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Total Synthesis of Lepadiformine Alkaloids using *N*-Boc α-Amino Nitriles as Trianion Synthons

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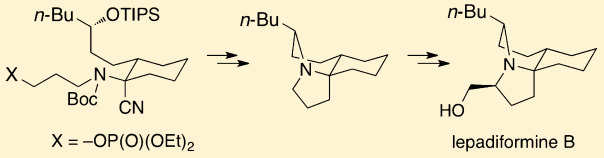
Supporting Information

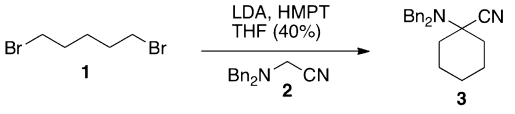
ABSTRACT: Lepadiformine A, B, and C were synthesized in an enantiomerically pure form using a reductive cyclization strategy. *N*-Boc α-amino nitriles were deprotonated and alkylated with enantiomerically pure dibromides to afford the first ring. The products were manipulated to introduce phosphate leaving groups, and subsequent reductive lithiation followed by intramolecular alkylation formed the second ring with high stereoselectivity. The third ring was formed by intramolecular displacement of a mesylate by the deprotected amine. Lepadiformine A and B contain a hydroxymethyl group adjacent to the amine. This appendage was introduced in a sequence using a Polonovski−Potier reaction as the key step. The synthetic strategy is stereoselective and convergent and demonstrates the utility of *N*-Boc α-amino nitriles as linchpins for alkaloid synthesis.



INTRODUCTION

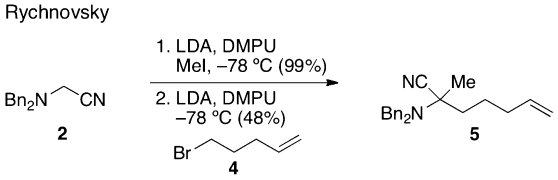
The use of stabilized carbanions to effect carbon−carbon bond formation is a long established strategy in organic synthesis.[1] Nitrile-stabilized anions (ketene iminates) have been applied to the construction of complex molecules by way of intermolecular alkylation and subsequent cyclization.[2] Stork used aminonitriles and cyanohydrin anions as aldehyde anion equivalents.[3,4] In a seminal report, Husson employed a double alkylation method to construct cyclohexyl aminonitriles from α,ω-alkyl bromides and di-*N*-benzyl cyanomethylamine **2** (eq 1).[5]

Husson



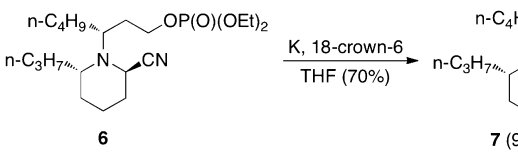
eq. (1)

Rychnovsky



eq. (2)

Grierson

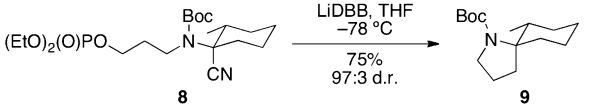


eq. (3)

We reported a sequential nitrile alkylation sequence to assemble tertiary α-aminonitriles as reductive carbolithiation precursors (eq 2).[6] Each of these strategies takes advantage of the high nucleophilicity of nitrile-stabilized anions.

Reduction of nitrile moieties for the stereoselective removal of nitrile groups is well documented in the literature.[7] These decyanation reactions presumably proceed through reactive alkyl metal species that are directly protonated under the reaction conditions. More recently, the formation of alkyl metal species by reductive metalation has been developed.[8] Reductive decyanation and cyclization of the resulting organometallic intermediate was first described in Grierson's synthesis of gephyrotoxin-16B (7) (eq 3).[9] These two transformations, the alkylation of nitrile-stabilized anions and a reductive decyanation followed by cyclization, can be combined to assemble complex structures rapidly and often stereoselectively. In this report, we provide a full account of the synthesis of lepadiformine alkaloids based on a sequential alkylation and reductive cyclization of α-aminonitriles.[10]

We have studied the reductive cyclization of α-heteronitriles for stereoselective syntheses of spirocyclic frameworks extensively.[11] Recent studies aimed toward expanding the synthetic scope of this methodology have shown that spiropyrrolidine moieties can be accessed from *exo*-cyclic α-aminonitriles in good yield and high diastereoselectivity (eq 4).[10,12] The



eq. (4)

structural similarity of spirocycle **9** to the core of fasicularin, cylindricine, and lepadiformine alkaloids captured our interest, and the fully substituted spiropyrrolidine core of these compounds arises naturally using this approach. We decided to develop the alkylation and reductive cyclization strategy with a synthetic approach to the lepadiformine alkaloids.[10]

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Lepadiformine A (Figure 1, **11**) was isolated by Biard and coworkers from the marine tunicate *Clavelina lepadiformis* off the coast of Tunisia.[13] Initial biological studies found moderate

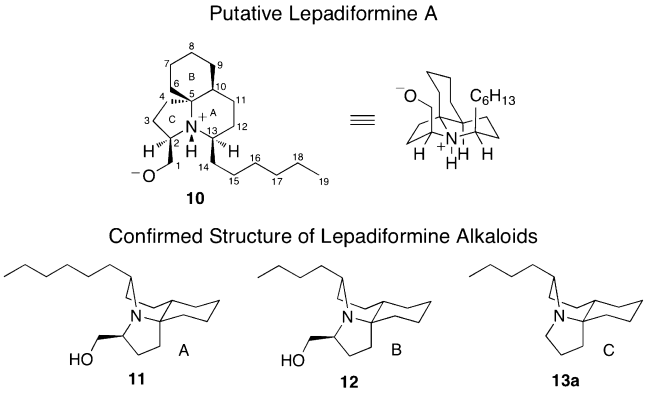

Figure 1. Lepadiformine alkaloids.

cytotoxic activity against various cell lines: nasopharnyx carcinoma (KB, IC_{50} = 9.20 μg/mL), human colon adenocarcinoma cells (HT29, IC_{50} = 0.75 μg/mL), and nonsmall-cell carcinoma (NSCLC-N6, IC_{50} = 6.10 μg/mL). Unequivocal assignment of the carbon skeleton was determined by ^{13}C NMR INADEQUATE experiments with the placement of the heteroatoms established from mass spectrometry fragmentation patterns. Clear assignment of the relative configuration was complicated by the poor resolution of the ^{1}H NMR signals leading to the incorrect *cis*-fused assignment of the A and B rings. Support for the controversial proposal of a zwitterionic species was provided by the low field singlet (~10 ppm) corresponding to a proton bound to one of the heteroatoms, the low chemical shifts of the carbons directly bonded to the nitrogen and the lack of chemical reactivity of the primary alcohol.

Inspired by the intriguing structure of lepadiformine, several groups attempted to prepare lepadiformine including Weinreb,[14] Kibayashi,[15] Pearson,[16] Oppolzer,[17] Funk,[18] Kim,[19] Hsung,[20] and Renaud[21] among others.[22] Synthetic work by Weinreb[14] and Pearson[16] determined the original zwitterionic structure **10** to be incorrect, and unambiguous assignment of the relative configuration (**11**) was accomplished by total synthesis of the racemate and X-ray crystallographic studies by the Kibayashi group.[15] Further work by Weinreb established the absolute configuration.[23] The synthetic challenge represented by this class of alkaloids has inspired several groups to complete total syntheses.[22,10]

In 2006, lepadiformines B (**12**) and C (**13a**), which contain a truncated four-carbon side chain, were isolated from the marine tunicate *Clavelina moluccensis* off the coast of Djibouti by the Sauviat group.[24] Biological studies showed moderate inhibition of cardiac inward rectifying K^+ channel for analogues **11** and **12**, and diminished activity for **13a**, which was attributed to the absence of the C-2 hydroxymethyl moiety. The absolute configuration of lepadiformine B and C were assumed to correspond to the absolute configuration of lepadiformine A. Lepadiformine C has attracted the attention of the synthetic community.[25]

We envisioned syntheses of lepadiformines A, B, and C from similar intermediates in a strategy that rapidly introduces all three rings from acyclic precursors. The retrosynthetic analysis involved an *N*-alkylation to form the tricyclic core with reductive cyclization providing the synthetically challenging spiropyrrolidine motif (Figure 2). Formation of the cyclohexane ring would be accomplished by double alkylation of chiral acyclic dibromides **15a,b** with α-aminonitrile **16**. The

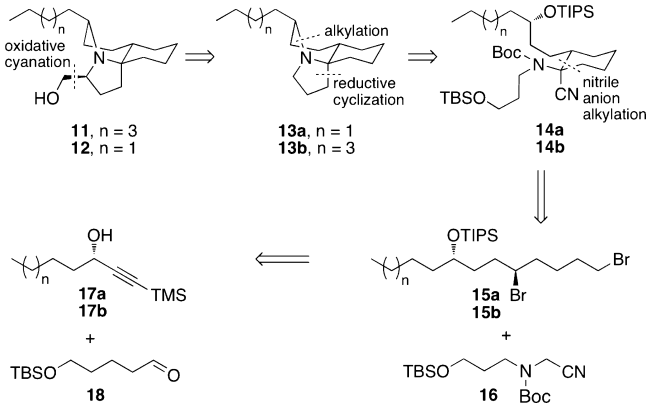

Figure 2. Retrosynthetic analysis of the lepadiformine alkaloids.

integral dibromide fragments would arise from alkyne reduction, TBS deprotection, and Appel-type[26] halogenation of alkynyl diol intermediates, whose stereochemical configurations would be installed by sequential Noyori-Ikariya transfer hydrogenations. The requisite precursors would originate from acetylide addition of a fragment derived from **17a,b**[27,28] and aldehyde **18**. The syntheses of lepadiformine A–C arising from this synthetic plan are presented below.[10]

RESULTS

The enantiomerically pure acyclic dibromide was prepared via the corresponding diol as outlined in Scheme 1. Synthesis of the dibromides **15a,b** began with the addition of lithium TMS-acetylide to aldehyde **19a,b** with subsequent oxidation to ynone **20a,b**. Reduction using the Noyori-Ikariya hydrogen-transfer catalyst Ru-(*p*-cymene)-TsDPEN (**21**), followed by removal of the trimethylsilyl group produced enantioenriched alcohols **22a,b**. Elaboration of the side chain proceeded by protection of the propargylic alcohol and addition of the lithiated alkyne to aldehyde **18** to give **23a,b**. Oxidation of the propargylic alcohols under Dondoni's modified Swern conditions,[29] followed by a second Noyori-Ikariya reduction gave (5*S*,8*S*)-**24a,b** as a single diastereomer. Conversion of propargylic alcohol **24a,b** to dibromide **15a,b** was initiated with alkyne reduction using Pt/C pretreated under H_2 atmosphere prior to addition of the alkyne, a procedure that proved unreliable on scale. Deleterious formation of ketone byproduct **26** was circumvented by use of platinum oxide and increasing the hydrogen pressure to 200 psi.[30] Subsequent removal of the TBS ether by treatment with PPTS in methanol afforded diols **27a,b**. Bromination of the diols to afford the double alkylation precursors **15a,b** was previously accomplished using NBS and triphenylphosphine in moderate yields, in part due to a difficult purification. Optimized conditions[26a] using bromine, triphenylphosphine, and triethylamine provided higher yields with greater consistency, improved purification, and eliminated the formation of a tetrahydropyran byproduct **28**. To examine whether an increase in the electrophilicity of the secondary bromide center would be beneficial in the double alkylation, dibromide **25** was also prepared in a similar fashion. Subsequent double alkylation studies with dibromide **25** were unsuccessful and were not explored further.

