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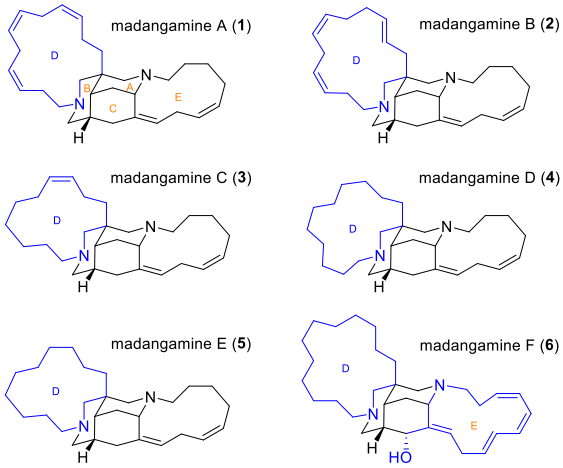
Abstract

The full details of a unified total synthesis of madangamine alkaloids are disclosed. Our central strategy is based on the construction of a common ABCE-tetracyclic system, followed by the late-stage installation of various D-rings. The common intermediate is assembled through *N*-acyliminium cyclization of a propargylsilane, and formation of the (*Z*,*Z*)-skipped diene. Stereoselective synthesis of the (*Z*,*Z*)-skipped diene is especially challenging, and is accomplished by the combination of *Z*-selective hydroboration of the 1,1-disubstituted allene and subsequent Migita-Kosugi-Stille coupling. Macrocyclic alkylation enables the late-stage variation of the D-rings on the common tetracyclic intermediate, resulting in the collective total syntheses of madangamines A-E. The synthetic madangamine alkaloids exhibited inhibitory activities against a variety of human cancer cell lines.

1. Introduction

In 1994, Andersen and co-workers reported the isolation of a new class of pentacyclic alkaloid, madangamine A (**1**), from the sponge *Xestospongia ingens* from the reefs of Madang, Papua New Guinea.[1,2a] Structurally, madangamine A (**1**) appeared to be derived biogenetically from a partially reduced bis-3-alkylpyridine precursor proposed by Whitehead and Baldwin as seen in the manzamine alkaloids, but possessed an unprecedented 2-azabicyclo[3.3.1]nonane structure. Andersen then reported isolation of madangamines B-E (**2**-**5**), which shared a common ABCE-tetracyclic ring system with a variety of D-rings.[2b] In 2007, the Berlinck group isolated madangamine F (**6**) from a different marine sponge *Pachychalina alcaloidifera*.[2c] Madangamines A (**1**) and F (**6**) exhibited in vitro cyctotoxicity against a variety of human cancer cell lines.[2a,c] However, biological activities of the other members of the madangamine family have not been examined because of their scarcity. Their unique architecture and the unexplored biological activities have inspired a number of



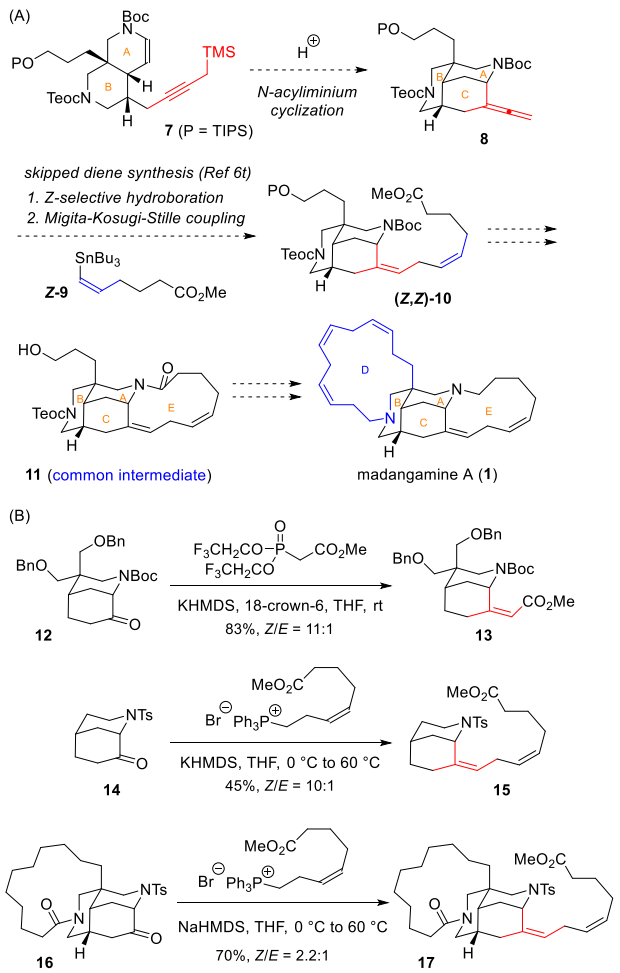
Scheme 1. Structures of madangamine alkaloids

synthetic chemists, culminating in the first total synthesis of madangamine D (**4**) by the Amat group in 2014.[3,4] They successfully provided a pure synthetic sample of madangamine D (**4**) for biological studies, which revealed cytotoxicity against human cancer cell lines. Although this landmark achievement suggested that a variable D-ring structure might be important for the cytotoxic spectrum of activity, resolving this issue would require the collective total synthesis of a series of madangamine alkaloids. Unfortunately, the Amat group constructed the variable D-ring in the middle stage of the total synthesis, causing difficulties in synthesizing other members of the madangamine alkaloids. In this article, we describe the full details of our unified total synthesis of madangamines A-E (**1**-**5**),[5] whose key steps were the *N*-acyliminium cyclization of a propargylsilane, and the subsequent construction of a skipped diene through stereoselective hydroboration of an allene. These reactions supplied a common ABCE-tetracyclic intermediate. The late-stage installation of a variety of D-rings enabled a

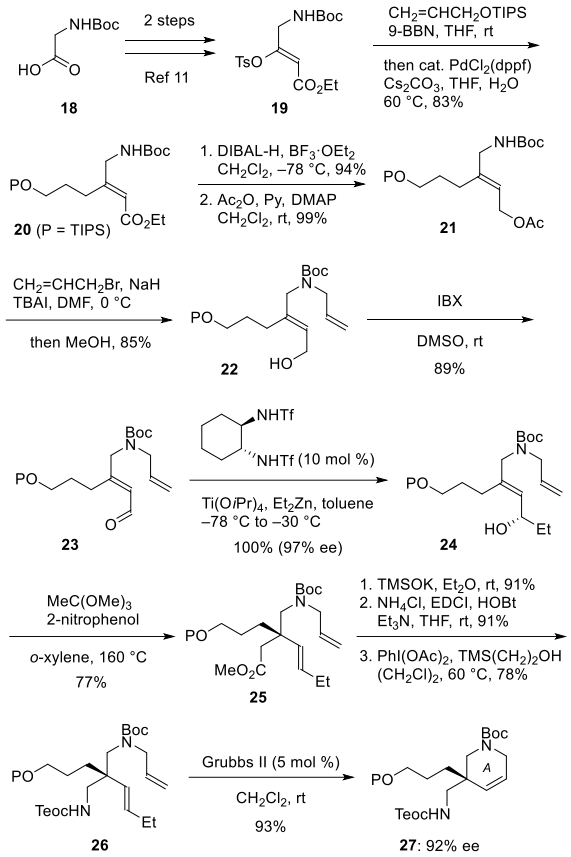
collective total synthesis of several madangamine alkaloids, which were tested for their inhibitory activities against a variety of human cancer cell lines.

2. Results and Discussion

To achieve the unified total synthesis of madangamine alkaloids, we planned the late-stage installation of various D-rings to the common ABCE-tetracyclic intermediate **11** (Scheme 2A). Synthesis of the common intermediate **11** has to solve two structural challenges; i) a diazatricyclic ABC-ring core, and ii) a skipped diene containing the *Z*-trisubstituted olefin. Historically, the construction of the unprecedented diazatricyclic system has drawns much more attention from synthetic chemists than the skipped diene. As a result, a number of solutions[3,4] including our racemic synthesis[5a] have been reported for the synthesis of the diazatricyclic system. On the other hand, the stereoselective synthesis of the skipped diene has been neglected as a synthetic issue.[6] Recent studies revealed that stereocontrol of the (*Z*)-trisubstituted olefin was a daunting task (Scheme 2B). The Kibayashi group documented the first model study of the skipped diene, in which the Still-Gennari olefination[7] of **12** formed (*Z*)-trisubstituted olefin **13**, and subsequent Migita-Kosugi-Stille coupling[8] installed the (*Z*,*Z*)-skipped diene.[4d] Amat and co-workers reported that their model



Scheme 2. (A) Synthetic plan toward the unified total synthesis of madangamine alkaloids. (B) Precedents for synthesis of the *Z*-trisubstituted olefin in the skipped diene of the madangamine alkaloids.



Scheme 3. Initial route to chiral A-ring moiety **27** through chirality transfer using the Claisen rearrangement.

compound exhibited better results by the Wittig reaction of **14** than the Still-Gennari modification to give (*Z*,*Z*)-skipped diene **15**.[3c] Unfortunately, low (*Z*)-selectivity was observed when applying the methodology to the fully functionalized intermediate **16** in their landmark total synthesis (*Z*/*E* = 2.2:1).[3e]

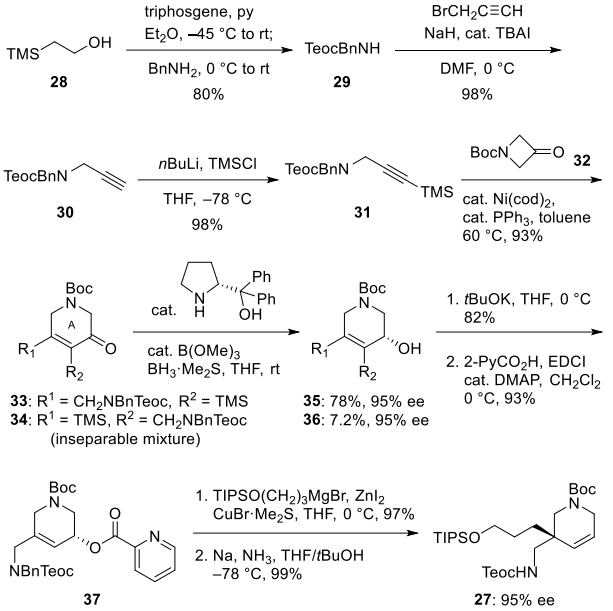
To solve these synthetic challenges of the madangamine alkaloids, we envisioned two consecutive processes involving *N*-acyliminium cyclization[9] of enamine **7** and stereoselective synthesis of skipped diene **(*Z*,*Z*)-10** from 1,1-disubstituted allene **8** (Scheme 2A). Protonation of enamine **7** would generate the transient *N*-acyliminium ion, which would form the diazatricyclic ABC-ring core through intramolecular cyclization. The resulting 1,1-disubstituted allene **8** could be a precursor of the (*Z*,*Z*)-skipped diene. We previously reported a stereodivergent synthesis of a skipped diene from an allene.[6t] The method consisted of hydroboration of the allene and subsequent Migita-Kosugi-Stille coupling[8] to give all four possible stereoisomers of the skipped diene. The key to success of this method was the stereodivergent hydroboration of the allene.[10] While hydroboration with sterically small 9-BBN gave a thermodynamic *E*-allylic alcohol, the reaction with sterically large $(Sia)_2BH$ provided a kinetic *Z*-allylic alcohol. Therefore, in the case of the madangamine alkaloids, hydroboration of 1,1-disubstituted allene **8** with $(Sia)_2BH$ would provide the *Z*-allylic alcohol, which could undergo the Migita-Kosugi-Stille coupling with (*Z*)-vinyl stannane **9**, giving skipped diene **(*Z*,*Z*)-10**. After the macrolactamization of **(*Z*,*Z*)-10**, the unified total synthesis of madangamines A-E would be accomplished from the common tetracyclic intermediate **11**.

The first synthetic task toward the unified total synthesis of the madangamine alkaloids was the enantioselective synthesis of A-ring **27** including a quaternary carbon center

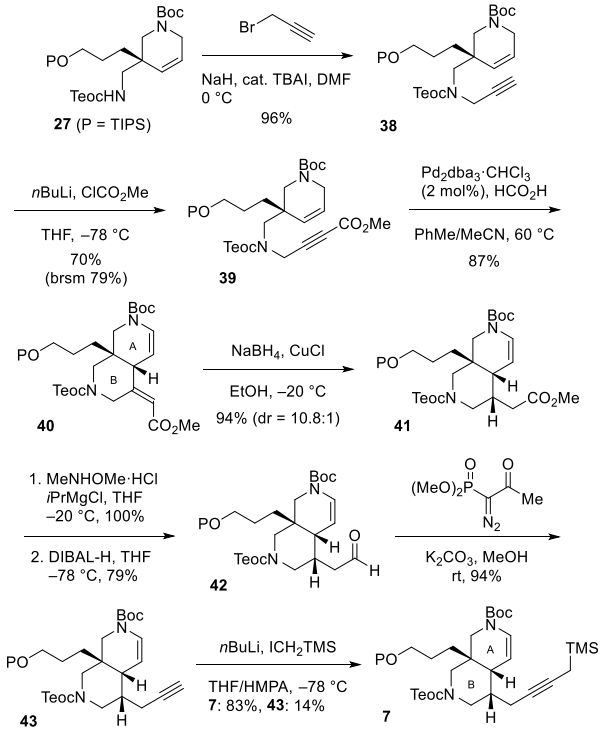
(Scheme 3). The synthesis commenced with the Suzuki-Miyaura coupling of known enol tosylate **19**, which was prepared from *N*-Boc glycine **18** in two steps, to form **20**.[11] After DIBAL-H reduction of **20** in the presence of $BF_3{\cdot}Et_2O$,[12] the resulting alcohol was protected as an acetate. *N*-Allylation of **21** and subsequent methanolysis of the acetate gave allylic alcohol **22**. The quaternary carbon center was constructed by the Johnson-type Claisen rearrangement of the chiral secondary alcohol. After IBX oxidation of allylic alcohol **22**,[13] the catalytic enantioselective alkylation of **23** provided allylic alcohol **24** in 97% ee.[14] A solution of **24** and trimethylorthoacetate was heated to 160 °C in the presence of 2-nitrophenol, installing the quaternary carbon center of **25**, which was isolated in 77% yield.[15] The resulting methyl ester **25** was converted to carbamate **26** by a three-step procedure including hydrolysis with TMSOK, condensation with ammonia and the Hofmann rearrangement.[16] Ring closing metathesis[17] of **26** furnished the A-ring moiety **27** in 93% yield and 92% ee. The enantiomeric excess of **27** was slightly decreased through the chirality transfer by the Claisen rearrangement.

An alternative robust route to A-ring moiety **27** was then examined to improve both the number of steps and the enantiomeric excess (Scheme 4). The synthesis began with preparation of protected *N*-benzyl amine **29**. After *N*-propargylation of **29**, the TMS group was installed at the terminal alkyne of **30**. We expected that this TMS group could control the regioselectivity in the subsequent nickel-catalyzed [4+2] cycloaddition[18] and the enantioselectivity in the CBS reduction.[19] Indeed, the [4+2] cycloaddition of alkyne **31** with azetidinone **32** took place smoothly under Louie's conditions to afford A-ring moiety **33** with high regioselectivity, along with minor regioisomer **34**. The CBS reduction of the inseparable mixture of **33** and **34** gave the desired allylic alcohol **35** in 78% yield with 95% ee, and **36** in 7.2% yield with 95% ee. The regioisomeric allylic alcohol **36** was separated at this stage. The TMS group in **35** was then removed by Brook rearrangement, and the remaining alcohol was converted to picolinate **37**. Anti-S_N2' reaction of **37** under Kobayashi's conditions installed the quaternary carbon center in 97% yield with complete regioselectivity and stereoselectivity.[20] The enantiomeric excess of the product was confirmed after removal of the benzyl group by Birch reduction, and was found to be well preserved (**27**, 99%, 95% ee).

With the chiral A-ring moiety **27** in hand, we turned our attention to the synthesis of the bicyclic AB-ring by palladium-catalyzed cycloisomerization (Scheme 5). The cyclization required methyl alkynoate **39**, which was prepared in a two-step procedure including *N*-propargylation of **27** and carbonylation of the terminal alkyne. The palladium-catalyzed cycloisomerization of **39** under Trost's conditions[21] smoothly took place at 60 °C in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (2 mol %) and HCO_2H in PhMe/MeCN = 49. The reaction provided the *cis*-fused bicyclic ring **40**[22] in 87% yield, associated with construction of the *N*-Boc-enamine group as an iminium ion equivalent. Next, Narisada's 1,4-reduction of α,β-unsaturated ester with $NaBH_4$ and CuCl gave **41** in 94% yield with 10.8:1 diastereoselectivity.[23] The methyl ester of **41** was converted to aldehyde **42** by stepwise reduction via the Weinreb amide.[24] Propargylsilane **7** was synthesized from aldehyde **42** by the Ohira-Bestmann reaction[25] and alkylation with (iodomethyl)trimethylsilane.



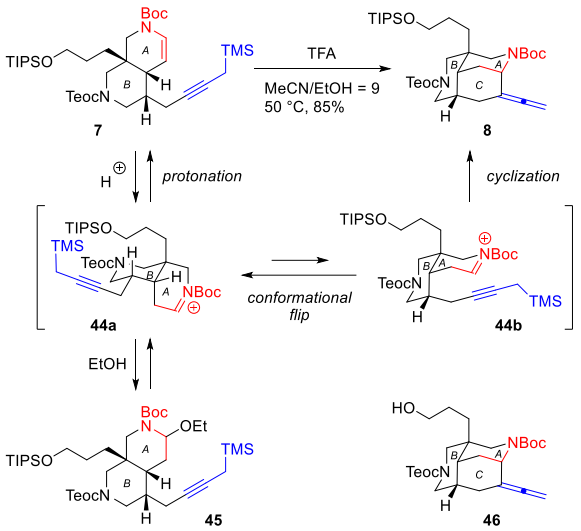
Scheme 4. Improved route to chiral A-ring moiety **27** through chirality transfer using S_N2' reaction.



Scheme 5. Synthesis of bicyclic AB-rings **7**.

The stage was now set for the crucial *N*-acyliminium cyclization to form the diazatricyclic ABC-ring core (Scheme 6). Addition of TFA to enamine **7** in MeCN/EtOH = 9 at 50 °C initiated protonation of the enamine to generate *N*-acyliminium ion **44a**. In the most stable conformation, the propargyl silane group of **44a** adopted the equatorial position and was located away from the *N*-acyliminium ion. Therefore, the cyclization required a conformational flip to place the propargyl silane in the axial position. Intramolecular allenylation then took place via the conformation of **44b**, providing 1,1-disubstituted allene **8** in 85% yield. The key to success was a combination of the

sterically small propargyl silane and the highly electrophilic *N*-acyliminium ion. Addition of ethanol was also important to form *N*,*O*-acetal **45** as a stable transient intermediate under equilibrium conditions. In addition, ethanol modulated the acidity of the reaction media. The reaction without ethanol took place at room temperature, but caused significant cleavage of the TIPS group (**8**: 52%; **46**: 32%). In contrast, the reaction with ethanol required a higher temperature at 50 °C, but formation of primary alcohol **46** was completely suppressed.

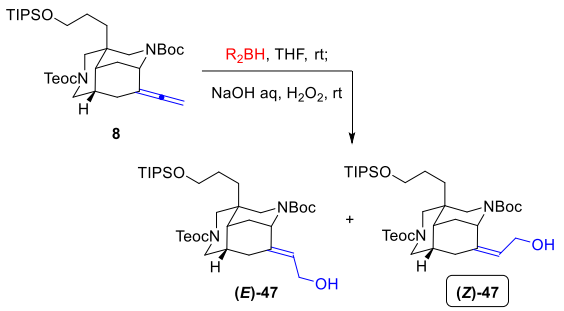


Scheme 6. Synthesis of 1,1-disubstituted allene **8** through *N*-acyliminium cyclization.

With 1,1-disubstituted allene **8** in hand, the next challenge was the stereoselective construction of the (*Z*,*Z*)-skipped diene (Table 1).[6t] First, *Z*-selective hydroboration of **8** was investigated with various organoborane reagents. Hydroboration of **8** with 9-BBN took place in both regioselective and stereoselective fashions to give allylic alcohol **(*E*)-47** as the major product after oxidative work-up (Table 1, Entry1, *E*:*Z* = 6.1:1). Use of $(Thx)BH_2$ and Cy_2BH resulted in moderate (*Z*)-stereoselectivities (Table 1, Entries 2 and 3). Gratifyingly, high (*Z*)-selectivity was realized with $(Sia)_2BH$ to afford allylic alcohol **(*Z*)-47** in 89% yield (Table 1, Entry 4, *E*:*Z* = 1:20).

