible diastereomers of **60** at C2 and C13 and have found that none of these stereoisomers correspond to lepadiformine. Another possibility which has not yet been tested is that lepadiformine is epimeric at C10 and thus is in the fasicularin (**12**) series.

In summary, we have described a stereoselective and convergent route to the pyrroloquinoline framework of the cylindricines/lepadiformine via an intramolecular nitrone dipolar cycloaddition involving a conjugated diene as the dipolarophile. In these studies, we have synthesized the putative structure of lepadiformine and have shown that the constitution of this alkaloid requires revision. Future work will require the development of alternative methodology to set the proper C2 stereochemistry found in the cylindricine series of marine alkaloids.

Experimental Section

5-Hydroxy-6-phenoxyhexan-2-one Oxime (19). To a 0 °C solution of acetone oxime (2.74 g, 37.5 mmol) in THF (125 mL) was added *n*BuLi (30 mL, 2.5 M solution in hexanes). The mixture was stirred at this temperature for 30 min, and a solution of 1,2-epoxy-3-phenoxypropane (3.38 mL, 25.0 mmol) in THF (25 mL) was then added. After warming to room temperature, the solution was stirred for 2 h, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The crude residue was crystallized from Et_2O/hexanes (1:4) to yield 4.79 g (86%) of oxime **19** as a white solid. An analytical sample was obtained by recrystallization from CH_2Cl_2/hexanes: mp 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (br s, 1H), 7.29 (t, J = 7.4 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.93 (d, J = 7.8 Hz, 2H), 4.05−3.90 (m, 3H), 3.30 (br s, 1H), 2.44 (t, J = 7.2 Hz, 2H), 1.93 (s, 3H), 1.86−1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.6, 129.5, 121.0, 114.5, 71.8, 69.2, 32.1, 29.5, 13.8; IR (CH_2Cl_2) 3244 (br), 2927, 1601, 1497, 1250 cm^{-1}; EIMS *m*/*z* (relative intensity) 223 (M^+, 4); HRMS calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1201.

(4*E*)-Undeca-1,4-dien-3-ol (24). To a solution of vinylmagnesium bromide (428 mL, 1 M in THF) in THF (500 mL) at 0 °C was added (*E*)-2-nonenal (59.0 mL, 357 mmol). The reaction was quenched after 15 min by the addition of a saturated aqueous NH_4Cl solution. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The product was distilled (85 °C, 12 mmHg) to

(27) Yasuda, S.; Hanaoka, M.; Arata, Y. *Chem. Pharm. Bull.* **1980**, *28*, 831.
(28) Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *15*, 237.
(29) Martin, E. L. *Org. React.* **1942**, *1*, 155.
(30) There seems to be little reason to further optimize the deoxygenation of ketone **52** since our synthetic compound **60** does not correspond to natural lepadiformine.
(31) We thank Professor J. F. Biard for the proton and carbon NMR spectra, as well as a sample of lepadiformine.
(32) We appreciate frequent helpful discussions and exchanges of information with Professor William H. Pearson.

afford 51.6 g (86%) of dienol **24** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (ddd, J = 17.2, 10.4, 5.7 Hz, 1H), 5.71 (ddt, J = 15.2, 6.6, 0.7 Hz, 1H), 5.49 (ddt, J = 15.4, 6.6, 1.3 Hz, 1H), 5.25 (dt, J = 17.3, 1.4 Hz, 1H), 5.12 (dt, J = 10.4, 1.3 Hz, 1H), 4.58 (t, J = 5.9 Hz, 1H), 2.04 (q, J = 6.8 Hz, 2H), 1.59 (t, J = 5.9 Hz, 1H), 1.43−1.26 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 132.8, 130.9, 114.5, 73.7, 32.1, 31.6, 29.0, 28.8, 22.5, 14.0; IR (neat) 3342, 985, 961, 920 cm^{-1}.

(4*E*,6*E*)-Trideca-4,6-dien-1-ol (26). A solution of alcohol **24** (5.00 g, 29.8 mmol), triethyl orthoacetate (109 mL, 595 mmol), propionic acid (400 μL, 5.36 mmol), and $Hg(OAc)_2$ (191 mg, 0.600 mmol) was heated at reflux. After 16 h, the reaction mixture was diluted with ether (200 mL) and washed with aqueous 3 N HCl. The organic layer was dried over $MgSO_4$ and concentrated to a yellow liquid. The crude residue was purified by flash chromatography (2% Et_2O/hexanes) to afford 2.8 g of a mixture of isomeric dienols which was used without further purification. The mixture was dissolved in THF (5 mL) and added to a suspension of 95% $LiAlH_4$ (470 mg, 11.8 mmol) in THF (40 mL) at 0 °C. After 15 min, the mixture was warmed to room temperature and quenched by the addition of $Na_2SO_4 \cdot 10H_2O$. After stirring for 30 min, the mixture was filtered, and the filtrate was concentrated. The crude product was purified by flash chromatography (10−20% Et_2O/hexanes gradient) to afford 836 mg (19% over 2 steps) of alcohol **26** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (m, 2H), 5.58 (m, 2H), 3.66 (t, J = 6.5 Hz, 2H), 2.15 (q, J = 7.2 Hz, 2H), 2.05 (q, J = 7.0 Hz, 2H), 1.66 (quin, J = 6.8 Hz, 2H), 1.38−1.26 (m, 9H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9, 131.0, 130.9, 130.0, 62.2, 32.5, 32.2, 31.7, 29.3, 28.8 (2C), 22.5, 14.0; IR (neat) 3342 (br), 985 cm.$^{-1}$