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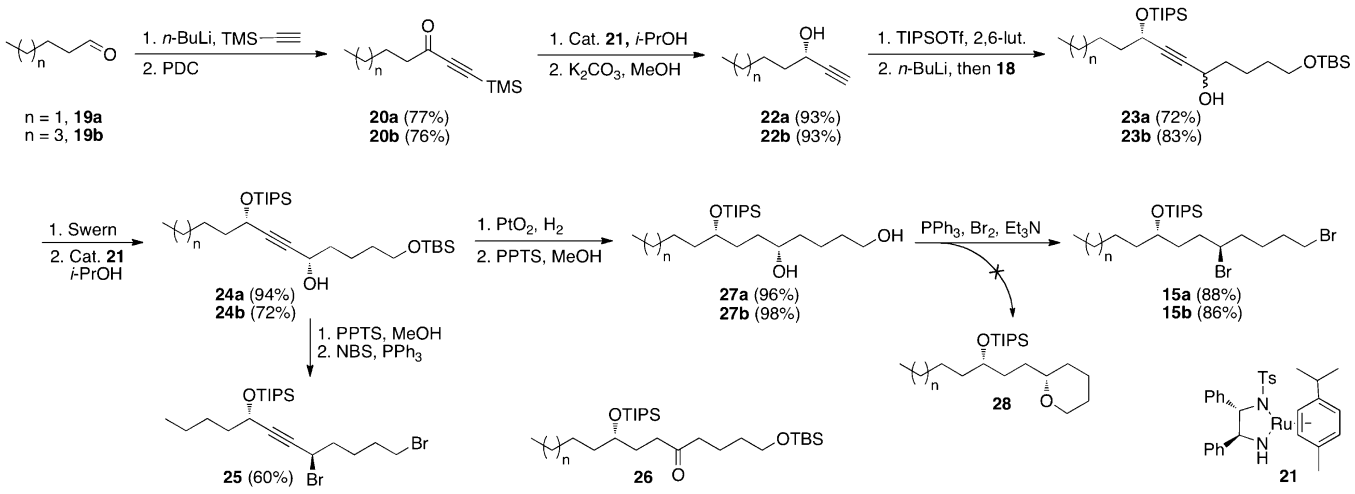
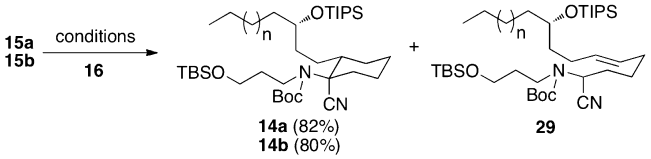
Scheme 1. Synthesis of the Dibromide Fragments



Synthesis of the α-aminonitrile **16** proceeded by protection of 3-amino-1-propanol as the TBS ether followed by cyanomethylation and protection of the amine as the Boc-carbamate.[10] With the coupling components in hand, a one-pot double nitrile anion alkylation with diastereomerically pure dibromide **15a** and α-aminonitrile **16** was conducted (Table 1). Treatment of **16** with base generates a nitrile anion that displaces the primary bromide of **15a**; a second equivalent of base forms another nitrile anion that then cyclizes via 6-*exo*-tet displacement of the secondary bromide. Initial studies were plagued by low yields and formation of elimination byproduct **29**. Procedural optimization did provide more consistent yields, albeit in the range of thirty percent. Alkylation with the more reactive propargyl bromide **25** was attempted, but none of the desired product was isolated. Apparently the strongly basic conditions of the reaction led to decomposition of the sensitive dibromide. Further optimization of the dialkylation with **15a** led to better results. Subsequent studies revealed that the use of less hindered bases, such as $LiNEt_2$ (entries 2 and 6), and elevated reaction temperature (entries 1 and 5) only promotes the formation of elimination byproduct **29**. An increase in yield was observed with the use of DMPU as the solvent, indicating that aggregation may be inhibiting complete reaction (entry 4). Addition of base at decreased temperature with warming to 0 °C favors formation of product and monoalkylated intermediate as well as suppresses the formation of eliminated byproduct (entry 8). After an exhaustive screen of reaction conditions, consistent 80% yields of **14a** were obtained with the use of freshly distilled DMPU in THF, addition of LDA (3.5 equiv) and slow increase in temperature from −78 − 0 °C (entry 8). The concentration of the reaction was not examined in depth, but lower yields were observed with a concentration less than 0.06 M.

Table 1. Nitrile Anion Double Alkylation for 14a



entry	base	temp. (°C)	solvent	yield
1	LDA (4 equiv)	−40	DMPU/THF (1:4)	3−35%
2	LDA (2 equiv), $LiNEt_2$ (2 equiv)	−40	DMPU/THF (1:2)	elim. (**29**)
3	LDA (3 equiv), KHMDS(2equiv)	−40	DMPU/THF (1:2)	49%
4	LDA (4 equiv)	−40	DMPU	49%
5	$LiNEt_2$ (3 equiv)	−20	THF	decomp.
6	$LiNEt_2$ (3 equiv)	−40	THF	decomp.
7	LDA (4.5 equiv)	−78 to 0	LiCl/THF	22%
8	LDA (3.5 equiv)	−78 to 0	DMPU/THF (1:1)	80−82%

The synthesis of lepadiformine A and B by an alkylation sequence with an elaborated chiral α-aminonitrile (**30**) containing the C2 side chain was also investigated (Figure 3).[31]

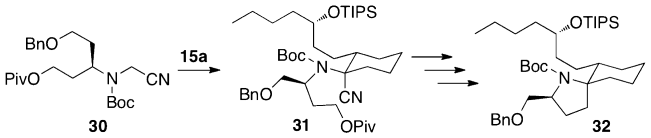


Figure 3. Alkylation and reductive cyclization of chiral aminonitrile.

Unfortunately, the double alkylation and reductive cyclization steps were problematic, affording the respective products, **31** and **32**, in an unoptimized 20 and 27% yield. These findings suggest that the presence of α-substitution to nitrogen in the nitrile results in increased steric hindrance and/or reduced nucleophilicity of the nitrile anion. These findings solidified the decision to use the simple α-aminonitrile **16** for the formation of the spiropyrrolidine framework with incorporation of the C2 side chain at a later stage.

With aminonitrile **14a,b** available in good yield, construction of the spiropyrrolidine system proceeded by deprotection of the TBS ether followed by phosphorylation to give reductive cyclization precursor **33a,b** (Scheme 2). Treatment of the phosphates **33a,b** with Freeman's reagent (lithium di-*tert*-butylbiphenylide, LiDBB)[32] afforded spiropyrrolidines **35a,b** as single diastereomers. Mechanistic studies to determine the origin of diastereoselectivity under reductive cyclization conditions indicate cyclization proceeds via a double inversion sequence with overall retention of configuration with respect to the nitrile starting material.[10]

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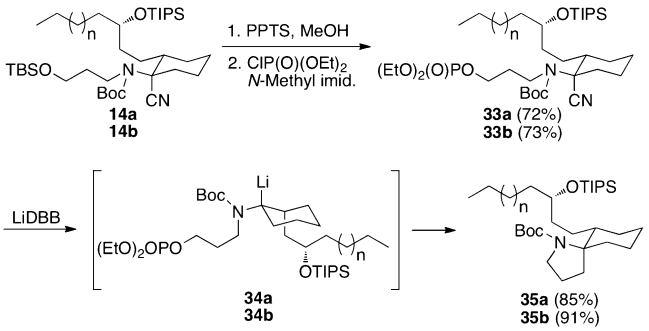
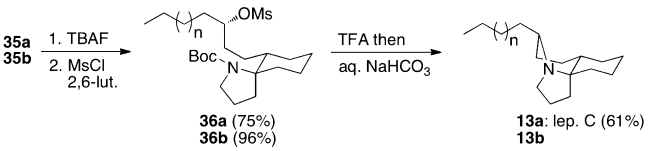
Scheme 2. Reductive Cyclization



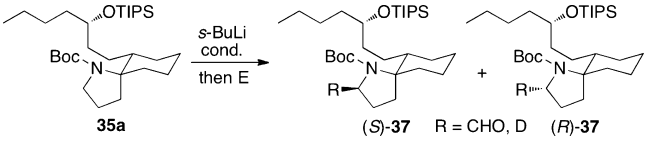
The synthesis of lepadiformine C (**13a**) and demethoxylepadiformine A (**13b**) proceeded with formation of the final ring via a mesylate intermediate as previously demonstrated by Kibayashi in the synthesis of (+)-cylindricine C.[22f] In this case, activation of the alcohol to mesylate **36a,b** was chosen to allow for facile Boc deprotection and *N*-alkylation/cyclization (Scheme 3). A previous attempt to effect cyclization using

Scheme 3. Synthesis of Lepadiformine C



CCl_4 and PPh_3 resulted in the formation of the trifluoroacetamide, which arose from the dehydration of residual TFA in the reaction mixture. Removal of the Boc group from **36a,b** with TFA followed by addition of saturated $NaHCO_3$ resulted in isolation of natural product **13a** and tricycle **13b** as a free amine. In order to compare the spectral data of synthetic lepadiformine C to that reported in the literature, **13a** was converted to the hydrochloride salt by treatment with anhydrous $HCl/CHCl_3$. The resultant synthetic material displayed

Table 2. *N*-Boc-pyrrolidine Formylation



entry	*T* (°C)	solvent	time	E	additive	yield (dr *S*:*R*)[a]
1	−78	Et_2O	3 h	**38**	**45**	31% (4:1)
2	−60 to −30	Et_2O	1 h	**39**	**45**	54% (1:7.4)
3	−60	Et_2O	3 h	**38** or **39**	**45**	20%
4	−30	THF	5 min	**40**	n/a	9%
5	−30	THF	5 min	**42**	n/a	21%
6	−78	Et_2O	3 h	**41**	**45**	3%
7	−78	Et_2O	3 h	**38**	**43**	34% (2:1)
8	−78	Me-THF	1 h	**38**	n/a	10%
9	−30	THF	5 min	**38** or **39**	n/a	43% (1:13.8)
10	−78	Et_2O	3 h	**38**	**44**	11% (1:2)
11	−78	Et_2O	2 h	CD_3OD	**45**	31% D incorp
12	−60	Et_2O	4 h	**38** or **39**	**45**	60%[b,c]

[a]The dr was determined by GC/MS. [b]4.4 equiv of *s*-BuLi or sequential addition of *s*-BuLi (5 × 1.3 equiv) and electrophile (5 × 1.3 equiv). [c]No recovered starting material.

spectroscopic data identical to those reported for the natural product with the exception of the optical rotation (vide infra).