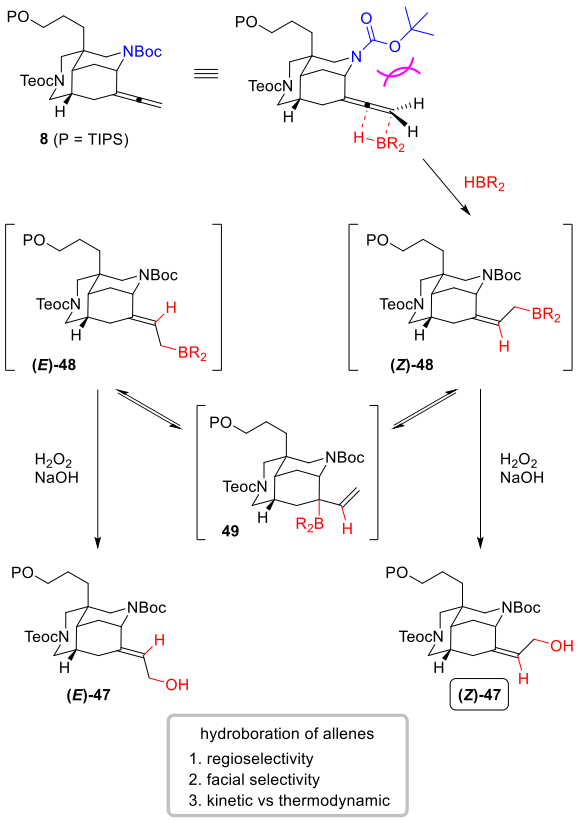
The mechanistic rational for the stereodivergent hydroboration of 1,1-disubstituted allene **8** is depicted in Scheme 7.[6t] In contrast to the hydroboration of alkenes and alkynes, the hydroboration of allenes requires precise control of three selectivities (regio-, facial-, and kinetic vs. thermodynamic). In the case of 1,1-disubstituted allene **8**, hydroboration took place regioselectively at the terminal position of the two olefins. The facial selectivity was controlled by the large Boc group. The organoborane reagents approached from the opposite side of the Boc group to avoid steric repulsion. Therefore, allylic borane **(*Z*)-48** would be formed in the initial step. The most challenging issue was control of the 1,3-allylic rearrangement. When a small organoborane reagent such as 9-BBN was used, **(*Z*)-48** quickly underwent two 1,3-allylic rearrangements[10,26] via **49** under equilibrium conditions, giving thermodynamically stable **(*E*)-48** which was converted to allylic alcohol **(*E*)-47** after oxidative work-up. On the other hand, use of sterically large $(Sia)_2BH$ prevented the 1,3-allylic rearrangement of **(*Z*)-48**, directly giving allylic alcohol **(*Z*)-47** as the major product. Thus, we demonstrated the stereodivergent hydroboration to produce either stereoisomer **(*E*)-47** or **(*Z*)-47** from the same allene **8** by simply changing organoborane reagents.

Table 1. Stereoselective hydroboration of 1,1-disubstituted allene **8**.



Entry	R_2BH	Combined Yield of **47** [%][c]	*E*:*Z* [c]
1[a]	9-BBN	83	6.1:1
2[b]	$(Thx)BH_2$	44	1:1.5
3[b]	Cy_2BH	78	1:4.7
4[b]	$(Sia)_2BH$	93	1:20

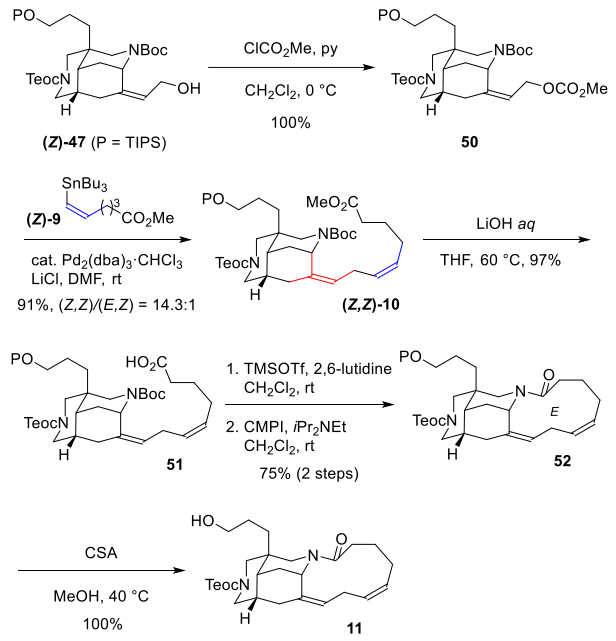
a) **8** (1 equiv), R_2BH (5 equiv), THF, rt, 3 h; then 3 M NaOH aq, 30% H_2O_2 aq, rt, 1 h. b) **8** (1 equiv), R_2BH (2 equiv), THF, rt, 10 min; then 3 M NaOH aq, 30% H_2O_2 aq, rt, 1 h. c) Yields and ratios of isolated products after purification by column chromatography are given.



Scheme 7. Mechanistic rationale for stereodivergent hydroboration of 1,1-disubstituted allene **8**.

We turned our attention to the Migita-Kosugi-Stille coupling[8] to provide skipped diene **(*Z*,*Z*)-10** (Scheme 8). The primary alcohol **(*Z*)-47** was converted to methyl carbonate **50**, which underwent a palladium-catalyzed coupling reaction with vinyl stannane **(*Z*)-9**, giving **(*Z*,*Z*)-10** in 91% yield. This is the first successful example of the stereoselective synthesis of the skipped diene in fully functionalized madangamine intermediates. Our results indicated that the developed sequence involving the stereodivergent hydroboration and subsequent coupling reaction could become a general approach to give access to skipped dienes comprised of trisubstituted olefins, which are often seen in a number of biologically active natural products.

The common tetracyclic intermediate of the madangamine alkaloids was then prepared from the skipped diene **(*Z*,*Z*)-10** in four steps (Scheme 8). Hydrolysis of the methyl ester and removal of the Boc group with TMSOTf provided the amino acid, which underwent macrolactamization with the Mukaiyama reagent (CMPI, 2-chloro-1-methylpyridinium iodide)[27] to construct the eleven-membered E-ring. The TIPS group of the resulting **52** was selectively removed with CSA in methanol without affecting the Teoc group, giving ABCE-tetracyclic common intermediate **11** in quantitative yield.



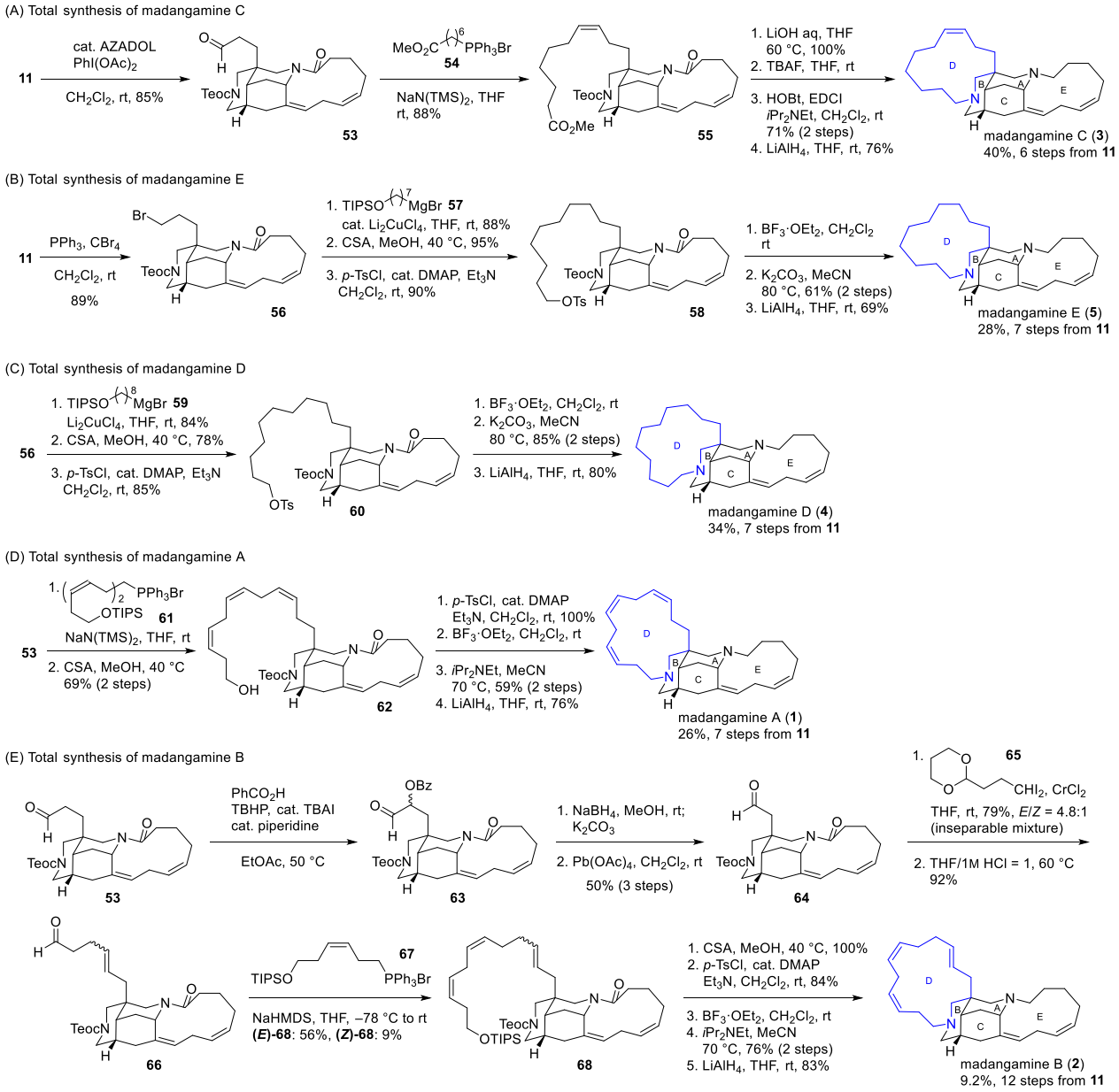
Scheme 8. Synthesis of common tetracyclic intermediate **11**.

As shown in parallel in Scheme 9, common ABCE-tetracyclic intermediate **11** was converted to each madangamine alkaloid. We began our collective total synthesis by targeting madangamine C (**3**), which possesses the thirteen-membered macrocyclic D-ring including the *cis*-olefin (Scheme 9A). The carbon framework of the D-ring was installed by AZADO oxidation of primary alcohol **11**,[28] followed by the Wittig coupling with **54**, giving **55** in 88% yield. After hydrolysis of the methyl ester and removal of the Teoc group, the resulting amino acid smoothly underwent macrolactamization with HOBt and EDCI to give the pentacyclic product in 71% yield over two steps.[3e] Reduction of the bismacrolactam with $LiAlH_4$ furnished madangamine C (**3**) in 76% yield. Thus, the total synthesis of madangamine C (**3**) was accomplished in 40% overall yield in six steps from the common intermediate **11**.

The next challenge was the synthesis of madangamine E (**5**) with a saturated thirteen-membered D-ring (Scheme 9B). Structurally, the saturated D-ring seemed to be simpler than the unsaturated series, but its construction proved to be more challenging because it had no functional bias such as a *cis*-olefin to facilitate the macrocyclization. Indeed, an initial attempt using the same macrolactamization procedure as in the synthesis of madangamine C (**3**) led to the formation of a significant amount of the dimer through intermolecular coupling. The Amat group employed a reaction sequence including ring-closing metathesis and hydrogenation to construct a saturated D-ring in their landmark total synthesis of madangamine D (**4**). However, their sequence was not applicable in our case because we installed the unsaturated E-ring prior to the D-ring for the efficient collective synthesis. Gratifyingly, we found that the following macrocyclic alkylation suppressed the unfavorable dimerization. Appel reaction of primary alcohol **11** provided bromide **56**, which underwent a copper-catalyzed alkylation with Grignard **57** reported by Cahiez and co-workers.[29] The TIPS group was then cleaved with CSA in methanol. The generated primary alcohol was then converted to tosylate **58**. Cleavage of the Teoc group in **58** provided the substrate for the macrocyclic alkylation. A solution of the resulting secondary amine in MeCN was heated to 80 °C in the presence of K_2CO_3. The macrocyclization took place smoothly in 61% yield over two steps without observation of dimerization. Finally, the total synthesis of madangamine E (**5**) was accomplished by $LiAlH_4$- reduction. Madangamine D (**4**), possessing the saturated fourteen-membered D-ring, was prepared in an identical fashion in 34% yield over seven steps from the common intermediate **11** (Scheme 9C).

In contrast to madangamines D and E, madangamine A (**1**) possesses a sensitive skipped (*Z*,*Z*,*Z*)-triene in the D-ring (Scheme 9D). The synthesis of madangamine A (**1**) started with the Wittig reaction of aldehyde **53** and subsequent cleavage of the TIPS group, affording skipped triene **62** as a single diastereomer. The skipped triene was a sensitive functional group, and limited the possible transformations for construction of the macrocyclic D-ring. For example, we first envisioned reductive amination or macrolactamization to form the D-ring, but the oxidation of primary alcohol **62** to form either an aldehyde or carboxylic acid resulted in significant decomposition. However, the macrocyclic alkylation that we developed proved to be highly general even for the D-ring including the sensitive skipped triene. After tosylation of **62** and removal of the Teoc group, macrocyclic alkylation with iPr_2NEt took place at 70 °C without causing elimination of the tosylate or isomerization of the skipped triene to the conjugated olefin. $LiAlH_4$-reduction of the macrolactam completed the total synthesis of madangamine A (**1**).

Synthesis of madangamine B (**2**) from the common intermediate **11** proved to be the most challenging because the position of the double bond was different from madangamines A (**1**) and C (**3**) (Scheme 9E). In fact, aldehyde **53** was not a productive intermediate to install the D-ring unit of madangamine B (**2**). After extensive study, we found that the aldehyde **64** was a possible intermediate to introduce the carbon chain of the D-ring, and could be prepared by a three-step sequence involving one-carbon dehomologation. First, α-oxybenzoylation of aldehyde **53** under Ishihara's conditions provided **63**, which underwent reduction of the aldehyde and subsequent hydrolysis in a one-pot process.[30] The resulting diol was converted to aldehyde **64** by oxidative cleavage with $Pb(OAc)_4$ in 50% yield over three steps.



Scheme 9. Unified total synthesis of madangamine alkaloids

$CrCl_2$-mediated Takai olefination[31] of aldehyde **64** with diiodide **65** provided an inseparable mixture of olefins in 79% yield (*E*:*Z* = 4.8:1). After hydrolysis of the cyclic acetal, the (*Z*,*Z*)-skipped diene **68** was formed by the Wittig reaction of **66** with **67** with complete *cis*-stereoselectivity. The two stereoisomers derived from the Takai olefination were separated at this stage. Finally, the macrocyclic alkylation and $LiAlH_4$-reduction completed the total synthesis of madangamine B (**2**).

With a series of synthetic madangamines A-E (**1**-**5**) in hand, their growth inhibitory activities were evaluated against thirteen human cancer cell lines including lung adenocarcinoma A549, melanoma CHL-1 and SK-MEL-28, colon carcinoma HCT116, cervix adenocarcinoma HeLa, fibrosarcoma HT1080, breast carcinoma MCF-7 and MDA-MB-23, pancreatic carcinoma Panc-1 and PK-1, prostate adenocarcinoma PC-3, bladder carcinoma T24, and acute monocytic leukemia THP1 (Table 2). All synthetic madangamines showed antiproliferative effects against these cancer cell lines, but their IC_{50} values were depended on the structure of the D-ring. The most potent alkaloids were madangamines A (**1**) and B (**2**), both of which contain the fifteen-membered D-rings with trienes. In contrast, madangamines D (**4**) and E (**5**) bearing saturated D-rings were less potent than other madangamines with unsaturated D-rings. In addition, madangamine C (**3**) containing a *cis*-olefin in the thirteen-membered D-ring demonstrated a slightly higher potency than madangamine E (**5**) with the saturated thirteen-membered D-ring. These results suggest an important role of the olefin groups in the D-rings for the cytotoxicity.

3. Conclusion

We accomplished a unified enantioselective total synthesis of madangamine alkaloids via a common ABCE-tetracyclic intermediate. The synthetic sequence includes a number of key transformations. First, the chiral diazatricyclic ABC-ring core was constructed through three cyclization events involving Ni-catalyzed [4+2] cycloaddition, palladium-catalyzed cycloisomerization and *N*-acyliminium cyclization of the propargylsilane. One of the most challenging issues in the synthesis was the stereoselecitve construction of the (*Z*,*Z*)-skipped diene, which was accomplished by *Z*-selective hydroboration/oxidation of the 1,1-disubstituted

Table 2. Cytotoxicity of synthetic madangamines A-E against various cancer cell lines (IC_{50} values in μM)[a)]

Cell Line	IC_{50} (μM)				
	Madangamine A (**1**)	Madangamine B (**2**)	Madangamine C (**3**)	Madangamine D (**4**)	Madangamine E (**5**)
A549	11.8	10.6	16.3	>20	>20
CHL-1	7.5	7.5	14.1	>20	>20
SK-MEL-28	8.8	10.0	18.9	>20	17.0
HCT116	7.4	7.4	13.3	16.3	19.8
HeLa	5.1	4.3	6.6	6.9	6.7
HT1080	6.2	6.7	8.7	>20	14.2
MCF-7	9.8	11.0	>20	>20	>20
MDA-MB-231	7.6	6.1	10.3	>20	13.5
Panc-1	11.8	10.8	18.3	>20	>20
PK-1	7.7	6.8	8.3	13.0	9.2
PC-3	8.4	9.8	14.9	>20	15.3
T24	12.1	10.8	16.3	>20	>20
THP1	6.1	3.3	3.4	7.4	5.0

a) Antiproliferative effects of tested compounds against human cancer cell lines in a 48 h growth inhibitory assay using the MTT method.

allene with $(Sia)_2BH$ and subsequent Migita-Kosugi-Stille coupling. The late-stage variation of the D-rings was realized from the common tetracyclic intermediate. The macrocyclic alkylation proved to be a general method for the synthesis of various types of D-rings. Our developed route enabled the supply of a series of synthetic madangamines for the first time, and elucidated the role of the D-rings in their proliferative effects against a variety of human cancer cell lines.

4. Experimental

General Details. Reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere. Toluene and DMSO were distilled from CaH_2. DMF and MeOH were distilled from $CaSO_4$. Pyridine was distilled from sodium hydroxide. Hexamethylphosphoric triamide was distilled from CaO. Toluene, DMSO, DMF, MeOH, pyridine, CH_2Cl_2, MeCN and EtOH were dried over activated 3Å molecular sieves. THF (dehydrated, stabilizer free) and Et_2O (dehydrated, stabilizer free) was purchased from KANTO CHEMICAL CO., INC. Commercial reagents were used without further purification. Thin-layer chromatography was performed on Merck 60 F_{254} precoated silica gel plates, which were visualized by exposure to UV (254 nm) or stained by submersion in *p*-anisaldehyde solution or ethanolic phosphomolybdic acid solution followed by heating on a hot plate. Flash column chromatography was performed on silica gel (Silica Gel 60 N; 63–210 or 40–50 mesh, KANTO CHEMICAL CO., INC.) and basic alumina (Alumina, Activated, about 200 mesh, WAKO PURE CHEMICAL INDUSTRIES, Ltd.). Preparative layer chromatography was performed on Merck PLC silica gel 60 F_{254}. ^1H NMR spectra were recorded at 500 MHz with JEOL ECA-500 spectrometer or 400 MHz with JEOL ECS-400 spectrometer. ^{13}C NMR spectra were recorded at 125 MHz with JEOL ECA-500 spectrometers. ^{19}F NMR spectra were recorded at 470 MHz with JEOL ECA-500 spectrometers. Chemical shifts are reported in ppm with reference to solvent signals [^1H NMR: $CDCl_3$ (7.26), C_6D_6 (7.16), $(CD_3)_2CO$ (2.05); ^{13}C NMR: $CDCl_3$ (77.16), C_6D_6 (128.06), $(CD_3)_2CO$ (206.26); ^{19}F NMR: C_6F_6 (–164.9)]. Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. MPLC was performed on Yamazen, YFLC AI-580. Infrared spectra were recorded using a BRUKER ALPHA FT-IR spectrometer. Mass spectra were measured with Waters, LCT Premier XE (ESI-TOF). Optical rotations were measured with a JASCO P-2100 polarimeter. Melting points were measured with a Yanaco MODEL MP-S3.