(4*E*,6*E*)-Trideca-4,6-dien-1-ol (26). To boronic acid[17] **29** (910 mg, 7.00 mmol) were added benzene (20 mL), (*E*)-1-iodooctene[18] (1.83 g, 7.70 mmol), tetrakis(triphenylphosphine)-palladium (404 mg, 0.350 mmol), and NaOEt (7.0 mL of a 2 M solution in ethanol), and the mixture was heated at reflux. After 2 h, the mixture was cooled to room temperature, and 15% aqueous NaOH (2 mL) was added followed by the dropwise addition of a 30% aqueous H_2O_2 solution (2 mL). The reaction mixture was diluted with brine and extracted with Et_2O. The organic extracts were combined, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography (10−15% EtOAc/hexanes gradient) to afford 593 mg (64%) of dienol **26** as a clear colorless oil.

(4*E*,6*E*)-1-Iodotrideca-4,6-diene (27). To a solution of triphenylphosphine (918 mg, 3.50 mmol) in CH_2Cl_2 (9 mL) at 0 °C were added imidazole (5.5 mg, 7.0 mmol) and iodine (890 mg, 3.50 mmol). After 30 min, a solution of alcohol **26** (343 mg, 1.75 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was warmed to room temperature and stirred for 40 min. Brine was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography (hexanes) to afford 510 mg (95%) of iodide **27** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (m, 2H), 5.60 (ddd, J = 14.1, 6.9, 6.9 Hz, 1H), 5.48 (ddd, J = 13.9, 6.9, 6.9 Hz, 1H), 3.18 (t, J = 6.9 Hz, 2H), 2.17 (q, J = 7.1 Hz, 2H), 2.05 (q, J = 7.0 Hz, 2H), 1.90 (quin, J = 7.0 Hz, 2H), 1.28 (m, 8H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 131.9, 129.8, 129.2, 33.1, 32.9, 32.6, 31.7, 29.2, 28.9, 22.6, 14.1, 6.4; IR (neat) 985 cm^{-1}.

Preparation of Oxime 30. To a solution of oxime **19** (4.07 g, 18.2 mmol) in THF (60 mL) at 0 °C was added *n*BuLi (23.0 mL, 2.5 M solution in hexanes). The mixture was warmed to room temperature and stirred for 45 min. After the solution was cooled to 0 °C, a solution of iodide **27** (6.13 g, 20.0 mmol) in THF (5 mL) was added. The mixture was warmed to room temperature and stirred for 16 h. The mixture was diluted with Et_2O and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (25−40% EtOAc/hexanes gradient) to yield 5.55 g (76%) of oxime isomers **30** as a white solid. Data for major isomer: mp 94−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (br s, 1H), 7.30 (t, J = 7.9 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 2H), 6.03 (m, 2H), 5.60 (m, 2H), 4.50 (br s, 1H), 4.03 (m, 1H), 3.94 (d, J = 5.5 Hz, 2H), 2.45 (t, J = 6.9 Hz, 2H), 2.40 (m, 2H), 2.10 (quin, J = 7.7 Hz, 4H), 1.88 (m, 2H), 1.59−1.30 (m, 12H), 0.92 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 158.5, 132.6, 131.5, 130.7, 130.1, 129.4, 120.9, 114.5, 71.6, 69.2, 32.5, 32.2, 31.7, 30.4, 29.6, 29.5, 29.3, 28.8, 27.8, 25.1, 22.5, 14.0; IR ($CHCl_3$) 3583, 3260 (br), 1599, 1588, 1241, 990 cm^{-1}; EIMS *m*/*z* (relative intensity) 401 (M^+, 3), 384 (M^+ − OH, 13), 294 (12), 276 (11), 236 (11), 94 (PhOH, 100); HRMS calcd for $C_{25}H_{39}NO_3$ 401.2930, found 401.2936.