Based on the established lithiation chemistry of *N*-Boc-pyrrolidines, a synthetic strategy using spiropyrrolidine **35a** to construct lepadiformine B (**12**) was initiated. Following a procedure developed by Beak,[33] spiropyrrolidine **35a** was lithiated and trapped with DMF to afford spiroprolinal **37** in 31% yield as a 4:1 mixture of chromatographically inseparable diastereomers (Table 2, entry 1).[34] The configuration of the major isomer was (*S*)-**37**, as demonstrated by the subsequent conversion to lepadiformine B (Scheme 4).[35] In an effort to improve the yield and diastereoselectivity of the reaction a number of conditions were examined. An increase in the temperature was found to moderately improve the yield with a concomitant reversal in diastereoselectivity (entry 2). Reaction times of greater than one hour at increased temperature also decreased yield (entry 3). Product formation was also highly electrophile-dependent. Of the electrophiles screened, DMF (**38**) and Weinreb amide **39** provided the highest yields (entries 1, 2, 9) with morpholine-4-carbaldehyde (**40**), methyl formate (**42**), and benzotriazole-1-methanol (**41**) proving unsatisfactory (entries 4, 5, 6). Unfortunately, neither the yields nor the selectivity for this transformation were satisfactory.

In an attempt to induce greater diastereoselectivity, the use of a chiral diamine ligand was explored. The desired stereochemistry of the lithiation/carbonylation required the use of a (+)-sparteine surrogate. O'Brien et al. reported on the use of chiral cyclohexyl diamine **43** on *N*-Boc-pyrrolidines in good yield and higher (Figure 4).[36] Formylation of spiropyrrolidine

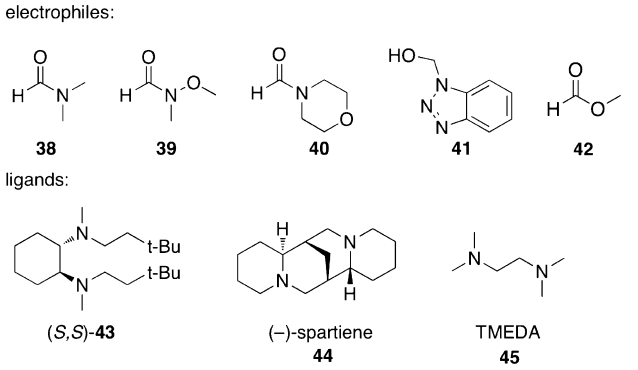


Figure 4. Examined electrophiles and diamine ligands.

35a using diamine **43** provided similar yields but lower diastereoselectivity (entry 7). A recent report by O'Brien on diamine-free lithiation/trapping of *N*-Boc-heterocycles provided a new avenue to improve the yield and, potentially, diastereoselectivity.[37] Use of the more coordinating solvent THF (or Me-THF) results in an *s*-BuLi/THF complex, which promoted lithiation similar to that of *s*-BuLi/TMEDA. At low temperatures the use of THF resulted in low yields (entry 8). Higher reaction temperatures gave higher yields but the undesired (*R*)-isomer was favored (entry 9). Due to the lack of complexation of (−)-sparteine to *s*-BuLi in THF or the faster rate of lithiation by *s*-BuLi/THF, the use of a chelating diamine in THF was not attempted. To determine the identity of the diastereomeric mixtures, a control reaction with (−)-sparteine (**44**) was conducted (entry 10). A deuterium incorporation study was conducted to examine whether deprotonation or trapping of the electrophile was insufficient. The deuterium incorporation of

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31% is congruent with the observed yields, suggesting that deprotonation is problematic (entry 11). With conditions capable of providing moderate yields and good diastereoselectivity for the undesired (*R*)-configuration (entries 2 and 12), an equilibration of the aldehyde to the (*S*)-configuration was attempted.

Inspection of the spirocycle **37** suggests the possibility of equilibrating the aldehyde (*R*)-**37** to a thermodynamically more stable (*S*)-**37** based on relief of steric strain. To test the hypothesis, spiropyrrolidine **37**, as a mixture of diastereomers, was subjected to a variety of conditions (Table 3). Initial attempts

Table 3. Attempted Equilibration of Spiropyrrolidine 37

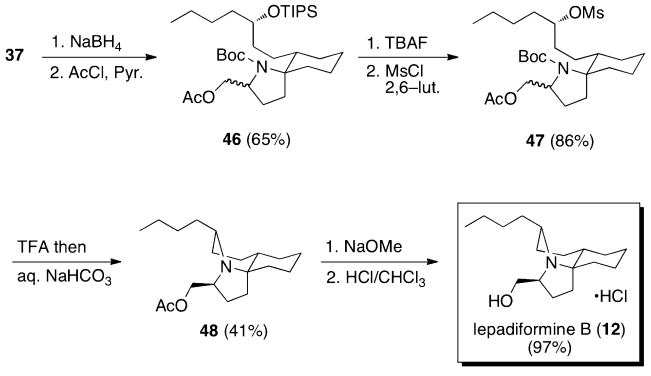
entry	base	solvent	temp (°C)	time	dr_i (*S*:*R*)	dr_f[a] (*S*:*R*)
1	Et_3N, SiO_2	Hexanes/EtOAc	22	48 h	1:7.4	1:3.5
2	Et_3N, SiO_2	Hexanes/EtOAc	22−90	4 d	4:1	2:1
3	DBU	DMF	22	48 h	4:1	3.4:1
4	pyrrolidine	DMF	22	48 h	4:1	97:3[b]
5	pyrrolidine	DMF	22	48 h	1:7.4	3:97[b]
6	K_2CO_3	MeOH	22	19 h	4:1	97:3[b]
7	K_2CO_3	MeOH	22	19 h	1:7.4	3:97[b]

[a]The dr was determined by GC/MS. [b]Formation of byproduct(s) resulted in supposed equilibration selectivity.

show convergence toward a 1:1 ratio of diastereomers, indicating no significant preference for either the *R* or *S* configuration (entries 1−3). The use of pyrrolidine and potassium carbonate were promising: a sample enriched in the (*S*)-isomer showed complete conversion to the desired diastereomer (entries 4 and 6). These results were then obfuscated by the conversion of an enriched (*R*)-isomer sample to the undesired (*R*)-isomer (entries 5 and 7). Analysis of the equilibrium reactions conducted by MS showed formation of an aldol byproduct, indicating that the observed increase in diastereomeric ratio was the result of an aldol addition reaction between the aldehyde reactants. This side reaction effectively removed the minor isomer to provide an increase in diastereomeric ratio; the outcome may be rationalized by postulating a diastereoselective aldol reaction between the (*R*)-aldehyde and the (*S*)-aldehyde that would preferentially remove *racemic* aldehyde from the mixture. Unfortunately, the increase in diastereomeric ratio was an impractical solution because it was accompanied by a reduction in yield.

The synthesis of lepadiformine B was completed from aldehyde **37** as outlined in Scheme 4. A mixture of diastereomeric aldehydes **37** (4:1 (*S*)-**37** to (*R*)-**37**, Table 2, entry 1) was

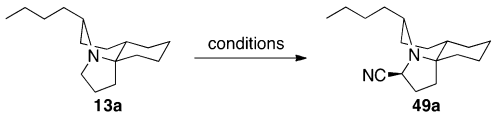
Scheme 4. Synthesis of Lepadiformine B



reduced with sodium borohydride, and the resultant alcohol was protected as the acetyl ester to afford **46** (4:1 diastereomeric mixture). Fluoride-mediated removal of the silyl protecting group, followed by activation of the alcohol as the mesylate provided *N*-alkylation precursor **47** as a mixture of diastereomers. Removal of the Boc group by TFA followed by neutralization provided *O*-acetyl-lepadiformine B (**48**) as a single stereoisomer. The stereoselectivity of the reaction may be attributed to the difference in the rates of cyclization for the two diastereomers: the less hindered (*S*)-isomer reacts faster compared to the undesired (*R*)-isomer. The moderate yield may be attributed to the formation of a number of byproducts. Products of an elimination pathway include the *O*-acetyl, *N*-acetyl (derived from an *O*- to *N*-acyl migration) and Boc-protected starting material. Unreacted free amine as well as acetate hydrolysis of the cyclized product (lepadiformine B) was also observed. Basic hydrolysis of the acetyl ester and acidification provided synthetic lepadiformine B (**12**) as the hydrochloride salt.

In an effort to install the C2 side chain in a more efficient and stereoselective fashion, a new route to convert lepadiformine C to lepadiformine B was proposed. Lepadiformine B would arise from a 3-step procedure involving oxidative cyanation, hydrolysis of the nitrile and reduction to the alcohol. Initial attempts at oxidative cyanation following the work of Murahashi were unsuccessful, with no perceptible formation of product (Table 4, entry 1).[38] Subsequent efforts using

Table 4. Oxidative α-Cyanation



entry	solvent	temp (°C)	reagents	yield (%)
1	CH_2Cl_2	22	$RuCl_3$, H_2O_2, AcOH, NaCN	0
2	CH_3CN	23−100	$C_7H_7^+BF_4^-$, KCN	0
3	CH_3CN	23−120	$C_7H_7^+BF_4^-$	0[a]
4	CH_2Cl_2	0−22	*m*-CPBA, TFAA, KCN	85

[a]Iminium ion formation control experiment.

aromatic cation tropylium tetrafluoroborate as reported by Lambert and Allen also showed no conversion (entry 2).[39] A control reaction was attempted to determine if iminium formation was possible under various reaction temperatures. The iminium salt was not observed upon treatment with tropylium salt in the absence of a nucleophile even at temperatures up to 120 °C (entry 3). The search for a more robust method led to the use of a Polonovski-Potier reaction (entry 4).[40] Formation of the *N*-oxide with peroxide followed by TFAA mediated rearrangement achieved iminium ion formation. Subsequent cyanide trapping provided aminonitrile **49a** as a 6:1 (*S*:*R*) ratio of diastereomers. Conversion of the nitrile to the aldehyde by DIBAL-H reduction was problematic, providing a 1:1 mixture of aldehyde and lepadiformine C. A revised route was explored to avoid the modest recovery observed in this step.