Unsaturated ester (20): 9-Borabicyclo[3.3.1]nonane (0.5 M solution in THF, 23 mL, 12 mmol) was added to a solution of (allyloxy)triisopropylsilane[32] (1.62 g, 7.56 mmol) and THF (3.8 mL) at 0 °C. The solution was allowed to warm to room temperature, maintained for 1 h at room temperature, and quenched with H_2O (1.6 mL, 91 mmol). This solution was added to a mixture of Cs_2CO_3 (4.93 g, 15.1 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (247 mg, 302 μmol). A solution of tosylate **19** (3.02 g, 7.56 mmol), H_2O (1.9 mL) and THF (19 mL) was then added to the resulting mixture. The mixture was allowed to warm to 60 °C, and stirred for 1 h. After cooling to 0 °C, the mixture was quenched with $NaBO_3\cdot 4H_2O$ (3.49 g, 22.7 mmol) and H_2O (19 mL) at 0 °C, stirred for 1 h at room temperature, and extracted with EtOAc (2x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:4) to give unsaturated ethyl ester **20** (2.77 g, 83%): a colorless oil; IR (film) 3368, 2943, 2867, 1719, 1517, 1463, 1367, 1247, 1178, 1105, 882, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.77 (s, 1H), 4.67 (brs, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.83 (d, *J* = 5.7 Hz, 2H), 3.75 (t, *J* = 6.3 Hz, 2H), 2.65 (t, *J* = 7.9 Hz, 2H), 1.75 (tt, *J* = 7.9, 6.3 Hz, 2H), 1.46 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.14–1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3 (C), 159.8 (C), 155.8 (C), 114.7 (CH), 79.9 (C), 63.4 (CH_2), 59.8

(CH_2), 46.3 (CH_2), 32.1 (CH_2), 28.5 (CH_3), 27.4 (CH_2), 18.1 (CH_3), 14.4 (CH_3), 12.1 (CH); HRMS (ESI), calcd for $C_{23}H_{45}NO_5SiNa^+$ $(M+Na)^+$ 466.2965, found 466.2962.

Allylic acetate (21): Boron trifluoride diethylether complex (3.0 mL, 25 mmol) was added to a solution of unsaturated ethyl ester **20** (9.99 g, 22.5 mmol) and CH_2Cl_2 (45 mL) at –78 °C. After maintaining for 30 min at –78 °C, diisobutylalminium hydride (1.0 M in hexane, 68 mL, 68 mmol) was added dropwise to the solution. This solution was quenched with saturated aqueous (+)-potassium sodium tartrate (50 mL), allowed to warm to room temperature, stirred for 3 h at room temperature, and extracted with EtOAc (3x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give allylic alcohol **69** (8.50 g, 94%): a colorless oil; IR (film) 3350, 2942, 2866, 1696, 1514, 1463, 1271, 1172, 1106, 882, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.62 (t, *J* = 6.9 Hz, 1H), 4.61 (brs, 1H), 4.17 (d, *J* = 6.9 Hz, 2H), 3.71 (d, *J* = 5.2 Hz, 2H), 3.68 (t, *J* = 5.7 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.65 (tt, *J* = 7.5, 5.7 Hz, 2H), 1.44 (s, 9H), 1.14–1.02 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0 (C), 140.0 (C), 125.2 (CH), 79.5 (C), 62.4 (CH_2), 58.6 (CH_2), 45.5 (CH_2), 31.5 (CH_2), 28.5 (CH_3), 25.0 (CH_2), 18.1 (CH_3), 12.1 (CH); HRMS (ESI), calcd for $C_{21}H_{43}NO_4SiNa^+$ $(M+Na)^+$ 424.2859, found 424.2861.

Acetic anhydride (5.8 mL, 61 mmol) was added to a solution of allyic alcohol **69** (12.3 g, 30.6 mmol), pyridine (5.0 mL, 61 mmol), *N*,*N*-dimethyl-4-aminopyridine (374 mg, 3.06 mmol) and CH_2Cl_2 (102 mL) at 0 °C. This solution was allowed to warm to room temperature, maintained for 1 h at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1/6) to give allylic acetate **21** (13.5 g, 99%): a colorless oil; IR (film) 3367, 2943, 2867, 1742, 1719, 1510, 1463, 1367, 1235, 1171, 1106, 882, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.49 (t, *J* = 6.9 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 2H), 4.53 (brs, 1H), 3.73 (d, *J* = 5.7 Hz, 2H), 3.70 (t, *J* = 6.1 Hz, 2H), 2.21 (t, *J* = 7.8 Hz, 2H), 2.04 (s, 3H), 1.65 (tt, *J* = 7.8, 6.1 Hz, 2H), 1.46 (s, 9H), 1.14–1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C), 155.9 (C), 142.8 (C), 119.6 (CH), 79.5 (C), 62.8 (CH_2), 60.8 (CH_2), 45.6 (CH_2), 32.0 (CH_2), 28.5 (CH_3), 25.6 (CH_2), 21.1 (CH_3), 18.1 (CH_3), 12.1 (CH); HRMS (ESI), calcd for $C_{23}H_{45}NO_5SiNa^+$ $(M+Na)^+$ 466.2965, found 466.2965.

Allylic alcohol (22): Sodium hydride (2.3 g, 61 mmol) was added to a solution of allylic acetate **21** (9.00 g, 20.3 mmol), allyl bromide (2.1 mL, 24 mmol), tetrabutylammonium iodide (750 mg, 2.03 mmol) and DMF (100 mL) at 0 °C. After maintaining for 2 h at this temperature, methanol (51 mL) was added to the solution. This solution was maintained at 0 °C for 30 min, quenched with saturated aqueous NH_4Cl (80 mL), and extracted with EtOAc/hexane = 1:3 (3x 80 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give allylic alcohol **22** (7.62 g, 85%): a colorless oil; IR (film) 3435, 2943, 2866, 1698, 1460, 1411, 1247, 1171, 1106, 882, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.77 (ddt, *J* = 16.9, 10.3, 5.8 Hz, 1H), 5.50 (t, *J* = 6.9 Hz, 1H), 5.12 (dt, *J* = 10.3, 1.2 Hz, 1H), 5.09 (dt, *J* = 16.9, 1.2 Hz, 1H), 4.21 (d, *J* = 6.9 Hz, 2H), 3.81 (brs, 2H), 3.77 (brs, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 2.16 (t, *J* = 7.2 Hz, 2H), 1.70–1.62 (m, 2H), 1.46 (s, 9H), 1.15–1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 155.7 (C), 138.6 (C), 134.0 (CH), 126.3 (CH), 116.5 (CH_2), 79.8 (C), 62.9 (CH_2), 58.9 (CH_2), 51.1 (CH_2), 48.7 (CH_2), 31.9 (CH_2), 28.5 (CH_3), 25.0 (CH_2), 18.1 (CH_3), 12.3 (CH); HRMS (ESI), calcd for $C_{24}H_{47}NO_4SiNa^+$ $(M+Na)^+$ 464.3172, found 464.3167.

Aldehyde (23): 2-Iodoxybenzoic acid (174 mg, 622 μmol) was added to a solution of allylic alcohol **22** (128 mg, 311 μmol) and DMSO (3.1 mL) at room temperature. This solution was maintained at this temperature for 1 h, quenched with H_2O (1 mL), and filtrated through a pad of Celite®. The resulting mixture was extracted with Et_2O (3x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel colomun chromatography (EtOAc/hexane 1:15 to 1:9) to give aldehyde **23** (122 mg, 89%): a colorless oil; IR (film) 2943, 2867, 1701, 1679, 1457, 1397, 1366, 1248, 1170, 1109, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 10.07 (d, *J* = 7.7 Hz, 1H), 5.85 (ddd, *J* = 7.7, 1.5, 1.4 Hz, 1H), 5.77 (dddd, *J* = 16.9, 10.3, 6.1, 5.7 Hz, 1H), 5.15 (dddd, *J* = 10.3, 1.5, 1.4, 1.2 Hz, 1H), 5.11 (dd, *J* = 16.9, 1.4 Hz, 1H), 4.04–3.90 (m, 2H), 3.85–3.72 (m, 2H), 3.75 (t, *J* = 6.1 Hz, 2H), 2.66–2.61 (m, 2H), 1.82–1.75 (m, 2H), 1.46 (s, 9H), 1.15–1.04 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 190.8 (CH), 162.4 (C), 155.5 (C), 133.6 (CH), 126.2 (CH), 117.2 (CH_2), 80.6 (C), 62.5 (CH_2), 51.6 (CH_2), 49.9 (CH_2), 33.0 (CH_2), 28.5 (CH_3), 26.1 (CH_2), 18.2 (CH_3), 12.3 (CH); HRMS (ESI), calcd for $C_{24}H_{46}NO_4Si^+$ $(M+H)^+$ 440.3196, found 440.3199.

Allylic alcohol (24): Isopropyl titanate (160 μL, 831 μmol) was added to a mixture of (1*R*)-*trans*-*N*,*N*'-1,2-cyclohexanediylbis(1,1,1-trifluoromethanesulfonamide) (10.5 mg, 27.7 μmol) and toluene (1.4 mL) at room temperature. The resulting mixture was heated to 40 °C, stirred for 20 min at this temperature, and cooled to –78 °C. Diethylzinc (1.1 M, 740 μL, 810 μmol) was added to the resulting solution at –78 °C and maintained for 10 min at this temperature. A solution of aldehyde **23** (122 mg, 277 μmol) and toluene (1.4 mL) was added dropwise to the solution at –78 °C and warmed to –30 °C. The solution was maintained for 2 h, and quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:12 to 1:5) to give allylic alcohol **24** (132 mg, 100%, 97% ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:100 (v/v), 1.0 mL/min, **24**: T_R= 12.6 min, ***ent*-24**: T_R= 10.8 min)): a colorless oil; $[\alpha]^{25}_D$ –7.3 (*c* 1.00, $CHCl_3$); IR (film) 3448, 2961, 2942, 2867, 1697, 1460, 1411, 1366, 1247, 1170, 1105, 882, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.76 (dddd, *J* = 16.9, 10.3, 5.8, 4.6 Hz, 1H), 5.24 (d, *J* = 8.9 Hz, 1H), 5.13–5.06 (m, 2H), 4.36 (ddd, *J* = 8.9, 6.6, 6.3 Hz, 1H), 3.95–3.65 (m, 6H), 2.22 (ddd, *J* = 13.5, 9.2, 6.9 Hz, 1H), 2.11 (ddd, *J* = 13.5, 9.2, 5.7 Hz, 1H), 1.73–1.57 (m, 3H), 1.55–1.43 (m, 1H), 1.46 (s, 9H), 1.15–1.05 (m, 21H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 155.7 (C), 138.0 (C), 134.1 (CH), 130.5 (CH), 116.5 (CH_2), 79.8 (C), 69.4 (CH), 63.1 (CH_2), 51.1 (CH_2), 48.7 (CH_2), 32.1 (CH_2), 30.7 (CH_2), 28.6 (CH_3), 25.3 (CH_2), 18.2 (CH_3), 12.4 (CH), 9.9 (CH_3); HRMS (ESI), calcd for $C_{26}H_{51}NO_4SiK^+$ $(M+K)^+$ 508.3224, found 508.3219.

Methyl ester (25): A sealed tube was charged with allylic alcohol **24** (36.6 mg, 77.9 mmol), 2-nitrophenol (10.8 mg, 77.9 mmol), trimethyl orthoacetate (200 μL, 1.60 mmol) and *o*-xylene (1.6 mL). The solution was heated to 160 °C, and maintained for 2 h at this temperature. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:29 to 1:7) to give methyl ester **24** (31.6 mg, 77%): a colorless oil; $[\alpha]^{28}_D$ +10.0 (*c* 1.00, $CHCl_3$); IR (film) 2960, 2944, 2866, 1739, 1699, 1462, 1405, 1366, 1247, 1172, 1103, 882, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.74 (ddt, *J* = 17.2, 10.6, 5.5 Hz, 1H), 5.45–5.34 (m, 2H), 5.09 (ddt,

J = 10.6, 1.5, 1.4 Hz, 1H), 5.05 (dtd, J = 17.2, 1.8, 1.4 Hz, 1H), 3.90–3.80 (m, 2H), 3.70–3.64 (m, 2H), 3.63 (s, 3H), 3.41 (d, J = 14.6 Hz, 1H), 3.31 (d, J = 14.6 Hz, 1H), 2.46 (d, J = 15.2 Hz, 1H), 2.42 (d, J = 15.2 Hz, 1H), 2.04 (qd, J = 7.5, 5.2 Hz, 2H), 1.66–1.50 (m, 4H), 1.44 (s, 9H), 1.13–1.03 (m, 21H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 172.3 (C), 156.6 (C), 134.6 (CH), 134.5 (CH), 130.7 (CH), 115.8 (CH_2), 79.7 (C), 64.2 (CH_2), 54.2 (CH_2), 51.7 (CH_2), 51.1 (CH_3), 43.5 (C), 39.2 (CH_2), 32.3 (CH_2), 28.6 (CH_3), 27.7 (CH_2), 26.1 (CH_2), 18.2 (CH_3), 13.9 (CH_3), 12.3 (CH); HRMS (ESI), calcd for $C_{29}H_{56}NO_5Si^+$ $(M+H)^+$ 526.3928, found 526.3930.

2-(Trimethylsilyl)ethyl carbamate (26): Potassium trimethylsilanolate (161 mg, 1.26 mmol) was added to a solution of methyl ester **25** (66.0 mg, 126 µmol) and Et_2O (2.5 mL) at room temperature. The solution was maintained for 18 h at room temperature, and quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:5) to give carboxylic acid **70** (58.9 mg, 91%): a colorless oil; $[\alpha]^{28}_D$ +53.4 (*c* 1.00, $CHCl_3$); IR (film) 3082, 2961, 2867, 1703, 1463, 1408, 1249, 1162, 1104, 920, 882, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.71 (dddd, J = 17.2, 10.3, 5.7, 4.9 Hz, 1H), 5.40 (dt, J = 15.8, 6.3 Hz, 1H), 5.31 (d, J = 15.8 Hz, 1H), 5.12 (dddd, J = 10.3, 1.7, 1.4, 1.2 Hz, 1H), 5.05 (dddd, J = 17.2, 1.7, 1.5, 1.4 Hz, 1H), 3.92 (dd, J = 16.3, 5.7 Hz, 1H), 3.75–3.58 (m, 3H), 3.55 (d, J = 14.9 Hz, 1H), 3.15–2.85 (m, 1H), 2.47 (d, J = 13.5 Hz, 1H), 2.43 (d, J = 13.5 Hz, 1H), 2.06 (qdd, J = 7.5, 6.3, 0.9 Hz, 2H), 1.80–1.65 (m, 1H), 1.55–1.44 (m, 3H), 1.46 (s, 9H), 1.12–1.03 (m, 21H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.1 (C), 158.3 (C), 134.0 (CH), 133.5 (CH), 131.8 (CH), 116.5 (CH_2), 81.6 (C), 63.8 (CH_2), 54.6 (CH_2), 52.8 (CH_2), 43.4 (C), 40.1 (CH_2), 33.3 (CH_2), 28.4 (CH_3), 27.4 (CH_2), 26.1 (CH_2), 18.2 (CH_3), 13.7 (CH_3), 12.3 (CH); HRMS (ESI), calcd for $C_{28}H_{54}NO_5Si^+$ $(M+H)^+$ 512.3771, found 512.3764.

1-Hydroxylbenzotriazole monohydrate (HOBt, 23.3 mg, 173 µmol) was added to a mixture of carboxylic acid **70** (58.9 mg, 115 µmol), NH_4Cl (35.3 mg, 230 µmol), EDCI (33.1 mg, 173 µmol), trimethylamine (40 µL, 290 µmol), and THF (2.3 mL) at room temperature. The mixture was stirred for 15 h at room temperature, and quenched with H_2O (3 mL). The resulting mixture was extracted with EtOAc (3x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:3) to give primary amide **71** (53.6 mg, 91%): a colorless oil; $[\alpha]^{26}_D$ +48.5 (*c* 1.00, $CHCl_3$); IR (film) 3345, 3191, 2960, 2943, 2866, 1681, 1621, 1464, 1407, 1249, 1162, 1102, 921, 883, 733, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 8.30–7.00 (m, 1H), 5.71 (dddd, J = 17.2, 10.3, 5.5, 5.2 Hz, 1H), 5.45–5.35 (m, 2H), 5.35–5.20 (m, 1H), 5.09 (ddt, J = 10.3, 1.7, 1.5 Hz, 1H), 5.04 (ddt, J = 16.9, 1.7, 1.5 Hz, 1H), 3.93–3.86 (m, 1H), 3.78–3.52 (m, 4H), 3.20–2.90 (m, 1H), 2.39 (d, J = 13.5 Hz, 1H), 2.28 (d, J = 13.5 Hz, 1H), 2.06 (qd, J = 7.5, 4.9 Hz, 2H), 1.80–1.65 (m, 1H), 1.58–1.40 (m, 3H), 1.44 (s, 9H), 1.12–1.03 (m, 21H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.7 (C), 157.6 (C), 134.9 (CH), 134.1 (CH), 131.3 (CH), 116.1 (CH_2), 80.4 (C), 64.0 (CH_2), 54.3 (CH_2), 52.4 (CH_2), 43.3 (C), 41.1 (CH_2), 33.2 (CH_2), 28.5 (CH_3), 27.6 (CH_2), 26.1 (CH_2), 18.2 (CH_3), 13.8 (CH_3), 12.3 (CH); HRMS (ESI), calcd for $C_{28}H_{54}N_2O_4SiK^+$ $(M+K)^+$ 549.3490, found 549.3496.

(Diacetoxyiodo)benzene (50.7 mg, 158 µmol) was added to a solution of primary amide **71** (53.6 mg, 105 µmol), 2-trimethylsilyl ethanol (150 µL, 1.10 mmol) and $(CH_2Cl)_2$ (2.1 mL) at room temperature. The solution was heated to 60 °C, and maintained for 15 h at this temperature. After cooling to room temperature, the solution was quenched with saturated aqueous $NaHCO_3$ (3 mL), and extracted with CH_2Cl_2 (3x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane 1:44 to 1:34) to give 2-(trimethylsilyl)ethyl carbamate **26** (51.3 mg, 78%): a colorless oil; $[\alpha]^{26}_D$ +29.5 (*c* 1.00, $CHCl_3$); IR (film) 3367, 2945, 2866, 1723, 1684, 1518, 1463, 1410, 1367, 1250, 1160, 1104, 883, 860, 838, 686 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.50–5.90 (m, 1H), 5.71 (dddd, J = 17.2, 10.3, 5.5, 5.2 Hz, 1H), 5.43 (dt, J = 16.3, 6.3 Hz, 1H), 5.27 (dt, J = 16.3, 1.5 Hz, 1H), 5.10 (dddd, J = 10.3, 1.5, 1.4, 1.2 Hz, 1H), 5.03 (dddd, J = 17.2, 1.7, 1.5, 1.5 Hz, 1H), 4.19–4.08 (m, 2H), 3.92–3.78 (m, 1H), 3.73 (dd, J = 16.1, 5.5 Hz, 1H), 3.68 (ddd, J = 9.8, 6.0, 5.7 Hz, 1H), 3.61 (ddd, J = 9.8, 6.6, 6.3 Hz, 1H), 3.35 (d, J = 14.7 Hz, 1H), 3.27 (dd, J = 13.5, 7.8 Hz, 1H), 3.13–2.90 (m, 1H), 2.99 (d, J = 14.7 Hz, 1H), 2.04 (qdd, J = 7.5, 6.3, 1.5 Hz, 2H), 1.66–1.54 (m. 1H), 1.52–1.26 (m, 3H), 1.45 (s, 9H), 1.13–1.03 (m, 21H), 1.00–0.95 (m, 3H), 0.98 (t, J = 7.5 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.43 (C), 157.41 (C), 133.9 (CH), 133.3 (CH), 131.6 (CH), 116.0 (CH_2), 80.2 (C), 64.0 (CH_2), 62.5 (CH_2), 52.4 (CH_2), 51.9 (CH_2), 44.6 (C), 42.8 (CH_2), 31.0 (CH_2), 28.4 (CH_3), 27.1 (CH_2), 26.4 (CH_2), 18.2 (CH_3), 17.9 (CH_2), 13.9 (CH_3), 12.1 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{33}H_{66}N_2O_5Si_2K^+$ $(M+K)^+$ 665.4147, found 665.4157.