Hydroxy Ketone 31. To a solution of oxime **30** (12.1 g, 7.46 mmol) in *p*-dioxane (150 mL) were added ammonium acetate (30.3 g, 392 mmol) and 50% aqueous acetic acid (15 mL). The mixture was stirred, and 20% aqueous titanium trichloride (56.0 g, 72.5 mmol) was added slowly at room temperature. The mixture was stirred for 20 min, diluted with Et_2O, and washed with aqueous 1 N HCl, a saturated aqueous $NaHCO_3$ solution, and brine. The organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 10.0 g (86%) of hydroxy ketone **31** as a white solid: mp 57−60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 8.7 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.8 Hz, 2H), 5.99 (m, 2H), 5.55 (m, 2H), 4.00−3.93 (m, 3H), 2.66 (t, J = 7.0 Hz, 2H), 2.60 (d, J = 3.8 Hz, 1H), 2.45 (t, J = 7.4 Hz, 2H), 2.05 (quin, J = 7.1 Hz, 4H), 1.86 (m, 2H), 1.56 (quin, J = 7.7 Hz, 2H), 1.33 (m, 10H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 158.4, 132.8, 131.4, 130.8, 130.1, 129.5, 121.1, 114.5, 71.8, 69.5, 42.7, 38.6, 32.6, 32.3, 31.7, 29.3, 28.9 (2C), 26.8, 23.4, 22.6; IR (CH_2Cl_2) 3588, 3452 (br), 1706, 1599, 1587, 1229, 990 cm^{-1}; ESIMS *m*/*z* (relative intensity) 409 ([M + Na]$^+$, 46), 369 ([M + H − H_2O]$^+$, 100); HRMS calcd for $C_{25}H_{38}O_3Na$ 409.2719, found 409.2734. Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.78; H, 9.82.

Siloxy Ketone 32. To a solution of hydroxy ketone **31** (10.0 g, 25.9 mmol) and imidazole (3.53 g, 51.8 mmol) in CH_2Cl_2 (130 mL) was added TBDPSCl (8.10 mL, 31.1 mmol). The mixture was stirred for 16 h, diluted with CH_2Cl_2, and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (3% EtOAc/hexanes) to afford 14.8 g (92%) of siloxy ketone **32** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.44−7.30 (m, 6H), 7.19 (m, 2H), 6.89 (m, 1H), 6.65 (m, 2H), 5.99 (m, 2H), 5.53 (m, 2H), 4.09 (quin, J = 5.5 Hz, 1H), 3.81 (AB of ABX, J_{AB} = 9.6 Hz, J_{AX} = 5.5 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 23.7 Hz, 2H), 2.46 (m, 2H), 2.29 (t, J = 7.3 Hz, 2H), 2.02 (m, 4H), 1.88 (m, 2H), 1.50 (m, 2H), 1.28 (m, 10H), 1.07 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 158.4, 135.8, 133.8, 133.7, 132.7, 131.4, 130.8, 130.1, 129.7, 129.6, 129.2, 127.6, 127.5, 120.6, 114.2, 70.6 (2C), 42.5, 37.8, 32.6, 32.3, 31.7, 29.3, 28.9 (2C), 28.1, 27.0, 23.3, 22.6, 19.4, 14.1; IR (neat) 1714, 1598, 1587, 1243, 988 cm^{-1}. Anal. Calcd for $C_{41}H_{56}O_3Si$: C, 78.79; H, 9.03. Found: C, 78.67; H, 9.08.

Formation of Ketal 33. To a solution of siloxy ketone **32** (14.8 g, 23.7 mmol) and *p*TsOH (1.35 g, 7.11 mmol) in benzene (120 mL) was added ethylene glycol (13 mL, 237 mmol). The flask was fitted with a Dean−Stark trap, and the mixture was heated at reflux for 16 h. The solution was cooled to room temperature, and an aqueous saturated $NaHCO_3$ solution was added. The mixture was extracted with Et_2O, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (3% EtOAc/hexanes) to afford 15.4 g (97%) of ketal **33** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.47−7.34 (m, 6H), 7.20 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.67 (d, J = 7.8 Hz, 2H), 6.01 (m, 2H), 5.57 (m, 2H), 4.09 (quin, J = 5.2 Hz, 1H), 3.88 (m, 6H), 2.06 (m, 4H), 1.74−1.27 (m, 18H), 1.09 (s, 9H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 136.0, 135.9, 134.1, 133.9, 132.5, 132.0, 130.5, 130.2, 129.6, 129.5, 129.2, 127.6, 127.4, 120.4, 114.3, 111.6, 71.3, 70.8, 64.8, 36.9, 32.6 (2C), 31.8, 31.7, 29.7, 29.4, 28.9, 28.5, 27.0, 23.4, 22.6, 19.4, 14.1; IR (neat) 1602, 1245, 987 cm^{-1}. Anal. Calcd for $C_{43}H_{60}O_4Si$: C, 77.20; H, 9.04. Found: C, 77.10; H, 9.15.

Alcohol 34. To a solution of ketal **33** (15.4 g, 23.1 mmol) in THF (65 mL) was added tetrabutylammonium fluoride (35 mL, 1 M solution in THF). The solution was stirred for 16 h, at which time the mixture was diluted with Et_2O and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (15−20% EtOAc/hexanes gradient) to afford 9.90 g (99%) of alcohol **34** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 8.2 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.8 Hz, 2H), 5.99 (m, 2H), 5.55 (m, 2H), 4.02−3.83 (m, 7H), 2.71 (br d, J = 3.0 Hz, 1H), 2.05 (quin, J = 6.9 Hz, 4H), 1.94−1.60 (m, 6H), 1.40−1.21 (m, 12H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 132.3, 131.7, 130.4, 130.1, 129.3, 120.8, 114.4, 111.4, 71.9, 69.9, 64.7, 36.8, 32.7, 32.4, 32.3, 31.6, 29.5, 29.2, 28.7, 27.3, 23.3, 22.4, 13.9; IR (neat) 3448 (br), 1595, 1588, 1243, 979 cm^{-1}. Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.13; H, 9.79.