An improved synthesis of lepadiformine A and B was realized by forgoing purification until hydrolysis of the aminonitrile to the methyl ester was complete. Following the procedure established above (Scheme 3), spiropyrrolidines **35a,b** were converted to the mesylates **36a,b** and cyclized to the lepadiformine skeleton. Without purification, the tertiary amines

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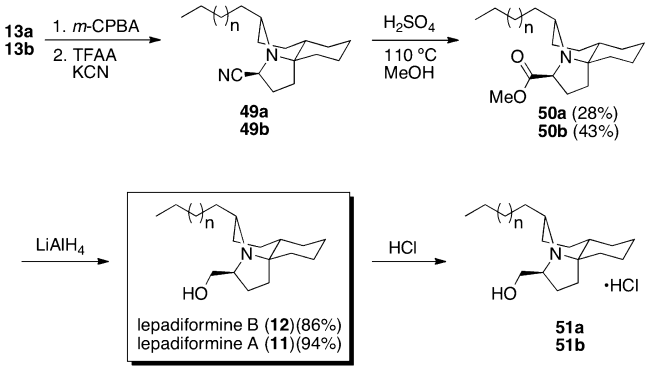
13a,b were subjected to a three-step sequence to provide the methyl esters **50a,b** in 28 and 43% overall yield as single diastereomers. The minor isomers from the aminonitriles **49a,b** did not lead to the corresponding methyl ester, perhaps due to inefficient hydrolysis of this more sterically encumbered nitrile. The sequence involved *N*-alkylation followed by formation of the *N*-oxide and modified Polonovski reaction to afford the aminonitriles **49a,b**. Hydrolysis of the nitrile to the methyl ester followed by reduction to the alcohol provided lepadiformine A (**11**). Lepadiformine B was prepared by an analogous sequence of transformations. Each natural product was isolated as a single stereoisomer (Scheme 5). The hydrochloride salts of

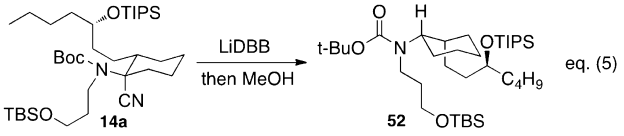
Scheme 5. Synthesis of Lepadiformine A and B



lepadiformine A and B matched the reported spectral data for the corresponding natural product. The optical rotation for lepadiformine A was +1.8 (lit. $[\alpha]^{22}_{D}$ = +4.0) and that for lepadiformine B was +3.2 (lit. $[\alpha]^{22}_{D}$ = +3.0).[24]

DISCUSSION

The key reductive cyclization reaction (e.g., **33a** to **35a**, Scheme 2) proved to be an efficient, stereoselective process. The mechanistic origin of selectivity was of interest and prompted an investigation aimed at identifying the configuration of the intermediate organolithium. Reductive lithiation of control substrate **14a** followed by protonation of the resultant organolithium gave *cis*-disubstituted cyclohexane **52** (eq 5). Assuming protonation

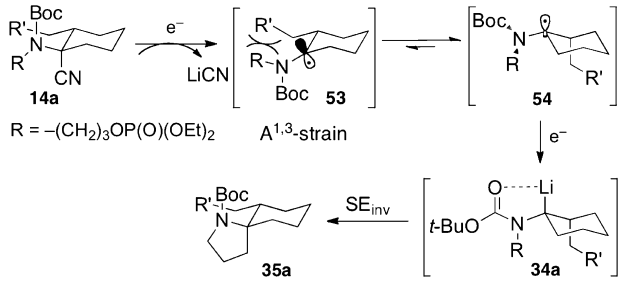


eq. (5)

proceeded with retention of configuration,[41] the mechanism of the reductive cyclization may proceed as proposed in Scheme 6. The radical intermediate **53**, stabilized by interaction with the nitrogen electrons, creates a sterically encumbered environment between the equatorial R′ group and the nitrogen R group (or *N*-Boc group) resulting in a conformational isomerization to produce radical **54**. Further reduction of radical **54** to alkyllithium **34a** allows for cyclization via a SE_{inv} pathway and leads to spiropyrrolidine **35a**. The overall stereochemical outcome of the event is cyclization with retention of configuration.

With any enantioselective natural product synthesis, unambiguous assignment of the absolute configuration is essential. Sauviat and co-workers reported an optical rotation of +11 for the hydrochloride salt of lepadiformine C. The synthetic hydrochloride salt of lepadiformine C described herein has an

Scheme 6. Proposed Mechanism for the Reductive Cyclization



optical rotation of −11. Further investigation revealed that the free base of synthetic **13a** gave the sign and magnitude (+11) reported by Sauviat. This data comparison indicated that either the reported rotation was of the free base and not the HCl salt or that the enantiomer of natural lepadiformine C was made. The latter seems unreasonable based on multiple factors. First, comparison of the first two Noyori-Ikariya reduction products to those reported in the literature confirms the stereochemistry and enantioselectivity as described herein.[23,42] Second, the stereoselective reduction of the alkynyl ketone with (*S*,*S*)-TsDPEN ruthenium catalyst gave the correct (*S*)-enantiomer and the second alkynyl ketone reduction with the same catalyst would give selectively the desired (*S*,*S*)-intermediate **24a**. This configuration was confirmed by Mosher's ester analysis. Third, with the stereochemistry of the alcoholic carbon used for the final bond formation clearly defined, formation of any other stereocenter than those described herein would produce a molecule that is inconsistent with the spectral data and not just the optical rotation. Most importantly, the optical rotation of synthetic lepadiformine B hydrochloride obtained from lepadiformine C is in agreement with the reported value. These results prove that synthesis of the desired enantiomer was achieved. Our current data indicate that natural lepadiformine A and B have the same absolute configuration. We propose that the configuration of lepadiformine C is the same as lepadiformine B, and that the discrepancy in optical rotation reported for the natural product should be discounted.

CONCLUSION

Lepadiformine A, B and C were synthesized enantioselectively using a double alkylation and subsequent reductive cyclization of an *exo*-cyclic α-aminonitrile. The syntheses described herein highlight the use of α-aminonitriles as trianion synthons that are capable of constructing fully substituted carbon centers in a stereoselective fashion. Furthermore, the reductive lithiation and cyclization transformation provides an innovative approach for constructing spiropyrrolidine frameworks and one that will be applicable to other synthetic problems.

EXPERIMENTAL SECTION

General Experimental Details. All moisture sensitive reactions were performed under a positive pressure of argon in flame- or oven-dried glassware using standard septa/syringe techniques. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), toluene (PhMe) were degassed and dried by filtration through alumina according to the procedure by Grubbs.[43] Chloroform ($CHCl_3$), ethyl acetate (EtOAc), nitromethane ($MeNO_2$), hexanes and acetonitrile (MeCN) were distilled over CaH_2 under nitrogen or argon at atmospheric pressure prior to use. All commercially available reagents were used as received, unless otherwise stated. Thin layer chromatography (TLC) was performed on Whatman K6F (250 μm) silica gel plates and visualized

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using *p*-anisaldehyde stain. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. ^{1}H NMR spectra are reported in ppm on the δ scale and referenced to the residual solvent peaks. The data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constant(s) in Hertz (Hz), and integration. ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (77.07 ppm). Unnumbered intermediates were assigned compound numbers sequentially as S1, S2, S3, etc.

Experimental Procedures. *(S)-Non-1-yn-3-ol (**22b**).* To a solution of (*S*)-1-(trimethylsilyl)non-1-yn-3-ol[44] (25.6 g, 121 mmol) in MeOH (500 mL) at 0 °C was added K_2CO_3 (20.0 g, 145 mmol). After 1 h the suspension was passed through a pad of Celite (2 cm) and concentrated to a yellow oil. Purification by column chromatography (6:1 pentane/Et_2O) gave the alcohol (16.3 g, 96%) as a clear oil. The spectral data matched those previously reported in the literature.

*(S)-(Non-1-yn-3-yloxy)triisopropylsilyl (**S1**).* To a solution of alcohol **22b** (5.00 g, 35.7 mmol) in CH_2Cl_2 (70.0 mL) at −78 °C was added 2,6-lutidine (8.31 mL, 71.3 mmol, 2.0 equiv) and TIPSOTf (11.5 mL, 42.8 mmol, 1.2 equiv). The mixture was allowed to warm to rt over 18 h and the reaction was quenched with saturated aq. $NaHCO_3$ (10 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (98:2 pentane/Et_2O) gave **S1** (10.2 g, 97%) as a clear oil: R_f = 0.77 (3:1 pentane/Et_2O); $[\alpha]_D^{22}$ = −32.6 (*c* = 1.0, $CHCl_3$); IR (thin film) 3313, 2943, 2868, 1464, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (td, *J* = 6.3, 6.3, 2.1 Hz, 1H), 2.38 (d, *J* = 2.0 Hz, 1H), 1.73−1.68 (m, 2H), 1.48 (m, 2H), 1.34−1.29 (m, 6H), 1.18−1.07 (m, 21H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ 85.9, 71.9, 63.0, 38.9, 31.8, 29.1, 24.9, 22.7, 18.1, 14.1, 12.3; HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{37}OSi$ $[M + H]^+$ 297.2614, found 297.2613.

*(8S)-Triisopropylsilyloxy-1-(tert-butyldimethylsiloxy)tetradec-6-yn-5-ol (**23b**).* To a solution of alkyne **S1** (6.70 g, 22.5 mmol) in THF/DMPU (8S/15, 100 mL) at −78 °C was added *n*-BuLi (10.2 mL of a 2.30 M solution in hexanes, 23.5 mmol) dropwise over 10 min. The solution was then warmed to −20 °C over 20 min. After cooling to −40 °C, aldehyde **18** (4.89 g, 22.6 mmol) was added over 1.2 h. After 20 min, the reaction was quenched with saturated aq. NH_4Cl (25 mL) and H_2O (25 mL), and the mixture was warmed to rt. After dilution of the mixture with Et_2O (50 mL) the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (gradient 98:2 pentane/Et_2O to 90:10 pentane/Et_2O) gave **23b** (9.99 g, 86%, 1:1 mixture of diastereomers) as a clear oil: R_f = 0.63 (4:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = −15.9 (*c* = 1.0, $CHCl_3$); IR (thin film) 3338, 2939, 2866, 1464 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (t, *J* = 6.3 Hz, 1H), 4.39 (q, *J* = 6.0, 1H), 3.62 (t, *J* = 6.5 Hz, 2H), 1.75 (dd, *J* = 5.5, 1.9 Hz, 1H), 1.72−1.66 (m, 4H), 1.57−1.40 (m, 6H), 1.38−1.26 (m, 6H), 1.18−1.05 (m, 20H), 0.90 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.9, 84.8, 63.1, 63.1, 62.6, 38.9, 37.6, 32.4, 31.8, 29.1, 26.0, 25.1, 22.7, 21.6, 18.4, 18.1, 14.1, 12.3, −5.3; HRMS (ESI) *m*/*z* Calcd for $C_{29}H_{60}NaO_3Si_2$ $[M + Na]^+$ 535.3979, found 535.3985.