A-ring (27): A solution of 2-(trimethylsilyl)ethyl carbamate **26** (48.9 mg, 78.0 µmol) and CH_2Cl_2 (1.6 mL) was heated to reflux, and maintained for 2 h at this temperature. The Grubbs 2nd generation catalyst (3.3 mg, 3.9 µmol) was then added to the solution at room temperature, and maintained for 3 h at this temperature. This solution was quenched with a solution of potassium 2-isocyanoacetate[33] (4.8 mg, 39 µmol) and MeOH (500 µL) at room temperature, maintained for 1 h, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:5) to give A-ring **27** (41.6 mg, 93%, 92% ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:85 (v/v), 1.0 mL/min, **27**: T_R= 7.2 min, ***ent*-27**: T_R= 8.5 min)): a colorless oil; $[\alpha]^{25}_D$ –9.0 (*c* 1.00, $CHCl_3$); IR (film) 3350, 2945, 2866, 1724, 1701, 1518, 1425, 1249, 1104, 860, 837, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.72 (d, J = 10.1 Hz, 1H), 5.58 (d, J = 10.1 Hz, 1H), 4.92 (m, 1H), 4.15 (t, J = 8.3 Hz, 2H), 4.00 (d, J = 18.3 Hz, 1H), 3.74 (d, J = 18.3 Hz, 1H), 3.67 (dt, J = 9.8, 6.3 Hz, 1H), 3.64 (dt, J = 9.8, 6.3 Hz, 1H), 3.55 (brs, 1H), 3.27 (dd, J = 13.8, 7.8 Hz, 1H), 3.09 (brs, 1H), 3.02–2.90 (m, 1H), 1.64–1.45 (m, 2H), 1.48 (s, 9H), 1.45–1.39 (m, 2H), 1.14–1.01 (m, 21H), 0.98 (t, J = 8.3 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 157.1 (C), 157.1 (C), 155.4 (C), 154.7 (C), 131.7 (CH), 131.0 (CH), 126.0 (CH), 125.3 (CH), 80.2 (C), 80.0 (C), 63.9 (CH_2), 63.9 (CH_2), 63.1 (CH_2), 62.9 (CH_2), 47.5 (CH_2), 46.4 (CH_2), 46.2 (CH_2), 46.2 (CH_2), 44.1 (CH_2), 43.1 (CH_2), 40.1 (C), 40.1 (C), 31.3 (CH_2), 31.2 (CH_2), 28.5 (CH_3), 28.5 (CH_3), 27.3 (CH_2), 27.3 (CH_2), 18.2 (CH_3), 18.2 (CH_3), 17.8 (CH_2), 17.8 (CH_2), 12.1 (CH), 12.1 (CH), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{29}H_{59}N_2O_5Si_2^+$ $(M+H)^+$ 571.3963, found 571.3991.

Carbamate (29): 2-Trimethylsilylethanol **28** (7.3 mL, 51 mmol) and pyridine (3.3 mL, 41 mmol) were added to a solution of triphosgene (5.02 g, 16.9 mmol) and Et_2O (250 mL) at –45 °C. The reaction mixture was stirred at this temperature for 1 h, then allowed to warm to room temperature, stirred for 3 h, and recooled to 0 °C. Benzylamine (11 mL, 100 mmol) was

then added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature, and stirred for 16 h. The resulting mixture was quenched with water (100 mL), and extracted with EtOAc (2x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give carbamate **29** (10.1 g, 80%): a colorless oil; IR (film) 3332, 2953, 1698, 1527, 1250, 1179, 1135, 1060, 1043, 969, 945, 860, 837, 752, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 5.05–4.65 (m, 1H), 4.37 (d, *J* = 5.7 Hz, 2H), 4.19 (t, *J* = 8.6 Hz, 2H), 0.99 (t, *J* = 8.6 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9 (C), 138.8 (C), 128.7 (CH), 127.6 (CH), 127.5 (CH), 63.3 (CH_2), 45.1 (CH_2), 17.9 (CH_2), –1.4 (CH_3); HRMS (ESI), calcd for $C_{13}H_{21}NO_2SiK^+$ $(M+K)^+$ 290.0979, found 290.0987.

Alkyne (30): Sodium hydride (63% in oil, 874 mg, 23.0 mmol) was added to a solution of carbamate **29** (3.84 g, 15.3 mmol), propargyl bromide (1.4 mL, 1.8 mmol), tetrabutylammonium iodide (565 mg, 1.53 mmol) and DMF (77 mL) at 0 °C. The solution was maintained at this temperature for 1 h, quenched with saturated aqueous NH_4Cl (50 mL), and extracted with hexane (3x 50 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:12) to give alkyne **30** (4.35 g, 98%): a colorless oil; IR (film) 2954, 1701, 1496, 1455, 1236, 1177, 1114, 945, 839, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.35–7.26 (m, 5H), 4.60 (s, 2H), 4.29–4.23 (m, 2H), 4.05 (brs, 1H), 3.96 (brs, 1H), 2.22 (t, *J* = 2.6 Hz, 1H), 1.05 (brs, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.3 (C), 156.3 (C), 137.1 (C), 137.1 (C), 128.7 (CH), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 127.6 (CH), 79.1 (CH), 79.1 (CH), 72.1 (C), 72.0 (C), 64.4 (CH_2), 64.4 (CH_2), 49.3 (CH_2), 49.0 (CH_2), 35.4 (CH_2), 35.1 (CH_2), 17.9 (CH_2), 17.9 (CH_2), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{16}H_{24}NO_2Si^+$ $(M+H)^+$ 290.1576, found 290.1571.

TMS alkyne (31): *n*-Butyllithium (1.63 M in hexane, 2.6 mL, 4.2 mmol) was added to a solution of alkyne **30** (1.17 g, 4.04 mmol) and THF (20 mL) at –78 °C. After maintaining for 10 min, chlorotrimethylsilane (620 µL, 4.9 mmol) was added to the solution at the same temperature. The mixture was maintained at –78 °C for 30 min, quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with hexane (2x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19) to give TMS alkyne **31** (1.43 g, 98%): a colorless oil; IR (film) 2956, 2178, 1704, 1455, 1415, 1250, 1235, 1178, 1114, 1012, 843, 762, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.34–7.25 (m, 5H), 4.59 (s, 2H), 4.25 (t, *J* = 8.6 Hz, 2H), 4.10 (brs, 1H), 3.97 (brs, 1H), 1.08–1.00 (m, 2H), 0.16 (s, 9H), 0.04 (s, 9H);^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.3 (C), 156.3 (C), 137.3 (C), 137.3 (C), 128.6 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 127.5 (CH), 100.9 (C), 100.9 (C), 89.2 (C), 89.0 (C), 64.3 (CH_2), 64.3 (CH_2), 49.4 (CH_2), 48.9 (CH_2), 36.4 (CH_2), 36.3 (CH_2), 17.9 (CH_2), 17.9 (CH_2), 0.0 (CH_3), 0.0 (CH_3), –1.3 (CH_3), –1.3 (CH_3); HRMS (ESI), calcd for $C_{19}H_{32}NO_2Si_2^+$ $(M+H)^+$ 362.1972, found 362.1979.

Allylic alcohol (35): In a glove box, $Ni(cod)_2$ (567 mg, 2.05 mmol) was added to a solution of alkyne **31** (7.41 g, 20.5 mmol), 1-Boc-3-azetidinone **32** (3.51 g, 20.5 mmol), triphenylphosphine (1.07 g, 4.10 mmol) and toluene (210 mL) at room temperature. The reaction vessel was removed from the glove box. The reaction was stirred at 60 °C for 6 h, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:6) to give an inseparable mixture of enone **33** and **34** (10.1 g, 93%): a colorless oil; IR (film) 2954, 1703, 1670, 1453, 1418, 1366, 1247, 1169, 1115, 843, 767, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C, a mixture of two regioisomers, signals of the major isomer are reported) δ 7.36–7.13 (m, 5H), 4.48 (brs, 2H), 4.35–4.26 (m, 4H), 4.07 (brs, 2H), 3.93 (brs, 2H), 1.49 (s, 9H), 1.06 (t, *J* = 8.6 Hz, 2H) 0.11 (s, 9H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C, a mixture of two regioisomers, signals of the major isomer are reported) δ 197.2 (C), 165.5 (C), 157.1 (C), 154.2 (C), 137.5 (C), 137.0 (C), 128.9 (CH), 127.9 (CH), 127.8 (CH), 80.8 (C), 64.7 (CH_2), 51.6 (CH_2), 50.8 (CH_2), 49.6 (CH_2), 44.7 (CH_2), 28.5 (CH_3), 18.2 (CH_2), 1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{27}H_{44}N_2O_5Si_2Na^+$ $(M+Na)^+$ 555.2686, found 555.2683.

Trimethylborate (310 µL, 2.80 mmol) was added to a solution of (*R*)-diphenyl(pyrrolidin-2-yl)methanol (595 mg, 2.35 mmol) in THF (39 mL) at room temperature. The resulting solution was maintained at room temperature for 1 h. Borane-methyl sulfide complex (1.1 mL, 12 mmol) was added to the solution. The solution was maintained for another 1 h. A solution of enone **33** and **34** (6.26 g, 11.7 mmol) and THF (78 mL) was added over 2 h using a syringe pump to the solution of the CBS reagent at room temperature. The resulting solution was maintained for an additional 3 h, and quenched with aqueous HCl (1 M, 50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (2x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/toluene 1:19 to 1:4) to afford a mixture of allylic alcohols **35** and **36**. The mixture of **35** and **36** were then separated by MPLC (Yamazen Ultra Pack Column D, 50×300 mm, EtOAc/hexane 11:89 to 32:68, 20 mL/min, **35**: T_R = 62.0 min, **36**: T_R = 58.0 min) to afford allylic alcohol **35** (4.89 g, 78%, 95% ee determined by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:9 (v/v), 1.0 mL/min, **35**: T_R= 6.7 min, ***ent*-35**: T_R= 11.5 min)) and **36** (452 mg, 7.2%, 95% ee determined by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:99 (v/v), 1.0 mL/min, **36**: T_R= 26.9 min, ***ent*-36**: T_R= 36.1 min)). Allylic alcohol **35**: a white amorphous solid; mp 34.0–35.5 °C; $[\alpha]^{21}_D$ –60.8 (*c* 1.00, $CHCl_3$); IR (film) 3444, 2954, 1699, 1453, 1422, 1366, 1250, 1172, 1135, 1062, 838, 766, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.32–7.19 (m, 5H), 4.44 (s, 2H), 4.28–4.10 (m, 6H), 3.93 (d, *J* = 13.5 Hz, 1H), 3.51 (d, *J* = 18.9 Hz, 1H), 2.96 (dd, *J* = 13.5, 2.9 Hz, 1H), 1.49 (s, 9H), 1.04 (t, *J* = 8.1 Hz, 2H), 0.10 (s, 9H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 157.3 (C), 157.0 (C), 155.4 (C), 155.4 (C), 145.3 (C), 144.2 (C), 137.4 (C), 137.4 (C), 135.6 (C), 135.6 (C), 128.7 (CH), 128.7 (CH), 127.6 (CH), 127.4 (CH), 127.4 (CH), 126.9 (CH), 80.1 (C), 80.1 (C), 66.0 (CH), 66.0 (CH), 64.3 (CH_2), 64.3 (CH_2), 49.9 (CH_2), 49.7 (CH_2), 49.7 (CH_2), 49.4 (CH_2), 48.2 (CH_2), 47.2 (CH_2), 44.9 (CH_2), 44.9 (CH_2), 28.5 (CH_3), 28.5 (CH_3), 18.2 (CH_2), 17.9 (CH_2), 0.4 (CH_3), 0.4 (CH_3), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{27}H_{46}N_2O_5Si_2Na^+$ $(M+Na)^+$ 557.2843, found 557.2843. Allylic alcohol **36**: a colorless oil; $[\alpha]^{25}_D$ –82.6 (*c* 1.00, $CHCl_3$); IR (film) 3428, 2954, 1698, 1453, 1422, 1366, 1250, 1172, 1130, 1062, 950, 856, 838, 760, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.35–7.13 (m, 5H), 4.66 (d, *J* = 14.9 Hz, 1H), 4.60 (d, *J* = 16.3 Hz, 1H), 4.30–4.17 (m, 3H), 4.04 (brs, 1H), 3.91 (brs, 2H), 3.79 (d, *J* = 14.9 Hz, 1H), 3.65 (brs, 1H), 3.39 (brs, 1H), 1.49 (s, 9H), 1.00 (t, *J* = 8.3 Hz, 2H),

0.05 (s, 9H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 158.4 (C), 155.1 (C), 143.6 (C), 137.4 (C), 136.1 (C), 128.8 (CH), 127.4 (CH), 126.9 (CH), 80.0 (C), 64.8 (CH_2), 63.2 (CH), 49.5 (CH_2), 48.7 (CH_2), 47.1 (CH_2), 47.1 (CH_2), 28.6 (CH_3), 18.1 (CH_2), 0.1 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{27}H_{46}N_2O_5Si_2Na^+$ $(M+Na)^+$ 557.2843, found 557.2839.

Picolinate (37): Potassium *tert*-butoxide (1.36 g, 12.1 mmol) was added to the solution of **35** (4.30 g, 8.04 mmol) and THF (80 mL) at 0 °C. The solution was maintained at 0 °C for 15 min, 1 M HCl was added to the solution until TLC analysis indicated the complete consumption of the TMS ether (total: 30 mL). The resulting mixture was extracted with EtOAc (2x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give allylic alcohol **72** (3.04 g, 82%): a colorless oil; $[\alpha]^{21}_D$ –26.2 (*c* 1.00, $CHCl_3$); IR (film) 3436, 2954, 1699, 1455, 1419, 1366, 1247, 1166, 1106, 1056, 936, 859, 838, 768, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.34–7.20 (m, 5H), 5.67–5.63 (m, 1H), 4.52 (d, *J* = 15.5 Hz, 1H), 4.42 (d, *J* = 15.5 Hz, 1H), 4.30–4.23 (m, 2H), 4.17–4.08 (m, 1H), 3.93–3.84 (m, 2H), 3.82 (d, *J* = 15.8 Hz, 1H), 3.66 (d, *J* = 18.6 Hz, 1H), 3.46 (d, *J* = 4.6 Hz, 2H), 1.48 (s, 9H), 1.08–1.02 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.9 (C), 155.2 (C), 137.8 (C), 135.5 (C), 128.7 (CH), 128.1 (CH), 127.5 (CH), 125.7 (CH), 80.3 (C), 64.3 (CH_2), 63.8 (CH), 50.1 (CH_2), 49.4 (CH_2), 47.9 (CH_2), 44.5 (CH_2), 28.6 (CH_3), 18.2 (CH_2), –1.4 (CH_3); HRMS (ESI), calcd for $C_{24}H_{38}N_2O_5SiNa^+$ $(M+Na)^+$ 485.2448, found 485.2454.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 1.89 g, 9.86 mmol) was added to a solution of alcohol **72** (3.04 g, 6.57 mmol), DMAP (80.3 mg, 657 μmol), 2-picolinic acid (1.13 g, 9.20 mmol), and CH_2Cl_2 (66 mL) at 0 °C. The solution was maintained at this temperature for 3 h, and quenched with H_2O (30 mL). The resulting mixture was extracted with CH_2Cl_2 (2x 30 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:1) to give picolinate **37** (3.48 g, 93%): a colorless oil; $[\alpha]^{21}_D$ –63.1 (*c* 1.00, $CHCl_3$); IR (film) 2954, 1740, 1698, 1454, 1421, 1366, 1245, 1169, 1129, 1044, 939, 858, 839, 750, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 8.77 (d, *J* = 4.3 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.81 (ddd, *J* = 7.8, 7.8, 1.5 Hz, 1H), 7.45 (dd, *J* = 7.8, 4.3 Hz, 1H), 7.32–7.21 (m, 5H), 5.81 (brs, 1H), 5.49 (brs, 1H), 4.50 (d, *J* = 15.5 Hz, 1H), 4.45 (d, *J* = 15.5 Hz, 1H), 4.29–4.23 (m, 2H), 4.04 (d, *J* = 17.8 Hz, 1H), 3.95 (d, *J* = 16.1 Hz, 1H), 3.89 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.83 (d, *J* = 16.1 Hz, 1H), 3.74 (d, *J* = 17.8 Hz, 1H), 3.60 (dd, *J* = 13.8, 4.6 Hz, 1H), 1.43 (s, 9H), 1.08–1.02 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 164.5 (C), 156.8 (C), 154.6 (C), 150.1 (CH), 148.4 (C), 139.0 (C), 137.5 (C), 136.8 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 126.8 (CH), 125.3 (CH), 120.9 (CH), 80.2 (C), 67.3 (CH), 64.2 (CH_2), 50.0 (CH_2), 49.3 (CH_2), 44.6 (CH_2), 44.3 (CH_2), 28.4 (CH_3), 18.1 (CH_2), –1.5 (CH_3); HRMS (ESI), calcd for $C_{30}H_{41}N_3O_6SiNa^+$ $(M+Na)^+$ 590.2662, found 590.2673.

A-ring (27): A 100 mL flask equipped with a rubber septa connected to a bubbler was charged with magnesium (turnings, 700 mg, 28.8 mmol) and THF (40 mL). (3-Bromopropoxy)-triisopropylsilane (4.5 mL, 16 mmol) was added to the mixture at room temperature over a period of 5 min. The resulting mixture was stirred vigorously for 1 h. The concentration of the Grignard reagent was determined as 0.26 M by titration with 1,10-phenanthroline method.[34]

The above Grignard reagent (0.26 M in THF, 31 mL, 7.5 mmol) was slowly added to a mixture of CuBr·Me_2S (918 mg, 4.46 mmol), ZnI_2 (1.42 g, 4.46 mmol), and THF (25 mL) at 0 °C. The resulting mixture was stirred at this temperature for 30 min. A solution of picolinate **37** (1.41 g, 2.48 mmol) and THF (25 mL) was added dropwise to the mixture dropwise at 0 °C. The mixture was stirred for 30 min, and quenched with saturated aqueous NH_4Cl (50 mL). The resulting mixture was extracted with hexane (2x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) and MPLC (Yamazen Ultra Pack Column B, 26×300 mm, EtOAc/hexane 18:82, 20 mL/min, **73**: T_R = 28.5 min) to afford S_N2' product **73** (1.58 g, 97%): a colorless oil; $[\alpha]^{21}_D$ +18.0 (*c* 1.00, $CHCl_3$); IR (film) 2945, 2866, 1699, 1464, 1419, 1365, 1249, 1175, 1144, 1103, 882, 858, 838, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.31–7.14 (m, 5H), 5.70 (d, *J* = 10.9 Hz, 1H), 5.64 (d, *J* = 10.9 Hz, 1H), 4.56 (d, *J* = 15.8 Hz, 1H), 4.51 (d, *J* = 15.8 Hz, 1H), 4.19 (dt, *J* = 10.6, 7.2 Hz, 2H), 3.85 (brs, 2H), 3.65 (t, *J* = 5.5 Hz, 2H), 3.54–3.25 (m, 4H), 1.60–1.41 (m, 13H), 1.12–1.04 (m, 21H), 1.05–0.96 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 157.9 (C), 155.4 (C), 138.4 (C), 132.8 (CH), 128.6 (CH), 127.6 (CH), 127.3 (CH), 124.4 (CH), 79.8 (C), 64.2 (CH_2), 63.9 (CH_2), 52.7 (CH_2), 52.0 (CH_2), 48.1 (CH_2), 43.5 (CH_2), 41.4 (C), 33.4 (CH_2), 28.6 (CH_3), 27.6 (CH_2), 18.2 (CH_3), 18.1 (CH_2), 12.3 (CH), –1.4 (CH_3); HRMS (ESI), calcd for $C_{36}H_{64}N_2O_5Si_2Na^+$ $(M+Na)^+$ 683.4252, found 683.4232.