Ketone 35. To a solution of oxalyl chloride (13.8 mL, 2 M solution in CH_2Cl_2) in CH_2Cl_2 (80 mL) at −60 °C was added DMSO (3.92 mL, 55.2 mmol) dropwise. The mixture was stirred for 15 min, and a solution of alcohol **34** (9.90 g, 23.0 mmol) in CH_2Cl_2 (20 mL) was then added. After the mixture was stirred for 15 min, TEA (16.0 mL, 115 mmol) was added and the mixture was warmed to room temperature. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (7% EtOAc/hexanes) to afford 9.15 g (93%) of ketone **35** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 8.6 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 5.99 (m, 2H), 5.55 (m, 2H), 4.57 (s, 2H), 3.90 (s, 4H), 2.62 (t, J = 7.3 Hz, 2H), 2.02 (m, 6H), 1.59 (m, 2H), 1.28 (m, 12H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 157.8, 132.6, 131.8, 130.6, 130.2, 129.6, 121.6, 114.5, 110.9, 87.1, 72.6, 64.9, 37.1, 33.6, 32.6, 32.4, 31.7, 30.4, 29.6, 29.3, 28.8, 23.4, 22.6, 14.0; IR (neat) 1721, 1600, 1244, 988 cm^{-1}; ESIMS m/z (relative intensity) 429 ([M + H]$^+$, 36), 367 (100), 349 (11); HRMS calcd for $C_{27}H_{41}O_4$ 429.3005, found 429.3023.

Oxime 36. To a solution of ketone **35** (9.15 g, 21.4 mmol) and pyridine (2.60 mL, 32.1 mmol) in ethanol (80 mL) was added hydroxylamine hydrochloride (1.78 g, 25.6 mmol). After stirring for 30 min, the mixture was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (15% EtOAc/hexanes) to afford 9.60 g (100%) of oxime **36** as a pale yellow oil, which was a 1:1 mixture of geometric isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.69 (s, 1H), 7.30 (m, 4H), 6.95 (m, 6H), 5.98 (m, 4H), 5.56 (m, 4H), 4.94 (s, 2H), 4.59 (s, 2H), 3.93 (s, 4H), 3.91 (s, 4H), 2.55 (m, 2H), 2.44 (m, 2H), 2.04 (q, J = 6.8 Hz, 8H), 1.90 (m, 4H), 1.62 (m, 4H), 1.37−1.21 (m, 24H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 158.3, 158.2, 157.9, 132.5, 131.9, 130.5, 130.3, 129.6, 129.5, 121.2, 114.7, 114.3, 111.2, 68.2, 64.9 (2C), 62.4, 36.9 (2C), 33.2, 32.6, 32.5 (2C), 31.8, 31.7, 29.7, 29.4, 28.9, 25.4, 23.4, 22.6, 20.5, 14.1; IR (neat) 3354 (br), 1595, 1590, 1237, 990 cm^{-1}. Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.50; H, 9.58.

Hydroxylamine 37. To a solution of oxime **36** (2.00 g, 4.50 mmol) in methanol (15 mL) at 0 °C was added a trace of bromocresol green followed by sodium cyanoborohydride (426 mg, 6.80 mmol). The solution was kept at pH = 4 by addition of a 2 M solution of HCl in methanol. The mixture was stirred for 2 h, and 15% aqueous KOH was then added until the solution became basic. The product was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (35% EtOAc/hexanes) to afford 1.90 g (95%) of hydroxylamine **37** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.95 (t, J = 7.3 Hz, 1H), 6.92 (d, J = 7.8 Hz, 2H), 6.00 (m, 2H), 5.58 (m, 2H), 4.01 (d, J = 5.3 Hz, 2H), 3.94 (s, 4H), 3.18 (quin, J = 5.7 Hz, 1H), 2.05 (m, 4H), 1.82−1.59 (m, 6H), 1.34 (m, 12H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 132.4, 131.8, 130.4, 130.2, 129.3, 120.8, 114.5, 111.4, 66.4, 64.8, 60.8, 37.0, 33.2, 32.5, 32.4, 31.6, 29.6, 29.3, 28.8, 23.4, 22.5, 14.0; IR (neat) 3264, 1599, 1587 cm^{-1}; EIMS m/z (relative intensity) 443 (M$^+$ − H_2, 3), 265 (34), 202 (27), 94 (PhOH, 100); HRMS calcd for $C_{27}H_{43}NO_4$ 445.3192, found 445.3175. Anal. Calcd for $C_{27}H_{43}NO_4$: C, 72.77; H, 9.73; N, 3.14. Found: C, 72.69; H, 9.85; N, 3.17.