*(8S)-Triisopropylsilyloxy-1-(tert-butyldimethylsiloxy)tetradec-6-yn-5-one (**S2**).* To a solution of oxalyl chloride (1.17 mL, 13.4 mmol) in CH_2Cl_2 (67 mL) at −78 °C was added dimethyl sulfoxide (1.60 mL, 22.6 mmol) in CH_2Cl_2 (33 mL) dropwise via addition funnel. The mixture was allowed to stir for 30 min before a solution of alcohol **23b** (5.27 g, 10.3 mmol) in CH_2Cl_2 (33 mL) was added via addition funnel over 20 min. After 30 min, $EtN(i\text{-}Pr)_2$ (6.3 mL, 40.0 mmol) was added dropwise by addition funnel, and the mixture was allowed to stir at −78 °C for 1 h. Upon warming for 30 min, the reaction mixture was poured on saturated aq. NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (96:4 pentane/Et_2O) gave the ynone (4.19 g, 80%) as a clear oil: R_f = 0.70 (4:1 hexanes/EtOAc); IR (thin film) 2944, 2865, 2208, 1682, 1464 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (t, *J* = 6.3 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 1.80−1.70 (m, 4H), 1.56−1.52 (m, 2H), 1.50−1.40 (m, 2H), 1.32−1.27 (m, 6H), 1.20−1.09 (m, 21H), 0.89 (s, 12H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 93.6, 83.2, 63.0, 62.7, 45.2, 38.2, 32.0, 31.9, 29.0, 25.9, 24.8, 22.6, 20.5, 18.3, 18.0, 14.1, 12.2, −5.3; HRMS (ESI) *m*/*z* Calcd for $C_{29}H_{58}NaO_3Si_2$ $[M + Na]^+$ 533.3822, found 533.3831.

*(5S,8S)-Triisopropylsilyloxy-1-(tert-butyldimethylsiloxy)tetradec-6-yn-5-ol (**24b**).* To a solution of ynone **S2** (4.19 g, 8.20 mmol) in OmniSolv *i*-PrOH (100 mL) was added Ru[(S,S)-TsDPEN](*η*-*p*-cymene) **21** (172 mg, 0.287 mmol, 3.5 mol %) producing a deep purple solution. After 24 h, the red solution was concentrated *in vacuo* to a dark red oil. Purification by column chromatography (95:5 pentane/Et_2O) gave **24b** (3.77 g, 90%) as a clear oil: R_f = 0.58 (4:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = −14.5 (*c* = 1.0, $CHCl_3$); IR (thin film) 3350, 2935, 2866, 1464 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (t, *J* = 6.3 Hz, 1H), 4.38 (q, *J* = 6.0 Hz, 1H), 3.62 (t, *J* = 6.5 Hz, 1H), 1.78 (d, *J* = 4.7 Hz, 1H), 1.74−1.66 (m, 4H), 1.58−1.53 (m, 2H), 1.52−1.47 (m, 2H), 1.46−1.40 (m, 2H), 1.35−1.25 (m, 7H), 1.15−1.03 (m, 21H), 0.89 (s, 12H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.9, 84.8, 63.1, 63.0, 62.6, 38.9, 37.6, 32.5,31.8, 29.1, 26.0, 25.1, 22.7, 21.6, 18.4, 18.1, 14.1, 12.3, −5.3; HRMS (ESI) *m*/*z* Calcd for $C_{29}H_{60}NaO_3Si_2$ $[M + Na]^+$ 535.3979, found 535.3970.

*(5S,8S)-Triisopropylsilyloxy-1-(tert-butyldimethylsiloxy)-tetradecan-5-ol (**S3**).* A Parr bomb with PtO_2 (0.050 g) and alkyne **24b** (9.45 g, 18.4 mmol) in EtOAc (35 mL) was charged to 200 psi with H_2 gas. After 10 h the suspension was filtered through a pad of Celite with EtOAc and concentrated *in vacuo* to give the alkane **S3** (9.50 g, 99%) as a clear oil: R_f = 0.54 (4:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = 2.9 (*c* = 1.0, $CHCl_3$); IR (thin film) 3367, 2935, 2864, 1464 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88−3.83 (m, 1H), 3.62 (t, *J* = 6.5 Hz, 3H), 1.69−1.66 (m, 1H), 1.65−1.34 (m, 12H), 1.34−1.23 (m, 8H), 1.07 (br s, 21H), 0.89 (br m, 11H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.3, 72.0, 63.2, 37.2, 36.4, 32.8, 32.1, 31.9, 31.8, 29.6, 26.0, 25.1, 22.7, 22.1, 18.3, 14.1, 12.7, −5.3; HRMS (ESI) *m*/*z* Calcd for $C_{29}H_{64}NaO_3Si_2$ $[M + Na]^+$ 539.4292, found 539.4279.

*(5S,8S)-Triisopropylsilyloxy-tetradecan-1,5-diol (**27b**).* To a solution of the alcohol **S3** (3.61 g, 6.98 mmol) in MeOH (40 mL) was added PPTS (1.93 g, 7.70 mmol, 1.1 equiv) and the mixture was stirred for 2 h. The mixture was then concentrated *in vacuo* and partitioned with EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (1:1 hexanes/EtOAc) gave **27b** (2.80 g, >99%) as a clear oil: R_f = 0.54 (1:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = 2.90 (*c* = 1.0, $CHCl_3$); IR (thin film) 3369, 2942, 2866, 1464 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90−3.83 (m, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 3.63−3.58 (m, 1H), 1.88 (br s, 1H), 1.77 (br s, 1H), 1.65−1.40 (m, 12H), 1.36−1.22 (m, 8H), 1.07 (br s, 21H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.2, 71.9, 62.8, 36.9, 36.4, 32.7, 32.1, 31.9, 31.8, 29.7, 25.2, 22.7, 21.9, 18.2, 14.1, 12.6; HRMS (ESI) *m*/*z* Calcd for $C_{23}H_{50}NaO_3Si$ $[M + Na]^+$ 425.3427, found 425.3427.

*(5R,8S)-Triisopropylsilyloxy-1,5-dibromododecane (**15b**).* To a suspension of triphenylphosphine (0.419 g, 1.60 mmol) and bromine (1.54 mL, 30.0 mmol) in toluene (125 mL) at 0 °C was added a solution of **27b** (5.50 g, 13.7 mmol) and triethylamine (4.81 mL, 34.3 mmol) in toluene (25 mL). After 12 h, the reaction mixture was diluted with Et_2O (100 mL) and filtered to remove the resultant precipitate. The filtrate was washed with 1N aq. $Na_2S_2O_3$ (25 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (98:2 hexanes/Et_2O) gave **15b** (6.24 g, 86%) as a clear oil: R_f = 0.60 (95:5 hexanes/EtOAc); $[\alpha]_D^{22}$ = 3.6 (*c* = 1.0, $CHCl_3$); IR (thin film) 2941, 2866, 1464 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (tt, *J* = 8.3, 8.3, 4.7, 4.7 Hz, 1H), 3.83 (quintet, *J* = 5.7 Hz, 1H), 3.42 (t, *J* = 6.8 Hz,

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2H), 1.91−1.80 (m, 5H), 1.75−1.67 (m, 1H), 1.63−1.45 (m, 5H), 1.29 (s, 9H), 1.07 (br s, 21H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.8, 58.4, 38.3, 36.9, 34.5, 34.2, 33.4, 32.2, 29.7, 26.3, 24.9, 22.7, 18.3, 14.2, 12.7; HRMS (APCI) m/z Calcd for $C_{23}H_{49}OSiBr_2$ $[M + H]^+$ 527.1921, found 527.1917.

Aminonitrile ***14b***. To a solution of α-aminonitrile **16** (2.24 g, 6.81 mmol) and dibromide **15b** (0.938 g, 5.68 mmol) in THF (45 mL) and DMPU (45 mL) at −78 °C was added LDA (14.2 mL of a 1.0 M solution in THF, 14.2 mmol, 2.5 equiv) over 20 min. The reaction was stirred for 1 h and slowly warmed to 0 °C over 1 h. The solution was cooled to −78 °C and LDA (5.69 mL of a 1.0 M solution in THF, 5.69 mmol, 1.0 equiv) was added dropwise over 10 min. The mixture was stirred for 10 min, warmed to 0 °C over 1 h, and the reaction was quenched with saturated aq. NH_4Cl (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (97:3 hexane/EtOAc) gave **14b** (3.16 g, 80%) as a clear oil: R_f = 0.48 (9:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = −2.2 (c = 1.5, $CHCl_3$); IR (thin film) 2931, 2866, 1697, 1466, 1392 cm^{-1}; ^{1}H NMR (500 MHz, Benzene-d_6, 343 K) δ 3.93 (app s, 1H), 3.75 (app d, J = 7.7 Hz, 2H), 3.66 (app s, 2H), 2.98 (brs, 1H), 2.64 (t, J = 13.2 Hz, 1H), 2.00 (brm, 2H), 1.95−1.83 (m, 3H), 1.82−1.71 (m, 1H)1.71−1.65 (m, 1H), 1.65−1.59 (m, 2H), 1.58−1.49 (m, 4H), 1.45 (s, 9H), 1.49−1.41 (m, 4H), 1.41−1.28 (m, 8H), 1.20−1.14 (m, 24H), 0.98 (s, 10H), 0.93 (app s, 3H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, Benzene−d_6, 343 K) δ 153.4, 117.7, 79.8, 72.5, 67.5, 61.0, 47.2, 41.3, 36.6, 34.2, 33.8, 33.6, 31.7, 29.54, 29.5, 28.0, 26.4, 25.7, 24.7, 24.6, 23.7. 22.4, 18.1, 18.0, 13.6, 12.8, −5.5; HRMS (ESI) m/z Calcd for $C_{39}H_{78}N_2NaO_4Si_2$ $[M + Na]^+$ 717.5398, found 717.5385.