Sodium (1.10 g, 47.8 mmol) was added to a solution of **73** (1.58 g, 2.39 mmol), *t*BuOH (0.7 mL), and NH_3/THF (25:24, 34 mL) at –78 °C. The resulting mixture was stirred for 15 min at –78 °C, quenched with solid NH_4Cl (3.84 g, 71.7 mmol), allowed to warm to room temperature, and diluted with water (20 mL). The resulting mixture was extracted with hexane (2x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:9) to give tetrahydropyridine **27** (1.34 g, 99%, 95% ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:85 (v/v), 1.0 mL/min, **27**: T_R= 6.9 min, ***ent*-27**: T_R= 8.0 min)): $[\alpha]^{21}_D$ –11.5 (*c* 1.00, $CHCl_3$).

Eneyne (38): Sodium hydride (63% in mineral oil, 257 mg, 6.75 mmol) was added to a solution of tetrahydropyridine **27** (2.57 g, 4.50 mmol), propargyl bromide (510 μL, 6.8 mmol), tetrabutylammonium iodide (166 mg, 450 μmol) and DMF (45 mL) at 0 °C. This solution was maintained at this temperature for 4 h, quenched with saturated aqueous NH_4Cl (25 mL), and extracted with EtOAc/hexane = 1/3 (3x 25 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:29 to 1:12) to give eneyne **38** (2.63 g, 96%): a colorless oil; $[\alpha]^{21}_D$ +10.5 (*c* 1.00, $CHCl_3$); IR (film) 3313, 2945, 2866, 1702, 1418, 1249, 1175, 1147, 1105, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.74–5.66 (m, 1H), 5.63 (ddd, *J* = 10.3, 2.0, 2.0 Hz, 1H), 4.25–4.17 (m, 2H), 4.10 (brs, 2H), 3.88 (d, *J* = 18.1 Hz, 1H), 3.82 (d, *J* = 18.1 Hz, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.48–3.36 (m, 1H), 3.43 (d, *J* = 14.9 Hz, 1H), 3.39 (d, *J* = 14.9 Hz, 1H), 3.33–3.24 (m, 1H), 2.17 (brs, 1H), 1.64–1.44 (m, 4H), 1.48 (s, 9H), 1.14–1.00 (m, 23H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 157.1 (C), 157.1 (C), 155.3 (C), 155.2 (C), 132.3 (CH), 131.9 (CH), 125.1 (CH), 124.6 (CH), 80.2–79.2 (C x4), 72.2–71.3 (CH x2), 64.3 (CH_2), 64.3 (CH_2), 63.9 (CH_2), 63.9 (CH_2), 52.8 (CH_2), 52.1 (CH_2), 48.0 (CH_2), 46.8 (CH_2), 43.7 (CH_2), 42.9 (CH_2), 41.2–40.4 (C x2), 38.4 (CH_2), 38.4 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 28.6 (CH_3), 28.6, (CH_3), 27.4 (CH_2), 27.4 (CH_2), 18.2 (CH_3), 18.2

(CH_3), 17.9 (CH_2), 17.8 (CH_2), 12.1 (CH), 12.1 (CH), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{32}H_{61}N_2O_5Si_2^+$ $(M+H)^+$ 609.4119, found 609.4130.

Methyl ynoate (39): *n*-Butyllithium (1.6 M in hexane, 1.3 mL, 2.2 mmol) was added to a solution of alkyne **38** (1.27 g, 2.09 mmol) and THF (21 mL) at –78 °C. After the solution was maintained for 15 min, methyl chloroformate (240 µL, 3.1 mmol) was added at the same temperature. The solution was maintained for 30 min, and quenched with saturated aqueous NH_4Cl (10 mL) at –78 °C. The resulting mixture was extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:5) to give a mixture of methyl ynoate **39** and alkyne **38**. The mixture was then separated by MPLC (Yamazen Ultra Pack Column B, 26×300 mm, EtOAc/hexane 24:76, 20 mL/min, **39**: T_R = 30.0 min, **38**: T_R = 28.0 min) to afford methyl ynoate **39** (969 mg, 70%, brsm 79%) and alkyne **38** (140 mg, 11%). **39**: a colorless oil; $[\alpha]^{25}_D$ +12.3 (*c* 1.00, $CHCl_3$); IR (film) 2945, 2866, 2239, 1702, 1462, 1423, 1250, 1175, 1104, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.76–5.69 (m, 1H), 5.60 (d, *J* = 10.3 Hz, 1H), 4.28–4.17 (m, 4H), 3.94–3.86 (m, 1H), 3.84–3.76 (m, 1H), 3.75 (s, 3H), 3.65 (t, *J* = 6.1 Hz, 2H), 3.56–3.32 (m, 1H), 3.42 (d, *J* = 14.9 Hz, 1H), 3.35 (d, *J* = 14.9 Hz, 1H), 3.25 (brs, 1H), 1.62–1.45 (m, 4H), 1.48 (s, 9H), 1.13–1.00 (m, 23H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.9 (C), 156.9 (C), 155.4 (C), 155.2 (C), 153.8 (C), 153.8 (C), 132.1 (CH), 131.7 (CH), 125.6 (CH), 125.2 (CH), 84.3 (C), 84.3 (C), 83.8 (C), 83.8 (C), 80.1 (C), 80.1 (C), 64.7 (CH_2), 64.7 (CH_2), 63.9 (CH_2), 63.9 (CH_2), 52.8 (CH_3), 52.8 (CH_3), 52.7 (CH_2), 52.7 (CH_2), 48.0 (CH_2), 46.7 (CH_2), 43.7 (CH_2), 43.0 (CH_2), 40.9 (C), 40.6 (C), 38.6 (CH_2), 38.5 (CH_2), 32.9 (CH_2), 32.1 (CH_2), 28.6 (CH_3), 28.6 (CH_3), 27.4 (CH_2), 27.4 (CH_2), 18.2 (CH_3), 18.2 (CH_3), 18.0 (CH_2), 17.9 (CH_2), 12.1 (CH), 12.1 (CH), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{34}H_{63}N_2O_7Si_2^+$ $(M+H)^+$ 667.4174, found 667.4173.

Unsaturated methyl ester (40): Tris(dibenzylidenacetone)-dipalladium chloroform adduct (39.4 mg, 38.1 µmol) was added to a solution of methyl ynoate **39** (1.27 g, 1.90 mmol), HCO_2H (350 µL, 9.5 mmol) and PhMe/MeCN = 49 (190 mL). The solution was heated to 60 °C, maintained for 1 h, quenched with saturated aqueous $NaHCO_3$ (50 mL) at room temperature, and extracted with EtOAc (3x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19) to give unsaturated methyl ester **40** (1.10 g, 87%): a colorless oil; $[\alpha]^{25}_D$ +62.0 (*c* 1.00, $CHCl_3$); IR (film) 2947, 2866, 1708, 1649, 1369, 1249, 1167, 1107, 858, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.07–6.77 (m, 1H), 5.76 (s, 1H), 5.01 (brs, 1H), 4.57 (brs, 1H), 4.40–4.12 (m, 1H), 4.19 (t, *J* = 8.6 Hz, 2H), 3.84–3.56 (m, 4H), 3.73 (s, 3H), 3.30 (d, *J* = 9.2 Hz, 1H), 2.88 (d, *J* = 13.8 Hz, 1H), 2.66 (brs, 1H), 1.68–1.36 (m, 4H), 1.50 (s, 9H), 1.12–0.99 (m, 23H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 166.1 (C), 166.1 (C), 156.6 (C), 156.4 (C), 155.9 (C), 155.9 (C), 152.7 (C), 152.2 (C), 127.0 (CH), 126.8 (CH), 118.4 (CH), 118.0 (CH), 103.3 (CH), 103.3 (CH), 81.5 (C), 81.5 (C), 63.9 (CH_2), 63.9 (CH_2), 63.7 (CH_2), 63.7 (CH_2), 51.4 (CH_3), 51.4 (CH_3), 46.7 (CH_2), 46.3 (CH_2), 46.0 (CH), 46.0 (CH_2), 45.6 (CH), 45.4 (CH_2), 44.2 (CH_2), 44.2 (CH_2), 37.4 (C), 37.2 (C), 32.0 (CH_2), 31.7 (CH_2), 28.3 (CH_3), 28.3 (CH_3), 26.7 (CH_2), 26.7 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 18.0 (CH_2), 17.9 (CH_2), 12.0 (CH), 12.0 (CH), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{34}H_{62}N_2O_7Si_2Na^+$ $(M+Na)^+$ 689.3993, found 689.3984.

Methyl ester (41): Copper (I) chloride (264 mg, 2.67 mmol) and $NaBH_4$ (101 mg, 2.67 mmol) were added to a solution of unsaturated methyl ester **40** (1.78 g, 2.67 mmol) and EtOH (27 mL) at –20 °C. Copper (I) chloride (264 mg, 2.67 mmol) and $NaBH_4$ (101 mg, 2.67 mmol) were added to the mixture every 15 min until TLC analysis indicated the complete consumption of unsaturated methyl ester **40** (total: CuCl 3.0 equiv., $NaBH_4$ 3.0 equiv.). The mixture was quenched with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (3x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was filtered through a pad of silica gel (EtOAc/hexane 1:19). Two diastereomers were then separated by MPLC (Yamazen Ultra Pack Column D, 50×300 mm, EtOAc/hexane 9:91 to 30:70, 45 mL/min, **41**: T_R = 38.0 min, **74**: T_R = 42.0 min) to afford methyl esters **41** (1.54 g, 86%) and **74** (142 mg, 7.9%). methyl ester **41**: a colorless oil; $[\alpha]^{25}_D$ –10.3 (*c* 1.00, $CHCl_3$); IR (film) 2946, 2865, 1742, 1703, 1652, 1436, 1367, 1250, 1168, 1110 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 79 °C) δ 7.20–6.90 (m, 1H), 4.43 (d, *J* = 8.3 Hz, 1H), 4.29 (t, *J* = 8.3 Hz, 2H), 4.12–3.96 (m, 1H), 3.94–3.72 (m, 2H), 3.64–3.54 (m, 2H), 3.38 (s, 3H), 2.92 (d, *J* = 13.2 Hz, 1H), 2.87 (d, *J* = 13.5 Hz, 1H), 2.52–2.40 (m, 2H), 2.23 (brs, 1H), 2.07 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.02 (dd, *J* = 15.8, 6.6 Hz, 1H), 1.65–1.49 (m, 4H), 1.42 (s, 9H), 1.17–1.05 (m, 21H), 1.02–0.95 (m, 2H), –0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 172.4 (C), 172.2 (C), 156.0 (C), 156.0 (C), 152.9 (C), 152.4 (C), 127.0 (CH), 126.8 (CH), 101.8 (CH), 101.4 (CH), 81.3 (C), 81.3 (C), 63.8 (CH_2), 63.7 (CH_2), 63.7 (CH_2), 63.6 (CH_2), 51.9 (CH_3), 51.9 (CH_3), 48.9 (CH_2), 47.9 (CH_2), 45.5 (CH_2), 45.1 (CH_2), 44.2 (CH_2), 43.9 (CH_2), 38.2 (CH), 37.5 (CH), 35.2 (CH_2), 35.0 (CH_2), 34.0 (C), 34.0 (C), 31.7 (CH), 31.4 (CH), 30.7 (CH_2), 30.5 (CH_2), 28.4 (CH_3), 28.4 (CH_3), 26.4 (CH_2), 26.4 (CH_2), 18.2 (CH_3), 18.2 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.1 (CH), 12.1 (CH), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{34}H_{64}N_2O_7Si_2Na^+$ $(M+Na)^+$ 691.4150, found 691.4172. methyl ester **74**: a colorless oil; $[\alpha]^{27}_D$ +30.6 (*c* 1.00, $CHCl_3$); IR (film) 2947, 2866, 1741, 1705, 1649, 1369, 1249, 1173, 1136, 1110 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 79 °C) δ 7.10–6.80 (m, 1H), 4.67 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.41–4.20 (m, 3H), 4.13 (d, *J* = 13.5 Hz, 1H), 4.00–3.75 (m, 1H), 3.61–3.52 (m, 2H), 3.37 (s, 3H), 3.28 (d, *J* = 13.8 Hz, 1H), 2.71 (d, *J* = 13.2 Hz, 1H), 2.45 (dd, *J* = 12.9, 12.9 Hz, 1H), 2.30 (d, *J* = 12.1 Hz, 1H), 2.02–1.88 (m, 2H), 1.62–1.46 (m, 2H), 1.44–1.38 (m, 1H), 1.42 (s, 9H), 1.36–1.17 (m, 2H), 1.15–1.03 (m, 21H), 1.01–0.95 (m, 2H), –0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 172.6 (C), 172.6 (C), 155.6 (C), 155.6 (C), 153.0 (C), 152.4 (C), 125.4 (CH), 125.0 (CH), 104.2 (CH), 103.7 (CH), 81.1 (C), 81.1 (C), 63.8 (CH_2), 63.8 (CH_2), 63.7 (CH_2), 63.7 (CH_2), 51.8 (CH_3), 51.8 (CH_3), 50.5 (CH_2), 50.5 (CH_2), 48.5 (CH_2), 48.3 (CH_2), 44.3 (CH_2), 43.6 (CH_2), 42.0 (CH), 41.8 (CH), 38.5 (CH), 38.5 (CH), 36.0 (CH_2), 35.8 (CH_2), 34.4 (C), 34.3 (C), 32.1 (CH_2), 32.1 (CH_2), 28.4 (CH_3), 28.4 (CH_3), 26.8 (CH_2), 26.7 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.0 (CH), 12.0 (CH), –1.3 (CH_3), –1.3 (CH_3); HRMS (ESI), calcd for $C_{34}H_{65}N_2O_7Si_2^+$ $(M+H)^+$ 669.4330, found 669.4363.

Aldehyde (42): A 200 mL flask equipped with a rubber septa connected to a bubbler was charged with magnesium (turnings, 751 mg, 30.9 mmol) and THF (47 mL). 1,2-Dibromoethane (12 µL, 140 µmol) and 2-bromopropane (2.64 mL, 28.2 mmol) were added to the mixture at room temperature over a period of 5 min. The resulting mixture was stirred vigorously for 1 h. The concentration of the resulting isopropylmagnesium bromide was determined as 0.38 M by titration with 1,10-phenanthroline method.[35]

Isopropylmagnesium bromide (0.38 M in THF, 24 mL, 9.2 mmol) was added to a mixture of methyl ester **41** (1.53 g, 2.29 mmol), MeNHOMe·HCl (447 mg, 4.58 mmol), and THF (12 mL) at –20 °C. The mixture was stirred for 15 min, quenched with saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3) to give Weinreb amide **75** (1.60 g, 100%): a colorless oil; $[\alpha]^{27}_D$ –3.9 (*c* 1.00, $CHCl_3$); IR (film) 2944, 2866, 1703, 1670, 1367, 1250, 1170, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.02–6.72 (m, 1H), 4.70 (brs, 1H), 4.17 (t, *J* = 8.4 Hz, 2H), 3.94–3.84 (m, 1H), 3.84–3.50 (m, 4H), 3.69 (s, 3H), 3.18 (s, 3H), 3.09–2.91 (m, 1H), 2.80 (d, *J* = 14.0 Hz, 1H), 2.60–2.42 (m, 3H), 2.41–2.30 (m, 2H), 1.63–1.46 (m, 4H), 1.49 (s, 9H), 1.13–1.03 (m, 21H), 1.00 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 172.5 (C), 172.2 (C), 156.1 (C), 156.1 (C), 153.0 (C), 152.5 (C), 126.7 (CH), 126.6 (CH), 102.4 (CH), 102.1 (CH), 81.2 (C), 81.2 (C), 63.9 (CH_2), 63.6 (CH_2), 63.6 (CH_2), 63.6 (CH_2), 61.4 (CH_3), 61.4 (CH_3), 49.0 (CH_2), 47.9 (CH_2), 45.4 (CH_2), 45.2 (CH_2), 44.4 (CH_2), 44.3 (CH_2), 38.8–37.0 (CH x4), 34.1 (C), 34.0 (C), 32.8–32.0 (CH_3 x2, CH_2 x2), 31.0 (CH), 30.9 (CH), 30.7 (CH_2), 30.5 (CH_2), 28.4 (CH_3), 28.4 (CH_3), 26.5 (CH_2), 26.5 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.0 (CH), 12.0 (CH), –1.4 (CH_3), –1.4 (CH_3); HRMS (ESI), calcd for $C_{35}H_{68}N_3O_7Si_2^+$ $(M+H)^+$ 698.4596, found 698.4590.

Diisobutylaluminium hydride (1.0 M in hexane, 3.4 mL, 3.4 mmol) was added to a solution of Weinreb amide **75** (1.60 g, 2.29 mmol) and THF (23 mL) at –78 °C. This solution was maintained at this temperature for 1 h, and quenched with saturated aqueous (+)-potassium sodium tartrate (50 mL). The resulting mixture was allowed to warm to room temperature, stirred for 1 h, and extracted with EtOAc (2x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give aldehyde **42** (1.46 g, 79%, 95% ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:19 (v/v), 1.0 mL/min, **42**: T_R= 5.3 min, ***ent*-42**: T_R= 6.9 min)): a colorless oil; $[\alpha]^{27}_D$ –7.6 (*c* 1.00, $CHCl_3$); IR (film) 2945, 2866, 2723, 1703, 1367, 1250, 1169, 1111, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 9.79 (s, 1H), 7.02–6.72 (m, 1H), 4.60(brs, 1H), 4.17 (t, *J* = 8.6 Hz, 2H), 3.91–3.77 (m, 1H), 3.75–3.55 (m, 4H), 3.09–2.94 (m, 1H), 2.83 (d, *J* = 14.3 Hz, 1H), 2.63–2.49 (m, 2H), 2.45 (dd, *J* = 17.8, 5.2 Hz, 1H), 2.38 (dd, *J* = 17.8, 6.9 Hz, 1H), 2.32 (brs, 1H), 1.63–1.52 (m, 2H), 1.51–1.45 (m, 2H), 1.50 (s, 9H), 1.14–1.03 (m, 21H), 1.00 (m 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 200.0 (CH), 156.1 (C), 152.7 (C), 127.4 (CH), 101.4 (CH), 81.4 (C), 63.82 (CH_2), 63.78 (CH_2), 49.3–47.5 (CH_2, broad), 45.7 (CH_2), 44.5 (CH_2), 44.3 (CH_2), 38.5 (CH), 34.3 (C), 31.1 (CH_2), 29.5 (CH), 28.5 (CH_3), 26.6 (CH_2), 18.2 (CH_3), 18.1 (CH_2), 12.3 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{33}H_{63}N_2O_6Si_2^+$ $(M+H)^+$ 639.4225, found 639.4222.

Alkyne (43): Ohira-Bestmann reagent (410 µL, 2.7 mmol) was added to a mixture of aldehyde **42** (1.15 g, 1.80 mmol), K_2CO_3 (498 mg, 3.60 mmol), and MeOH (18 mL) at room temperature. The mixture was stirred for 3 h, and quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C. The resulting mixture was extracted with hexane (2x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give alkyne **43** (1.07 g, 94%): a colorless oil; $[\alpha]^{27}_D$ –16.4 (*c* 1.00, $CHCl_3$); IR (film) 3313, 2945, 2866, 1704, 1652, 1465, 1435, 1412, 1366, 1250, 1169, 1146, 1111, 883, 859, 839, 766, 722, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.84 (brs, 1H), 4.65 (brs, 1H), 4.17 (t, *J* = 8.3 Hz, 2H), 3.99 (brs, 1H), 3.81 (brs, 1H), 3.74–3.52 (m, 3H), 3.08–2.92 (m, 1H), 2.76 (d, *J* = 13.2 Hz, 1H), 2.52–2.42 (m, 2H), 2.28–2.08 (m, 3H), 1.99 (m, 1H), 1.60–1.48 (m, 4H), 1.49 (s, 9H), 1.09–1.04 (m, 21H), 1.00 (t, *J* = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.1 (C), 152.7 (C), 127.1 (CH), 101.5 (CH), 81.4 (C), 81.2 (C), 70.2 (CH), 63.9 (CH_2), 63.6 (CH_2), 49.6–47.8 (br, CH_2), 45.6 (CH_2), 44.2 (CH_2), 37.8 (CH), 34.3 (C), 34.2 (CH), 30.8 (CH_2), 28.5 (CH_3), 26.6 (CH_2), 19.9 (CH_2), 18.2 (CH_3), 18.1 (CH_2), 12.3 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{34}H_{63}N_2O_5Si_2^+$ $(M+H)^+$ 635.4276, found 635.4271.