Formation of Nitrone Diene 40. A mixture of hydroxylamine **37** (8.45 g, 19.0 mmol) and aqueous 3 N HCl (60 mL) in THF (120 mL) was stirred at room temperature for 3.5 h. The solution was diluted with EtOAc and then washed with water, 5% aqueous NaOH solution, and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10% MeOH/EtOAc) to afford 6.73 g (92%) of nitrone diene **40** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, J = 8.0 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 7.9 Hz, 2H), 5.98 (m, 2H), 5.53 (m, 2H), 4.67 (dd, J = 10.1, 3.5 Hz, 1H), 4.31 (m, 1H), 4.14 (dd, J = 10.1, 2.8 Hz, 1H), 2.82 (dt, J = 15.9, 8.5 Hz, 1H), 2.61 (m, 2H), 2.44 (dt, J = 15.2, 7.1 Hz, 1H), 2.29 (q, J = 7.5 Hz, 2H), 2.06 (quin, J = 7.5 Hz, 4H), 1.58−1.26 (m, 12H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 148.7, 132.6, 131.2, 130.7, 130.0, 129.3, 121.0, 114.5, 72.0, 66.3, 32.4, 32.0, 31.6, 30.1, 29.2, 29.0, 28.7, 26.4, 24.4, 22.4, 19.6, 13.9; IR (neat) 1602, 1590, 1237, 985 cm^{-1}; EIMS m/z (relative intensity) 383 (M$^+$, 6), 367 (8), 276 (58), 202 (33), 94 (PhOH, 100); HRMS calcd for $C_{25}H_{37}NO_2$ 383.2824, found 383.2833.

5-(Hex-5′-enyl)-2-phenoxymethyl-2,3-dihydro4*H*-pyrrole 1-Oxide (41). A mixture of ketal **38** (0.68 g, 2.03 mmol) and 3 N aqueous HCl (2 mL) in THF (20 mL) was stirred at room temperature overnight. The mixture was diluted with water, extracted with EtOAc, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 4:1 EtOAc/MeOH to yield 0.48 g (87%) of nitrone **41** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35−1.55 (m, 4H), 1.99−2.06 (m, 2H), 2.18−2.26 (m, 2H), 2.36−2.79 (m, 4H), 4.07 (dd, J = 2.8, 10.1 Hz, 1H), 4.24 (br s, 1H), 4.62 (dd, J = 3.4, 10.1 Hz, 1H), 4.87−4.98 (m, 2H), 5.65−5.78 (m, 1H), 6.84−7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 24.2, 26.3, 28.4, 30.0, 33.1, 66.2, 71.9, 114.4, 114.5, 120.9, 129.2, 138.1, 148.8, 158.2; IR (neat) 3385 (br), 2927 (br), 1600, 1497, 1245 cm^{-1}; EIMS m/z (relative intensity) 273 (M$^+$, 4); CIMS m/z (relative intensity) 274 (MH$^+$, 100); HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1726.

Cycloaddition of Nitrone 41. A solution of nitrone **41** (0.23 g, 0.84 mmol) in *m*-xylene (10 mL) was heated at 150 °C for 48 h. The solvent was removed, and the residue was purified by flash chromatography eluting first with 1:20 EtOAc/hexanes to afford 108 mg (47%) of the less polar compound **46** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42−1.65 (m, 4H), 1.69−1.83 (m, 6H), 2.03−2.10 (m, 2H), 2.22−2.26 (m, 2H), 3.37−3.46 (m, 1H), 3.84 (t, J = 8.9 Hz, 1H), 4.30 (dd, J = 4.0, 8.9 Hz, 1H), 4.72 (br d, J = 8.9 Hz, 1H), 6.90−7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 23.5, 25.6, 33.2, 33.5, 40.0, 41.2, 66.5, 71.0, 72.8, 79.7, 114.3, 120.4, 129.2, 158.8; IR (neat) 2918, 1599, 1496, 1245 cm^{-1}; EIMS m/z (relative intensity) 273 (M$^+$, 8); CIMS m/z (relative intensity) 274 (MH$^+$, 99); HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1728. Further elution with 1:10 EtOAc/hexanes furnished the more polar product **44**, 51 mg (22%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23−2.31 (m, 12H), 2.43−2.51 (m, 1H), 3.46−3.56 (m, 1H), 3.80−3.88 (m, 2H), 4.20 (t, J = 7.9 Hz, 1H), 4.26 (dd, J = 4.3, 9.0 Hz, 1H), 6.90−7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 22.9, 23.1, 26.5, 32.8, 34.1, 45.0, 65.3, 71.0, 71.5, 71.6, 114.5, 120.6, 129.3, 158.9; IR (neat) 2930, 1600, 1496, 1246 cm^{-1}; EIMS m/z (relative intensity) 273 (M$^+$, 10); HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1728.