Amino Alcohol ***S4***. To a solution of **14b** (3.16 g, 4.54 mmol) in MeOH (130 mL) was added PPTS (1.26 g, 4.99 mmol). The mixture was stirred at rt for 12 h then concentrated *in vacuo* and partitioned with EtOAc (50 mL) and water (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (4:1 hexane/EtOAc) gave the alcohol (2.04 mg, 77%) as a clear oil: R_f = 0.44 (2:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = −5.0 (c = 1.15, $CHCl_3$); IR (thin film) 3471, 2935, 2866, 1697, 1466, 1392 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 343 K) δ 3.93 (quintet, J = 5.1 Hz, 1H), 3.75−3.62 (m, 2H), 3.50 (t, J = 6.0 Hz, 2H), 2.87 (brs, 1H), 2.51 (t, J = 11.5 Hz, 1H), 1.95−1.71 (m, 6H), 1.70−1.57 (m, 3H), 1.57−1.46 (m, 5H), 1.41 (s, 9H), 1.46−1.39 (m, 4H), 1.39−1.26 (m, 7H), 1.25−1.02 (m, 24H), 0.93 (brt, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6, 343 K) δ 153.9, 117.7, 80.4, 72.4, 67.0, 59.4, 46.3, 41.5, 36.5, 34.3, 33.8, 33.4, 31.7, 29.5, 29.48, 27.9, 26.3, 24.7, 24.6, 23.6, 22.4, 18.0, 13.6, 12.8; HRMS (ESI) m/z Calcd for $C_{33}H_{64}N_2NaO_4Si$ $[M + Na]^+$ 603.4533, found 603.4531.

Diethylphosphate ***33b***. To a solution of the alcohol **S4** (127 mg, 0.219 mmol) in THF (6 mL) at 0 °C was added *N*-methylimidazole (841 μL, 0.876 mmol) followed by diethyl chlorophosphate (548 μL, 0.657 mmol). After 2.5 h, saturated aq. $NaHCO_3$ (2.0 mL) and brine (2.0 mL) were added and the mixture was diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (5 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (2:1 hexanes/EtOAc) gave **33b** (149 mg, 95%) as a clear oil: R_f = 0.27 (4:3 hexanes/EtOAc); $[\alpha]_D^{22}$ = −2.7 (c = 1.35, $CHCl_3$); IR (thin film) 2935, 2866, 1697, 1466, 1392, 1369 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.08 (dd, J = 5.9 Hz, 2H), 4.00 (quint, J = 6.9 Hz, 4H), 3.91 (brm, 1H), 3.80−3.62 (m, 2H), 3.05 (brs, 1H), 2.61 (brs, 1H), 2.15−1.95 (m, 2H), 1.95−1.80 (m, 2H), 1.80−1.70 (m, 2H), 1.70−1.57 (m, 3H), 1.50−1.45 (m, 5H), 1.43 (s, 9H), 1.45−1.38 (m, 2H), 1.35−1.27 (app s, 8H), 1.18 (s) and 1.02 (s, 19H), 1.15−1.03 (m, 9H), 0.92 (brt, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.1, 117.7, 80.2, 72.2, 64.8 (d, $^2J_{PC}$ = 6.3 Hz), 63.1 (ddd, $^2J_{PC}$ = 2.8 Hz), 41.0, 36.5, 34.0, 33.6, 31.9, 31.2 (d, $^2J_{PC}$ = 6.3 Hz), 29.7, 29.4, 27.9, 26.2, 24.7, 24.6, 23.7, 22.6, 18.1 (d, $^3J_{PC}$ = 2.5 Hz), 15.8 (d, $^3J_{PC}$ = 6.3 Hz), 13.9, 12.7; HRMS (ESI) m/z Calcd for $C_{37}H_{73}N_2NaO_7SiP$ $[M + Na]^+$ 739.4822, found 739.4815.

Spiropyrrolidine ***35b***. An oven-dried round−bottom flask equipped with a glass stir bar was cooled under vacuum and backfilled with argon. The flask was charged with 1,10-phenanthroline (1 crystal), and a solution of phosphate **33b** (159 mg, 0.222 mmol) in THF (5.5 mL). The solution was cooled to −78 °C and *n*-BuLi (ca. 2 M solution in hexane) was added until a dark brown color persisted (2 drops). To that solution at −78 °C was added LiDBB (~0.5 M, 0.98 mL, 0.488 mmol) *via* syringe in a steady stream over 30 s to produce a solution that remained dark green for at least 20 s. The mixture was stirred for 1.5 h, then diluted with MeOH (0.1 mL) and saturated aq. NH_4Cl (1 mL). The reaction mixture was diluted with Et_2O (4 mL), the aqueous layer was separated and extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a light yellow viscous solid. Purification by column chromatography (gradient 97:3 hexane/CH_2Cl_2 then 98:2 hexane/EtOAc to 95:5 hexane/EtOAc) gave **35b** (108 mg, 91%) as a clear oil: R_f = 0.29 (95:5 hexanes/EtOAc); $[\alpha]_D^{22}$ = −19.1 (c = 3.0, $CHCl_3$); IR (thin film) 2935, 2866, 1693, 1462, 1381 cm^{-1}; ^{1}H NMR (500 MHz, Benzene-d_6, minor rotamer peaks denoted by *) δ 4.05−3.95 (m, 1H), 3.70* (app. quint, J = 5.8 Hz) 3.48−3.40 (m, 1H), 3.26* (dd, J = 8.2 Hz), 2.94 (t, J = 11.9 Hz, 1H), 2.70* (dt, J = 3.6, 13.0 Hz), 1.95−1.85 (m, 1H), 1.85−1.75 (m, 1H), 1.75−1.62 (m, 3H), 1.54 (s, 9H), 1.50−1.43 (m, 3H), 1.43−1.29 (m, 9H), 1.29−1.09 (m, 20H), 1.09−0.99 (m, 1H) 0.93 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, Benzene-d_6, 343K, minor rotamer denoted by *) δ 154.9, 78.6, 73.9*, 73.6, 68.2, 49.4*, 49.1, 44.0, 39.6, 37.5, 37.3*, 37.2*, 35.5, 34.0*, 32.7*, 32.7, 30.8, 30.5, 29.3*, 29.1*, 27.2, 26.8, 26.2, 25.6*, 25.6, 25.2, 24.4, 24.3*, 23.4, 21.6*, 21.5, 19.0*, 18.9, 14.5, 13.7; HRMS (ESI) m/z Calcd for $C_{32}H_{63}NNaO_3Si$ $[M + Na]^+$ 560.4475, found 560.4461.

Prolinal ***37***. To a solution of spiropyrrolidine **35a** (200 mg, 0.390 mmol) and TMEDA (76 μL, 0.51 mmol) in Et_2O (3.5 mL) at −78 °C was added *s*-BuLi (392 μL of a 1.3 M solution in cyclohexane, 0.51 mmol). After 3 h, DMF (46 μL, 0.59 mmol) was added followed by saturated aq. NH_4Cl (1.5 mL) and water (1 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (98:2 hexanes/EtOAc) gave **37** (64 mg, 31%, 86% brsm, 4:1 dr) as a clear oil as well as recovered spiropyrrolidine (126 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57−9.30 (rotameric doublet, J = 3.4 Hz, 1H), 4.30−4.21 (m, 1H), 4.08 (dt, J = 7.5, 3.1 Hz, 1H), 3.80 (quintet, J = 5.3 Hz, 2H), 2.58−2.49 (m, 1H), 2.38 (dt, 1H), 2.34−2.12 (m, 1H), 2.10−1.61 (m, 12H), 1.58−1.44 (m, 11H), 1.42−1.36 (diastereo and rotameric singlets, 11H), 1.36−1.20 (m, 13H), 1.05 (diasteriomeric singlets, 32H), 0.94−0.84 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 152.3, 80.4, 72.4, 69.9, 67.8, 66.4, 42.6, 40.7, 36.2, 35.5, 34.2, 29.4, 28.3, 27.0, 26.2, 25.7, 24.3, 23.5, 23.1, 18.3, 14.2, 12.7, 201.3, 154.5, 80.7, 72.0, 68.9, 67.1, 66.7, 41.2, 36.1, 35.7, 34.6, 29.7, 28.5, 26.9, 25.8, 25.1, 24.4, 23.1, 18.3, 14.2, 12.7; IR (thin film) 2931, 1739, 1712, 1674, 1462 cm^{-1}; HRMS (ESI) m/z calcd for $C_{31}H_{59}NNaO_4Si$ $[M + Na]^+$ 560.4111, found 560.4105.

Alcohol ***S5***. To a solution of prolinal **37** (34 mg, 0.063 mmol) in EtOH (1 mL) at 0 °C was added sodium borohydride (3.1 mg, 0.082 mmol). The reaction mixture was heated to 70 °C for 45 min, cooled to r.t., and partitioned between Et_2O (2 mL) and brine (2 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (9:1 hexanes/EtOAc) gave **S5** (23 mg, 68%, 4:1 dr) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (brs, 1H), 4.20−4.11 (m, 1H), 4.08−3.98 (m, 1H), 3.88−3.82 (m, 1H), 3.82−3.75 (m, 1H), 3.72−3.58 (m, 2H), 2.38−2.13 (m, 2H), 2.10−1.95 (m, 2H), 1.94−1.77 (m, 3H), 1.77−1.55 (m, 8H), 1.48 (s, 8H), 1.47 (s, 8H), 1.46 (s, 4H), 1.40−1.20 (m, 14H), 1.06 (s, 8H), 1.05 (s, 24H), 1.00−0.80 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 80.4, 72.4, 72.0, 69.3, 68.6, 62.8, 42.2, 39.0, 36.7, 36.2, 35.6, 34.7, 31.5, 28.6, 26.8, 26.3, 25.2, 24.5, 23.1, 18.3, 12.7; IR (thin film) 3130, 2930, 1720 cm^{-1}; HRMS (ESI) m/z calcd for $C_{31}H_{61}NO_4SiNa$ $[M + Na]^+$ 562.4268, found 562.4269.

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Acetate ***46***. To a solution of alcohol **S5** (23 mg, 0.046 mmol) in CH_2Cl_2 (0.5 mL) was added acetyl chloride (15 μL, 0.21 mmol), pyridine (14 μL, 0.17 mmol) and DMAP (0.6 mg, 0.005 mmol), respectively. After 12 h, the mixture was diluted with CH_2Cl_2, and the reaction was quenched with saturated aq. NH_4Cl (2 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (9:1 hexanes/EtOAc) gave **46** (24 mg, 95%, 4:1 dr) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29−4.07 (m, 2H), 4.07−3.92 (m, 1H), 3.90−3.75 (m, 1H), 2.56−2.46 (m, 1H), 2.35−2.15 (m, 1H), 2.14−2.02 (m, 4H), 2.00−1.77 (m, 3H), 1.75−1.56 (m, 7H), 1.51−1.42 (m, 13H), 1.41−1.20 (m, 11H), 1.06 (s, 10H), 1.05 (s, 13H), 0.99−0.80 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) major diastereomer: δ 170.9, 152.7, 79.2, 72.5, 68.9, 65.2, 58.1, 42.1, 40.0, 38.5, 36.2, 34.2, 31.1, 29.7, 28.5, 27.0, 26.3, 25.8, 24.2, 21.0, 18.2, 12.7; minor diastereomer: 171.1, 153.9, 79.7, 72.4, 68.2, 64.6, 58.3, 41.3, 39.6, 36.1, 34.7, 31.7, 29.6, 28.6, 26.8, 26.2, 25.7, 25.3, 24.3, 21.1, 18.3, 12.6; cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{63}NO_5SiNa$ $[M + Na]^+$ 604.4373, found 604.4368.