Propargylsilane (7): *n*-Butyllithium (1.6 M in hexane, 1.1 mL, 1.8 mmol) was added to a solution of alkyne **43** (1.07 g, 1.68 mmol) and THF (15 mL) at –78 °C. After maintaining for 15 min, (iodomethyl)trimethylsilane (300 µL, 2.0 mmol) and HMPA (2 mL) were added to the solution at –78 °C. The mixture was stirred for 30 min at –78 °C, quenched with saturated aqueous NH_4Cl (10 mL) at the same temperature, and extracted with hexane (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give a mixture of propargylsilane **7** and alkyne **43**. The mixture was then separated by MPLC (Yamazen Ultra Pack Column B, 26×300 mm, EtOAc/hexane 7:93 to 30:70, 20 mL/min, **7**: T_R = 25.5 min, **43**: T_R = 28.5 min) to afford propargylsilane **7** (1.01 g, 83%) and alkyne **43** (149 mg, 14%). propargylsilane **7**: a colorless oil; $[\alpha]^{25}_D$ –21.1 (*c* 1.00, $CHCl_3$); IR (film) 2953, 2866, 1705, 1465, 1435, 1366, 1250, 1170, 1110, 946, 854, 765, 722, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.00–8.68 (m, 1H), 4.80–4.60 (m, 1H), 4.16 (t, *J* = 8.0 Hz, 2H), 4.00–3.90 (m, 1H), 3.83 (brs, 1H), 3.74–3.56 (m, 3H), 2.98 (brs, 1H), 2.74 (d, *J* = 13.5 Hz, 1H), 2.48 (brs, 1H), 2.42 (t, *J* = 11.8 Hz, 1H), 2.26–2.16 (m, 1H), 2.16–2.00 (m, 2H), 1.60–1.48 (m, 4H), 1.50 (s, 9H), 1.43 (m, 2H), 1.10–1.04 (m, 21H), 1.00 (t, *J* = 8.9 Hz, 2H), 0.10 (s, 9H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.2 (C), 152.8 (C), 126.8 (CH), 102.3 (CH), 81.2 (C), 79.6 (C), 75.5 (C), 64.0 (CH_2), 63.6 (CH_2), 49.8–47.6 (br, CH_2), 45.6 (CH_2), 44.5 (CH_2), 38.0 (CH), 34.6 (CH), 34.3 (C), 30.9 (CH_2), 28.5 (CH_3), 26.7 (CH_2), 20.5 (CH_2), 18.22 (CH_3), 18.19 (CH_2), 12.3 (CH), 7.3 (CH_2), –1.3 (CH_3), –1.8 (CH_3); HRMS (ESI), calcd for $C_{38}H_{73}N_2O_5Si_3^+$ $(M+H)^+$ 721.4827, found 721.4825.

Tricyclic core (8): Trifluoroacetic acid (33 µL, 430 µmol) was added to a solution of propargylsilane **7** (208 mg, 288 µmol) and MeCN/EtOH = 9 (29 mL). The solution was heated to 50 °C, maintained for 5 h, quenched with Et_3N (80 µL, 580 µmol) at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:14) and MPLC (Yamazen Ultra Pack Column B, 26×300 mm, EtOAc/hexane 7:93 to 30:70, 20 mL/min, **8**: T_R = 23.0 min) to afford tricyclic core **8** (158 mg, 85%): a colorless oil; $[\alpha]^{25}_D$ +40.8 (*c* 1.00, $CHCl_3$); IR (film) 3449, 2945, 2865, 1958, 1696, 1463, 1437, 1365, 1250, 1174, 1105, 839, 765, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.00–4.55 (m, 3H), 4.19 (t, *J* = 8.6 Hz, 2H), 4.09–3.95 (m, 1H), 3.92–3.75 (m, 1H), 3.73–3.58 (m, 3H), 3.13 (d, *J* = 13.5 Hz, 1H), 2.87 (d, *J* = 12.3 Hz, 1H), 2.63 (d, *J* = 13.2 Hz, 1H), 2.62–2.50 (m, 1H), 2.35 (dd, *J* = 15.8, 6.6 Hz, 1H), 2.15 (ddd, *J* = 13.2, 3.2, 3.2 Hz, 1H), 2.00 (brs, 1H), 1.70–1.66 (m, 1H), 1.55–1.40 (m, 14H), 1.11–1.05 (m, 21H), 1.01 (t, *J* = 8.6 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 205.5 (C), 156.8 (C), 155.8 (C), 99.6 (C), 79.7 (C), 74.0 (CH_2), 63.93 (CH_2), 63.88 (CH_2), 51.1 (CH_2), 49.3 (CH), 49.1 (CH_2), 47.4 (CH_2), 36.0–34.9 (br,

C x1, CH x1), 34.8 (CH), 33.0 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 28.6 (CH_3), 27.0 (CH_2), 18.2 (CH_3), 18.1 (CH_2), 12.3 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{35}H_{65}N_2O_5Si_2^+$ $(M+H)^+$ 649.4432, found 649.4434.

***Z*-Allylic alcohol ((*Z*)-47)**: 2-Methyl-2-butene (1.7 mL, 16 mmol) was added to borane THF complex (0.92 M in THF, 8.0 mL, 7.4 mmol) at 0 °C. The solution was maintained at this temperature for 1 h to give disiamylborane (calculated as 0.76 M in THF).

Disiamylborane (0.76 M, 6.0 mL, 4.6 mmol) was added to a solution of allene **8** (1.48 g, 2.28 mmol) and THF (23 mL) at room temperature. The solution was maintained for 10 min at room temperature, and quenched with NaOH aq (3 M, 10 mL) and 30% H_2O_2 aq (10 mL) at 0 °C. The resulting mixture was maintained for 1 h at 0 °C, and extracted with EtOAc (2x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give *Z*-allylic alcohol **(*Z*)-47** (1.34 g, 88%) and *E*-allylic alcohol **(*E*)-47** (65.7 mg, 4.3%). **(*Z*)-47**: a colorless oil; $[\alpha]^{27}_D$ +4.3 (*c* 1.00, $CHCl_3$); IR (film) 3450, 2945, 2866, 1688, 1463, 1437, 1415, 1250, 1175, 1132, 1105, 838, 765, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.68–5.38 (m, 1H), 5.18–4.90 (m, 1H), 4.46–4.33 (m, 1H), 4.30–4.12 (m, 2H), 4.01 (d, *J* = 12.3 Hz, 1H), 3.92–3.76 (m, 2H), 3.74–3.63 (m, 2H), 3.58 (d, *J* = 14.1 Hz, 1H), 3.38 (brs, 1H), 3.10 (d, *J* = 14.1 Hz, 1H), 2.86 (d, *J* = 12.3 Hz, 1H), 2.63 (d, *J* = 13.5 Hz, 1H), 2.51 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.28 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.15 (ddd, *J* = 13.5, 3.5, 3.5 Hz, 1H), 1.99–1.91 (m, 1H), 1.70–1.65 (m, 1H), 1.58–1.35 (m, 14H), 1.12–1.04 (m, 21H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.8 (C), 156.7 (C), 140.4 (C), 125.2 (CH), 80.7 (C), 63.9 (CH_2), 63.9 (CH_2), 57.1 (CH_2), 51.1 (CH_2), 49.1 (CH_2), 48.1 (CH_2), 44.3 (CH), 35.9 (CH), 35.6 (CH), 35.4 (CH_2), 35.0 (C), 33.4 (CH_2), 29.5 (CH_2), 28.7 (CH_3), 27.0 (CH_2), 18.2 (CH_3), 18.1 (CH_2), 12.3 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{35}H_{66}N_2O_6Si_2Na^+$ $(M+Na)^+$ 689.4357, found 689.4359. **(*E*)-47**: a colorless oil; $[\alpha]^{27}_D$ +11.1 (*c* 1.00, $CHCl_3$); IR (film) 3461, 2944, 2866, 1693, 1463, 1437, 1414, 1366, 1250, 1175, 1132, 1104, 838, 765, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.80–5.40 (m, 1H), 4.80–4.35 (m, 1H), 4.26–4.13 (m, 3H), 4.09 (dd, *J* = 12.9, 5.7 Hz, 1H), 4.08–3.96 (m, 1H), 3.84 (d, *J* = 11.8 Hz, 1H), 3.74–3.57 (m, 3H), 3.13–2.95 (m, 1H), 2.87 (d, *J* = 12.6 Hz, 1H), 2.70–2.54 (m, 2H), 2.24 (dd, *J* = 15.5, 12.9 Hz, 1H), 2.13 (ddd, *J* = 13.5, 3.8, 3.8 Hz, 1H), 1.98–1.86 (m, 1H), 1.72–1.65 (m, 1H), 1.60–1.38 (m, 14H), 1.12–1.04 (m, 21H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.8 (C), 156.8 (C), 155.7 (C), 155.4 (C), 139.1 (C), 138.5 (C), 126.6 (CH), 125.5 (CH), 79.7 (C), 79.7 (C), 63.9 (CH_2), 63.9 (CH_2), 63.8 (CH_2), 63.7 (CH_2), 58.4 (CH_2), 58.4 (CH_2), 53.0 (CH), 51.8 (CH), 50.9 (CH_2), 50.7 (CH_2), 49.0 (CH_2), 48.8 (CH_2), 47.1 (CH_2), 47.1 (CH_2), 35.8 (CH), 35.8 (CH), 35.1 (C), 35.0 (CH), 34.8 (CH), 34.7 (C), 32.8 (CH_2), 32.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.6 (CH_2), 28.6 (CH_3), 28.6 (CH_3), 28.5 (CH_2), 26.8 (CH_2), 26.8 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.0 (CH), 12.0 (CH), –1.3 (CH_3), –1.3 (CH_3); HRMS (ESI), calcd for $C_{35}H_{66}N_2O_6Si_2Na^+$ $(M+Na)^+$ 689.4357, found 689.4354.

Allylic carbonate (50): Methyl chloroformate (140 µL, 1.8 mmol) was added to a solution of allylic alcohol **(*Z*)-47** (614 mg, 920 µmol), pyridine (150 µL, 1.8 mmol) and CH_2Cl_2 (9.0 mL) at 0 °C. This solution was maintained for 2 h at 0 °C, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give allylic carbonate **50** (670 mg, 100%): a colorless oil; $[\alpha]^{28}_D$ +49.6 (*c* 1.00, $CHCl_3$); IR (film) 2926, 2865, 1750, 1695, 1463, 1440, 1366, 1266, 1252, 1175, 1131, 945, 838, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.40 (t, *J* = 6.9 Hz, 1H), 5.22–4.90 (m, 2H), 4.78–4.46 (m, 1H), 4.25–4.12 (m, 2H), 4.09–3.94 (m, 1H), 3.90–3.79 (m, 1H), 3.77 (s, 3H), 3.74–3.56 (m, 3H), 3.07 (d, *J* = 14.4 Hz, 1H), 2.85 (d, *J* = 12.3 Hz, 1H), 2.63 (d, *J* = 12.6 Hz, 1H), 2.63–2.50 (m, 1H), 2.32 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.16 (ddd, *J* = 13.5, 3.4, 3.4 Hz, 1H), 2.02–1.91 (m, 1H), 1.72–1.66 (m, 1H), 1.60–1.35 (m, 14H), 1.12–1.04 (m, 21H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.8 (C), 156.8 (C), 155.8 (C), 155.8 (C), 155.3 (C), 155.2 (C), 143.6 (C), 142.9 (C), 119.7 (CH), 118.6 (CH), 80.4 (C), 79.8 (C), 64.2 (CH_2), 64.1 (CH_2), 63.9 (CH_2), 63.8 (CH_2), 63.8 (CH_2), 63.7 (CH_2), 54.8 (CH_3), 54.7 (CH_3), 50.8 (CH_2), 50.7 (CH_2), 48.8 (CH_2), 48.6 (CH_2), 47.3 (CH_2), 47.1 (CH_2), 45.1 (CH), 43.9 (CH), 35.6 (CH), 35.5 (CH), 35.4 (CH), 35.1 (CH_2), 35.1 (CH_2), 34.9 (C), 34.8 (CH), 34.7 (C), 32.8 (CH_2), 32.7 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 28.6 (CH_3), 28.5 (CH_3), 26.8 (CH_2), 26.8 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.0 (CH), 12.0 (CH), –1.3 (CH_3), –1.3 (CH_3); HRMS (ESI), calcd for $C_{37}H_{68}N_2O_8Si_2Na^+$ $(M+Na)^+$ 747.4412, found 747.4404.

Skipped diene ((*Z*,*Z*)-10): A solution of allylic carbonate **50** (667 mg, 920 µmol), vinylstannane **9** (960 mg, 2.30 mmol) and DMF (9.2 mL) was added to a mixture of LiCl (195 mg, 4.60 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (47.6 mg, 46.0 µmol) at room temperature. After stirring at room temperature for 1 h, the mixture was quenched with KF aq (1 M, 5 mL) at 0 °C, stirred for 1 h at room temperature, and extracted with hexane (3x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:14) to afford a mixture of skipped dienes **(*Z*,*Z*)-10** and **(*E*,*Z*)-10**. Two skipped dienes were then separated by MPLC (Yamazen Ultra Pack Column B, 26×300 mm, Et_2O/hexane 1:4 to 2:3, 20 mL/min, **(*Z*,*Z*)-10**: T_R = 32.0 min, **(*E*,*Z*)-10**: T_R = 36.0 min) to afford skipped diene **(*Z*,*Z*)-10** (611 mg, 85%) and skipped diene **(*E*,*Z*)-10** (42.6 mg, 6%). Skipped diene **(*Z*,*Z*)-10**: a colorless oil; $[\alpha]^{26}_D$ +26.5 (*c* 1.00, $CHCl_3$); IR (film) 2946, 2866, 1741, 1692, 1463, 1436, 1414, 1250, 1175, 1131, 859, 839, 765, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.40–5.27 (m, 2H), 5.23–4.90 (m, 2H), 4.25–4.10 (m, 2H), 4.10–3.91 (m, 1H), 3.91–3.78 (m, 1H), 3.77–3.55 (m, 6H), 3.12 (d, *J* = 14.0 Hz, 1H), 3.05–2.90 (m, 2H), 2.84 (d, *J* = 13.2 Hz, 1H), 2.61 (d, *J* = 12.6 Hz, 1H), 2.55 (dd, *J* = 13.7, 13.7 Hz, 1H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.26 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.16–2.07 (m, 3H), 1.98–1.89 (m, 1H), 1.70 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.78–1.63 (m, 1H), 1.60–1.40 (m, 13H), 1.35–1.26 (m, 1H), 1.13–1.04 (m, 21H), 1.00 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 174.3 (C), 174.1 (C), 156.8 (C), 156.8 (C), 155.4 (C), 155.2 (C), 136.8 (C), 136.1 (C), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 124.9 (CH), 123.9 (CH), 79.8 (C), 79.4 (C), 63.9 (CH_2), 63.9 (CH_2), 63.8 (CH_2), 63.8 (CH_2), 51.6 (CH_3), 51.5 (CH_3), 50.9 (CH_2), 50.7 (CH_2), 49.0 (CH_2), 48.7 (CH_2), 47.2 (CH_2), 47.2 (CH_2), 45.2 (CH), 44.0 (CH), 35.9 (CH), 35.7 (CH), 35.6 (CH_2), 35.6 (CH), 35.3 (CH_2), 35.22 (C), 35.18 (CH), 34.9 (C), 33.60 (CH_2), 33.56 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 29.7 (CH_2), 28.63 (CH_3), 28.57 (CH_3), 26.9 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 18.2 (CH_3), 18.2 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.1 (CH), 12.1 (CH), –1.3 (CH_3), –1.3 (CH_3); HRMS (ESI), calcd for $C_{42}H_{76}N_2O_7Si_2Na^+$ $(M+Na)^+$ 799.5089, found 799.5090. Skipped diene **(*E*,*Z*)-10**: a colorless oil; $[\alpha]^{24}_D$ +2.1 (*c* 1.00, $CHCl_3$); IR (film) 2946, 2866, 1741, 1694, 1463, 1436, 1414, 1366, 1318, 1250, 1175, 1131, 882, 860, 839, 765, 687

cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.54–5.06 (m, 3H), 4.78–4.36 (m, 1H), 4.25–4.10 (m, 2H), 4.12–3.94 (m, 1H), 3.92–3.76 (m, 1H), 3.74–3.56 (m, 5H), 3.61 (d, *J* = 14.4 Hz, 1H), 3.16–2.94 (m, 1H), 2.87 (d, *J* = 13.5 Hz, 1H), 2.77 (ddd, *J* = 16.1, 6.3, 6.3 Hz, 1H), 2.70–2.50 (m, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.26–2.16 (m, 1H), 2.16–2.05 (m, 3H), 1.98–1.85 (m, 1H), 1.70 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.74–1.64 (m, 1H), 1.60–1.37 (m, 14H), 1.13–1.04 (m, 21H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 174.1 (C), 174.1 (C), 156.8 (C), 156.8 (C), 155.9 (C), 155.3 (C), 136.6 (C), 135.9 (C), 129.1 (CH), 129.0 (CH), 128.91 (CH), 128.87 (CH), 126.1 (CH), 124.8 (CH), 79.5 (C), 79.5 (C), 63.9 (CH_2), 63.8 (CH_2), 63.8 (CH_2), 63.7 (CH_2), 53.3 (CH), 52.0 (CH), 51.6 (CH_3), 51.6 (CH_3), 50.9 (CH_2), 50.7 (CH_2), 49.1 (CH_2), 48.9 (CH_2), 47.2 (CH_2), 47.0 (CH_2), 36.0 (CH), 35.5 (CH), 35.2 (C), 35.1 (CH), 34.74 (CH), 34.69 (C), 33.5 (CH_2), 33.5 (CH_2), 32.8 (CH_2), 32.3 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 28.6 (CH_3), 28.6 (CH_3), 28.4 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.7 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 24.8 (CH_2), 24.8 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.0 (CH), 12.0 (CH), –1.3 (CH_3), –1.3 (CH_3); HRMS (ESI), calcd for $C_{42}H_{76}N_2O_7Si_2Na^+$ $(M+Na)^+$ 799.5089, found 799.5094.

Carboxylic acid (51): Aqueous LiOH (1 M, 2.6 mL) was added to a solution of ***(Z,Z)*-10** (611 mg, 786 µmol) and THF (5.3 mL). The mixture was heated to 60 °C, maintained for 10 h at 60 °C, quenched with saturated aqueous NH_4Cl (5 mL) at room temperature, and extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give carboxylic acid **51** (583 mg, 97%): a colorless oil; $[\alpha]^{29}_D$ +26.1 (*c* 1.00, $CHCl_3$); IR (film) 3158, 2944, 2866, 1736, 1691, 1463, 1438, 1415, 1366, 1321, 1250, 1175, 1132, 882, 858, 839, 765, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.42–5.25 (m, 2H), 5.25–4.90 (m, 2H), 4.30–4.10 (m, 2H), 4.10–3.90 (m, 1H), 3.90–3.77 (m, 1H), 3.77–3.58 (m, 3H), 3.13 (d, *J* = 12.9 Hz, 1H), 3.05–2.74 (m, 2H), 2.84 (d, *J* = 12.3 Hz, 1H), 2.70–2.46 (m, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.32–2.20 (m, 1H), 2.20–2.06 (m, 3H), 1.98–1.86 (m, 1H), 1.72 (tt, *J* = 7.5, 7.2 Hz, 2H), 1.70–1.63 (m, 1H), 1.60–1.36 (m, 13H), 1.36–1.25 (m, 1H), 1.13–1.03 (m, 21H), 1.01 (t, *J* = 8.4 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 179.0 (C), 178.7 (C), 156.9 (C), 156.9 (C), 155.3 (C), 155.3 (C), 136.8 (C), 136.0 (C), 129.6 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 125.1 (CH), 123.9 (CH), 79.9 (C), 79.7 (C), 63.9 (CH_2), 63.9 (CH_2), 63.8 (CH_2), 63.8 (CH_2), 50.9 (CH_2), 50.7 (CH_2), 49.0 (CH_2), 48.7 (CH_2), 47.1 (CH_2), 47.1 (CH_2), 45.2 (CH), 44.1 (CH), 35.9 (CH), 35.7 (CH), 35.5 (CH_2), 35.5 (CH), 35.3 (C), 35.2 (CH_2), 35.1 (CH), 34.9 (C), 33.5 (CH_2), 33.5 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 28.61 (CH_3), 28.58 (CH_3), 26.8 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 26.0 (CH_2), 26.0 (CH_2), 24.73 (CH_2), 24.67 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 17.9 (CH_2), 17.9 (CH_2), 12.0 (CH), 12.0 (CH), –1.3 (CH_3), –1.3 (CH_3); HRMS (ESI), calcd for $C_{41}H_{74}N_2O_7Si_2Na^+$ $(M+Na)^+$ 785.4932, found 785.4937.