5-(Hept-5′-enyl)-2-phenoxymethyl-2,3-dihydro-4*H*-pyrrole 1-Oxide (42). A mixture of ketal **39** (1.02 g, 2.93 mmol) and 3 N aqueous HCl (3 mL) in THF (30 mL) was stirred at room temperature for 4.5 h. The mixture was diluted with water, extracted with EtOAc, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 4:1 EtOAc/MeOH to yield 0.65 g (78%) of nitrone **42** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34−1.44 (m, 2H), 1.46−1.60 (m, 2H), 1.62 (d, J = 4.6 Hz, 3H), 1.96−2.02 (m, 2H), 2.24−2.32 (m, 2H), 2.41−2.85 (m, 4H), 4.13 (dd, J = 2.8, 10.1 Hz, 1H), 4.29 (br s, 1H), 4.67 (dd, J = 3.4,

10.1 Hz, 1H), 5.33−5.45 (m, 2H), 6.87−7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.7, 24.5, 26.6, 29.3, 30.2, 32.1, 66.5, 72.1, 114.6, 121.1, 125.1, 129.4, 130.8, 149.3, 158.4; IR (neat) 2928, 1599, 1497, 1454, 1244 cm^{-1}; EIMS *m*/*z* (relative intensity) 287 (M^+, 3).

Cycloaddition of Nitrone 42. A solution of nitrone **42** (0.097 g, 0.338 mmol) in toluene (2 mL) was heated in a sealed tube at 120 °C for 72 h. The solvent was removed, and the residue was purified by flash chromatography eluting with 1:10 EtOAc/hexanes to afford 14 mg (15%) (38% based on recovered nitrone) of cycloadduct **45** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.30 (m, 2H), 1.33 (d, J = 6.0 Hz, 3H), 1.51−1.84 (m, 8H), 1.95−2.02 (m, 2H), 2.24−2.33 (m, 1H), 3.49−3.57 (m, 1H), 3.81 (t, J = 9.0 Hz, 1H), 4.22 (dd, J = 6.0, 10.8 Hz, 1H), 4.30 (dd, J = 4.0, 9.0 Hz, 1H), 6.90−7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.0, 22.4, 23.6, 26.9, 32.2, 34.9, 52.1, 66.6, 70.6, 72.4, 79.5, 114.4, 120.5, 129.4, 158.9; IR (neat) 2927, 1600, 1497, 1247 cm^{-1}; EIMS *m*/*z* (relative intensity) 287 (M^+, 4.6); HRMS calcd for $C_{18}H_{25}NO_2$ 287.1885, found 287.1870.

Isoxazolidine 43. A solution of nitrone diene **40** (485 mg, 1.27 mmol) in DMSO (7.0 mL) was heated at 195 °C in a sealed tube for 16 h. The solvent was removed, and the residue was purified by flash chromatography (10% EtOAc/hexanes) to afford 305 mg (63%) of isoxazolidine **43** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.92 (m, 3H), 5.66 (dt, J = 15.2, 6.7 Hz, 1H), 5.37 (dd, J = 15.2, 8.3 Hz, 1H), 4.43 (dd, J = 10.8, 8.4 Hz, 1H), 4.32 (dd, J = 9.0, 3.9 Hz, 1H), 3.81 (t, J = 9.0 Hz, 1H), 3.51 (m, 1H), 2.30 (m, 1H), 2.02 (m, 4H), 1.80−1.53 (m, 8H), 1.39−1.16 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 135.8, 130.2, 129.3, 120.5, 114.4, 85.7, 72.3, 70.7, 66.2, 50.4, 34.6, 32.2, 31.7, 31.6, 28.9, 28.7, 26.4, 23.6, 22.5, 21.6, 20.9, 14.0; IR (neat) 1602, 1584, 1243, 950 cm^{-1}; EIMS *m*/*z* (relative intensity) 383 (M^+, 39), 366 (17), 276 (100), 218 (23); HRMS calcd for $C_{25}H_{37}NO_2$ 383.2824, found 383.2822.

Amino Alcohol 49. To a solution of isoxazolidine **43** (200 mg, 0.522 mmol) in AcOH:H_2O (1:1, 3 mL) was added Zn dust (680 mg, 10.4 mmol), and the mixture was heated at 45 °C for 3 h. The solution was cooled, basified with 15% aqueous NaOH, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (2.5−5% MeOH/CH_2Cl_2) to afford 183 mg (91%) of amino alcohol **49** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 5.67 (dt, J = 15.1, 6.6 Hz, 1H), 5.39 (dd, J = 15.2, 8.1 Hz, 1H), 4.45 (t, J = 8.8 Hz, 1H), 4.00 (AB of ABX, J_{AB} = 9.5 Hz, J_{AX} = 7.3 Hz, J_{BX} = 7.7 Hz, $\Delta\upsilon_{AB}$ = 33.4 Hz, 2H), 3.49 (m, 1H), 2.10−1.68 (m, 11H), 1.55−1.20 (m, 16H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 132.3, 131.7, 129.4, 120.9, 114.4, 73.4, 68.2, 66.3, 56.7, 46.0, 37.7, 34.2, 32.1, 31.6, 29.0, 28.7, 28.2, 25.4, 24.1, 22.5, 19.7, 14.0; IR (neat) 3025 (br), 3025, 1596, 1237, 967 cm^{-1}; CIMS *m*/*z* (relative intensity) 386 (MH^+, 6), 368 ($MH^+ - H_2O$, 21), 274 ($MH^+ - PhOH - H_2O$, 7), 260 (6), 69 (100); HRMS calcd for $C_{25}H_{39}NO_2$ 385.2981, found 385.2997. Anal. Calcd for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.71; H, 10.20; N, 3.59.