Alcohol ***S6***. To a solution of **46** (23 mg, 0.040 mmol) in THF (0.8 mL) at 0 °C was added TBAF (53 μL of a 1 N solution in THF, 0.053 mmol) and the mixture was stirred at rt. After 12 h, the solution was diluted with Et_2O (1 mL) followed by water (1 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (2:1 hexane/EtOAc) gave **S6** (15 mg, 91%, 4:1 dr) as a clear oil: R_f = 0.21 (4:1 hexanes/EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33−4.19 (m, 1H), 4.19−4.09 (m, 2H), 4.09−3.88 (m, 3H), 3.60−3.47 (m, 2H), 2.67−2. 57 (m, 1H), 2.50−2.42 (m, 1H), 2.37−2.09 (m, 3H), 2.10 (s, 4H), 2.05 (s, 2H), 2.00−1.77 (m, 6H), 1.76−1.51 (m, 14H), 1.48 (s, 4H), 1.45 (s, 14H), 1.44−1.10 (m, 23H), 0.90 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) major diastereomer: δ 170.9, 153.0, 126.7, 79.4, 72.8, 68.9, 65.1, 58.2, 40.1, 38.4, 37.1, 35.4, 31.4, 29.8, 28.6, 27.8, 26.3, 25.8, 24.2, 22.8, 21.0, 14.1; minor distereomer: 171.1, 154.0, 125.7, 79.9, 72.5, 69.6, 64.6, 58.3, 39.5, 36.9, 36.0, 31.8, 30.8, 29.6, 28.6, 27.9, 26.2, 25.8, 24.3, 22.8, 21.1, 14.2; IR (thin film) 3243, 2934, 2893, 1710, 1695 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{43}NO_5Na$ $[M + Na]^+$ 448.3039, found 448.3022.

Mesylate ***47***. To a solution of alcohol **S6** (10 mg, 0.024 mmol) in CH_2Cl_2 (0.5 mL) was added 2,6-lutidine (8.2 μL, 0.070 mmol) followed by methanesulfonyl chloride (4.2 μL, 0.053 mmol). After 12 h, water (2 mL) and CH_2Cl_2 (2 mL) were added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (4:1 hexane/EtOAc) gave the product (12 mg, >95%, 4:1 dr) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75−4.61 (m, 1H), 4.31−4.18 (m, 1H), 4.16−4.07 (m, 1H), 4.07−4.00 (m, 1H), 3.99−3.89 (m, 1H), 2.99 (three s, 3H), 2.60−2.45 (m, 1H), 2.30−2.13 (m, 1H), 2.07 (two s, 3H), 1.98−1.75 (m, 3H), 1.75−1.61 (m, 5H), 1.46 (two s, 10H), 1.40−1.28 (m, 5H), 1.28−1.09 (m, 2H), 1.08−0.95 (m, 1H), 0.95−0.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) major diastereomer: δ 170.9, 152.8, 84.8, 79.4, 68.7, 65.1, 58.2, 39.7, 38.8, 38.6, 34.3, 33.3, 32.8, 29.7, 28.6, 27.1, 26.3, 25.7, 24.1, 22.5, 21.1, 19.8, 14.0; minor diastereomer: 171.1, 153.9, 83.8, 79.9, 68.1, 64.7, 58.4, 38.7, 38.6, 34.5, 33.4, 32.3, 29.5, 28.7, 27.2, 26.2, 26.1, 24.2, 22.6, 21.1, 19.9, 14.1; IR (thin film) 2934, 2865, 1710, 1695 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{45}NO_7SNa$ $[M + Na]^+$ 526.2814, found 526.2818.

Tricycle ***48***. To a solution of mesylate **47** (12.0 mg, 0.024 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added TFA (73 μL, 0.95 mmol). After stirring for 1.5 h, volatile materials were removed *in vacuo* and the residue was dissolved in THF (0.5 mL), followed by addition of saturated aq. $NaHCO_3$ (0.5 mL). After 14 h, $CHCl_3$ (2 mL) was added and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (gradient 200:9:1 $CHCl_3$/MeOH/NH_4OH) gave the compound **48** (3.0 mg, 41%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.73 (t, *J* = 8.4 Hz, 1H), 3.42−3.30 (brm, 1H), 3.20−3.07 (brm, 1H), 2.05 (s, 3H), 1.94−1.86 (m, 1H), 1.80−1.56 (m, 10H), 1.56−1.43 (m, 4H), 1.43−1.15 (m, 9H), 1.04 (dq, *J* = 12.5, 3.5 Hz, 1H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 70.56, 67.9, 56.5, 53.6, 41.2, 37.9, 34.1, 30.9, 30.0, 28.4, 28.0, 26.4, 24.5, 24.0, 23.1, 22.5, 21.2, 14.2; cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{33}O_2NH$ $[M + H]^+$ 308.2589, found 308.2587.

*Lepadiformine B (****12****)*. To a solution of the tricyclic acetate **48** (3.0 mg, 0.010 mmol) in MeOH (0.2 mL) was added sodium methoxide (5 mg, 0.10 mmol). After 1 h, EtOAc (1 mL) and saturated aq. NH_4Cl (1 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried over K_2CO_3 and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (gradient 200:9:1 $CHCl_3$/MeOH/NH_4OH) gave lepadiformine B (**12**) (2.6 mg, >95%) as a clear oil. Lepadiformine B was converted to the HCl salt by treatment with anhydrous HCl/$CHCl_3$ (1.0 mL) followed by concentration *in vacuo*. The spectral data matched those previously reported in the literature.[24]

Alcohol ***S7***. To a solution of TIPS ether **35b** (380 mg, 0.706 mmol) in THF (11 mL) at 0 °C was added TBAF (560 μL of a 1 N solution in THF, 0.560 mmol). After 12 h at 0 °C, the solution was diluted with Et_2O (10 mL) and poured on water (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (4:1 hexane/EtOAc) gave **S7** (206 mg, 97%) as a clear oil: R_f = 0.21 (4:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = −27.3 (*c* = 0.37, $CHCl_3$); IR (thin film) 3464, 2927, 2858, 1693, 1682, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, minor rotamer denoted by *) δ 3.76−3.70* (m), 3.60−3.50 (m, 1H), 3.50−3.39 (m, 1H), 3.23−3.15* (m, 1H), 3.08−3.00 (app. t, *J* = 10.0 Hz, 1H), 2.55 (dt, *J* = 13.7, 4.2 Hz, 1H), 2.40−2.32* (m), 2.25−2.18* (m), 2.04 (app. s, 1H), 1.85 (app. d, *J* = 11.9 Hz, 1H), 1.71−1.64 (m, 9H), 1.51 (s, 9H), 1.43−1.25 (m, 11H), 1.24−1.11 (m, 1H), 1.11−0.95 (m, 1H), 0.82 (t, *J* = 6.6 Hz, 3H), 0.88−0.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 78.5, 73.1, 72.1*, 68.2, 49.1*, 49.0, 43.4*, 41.0, 38.3, 38.0*, 36.7*, 35.7, 34.4, 32.4, 31.5*, 30.1, 29.9, 29.8, 28.7, 27.5, 26.8*, 26.3, 26.2, 26.1*, 24.9*, 24.7, 23.1, 22.5, 22.0*, 14.4; HRMS (ESI) *m*/*z* Calcd for $C_{23}H_{43}NNaO_3$ $[M + Na]^+$ 404.3141, found 404.3134.

Mesylate ***36b***. To a solution of alcohol **S7** (206 mg, 0.540 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added 2,6−lutidine (115 μL, 0.840 mmol) followed by methanesulfonyl chloride (49 μL, 0.630 mmol). After 12 h at 0 °C, the reaction mixture was poured on water (3 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (4:1 hexane/EtOAc) gave **36b** (238 mg, 96%) as a clear oil: R_f = 0.45 (3:1 hexanes/EtOAc); $[\alpha]_D^{22}$ = −28.2 (*c* = 1.0, $CHCl_3$); IR (thin film) 2931, 2862, 1693, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, minor rotamer denoted by *) δ 4.68 (m, 1H), 3.72−3.65* (m), 3.48−3.34 (m, 1H), 3.29−3.21 (m, 1H), 2.93−2.84 (m, 1H), 2.63 (dt, *J* = 13.3, 3.7 Hz, 1H), 2.47* (s, 1H), 2.35 (s, 2H), 2.30−2.23* (m), 2.23−2.13* (m), 1.77−1.69 (m, 1H), 1.69−1.62 (m, 2H), 1.62−1.55 (m, 3H), 1.55 (s, 9H), 1.48−1.41 (m, 1H), 1.40−1.30 (m, 4H), 1.29−1.23 (m, 2H), 1.22−1.09 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.81 (dq, *J* = 12.7, 3.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7*, 152.9, 83.6, 82.4*, 78.6*, 77.9, 67.4, 66.8*, 49.1*, 48.7, 43.0*, 40.4, 37.9, 35.4*, 34.9*, 34.6, 34.2, 33.5*, 32.9, 31.7, 31.1*, 30.0, 29.6, 29.5*, 29.1, 28.4, 26.3*, 26.0, 25.7, 25.2*, 25.0, 24.4*, 24.3, 22.7, 22.3, 21.7*, 14.0; HRMS (ESI) *m*/*z* Calcd for $C_{24}H_{45}NNaO_5S$ $[M + Na]^+$ 482.2916, found 482.2902.