Tetracyclic core (52): 2,6-Lutidine (74 µL, 640 µmol) and TMSOTf (58 µL, 320 µmol) were added to a solution of carboxylic acid **51** (122 mg, 160 µmol) and CH_2Cl_2 (1.6 mL) at room temperature. 2,6-Lutidine (7.4 µL, 64 µmol) and TMSOTf (5.8 µL, 32 µmol) were added to the solution every 15 min until TLC analysis indicated the complete consumption of carboxylic acid **51** (total: 2,6-lutidine 5.6 equiv., TMSOTf 2.8 equiv.). The resulting solution was quenched with Et_3N (76 µL, 550 µmol) and concentrated. The residue was filtrated through a pad of silica gel ($CHCl_3$/MeOH 29:1) to give amino acid, which was immediately used in the next reaction without further purification.

2-Chloro-1-methylpyridinium iodide (CMPI, 204 mg, 800 µmol) was added to a solution of the above amino acid, DIPEA (140 µL, 800 µmol) and CH_2Cl_2 (160 mL) at room temperature. The solution was maintained for 16 h at room temperature, quenched with saturated aqueous NH_4Cl (50 mL), and extracted with CH_2Cl_2 (2x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give tetracyclic core **52** (77.0 mg, 75% for 2 steps, 95% ee by HPLC (CHIRALPAK AD-H, 250×4.6 mm, UV 210 nm, *i*PrOH/hexane 1:20 (v/v), 1.0 mL/min, **52**: T_R= 31.5 min, ***ent*-52**: T_R= 22.2 min)): a colorless oil; $[\alpha]^{28}_D$ +87.0 (*c* 1.00, $CHCl_3$); IR (film) 2944, 2865, 1697, 1633, 1438, 1249, 1103, 923, 882, 859, 764, 731, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.62–5.48 (m, 1H), 5.48–5.34 (m, 1H), 5.34–5.10 (m, 1H), 5.10–4.90 (m, 1H), 4.38–4.08 (m, 3H), 4.08–3.92 (m, 1H), 3.94–3.75 (m, 1H), 3.74–3.52 (m, 2H), 3.22–3.02 (m, 1H), 3.00–2.77 (m, 2H), 2.76–2.35 (m, 4H), 2.35–1.88 (m, 6H), 1.88–1.66 (m, 2H), 1.64–1.23 (m, 6H), 1.12–0.98 (m, 23H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.5 (C), 156.8 (C), 137.2 (C), 129.2 (CH), 128.0 (CH), 125.5 (CH), 63.91 (CH_2), 63.86 (CH_2), 50.9 (CH_2), 49.1 (CH_2), 48.1 (CH), 45.2 (CH_2), 36.3 (C), 35.8 (CH), 35.1 (CH), 34.5 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 30.6 (CH_2), 27.8 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 25.8 (CH_2), 18.2 (CH_3), 18.2 (CH_2), 12.3 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{36}H_{65}N_2O_4Si_2^+$ $(M+H)^+$ 645.4483, found 645.4487.

Common intermediate (11): 10-Camphorsulfonic acid (CSA, 55.3 mg, 238 µmol) was added to a solution of tetracyclic core **52** (77.0 mg, 119 µmol) and MeOH (2.4 mL) at room temperature. The solution was heated to 40 °C, maintained for 1 h at 40 °C, quenched with Et_3N (66 µL, 480 µmol) at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 19:1) to give common intermediate **11** (58.2 mg, 100%): a white amorphous solid; mp 45.0–47.0 °C; $[\alpha]^{26}_D$ +43.1 (*c* 1.00, $CHCl_3$); IR (film) 3413, 2950, 2921, 1693, 1613, 1438, 1249, 1059, 936, 859, 839, 754, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.70–5.50 (m, 1H), 5.46–5.32 (m, 1H), 5.32–5.15 (m, 1H), 5.12–4.94 (m, 1H), 4.39–4.26 (m, 1H), 4.25–4.15 (m, 2H), 4.10–3.80 (m, 2H), 3.70–3.60 (m, 1H), 3.55–3.45 (m, 1H), 3.10 (ddd, *J* = 14.9, 9.5, 9.5 Hz, 1H), 2.94–2.76 (m, 2H), 2.76–2.64 (m, 1H), 2.64–2.40 (m, 3H), 2.35–1.90 (m, 6H), 1.90–1.74 (m, 1H), 1.74–1.53 (m, 4H), 1.53–1.36 (m, 2H), 1.22–1.09 (m, 1H), 1.02 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.8 (C), 156.8 (C), 136.8 (C), 129.0 (CH), 128.1 (CH), 126.4 (CH), 63.9 (CH_2), 62.9 (CH_2), 50.9 (CH_2), 49.2 (CH_2), 48.4 (CH), 43.5 (CH_2), 37.1 (CH), 36.8 (C), 34.9 (CH), 33.9 (CH_2), 32.6 (CH_2), 31.8 (CH_2), 30.6 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{27}H_{45}N_2O_4Si^+$ $(M+H)^+$ 489.3149, found 489.3153.

Aldehyde (53): AZADOL® (1.8 mg, 11.9 µmol) and $PhI(OAc)_2$ (57.5 mg, 179 µmol) were added to a solution of alcohol **11** (58.2 mg, 119 µmol) and CH_2Cl_2 (2.4 mL) at room temperature. The solution was maintained for 17 h, quenched with saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2 (2x 2 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2 to EtOAc) to give aldehyde **53** (49.2 mg, 85%): a colorless oil; $[\alpha]^{26}_D$ +122 (*c* 1.00, $CHCl_3$); IR (film) 2951, 2919, 1724, 1693, 1626, 1439, 1248, 1087, 1044, 936, 859, 839, 761, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ

9.73 (s, 1H), 5.70–5.48 (m, 1H), 5.46–5.31 (m, 1H), 5.30–5.14 (m, 1H), 5.12–4.92 (m, 1H), 4.34–4.10 (m, 3H), 4.08–3.75 (m, 2H), 3.09 (ddd, *J* = 14.9, 9.5, 9.2 Hz, 1H), 2.96–2.75 (m, 2H), 2.75–2.41 (m, 5H), 2.33 (ddd, *J* = 17.2, 11.2, 5.2 Hz, 1H), 2.28–1.93 (m, 6H), 1.91–1.72 (m, 2H), 1.71–1.57 (m, 1H), 1.50–1.32 (m, 3H), 1.00 (t, *J* = 8.6 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 201.1 (CH), 173.4 (C), 156.6 (C), 136.6 (C), 129.0 (CH), 128.0 (CH), 126.4 (CH), 64.0 (CH_2), 50.8 (CH_2), 49.2 (CH_2), 48.2 (CH), 43.1 (CH_2), 38.3 (CH_2), 37.1 (CH), 36.3 (C), 34.8 (CH), 34.0 (CH_2), 32.5 (CH_2), 30.6 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{27}H_{43}N_2O_4Si^+$ $(M+H)^+$ 487.2992, found 487.2991.

Methyl ester (55): In a glove box, sodium hexamethyldisilazide (25.1 mg, 137 µmol) was added to a mixture of phosphonium salt **54** (67.9 mg, 140 µmol) and THF (1.0 mL) at room temperature. After stirring for 5 min, a solution of aldehyde **53** (19.6 mg, 40.3 µmol) and THF (1.0 mL) was added to the mixture of the ylide. The reaction vessel was removed from the glove box, and stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL), and extracted with EtOAc (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:3) to give methyl ester **55** (21.8 mg, 88%): a colorless oil; $[\alpha]^{26}_D$ +92.0 (*c* 1.00, $CHCl_3$); IR (film) 2926, 2856, 1738, 1695, 1631, 1437, 1249, 859, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.62–5.47 (m, 1H), 5.47–5.10 (m, 4H), 5.10–4.88 (m, 1H), 4.30–4.10 (m, 3H), 4.10–3.76 (m, 2H), 3.66 (s, 3H), 3.12 (dt, *J* = 14.4, 9.5 Hz, 1H), 3.00–2.76 (m, 2H), 2.76–2.38 (m, 3H), 2.64 (d, *J* = 13.5 Hz, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.34–1.86 (m, 10H), 1.85–1.52 (m, 5H), 1.50–1.18 (m, 7H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 174.2 (C), 173.4 (C), 156.8 (C), 137.1 (C), 130.3 (CH), 129.5 (CH), 129.2 (CH), 128.0 (CH), 125.7 (CH), 63.9 (CH_2), 51.4 (CH_3), 50.9 (CH_2), 49.2 (CH_2), 48.1 (CH), 44.7 (CH_2), 36.7 (C), 36.3 (CH_2), 36.1 (CH), 35.1 (CH), 34.4 (CH_2), 34.2 (CH_2), 32.9 (CH_2), 30.7 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 27.8 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 25.8 (CH_2), 25.1 (CH_2), 21.3 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{35}H_{57}N_2O_5Si^+$ $(M+H)^+$ 613.4037, found 613.4037.

Madangamine C (3): Aqueous LiOH (1 M, 0.6 mL) was added to a solution of ester **55** (21.8 mg, 35.6 µmol) and THF (1.2 mL). The mixture was heated to 60 °C, maintained for 5 h at that temperature, quenched with saturated aqueous NH_4Cl (1 mL) at room temperature, and extracted with EtOAc (2x 5 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1) to give carboxylic acid **76** (21.3 mg, 100%): a colorless oil; $[\alpha]^{26}_D$ +104 (*c* 1.00, $CHCl_3$); IR (film) 3141, 2925, 2855, 1696, 1631, 1590, 1439, 1249, 932, 859, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.66–5.48 (m, 1H), 5.48–5.10 (m, 4H), 5.10–4.90 (m, 1H), 4.34–4.10 (m, 3H), 4.10–3.74 (m, 2H), 3.11 (dt, *J* = 14.0, 9.2 Hz, 1H), 3.00–2.77 (m, 2H), 2.77–2.40 (m, 3H), 2.63 (d, *J* = 13.2 Hz, 1H), 2.38–2.25 (m, 3H), 2.24–1.86 (m, 9H), 1.86–1.56 (m, 5H), 1.54–1.15 (m, 7H), 1.02 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 176.7 (C), 173.9 (C), 156.9 (C), 136.8 (C), 130.4 (CH), 129.5 (CH), 129.2 (CH), 128.0 (CH), 126.0 (CH), 64.0 (CH_2), 51.0 (CH_2), 49.2 (CH_2), 48.2 (CH), 44.7 (CH_2), 36.8 (C), 36.3 (CH), 36.2 (CH_2), 35.1 (CH), 34.3 (CH_2), 34.1 (CH_2), 32.9 (CH_2), 30.7 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 25.8 (CH_2), 24.8 (CH_2), 21.3 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{34}H_{55}N_2O_5Si^+$ $(M+H)^+$599.3880, found 599.3878.

Tetrabutylammonium fluoride (1.0 M in THF, 160 µL, 160 µmol) was added to a solution of carboxylic acid **76** (23.4 mg, 39.1 µmol) and THF (3.9 mL) at room temperature. This solution was maintained for 5 h, and concentrated to give amino acid, which was immediately used in the next reaction without further purification.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 37.5 mg, 196 µmol) was added to a solution of the above amino acid, *i*Pr_2EtN (67 µL, 390 µmol), HOBt (26.6 mg, 196 µmol), and CH_2Cl_2 (39 mL) at room temperature. The solution was maintained for 24 h, quenched with saturated aqueous NH_4Cl (20 mL), and extracted with CH_2Cl_2 (2x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 3:1) to pentacyclic bislactam **77** (12.1 mg, 71% for 2 steps): a colorless oil; $[\alpha]^{26}_D$ +144 (*c* 1.00, $CHCl_3$); IR (film) 2925, 2856, 1628, 1446, 1270, 1247, 923, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (t, *J* = 7.8 Hz, 1H), 5.50 (td, *J* = 10.6, 4.3 Hz, 1H), 5.45–5.30 (m, 2H), 5.20 (td, *J* = 9.8, 4.3 Hz, 1H), 4.98 (brs, 1H), 4.45 (d, *J* = 13.8 Hz, 1H), 4.26 (d, *J* = 13.2 Hz, 1H), 3.59 (d, *J* = 13.7 Hz, 1H), 3.17 (dt, *J* = 14.6, 10.1 Hz, 1H), 2.93 (d, *J* = 13.7 Hz, 1H), 2.81 (d, *J* = 13.8 Hz, 1H), 2.76–2.66 (m, 2H), 2.59–2.21 (m, 7H), 2.20–1.48 (m, 13H), 1.48–1.10 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0 (C), 173.8 (C), 136.2 (C), 129.7 (CH), 129.5 (CH), 128.3 (CH), 128.0 (CH), 126.8 (CH), 52.5 (CH_2), 48.0 (CH), 46.4 (CH_2), 43.6 (CH_2), 39.7 (CH), 36.6 (C), 34.43 (CH), 34.36 (CH_2), 34.1 (CH_2), 33.7 (CH_2), 32.5 (CH_2), 30.3 (CH_2), 28.2 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 25.0 (CH_2), 23.3 (CH_2), 22.9 (CH_2), 21.7 (CH_2); HRMS (ESI), calcd for $C_{28}H_{41}N_2O_2^+$ $(M+H)^+$ 437.3168, found 437.3167.

In a glove box, $LiAlH_4$ (1.0 M in THF, 140 µL, 140 µmol) was added to a solution of pentacyclic bislactam **77** (6.3 mg, 14 µmol) and THF (1.4 mL) at room temperature. The reaction vessel was removed from the glove box, stirred at room temperature for 6 h, cooled to 0 °C, and quenched with a few drops of distilled water. The resulting suspension was dried over Na_2SO_4, and filtrated. The solid was washed with Et_2O (3 mL). The resulting filtrate was then concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:19 to 1:5) to give madangamine C (**3**) (4.5 mg, 76%): a colorless oil; $[\alpha]^{26}_D$ +133 (*c* 0.09, EtOAc); IR (film) 2928, 2857, 1458, 1438, 1126, 722, 685, 497 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 65 °C) δ 5.49–5.35 (m, 3H), 5.20 (dt, *J* = 11.5, 3.2 Hz, 1H), 5.23–5.13 (m, 1H), 3.72 (t, *J* = 3.2 Hz, 1H), 3.42 (dd, *J* = 12.1, 1.2 Hz, 1H), 3.35 (dt, *J* = 13.5, 11.5 Hz, 1H), 3.13 (ddt, *J* = 16.3, 12.1, 3.2 Hz, 1H), 2.83 (ddd, *J* = 13.8, 11.8, 5.2 Hz, 1H), 2.74 (dd, *J* = 12.1, 1.7 Hz, 1H), 2.73 (ddd, *J* = 12.0, 3.7, 2.0 Hz, 1H), 2.68 (d, *J* = 12.1 Hz, 1H), 2.60 (td, *J* = 13.8, 4.3 Hz, 1H), 2.36 (dt, *J* = 12.6, 3.2 Hz, 1H), 2.33 (d, *J* = 10.9 Hz, 1H), 2.36–2.01 (m, 9H), 2.16 (dd, *J* = 10.9, 3.5 Hz, 1H), 1.89–1.78 (m, 2H), 1.76–1.57 (m, 3H), 1.57–1.07 (m, 10H), 1.53 (d, *J* = 12.1 Hz, 1H), 1.27 (dt, *J* = 12.6, 3.2 Hz, 1H), 0.90 (ddt, *J* = 12.0, 9.5, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6, 65 °C) δ 139.2 (C), 133.8 (CH), 129.2 (CH), 129.2 (CH), 129.1 (CH), 122.0 (CH), 63.4 (CH_2), 62.7 (CH_2), 56.2 (CH_2), 55.6 (CH_2), 53.7 (CH_2), 51.6 (CH), 40.0 (CH), 38.6 (CH_2), 38.2 (C), 37.4 (CH), 36.3 (CH_2), 32.1 (CH_2), 30.2 (CH_2), 28.0 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 25.5 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 23.4 (CH_2); HRMS (ESI), calcd for $C_{28}H_{45}N_2^+$ $(M+H)^+$ 409.3583, found 409.3585.

Bromide (56): Carbon tetrabromide (17.6 mg, 531 µmol) was added to a solution of alcohol **11** (17.3 mg, 35.4 µmol), PPh_3 (13.9 mg, 53.1 µmol) and CH_2Cl_2 (1.2 mL) at room

temperature. The solution was maintained for 1 h, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:3) to give bromide **56** (17.4 mg, 89%): a colorless oil; $[\alpha]^{22}_D$ +86.7 (*c* 1.00, $CHCl_3$); IR (film) 2950, 2916, 1693, 1627, 1438, 1248, 858, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.65–5.50 (m, 1H), 5.48–5.33 (m, 1H), 5.33–5.15 (m, 1H), 5.14–4.94 (m, 1H), 4.30–4.10 (m, 3H), 4.08–3.95 (m, 1H), 3.94–3.80 (m, 1H), 3.45–3.35 (m, 1H), 3.33–3.25 (m, 1H), 3.12 (ddd, *J* = 14.6, 9.8, 9.2 Hz, 1H), 2.96–2.78 (m, 2H), 2.76–2.64 (m, 1H), 2.64–2.40 (m, 3H), 2.36–1.64 (m, 10H), 1.59–1.34 (m, 4H), 1.02 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.4 (C), 156.7 (C), 136.8 (C), 129.1 (CH), 128.0 (CH), 126.1 (CH), 64.0 (CH_2), 50.9 (CH_2), 49.2 (CH_2), 48.1 (CH), 44.2 (CH_2), 36.6 (C), 36.5 (CH), 34.9 (CH), 34.8 (CH_2), 34.23 (CH_2), 34.17 (CH_2), 32.7 (CH_2), 30.6 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 25.7 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{27}H_{44}N_2O_3SiBr^+$ $(M+H)^+$ 551.2305, found 551.2304.

Tosylate (58): A 30 mL flask equipped with a rubber septa connected to a bubbler was charged with magnesium (turnings, 41.5 mg, 1.71 mmol) and THF. ((7-Bromoheptyl)oxy)-triisopropylsilane **78** (333 mg, 948 µmol) was added to the mixture at room temperature over a period of 5 min. The resulting mixture was stirred vigorously for 1 h. The concentration of the resulting Grignard reagent **57** was determined as 0.26 M by titration with 1,10-phenanthroline method.[33]

A 20 mL flask was charged with copper (II) chloride (2.1 mg, 16 µmol) and LiCl (1.3 mg, 32 µmol). The reagent was heated under reduced pressure until blue copper (II) chloride became orange. A solution of bromide **56** (17.4 mg, 31.5 µmol) and THF (3.2 mL) was added to the solids via cannula at room temperature. The solution of Grignard reagent **57** (0.26 M in THF, 910 µL, 240 µmol) was then added to the resulting solution at room temperature. The solution was maintained for 30 min at room temperature, and quenched with saturated aqueous NH_4Cl (3 mL). The resulting mixture was extracted with EtOAc (2x 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:12) to give alkylation product **79** (20.5 mg, 88%): a colorless oil; $[\alpha]^{23}_D$ +85.8 (*c* 1.00, $CHCl_3$); IR (film) 2927, 2863, 1698, 1633, 1462, 1438, 1249, 1105, 859, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.60–5.48 (m, 1H), 5.48–5.35 (m, 1H), 5.35–5.12 (m, 1H), 5.10–4.90 (m, 1H), 4.25–4.10 (m, 3H), 4.06–3.92 (m, 1H), 3.92–3.75 (m, 1H), 3.69 (t, *J* = 6.6 Hz, 2H), 3.13 (ddd, *J* = 13.6, 10.5, 9.2 Hz, 1H), 2.96–2.77 (m, 2H), 2.77–2.65 (m, 1H), 2.61 (d, *J* = 13.2 Hz, 1H), 2.64–2.37 (m, 2H), 2.36–2.23 (m, 1H), 2.23–1.90 (m, 5H), 1.87–1.75 (m, 1H), 1.75–1.66 (m, 1H), 1.54 (tt, *J* = 6.9, 6.6 Hz, 2H), 1.50–1.14 (m, 18H), 1.12–1.05 (m, 21H), 1.02 (t, *J* = 8.6 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.5 (C), 156.8 (C), 137.2 (C), 129.2 (CH), 128.0 (CH), 125.6 (CH), 63.9 (CH_2), 63.7 (CH_2), 51.0 (CH_2), 49.2 (CH_2), 48.1 (CH), 45.1 (CH_2), 36.6 (C), 36.4 (CH_2), 36.0 (CH), 35.2 (CH), 34.4 (CH_2), 33.3 (CH_2), 32.9 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 29.71 (CH_2), 29.66 (CH_2), 29.62 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 23.2 (CH_2), 18.2 (CH_3, CH_2), 12.4 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{43}H_{79}N_2O_4Si_2^+$ $(M+H)^+$ 743.5578, found 743.5580.