Preparation of Tricyclic Ketone 52. To a suspension of Dess−Martin periodinane (325 mg, 0.768 mmol) in CH_2Cl_2 (1 mL) was added *tert*-butyl alcohol (98 μL, 1.02 mmol). After stirring for 15 min, the suspension was added slowly to a solution of alcohol **49** (197 mg, 0.512 mmol) in CH_2Cl_2 (2.5 mL). After 40 min, the reaction mixture was quenched by the addition of a 15% aqueous NaOH solution. The mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography (5% EtOAc/hexanes) to afford 139 mg (71%) of tricyclic ketone **52** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 2H), 6.93 (m, 3H), 3.92 (dd, J = 9.0, 4.5 Hz, 1H), 3.70 (t, J = 8.9 Hz, 1H), 3.47 (m, 1H), 3.31 (m, 1H), 2.64 (dd, J = 15.5, 5.2 Hz, 1H), 2.51 (br s, 1H), 2.29 (m, 2H), 2.21 (dd, J = 15.5, 6.9 Hz, 1H), 2.10 (m, 2H), 1.85 (m, 2H), 1.70−1.20 (m, 16H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 158.8, 129.2, 120.4, 114.3, 72.0, 68.0, 63.6, 58.7, 50.7, 43.0, 40.4, 36.9, 36.2, 31.7, 29.2, 26.0, 25.9, 24.3, 23.0, 22.4, 21.5, 13.9; IR (neat) 1707, 1602, 1584, 1243 cm^{-1}; CIMS *m*/*z* (relative intensity) 384 (MH^+, 11), 290 ($MH^+ - PhOH - H_2O$, 7), 276 (9), 69 (100); HRMS calcd for $C_{25}H_{37}NO_2$ 383.2824, found 383.2815. Anal. Calcd for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.26; H, 9.77; N, 3.61.

Clemmensen Reduction of Ketone 52. Concentrated HCl (1.5 mL) was added to a solution of tricyclic ketone **52** (82.0 mg, 0.214 mmol) in toluene (750 μL). Zn(Hg) (100 mg) was added, and the mixture was heated to 90 °C and stirred for 16 h. Additional Zn(Hg) (100 mg) and concentrated HCl (1 mL) was added, and after 7 h the reaction mixture was cooled to room temperature, basified with a 15% aqueous NaOH solution, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography (5−10% EtOAc/hexanes gradient) to afford 40 mg (51%) of olefin **58** and 5 mg of tricyclic indolizidine **59** (6%). Data for olefin **58**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.93 (m, 3H), 5.35 (br d, J = 6.5 Hz, 1H), 4.00 (dd, J = 9.1, 4.1 Hz, 1H), 3.76 (t, J = 8.4 Hz, 1H), 3.25 (m, 1H), 2.90 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 2.33 (m, 1H), 2.18−1.95 (m, 4H), 1.75−1.10 (m, 19H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 143.0, 129.3, 120.4, 114.7, 114.5, 73.0, 63.6, 62.9, 54.8, 40.8, 35.6, 34.6, 34.5, 31.9, 29.7, 27.9, 27.3, 27.0, 25.1, 24.5, 22.7, 14.1; IR (neat) 1602, 1590, 1243 cm^{-1}; CIMS *m*/*z* (relative intensity) 386 (MH^+, 80), 274 ($MH^+ - PhOH$, 93), 260 (100); HRMS calcd for $C_{25}H_{38}NO$ 368.2953, found 368.2929.

Hydrogenation of Olefin 58. To a solution of olefin **58** (32.6 mg, 0.089 mmol) in ethanol (1.5 mL) under argon was added 10% Pd/C (100 mg). The flask was evacuated and filled with H_2. After 6 h, the reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by flash chromatography (2.5−10% EtOAc/hexanes gradient) to afford 23 mg (70%) of indolizidine **59** as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.91 (m, 3H), 3.82 (dd, J = 8.9 Hz, 1H), 3.60 (t, J = 8.8 Hz, 1H), 3.31 (m, 1H), 2.79 (m, 1H), 2.10−1.18 (m, 27H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 129.4, 120.4, 114.5, 72.6, 63.6, 63.2, 56.2, 36.5, 36.4, 36.0, 35.8, 32.0, 30.5, 29.6, 27.9, 26.2, 25.8, 25.3, 22.7, 22.0, 21.0, 14.1; IR (neat) 1600, 1586, 1244 cm^{-1}; CIMS *m*/*z* (relative intensity) 370 (MH^+, 24), 336 (7), 276 ($MH^+ - PhOH$, 58), 262 (100); HRMS calcd for $C_{25}H_{40}NO$ 370.3110, found 370.3122. The picrate salt of amine **59** was recrystallized from CH_2Cl_2/hexanes (1/1) by slow evaporation for X-ray analysis (see Figure 1).