Tricycle ***13b***. To a solution of mesylate **36b** (169 mg, 0.444 mmol) in dry CH_2Cl_2 (4.4 mL) at 0 °C was added TFA (657 μL, 8.88 mmol). After stirring for 1 h, $CHCl_3$ (6.0 mL) and saturated aq. $NaHCO_3$ (6.0 mL) were added, respectively. After 3.5 h, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried over K_2CO_3 and concentrated

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in vacuo to give a yellow oil. The crude material was carried on without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.45−3.35 (brm, 2H), 2.75 (dt, J = 10.6, 7.3 Hz, 1H), 2.0−1.83 (m, 4H), 1.83−1.63 (m, 6H), 1.63−1.54 (m, 2H), 1.54−1.39 (m, 3H), 1.39−1.24 (m, 3H), 1.24−1.03 (m, 10H), 0.96 (dq, J = 12.9, 3.6 Hz, 1H), 0.76 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.4, 72.3, 54.3, 46.7, 38.1, 35.5, 32.0, 31.5, 29.8, 29.1, 27.8, 26.2, 25.4, 23.9, 22.6, 22.5, 20.3, 14.0; IR (thin film) 3425, 2931, 2862, 1469 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{33}NH$ $[M + H]^-$ 264.2691, found 264.2693.

General Procedure for Oxidative Cyanation. To a 0.1 M solution of **13a,b** in CH_2Cl_2 at 0 °C was added a 0.67 M solution of *m*−CPBA (1.1 equiv) in CH_2Cl_2 dropwise. After complete conversion of the amine to the *N*−oxide, saturated aq. Na_2CO_3 was added and the mixture was warmed to r.t. The aqueous layer was extracted with $CHCl_3$ (3×) and dried over Na_2SO_4 and concentrated to a yellow oil. To a 0.1 M solution of the crude *N*-oxide in CH_2Cl_2 at 0 °C was added TFAA (5.0 equiv) and potassium cyanide (5.0 equiv), respectively. After stirring for 1.5 h, water was added and the pH adjusted to ∼5 with potassium acetate. After 30 min, saturated aq. Na_2CO_3 and $CHCl_3$ were added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3×). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. The crude nitrile was carried on without further purification.

C4 Tricyclic Aminonitrile ***49a***. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93* (dd, J = 2.9, 4.3 Hz, 0.16H), 3.75 (dd, J = 6.8, 10.4, 1H), 3.19−3.11 (m, 1H), 3.11−3.04* (m, 0.18H), 2.20 (quint, J = 6.5 Hz, 1H), 2.12−2.00 (m, 1H), 1.94−1.86* (m, 0.5H), 1.82 (dd, J = 6.8, 12.8 Hz, 1H), 1.80−1.68 (m, 2H), 1.68−1.62 (m, 4H), 1.62−1.49 (m, 5H), 1.49−1.38 (m, 5H), 1.38−1.17 (m, 11H), 0.97 (dq, J = 3.2, 12.6 Hz, 1H), 0.91 (t, J = 7.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.0, 77.2, 67.4, 52.5, 47.4, 39.7, 38.8, 33.9, 29.8, 29.5, 27.6, 26.2, 24.5, 22.7, 22.6, 22.3, 14.1; minor isomer: 49.9, 49.2, 42.1, 38.0, 33.8, 29.6, 29.5, 29.3, 28.1, 27.3, 26.4, 24.8, 22.9, 14.1; IR (thin film) 2931, 2862, 2237 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{28}N_2H$ $[M + H]^+$ 261.2331, found 261.2337; $C_{16}H_{28}N$ $[M - CN]^+$ 234.2222, found 234.2229.

C6 Tricyclic Aminonitrile ***49b***. ^{1}H NMR (500 MHz, $CDCl_3$, minor isomer denoted by *) δ 3.93* (app. s, 0.18H), 3.75 (dd, J = 6.7, 10.4, 1H), 3.20−3.11 (m, 1H), 3.11−3.04* (app. dq, J = 7.2, 14.1 Hz, 0.18H), 2.20 (quint., J = 6.6, 1H), 2.13−2.00 (m, 2H), 1.94−1.86* (m, 1H), 1.82 (dd, J = 6.7, 12.7, 2H), 1.79−1.68 (m, 3H), 1.68−1.61 (m, 4H), 1.61−1.55 (m, 2H), 1.55−1.48 (m, 4H), 1.47−1.35 (m, 5H), 1.35−1.17 (m, 20H), 1.17−1.05* (m, 0.5H), 0.97 (dq, J = 3.2, 12.6, 1H), 0.91 (brm, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.0, 77.3, 67.5, 52.6, 47.4, 39.7, 38.8, 34.3, 30.2, 29.9, 29.8, 29.4, 27.6, 27.3, 24.5, 22.7, 22.6, 22.3, 14.1; minor isomer: 123.8, 49.9, 49.2, 42.1, 38.0, 34.1, 29.7, 29.6, 29.4, 28.1, 27.3, 27.1, 26.4, 24.8, 22.9, 14.0; IR (thin film) 2931, 2858, 2360, 2341, 1778 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{32}N_2Na$ $[M + Na]^+$ 311.2463, found 311.2454.

General Procedure for Hydrolysis of Aminonitrile to Methyl Ester. A 0.17 M solution of nitrile in $MeOH/H_2SO_4$ (20:1) was heated to 110 °C in a sealed tube. After 3 days, the solution was cooled to 0 °C and adjusted to pH 8 with saturated aq. $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3×). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a brown oil. Purification by column chromatography (4:1 hexane/EtOAc) gave the methyl ester as a yellow oil.

C4 Methyl Ester ***50a***. Starting from mesylate **36a** (63.0 mg, 0.146 mmol) the sequence provided 12 mg (28% over 5 steps) of product; R_f = 0.29 (4:1 hexanes/EtOAc); $[\alpha]^{22}_D$ −43.0 (c 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74−3.66 (m, 1H), 3.69 (s, 3H), 3.21−3.13 (m, 1H), 2.06 (dt, J = 6.6, 10.5, 1H), 1.80 (quint, J = 6.7, 2H), 1.80−1.70 (m, 1H), 1.70−1.60 (m, 3H), 1.60−1.51 (m, 2H), 1.51−1.38 (m, 5H), 1.38−1.14 (m, 7H), 1.14−1.04 (m, 1H), 1.00 (dq, J = 3.2, 12.6, 1H), 0.85 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 77.3, 67.7, 61.5, 53.0, 52.0, 39.8, 38.6, 33.7, 30.6, 29.6, 29.4, 28.1, 26.4, 24.6, 23.1, 23.0, 22.1, 14.2; IR (thin film) 2931, 2862, 1732 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{31}NO_2H$ $[M + H]^+$ 294.2433, found 294.2433.

C6 Methyl Ester ***50b***. Starting from mesylate **36b** (204 mg, 0.444 mmol) the sequence provided 61 mg (43% over 5 steps) of product; R_f = 0.22 (4:1 hexanes/EtOAc); $[\alpha]^{22}_D$ −2.9 (c 2.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71−3.65 (m, 1H), 3.68 (s, 3H), 3.20−3.12 1.24 (m, 6H), 1.24−1.11 (m, 6H), 1.11−1.04 (m, 1H), 0.99 (dq, J = 3.4, 12.7, 1H), 0.85 (t, J = 6.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 77.4, 67.7, 61.5, 53.1, 52.0, 39.8, 38.6, 34.1, 31.9, 30.6, 29.5, 28.1, 27.4, 26.4, 24.6, 23.1, 22.7, 22.1, 14.2; IR (thin film) 2927, 2858, 2360, 2341, 1732, 1462 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{35}NO_2H$ $[M + H]^+$ 322.2746, found 322.2741.

General Procedure for Methyl Ester Reduction. To a 0.31 M solution of methyl ester in Et_2O at 0 °C was added lithium aluminum hydride (1.5 equiv). After 30 min at r.t., the reaction was quenched by sequential addition of water (x mL), 4 M NaOH (x mL), and water ($2x$ mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O ($3x$). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the natural product as a pale-yellow oil. The natural product was converted to the HCl salt by treatment with anhydrous $HCl/CHCl_3$ (1.0 mL) followed by concentration *in vacuo*. The spectral data matched those previously reported in the literature.[13,24]

*Lepadiformine B (Hydrochloride Salt) (****51a****)*. Starting from methyl ester **50a** (8 mg, 0.03 mmol), 7 mg (86%) of the HCl salt of the natural product **12** was obtained; $[\alpha]^{22}_D$ = +3.2 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.2 (brs, 1H), 5.24 (brs, 1H), 4.18 (d, J = 13.0, 1H), 3.68 (t, J = 10.7, 1H), 3.62 (d, J = 12.8, 2H), 2.55−2.48 (brm, 1H), 2.40 (brdq, J = 8.3, 12.6, 1H), 2.17 (app s, 2H), 2.06 (dd, J = 6.8, 12.8, 2H), 1.95 (app t, J = 12.9, 2H), 1.88−1.71 (m, 4H), 1.68 (app d, J = 9.2, 3H), 1.58−1.40 (m, 3H), 1.40−1.28 (m, 7H), 1.28−1.15 (m, 3H), 1.10−0.98 (brm, 1H), 0.91 (t, J = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.4, 63.6, 60.1, 58.8, 36.3, 33.9, 30.9, 29.7, 28.6, 26.6, 25.1, 24.4, 23.4, 22.7, 22.6, 19.3, 14.1; cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{31}NOH$ $[M + H]^+$ 266.2484, found 266.2480.

*Lepadiformine A (hydrochloride salt)(****51b****)*. Starting from methyl ester **50b** (20 mg, 0.06 mmol) 19 mg (94%) of the HCl salt of the natural product **11** was obtained; $[\alpha]^{22}_D$ = +1.8 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.1 (brs, 1H), 4.15 (d, J = 12.4 Hz, 1H), 3.70−3.56 (m, 3H), 2.50−2.43 (brm, 1H), 2.37 (brdq, J = 7.2, 12.9 Hz, 1H), 2.15 (app s, 2H), 2.04 (dd, J = 7.0, 12.9 Hz, 2H), 1.99−1.89 (m, 2H), 1.86−1.71 (m, 4H), 1.66 (app d, J = 10.1 Hz, 3H), 1.56−1.42 (m, 2H), 1.42−1.35 (m, 3H), 1.35−1.29 (m, 5H), 1.29−1.15 (brm, 10H), 1.02 (brdq, J = 3.1, 12.6 Hz, 1H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.3, 63.5, 60.0, 58.8, 36.2, 33.8, 31.7, 30.8, 29.9, 29.1, 26.5, 26.4, 25.0, 24.3, 23.3, 22.6, 22.5, 19.2, 14.1; cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{35}NOH$ $[M + H]^+$ 294.2797, found 294.2798.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Proton and Carbon NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Professor Gilbert Stork on the occasion of his 90th Birthday.

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(35) The configuration assignments of (*S*)-**37** and (*R*)-**37** were consistent with the enantioselective metalations using (−)-sparteine (**44**) and O'Brien's (+)-sparteine surrogate, diamine **43**. Metalation with (−)-sparteine (Table 2, entry 10) favors the (*R*) product, and metalation with diamine **43** (Table 2, entry 7) favors the (*S*) product.
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