2-*epi*-Cylindricine C (53). To a solution of ketone **52** (15 mg, 0.039 mmol) in benzene (6 mL) was added ethylene glycol (0.190 mL, 3.39 mmol), followed by a catalytic amount of PPTS. The reaction flask was fitted with a Dean−Stark trap, and the mixture was heated at reflux and stirred for 48 h. The reaction mixture was cooled to room temperature and concentrated. The mixture was diluted with EtOAc and washed with a 15% NaOH solution. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude reaction mixture was purified by preparative TLC (5% EtOAc/hexanes, 4 elutions) to afford 5.9 mg (35%) of the ketal as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 2H), 6.92 (m, 3H), 4.07−3.87 (m, 4H), 3.80 (dd, J = 9.0, 4.5 Hz, 1H), 3.65 (t, J = 9.0 Hz, 1H), 3.32 (m, 1H), 2.93 (m, 1H), 2.30−1.20 (m, 25H), 0.88 (m, 3H).

Anhydrous ammonia (5 mL) was added to a solution of the ketal (0.014 mmol) in 0.800 mL of EtOH at −50 °C. Lithium wire (100 mg) was added in portions over 2 h, and the reaction mixture was diluted with aqueous NH_4Cl solution. The mixture was slowly warmed to room temperature, allowing the ammonia to evaporate. The crude product was partitioned between EtOAc and water, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude reaction mixture was purified by flash chromatography (5% EtOAc/hexanes) to afford 3.9 mg of a mixture of the desired reduction product and starting material (2.5:1 ratio).

The mixture was dissolved in THF (1 mL), 3 N aqueous HCl (0.250 mL) was added, and the reaction was stirred for 16 h.

The reaction mixture was basified with a 15% NaOH solution and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10−50% EtOAc/hexanes gradient) to afford 1 mg (24%) of 2-*epi*-cylindricine C (**53**) as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (dd, J = 10.6, 4.0 Hz, 1H), 3.40−3.28 (m, 2H), 3.23 (t, J = 5.9 Hz, 1H), 2.78 (m, 1H), 2.67 (dd, J = 15.7, 5.9 Hz, 1H), 2.54 (m, 1H), 2.26 (m, 1H), 2.17 (dd, J = 15.4, 6.0 Hz, 1H), 2.09−2.02 (m, 2H), 1.84−1.20 (m, 19H), 0.88 (t, J = 7.2 Hz, 3H); CIMS *m*/*z* (relative intensity) 308 (MH^+, 56), 290 (8), 276 (20), 222 (9).

Tricyclic Amino Alcohol 60. Anhydrous ammonia (6 mL) was added to a solution of indolizidine **59** in 2 mL of THF/EtOH (1/4) at −50 °C. Lithium wire (200 mg) was added in portions over 2 h, and after stirring for an additional 2 h, the reaction was quenched with an aqueous NH_4Cl solution. The mixture was slowly warmed to room temperature, allowing the ammonia to evaporate. The crude product was partitioned between ether and water, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. As shown in the ^{1}H NMR spectrum, the crude product obtained was a 2:3 mixture of starting material:reduction product and therefore the mixture was resubmitted to the above procedure. The resulting residue was dissolved in THF (1 mL), and 2 N HCl in methanol (0.100 mL) was added. After stirring for 6 h at room temperature, the mixture was basified with a 15% aqueous NaOH solution and extracted with ether. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (20% EtOAc/hexanes and then 0.5% NH_4OH/9.5% MeOH/90% CH_2Cl_2) to afford 18 mg (71%) of amino alcohol **60** as a pale yellow oil: IR (neat) 3436 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (dd, J = 10.3, 3.2 Hz, 1H), 3.27 (d, J = 10.3 Hz, 1H), 3.13 (m, 1H), 2.65 (m, 1H), 2.12−1.17 (m, 27H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.1, 63.5, 63.1, 54.2, 37.1, 35.8, 31.9, 30.2, 29.5, 28.1, 26.1, 25.1, 22.7, 21.7, 21.0, 14.1; ESIMS *m*/*z* (relative intensity) 294 ($[M + H]^+$, 100), 278 (5); HRMS calcd for $C_{19}H_{36}NO$ 294.2797, found 294.2785.

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Supporting Information Available: Experimental details for preparation of nitrone precursors **38** and **39**, proton and carbon NMR spectra of new compounds, and the NOESY spectrum of tricyclic ketone **52**. This material is available free of charge via the Internet at http://pubs.acs.org.

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