10-Camphorsulfonic acid (CSA, 17.6 mg, 75.9 µmol) was added to a solution of alkylation product **79** (28.2 mg, 37.9 µmol) and MeOH (1.3 mL) at room temperature. The solution was heated to 40 °C, maintained for 1 h at 40 °C, quenched with Et_3N (21 µL, 150 µmol) at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:1) to give alcohol **80** (21.1 mg, 95%): a colorless oil; $[\alpha]^{27}_D$ +90.4 (*c* 1.00, $CHCl_3$); IR (film) 3421, 2927, 2854, 1695, 1616, 1437, 1248, 859, 838, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.64–5.46 (m, 1H), 5.46–5.34 (m, 1H), 5.34–5.12 (m, 1H), 5.08–4.84 (m, 1H), 4.26–4.10 (m, 3H), 4.08–3.92 (m, 1H), 3.92–3.74 (m, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.12 (ddd, *J* = 13.5, 10.1, 9.7 Hz, 1H), 2.98–2.76 (m, 2H), 2.76–2.64 (m, 1H), 2.60 (d, *J* = 13.5 Hz, 1H), 2.64–2.36 (m, 2H), 2.35–2.22 (m, 1H), 2.22–1.90 (m, 5H), 1.87–1.74 (m, 1H), 1.73–1.64 (m, 1H), 1.57 (tt, *J* = 7.2, 6.6 Hz, 2H), 1.45–1.10 (m, 18H), 1.02 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.5 (C), 156.8 (C), 137.1 (C), 129.2 (CH), 128.0 (CH), 125.6 (CH), 63.9 (CH_2), 63.1 (CH_2), 51.0 (CH_2), 49.1 (CH_2), 48.1 (CH), 45.0 (CH_2), 36.6 (C), 36.3 (CH_2), 36.1 (CH), 35.1 (CH), 34.5 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 30.6 (CH_2), 30.4 (CH_2), 29.6 (CH_2), 29.52 (CH_2), 29.52 (CH_2), 29.46 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 23.2 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{34}H_{59}N_2O_4Si^+$ $(M+H)^+$ 587.4244, found 587.4244.

p-Toluenesulfonyl chloride (13.7 mg, 71.8 µmol) was added to a solution of alcohol **80** (21.1 mg, 35.9 µmol), Et_3N (20 µL, 140 µmol), DMAP (0.9 mg, 7.2 µmol) and CH_2Cl_2 (1.2 mL) at room temperature. The solution was maintained at room temperature for 15 h, and quenched with saturated aqueous NH_4Cl (3 mL). The resulting mixture was extracted with CH_2Cl_2 (2x 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:12 to 1:1) to give tosylate **58** (23.9 mg, 90%): a colorless oil; $[\alpha]^{25}_D$ +84.9 (*c* 1.00, $CHCl_3$); IR (film) 2927, 2856, 1693, 1612, 1441, 1358, 1249, 1176, 925, 838, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 5.62–5.46 (m, 1H), 5.46–5.33 (m, 1H), 5.33–5.10 (m, 1H), 5.10–4.84 (m, 1H), 4.25–4.10 (m, 3H), 4.03 (t, *J* = 6.6 Hz, 2H), 4.06–3.91 (m, 1H), 3.90–3.72 (m, 1H), 3.12 (ddd, *J* = 13.8, 9.8, 9.2 Hz, 1H), 3.00–2.76 (m, 2H), 2.76–2.64 (m, 1H), 2.59 (d, *J* = 13.5 Hz, 1H), 2.64–2.48 (m, 2H), 2.44 (s, 3H), 2.34–2.21 (m, 1H), 2.21–1.90 (m, 5H), 1.86–1.73 (m, 1H), 1.72–1.67 (m, 1H), 1.63 (tt, *J* = 6.9, 6.6 Hz, 2H), 1.45–1.10 (m, 18H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.5 (C), 156.8 (C), 144.6 (C), 137.2 (C), 134.0 (C), 129.9 (CH), 129.2 (CH), 128.0 (CH), 128.0 (CH), 125.6 (CH), 70.8 (CH_2), 63.9 (CH_2), 51.0 (CH_2), 49.2 (CH_2), 48.1 (CH), 45.0 (CH_2), 36.6 (C), 36.3 (CH_2), 36.1 (CH), 35.1 (CH), 34.5 (CH_2), 32.9 (CH_2), 32.9 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 29.55 (CH_2), 29.45 (CH_2), 29.09 (CH_2), 29.05 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 23.2 (CH_2), 21.7 (CH_3), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{41}H_{65}N_2O_6SiS^+$ $(M+H)^+$ 741.4333, found 741.4329.

Madangamine E (5): Boron trifluoride ethyl ether complex (10 µL, 76 µmol) was added to a solution of tosylate **58** (11.2 mg, 15.1 µmol) and CH_2Cl_2 (1.5 mL) at room temperature. The solution was maintained for 30 min, quenched with Et_3N (21 µL, 150 µmol) at room temperature. The solution was concentrated to give the corresponding amine, which was immediately used in the next step without further purification.
Potassium carbonate (10.4 mg, 75.5 µmol) was added to a solution of the above amine and MeCN (15 mL) at room temperature. The resulting solution was heated to 80 °C, maintained for 80 h at 80 °C, and concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:9 to 1:2) to give macrocyclic amine **81** (3.9 mg, 61% for 2 steps): a colorless oil; $[\alpha]^{27}_D$ –9.1 (*c* 0.50, EtOAc); IR (film) 2925, 2856, 1629, 1447, 678 cm^{-1}; ^1H NMR (500

MHz, C_6D_6, 1.4:1 mixture of rotamers) δ 5.87–5.79 (m, 5/12H), 5.44–5.17 (m, 3H), 4.74–4.67 (m, 7/12H), 4.55 (d, *J* = 14.0 Hz, 7/12H), 3.40 (ddd, *J* = 14.9, 10.6, 10.0 Hz, 5/12H), 3.23 (d, *J* = 14.0 Hz, 7/12H), 3.16 (d, *J* = 13.5 Hz, 5/12H), 3.13–3.02 (m, 5/12H), 2.81 (ddd, *J* = 14.6, 9.5, 8.9 Hz, 7/12H), 2.69 (d, *J* = 13.5 Hz, 5/12H), 2.72–2.61 (m, 7/12H), 2.50–1.10 (m, 36H); ^{13}C NMR (125 MHz, C_6D_6, mixture of two rotamers) δ 172.1 (C), 169.7 (C), 138.9 (C), 137.4 (C), 129.3 (CH), 129.0–127.0 (CH x3), 126.4 (CH), 124.8 (CH), 60.4 (CH_2), 59.4 (CH_2), 59.3 (CH_2), 58.8 (CH_2), 57.5 (CH_2), 57.2 (CH_2), 52.2 (CH_2), 48.6 (CH), 46.3 (CH_2), 44.9 (CH), 36.9 (C), 36.7 (C), 35.9 (CH_2), 35.8 (CH_2), 35.2 (CH), 35.0 (CH_2), 34.6 (CH), 33.0 (CH_2), 32.7 (CH), 31.7 (CH_2), 30.1 (CH_2), 28.8 (CH_2), 28.4 (CH), 27.9 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 27.14 (CH_2), 27.08 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 25.04 (CH_2), 24.97 (CH_2), 24.87 (CH_2), 24.65 (CH_2), 24.56 (CH_2), 24.4 (CH_2), 23.7 (CH_2), 23.2 (CH_2), 22.1 (CH_2), 20.7 (CH_2); HRMS (ESI), calcd for $C_{28}H_{45}N_2O^+$ $(M+H)^+$ 425.3532, found 425.3532.

In a glove box, $LiAlH_4$ (1.0 M in THF, 74 µL, 74 µmol) was added to a solution of macrocyclic amine **81** (6.3 mg, 15 µmol) and THF (1.5 mL) at room temperature. The reaction vessel was removed from the glove box, stirred at room temperature for 8 h, cooled to 0 °C, and quenched with a few drops of distilled water. The resulting suspension was dried over Na_2SO_4, and filtrated. The solid was washed with Et_2O (3 mL). The resulting filtrate was then concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:19 to 1:5) to give madangamine E (**5**) (4.2 mg, 69%): a colorless oil; $[\alpha]^{22}_D$ +90.9 (*c* 0.40, EtOAc); IR (film) 2925, 2853, 1458, 1445, 1350, 1129, 1116, 923, 862, 722 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.46 (td, *J* = 10.9, 4.3 Hz, 1H), 5.41 (tdd, *J* = 10.9, 6.3, 1.4 Hz, 1H), 5.20 (dt, *J* = 11.5, 2.6 Hz, 1H), 3.71 (t, *J* = 2.9 Hz, 1H), 3.34 (dt, *J* = 13.5, 11.5 Hz, 1H), 3.30 (d, *J* = 12.1 Hz, 1H), 3.02 (ddt, *J* = 15.8, 12.6, 2.6 Hz, 1H), 2.85 (ddd, *J* = 13.7, 11.7, 5.4 Hz, 1H), 2.63 (m, 1H), 2.58 (d, *J* = 12.0 Hz, 1H), 2.70–2.56 (m, 1H), 2.46 (d, *J* = 12.1 Hz, 1H), 2.36 (dt, *J* = 12.0, 2.9 Hz, 1H), 2.25 (m, 1H), 2.39–2.20 (m, 4H), 2.12 (ddd, *J* = 12.9, 4.6, 3.7 Hz, 1H), 1.95–1.74 (m, 4H), 1.83 (d, *J* = 12.0 Hz, 1H), 1.72–1.61 (m, 1H), 1.61–1.09 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.1 (C), 129.1 (CH), 129.0 (CH), 122.1 (CH), 62.3 (CH_2), 60.1 (CH_2), 57.4 (CH_2), 56.3 (CH_2), 55.3 (CH_2), 51.8 (CH), 39.0 (CH_2), 37.0 (C), 36.6 (CH), 36.5 (CH), 35.4 (CH_2), 32.2 (CH_2), 27.3 (CH_2), 27.1 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 25.11 (CH_2), 25.09 (CH_2), 24.81 (CH_2), 24.76 (CH_2), 24.2–23.4 (CH_2, br), 22.8 (CH_2); HRMS (ESI), calcd for $C_{28}H_{47}N_2^+$ $(M+H)^+$ 411.3739, found 411.3743.

Tosylate (60): A 30 mL flask equipped with a rubber septa connected to a bubbler was charged with magnesium (turnings, 60.0 mg, 2.47 mmol) and THF. ((8-bromooctyl)-oxy)triisopropylsilane[34] (500 mg, 1.37 mmol) was added to the mixture at room temperature over a period of 5 min. The resulting mixture was stirred vigorously for 1 h. The concentration of the resulting Grignard reagent **59** was determined as 0.26 M by titration with 1,10-phenanthroline method.[33]

A 30 mL flask was charged with copper (II) chloride (49.2 mg, 364 µmol) and LiCl (30.8 mg, 727 µmol). The reagent was heated under reduced pressure until blue copper (II) chloride became orange. A solution of bromide **56** (40.1 mg, 72.7 µmol) and THF (3.6 mL) was added to copper (II) chloride via cannula at room temperature. The solution of Grignard reagent **59** (0.26 M in THF, 840 µL, 220 µmol) was then added to the resulting solution at room temperature. The solution of the Grignard reagent was added until TLC analysis indicated the complete consumption of bromide **56** (total: 2.5 mL). The resulting solution was maintained for 30 min at room temperature, quenched with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (2x 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:12) to give TIPS ether **82** (46.3 mg, 84%): a colorless oil; $[\alpha]^{22}_D$ +80.2 (*c* 1.00, $CHCl_3$); IR (film) 2927, 2863, 1698, 1633, 1463, 1437, 1249, 1105, 859, 838, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.60–5.48 (m, 1H), 5.46–5.34 (m, 1H), 5.32–5.12 (m, 1H), 5.10–4.90 (m, 1H), 4.25–4.10 (m, 3H), 4.08–3.91 (m, 1H), 3.90–3.75 (m, 1H), 3.68 (t, *J* = 6.6 Hz, 2H), 3.12 (ddd, *J* = 14.9, 10.0, 8.3 Hz, 1H), 2.93–2.76 (m, 2H), 2.75–2.37 (m, 3H), 2.60 (d, *J* = 13.8 Hz, 1H), 2.36–1.90 (m, 6H), 1.86–1.75 (m, 1H), 1.74–1.65 (m, 1H), 1.57–1.50 (m, 2H), 1.45–1.15 (m, 20H), 1.12–1.04 (m, 21H), 1.02 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.5 (C), 156.9 (C), 137.2 (C), 129.3 (CH), 128.0 (CH), 125.6 (CH), 63.9 (CH_2), 63.8 (CH_2), 51.0 (CH_2), 49.2 (CH_2), 48.1 (CH), 45.1 (CH_2), 36.6 (C), 36.4 (CH_2), 36.0 (CH), 35.2 (CH), 34.5 (CH_2), 33.3 (CH_2), 32.9 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 29.82 (CH_2), 29.78 (CH_2), 29.76 (CH_2), 29.71 (CH_2), 29.66 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 23.3 (CH_2), 18.2–18.0 (CH_2, CH_3), 12.4 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{44}H_{81}N_2O_4Si_2^+$ $(M+H)^+$ 757.5735, found 757.5732.

10-Camphorsulfonic acid (CSA, 28.5 mg, 123 µmol) was added to a solution of TIPS ether **82** (46.4 mg, 61.3 µmol) and MeOH (2.0 mL) at room temperature. The solution was heated to 40 °C, maintained for 3 h at 40 °C, quenched with Et_3N (40 µL, 310 µmol) at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:1) to give alcohol **83** (28.7 mg, 78%): a colorless oil; $[\alpha]^{22}_D$ +110 (*c* 1.00, $CHCl_3$); IR (film) 3423, 2926, 2854, 1695, 1613, 1438, 1248, 859, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.60–5.48 (m, 1H), 5.46–5.34 (m, 1H), 5.34–5.12 (m, 1H), 5.10–4.90 (m, 1H), 4.26–4.10 (m, 3H), 4.07–3.91 (m, 1H), 3.90–3.75 (m, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.12 (ddd, *J* = 14.4, 10.0, 9.2 Hz, 1H), 2.93–2.76 (m, 2H), 2.75–2.37 (m, 3H), 2.60 (d, *J* = 13.5 Hz, 1H), 2.34–1.90 (m, 6H), 1.87–1.74 (m, 1H), 1.74–1.66 (m, 1H), 1.57 (tt, *J* = 7.2, 6.9 Hz, 2H), 1.45–1.10 (m, 20H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.5 (C), 156.9 (C), 137.2 (C), 129.3 (CH), 128.0 (CH), 125.6 (CH), 63.9 (CH_2), 63.2 (CH_2), 51.0 (CH_2), 49.2 (CH_2), 48.1 (CH), 45.0 (CH_2), 36.6 (C), 36.4 (CH_2), 36.1 (CH), 35.2 (CH), 34.5 (CH_2), 33.1 (CH_2), 32.9 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 29.7 (CH_2 x2), 29.62 (CH_2), 29.60 (CH_2), 29.54 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 23.2 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{35}H_{61}N_2O_4Si^+$ $(M+H)^+$ 601.4401, found 601.4405.

p-Toluenesulfonyl chloride (19.1 mg, 100 µmol) was added to a solution of alcohol **83** (30.1 mg, 50.1 µmol), Et_3N (28 µL, 200 µmol), DMAP (1.2 mg, 10.0 µmol) and CH_2Cl_2 (1.0 mL) at room temperature. The solution was maintained at room temperature for 15 h, and quenched with saturated aqueous NH_4Cl (1 mL). The resulting mixture was extracted with CH_2Cl_2 (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:12 to 1:1) to give tosylate **60** (32.3 mg, 85%): a colorless oil; $[\alpha]^{22}_D$ +84.4 (*c* 1.00, $CHCl_3$); IR (film) 2926, 2854, 1694, 1629, 1437, 1361, 1248, 1176, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 5.60–5.48 (m, 1H), 5.48–5.34 (m, 1H), 5.34–5.14 (m, 1H), 5.10–4.90 (m, 1H), 4.27–4.10 (m, 3H), 4.04

(t, *J* = 6.6 Hz, 2H), 4.08–3.91 (m, 1H), 3.91–3.75 (m, 1H), 3.12 (ddd, *J* = 13.5, 10.1, 9.5 Hz, 1H), 2.94–2.76 (m, 2H), 2.76–2.38 (m, 3H), 2.60 (d, *J* = 13.7 Hz, 1H), 2.45 (s, 3H), 2.34–1.90 (m, 6H), 1.88–1.74 (m, 1H), 1.74–1.68 (m, 1H), 1.64 (tt, *J* = 6.9, 6.6 Hz, 2H), 1.45–1.10 (m, 20H), 1.02 (t, *J* = 8.6 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.5 (C), 156.8 (C), 144.6 (C), 137.1 (C), 134.0 (C), 129.9 (CH), 129.3 (CH), 128.0 (CH x2), 125.6 (CH), 70.8 (CH_2), 63.9 (CH_2), 51.0 (CH_2), 49.2 (CH_2), 48.1 (CH), 45.0 (CH_2), 36.6 (C), 36.4 (CH_2), 36.1 (CH), 35.2 (CH), 34.5 (CH_2), 32.9 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 29.7 (CH_2), 29.63 (CH_2), 29.59 (CH_2), 29.50 (CH_2), 29.11 (CH_2), 29.10 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 23.2 (CH_2), 21.7 (CH_3), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{42}H_{67}N_2O_6SiS^+$ $(M+H)^+$ 755.4489, found 755.4461.

Madangamine D (4): Boron trifluoride ethyl ether complex (22 µL, 170 µmol) was added to a solution of tosylate **60** (32.3 mg, 42.8 µmol) and CH_2Cl_2 (4.3 mL) at room temperature. The solution was maintained for 30 min, quenched with Et_3N (24 µL, 170 µmol) at room temperature. The solution was concentrated to give the corresponding secondary amine, which was immediately used in the next step without further purification.

Potassium carbonate (59.2 mg, 428 µmol) was added to a solution of the above secondary amine and MeCN (43 mL) at room temperature. The resulting solution was heated to 80 °C, maintained for 72 h at 80 °C, and concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:9 to 1:2) to give macrocyclic amine **84** (15.9 mg, 85% for 2 steps): a colorless oil; $[\alpha]^{24}_D$ +55.1 (*c* 1.00, $CHCl_3$); IR (film) 2926, 2856, 1630, 1446, 678 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 3.4:1 mixture of rotamers, signals of the major rotamer are reported) δ 5.45–5.16 (m, 3H), 4.77–4.68 (m, 1H), 4.57 (d, *J* = 14.1 Hz, 1H), 3.35 (d, *J* = 14.1 Hz, 1H), 3.02–2.80 (m, 2H), 2.61 (d, *J* = 11.5 Hz, 1H), 2.64–2.52 (m, 1H), 2.45–2.33 (m, 2H), 2.32–2.14 (m, 4H), 2.12–1.81 (m, 4H), 1.77 (d, *J* = 11.5 Hz, 1H), 1.75–1.66 (m, 2H), 1.66–1.56 (m, 2H), 1.52–0.95 (m, 20H), 0.87–0.78 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6, mixture of two rotamers, signals of the major rotamer are reported) δ 172.4 (C), 139.0 (C), 129.2 (CH), 129.0–127.0 (CH), 124.4 (CH), 60.1 (CH_2), 59.3 (CH_2), 57.1 (CH_2), 48.2 (CH), 44.7 (CH_2), 37.2 (C), 37.1 (CH), 35.9–35.7 (CH, CH_2), 35.0 (CH_2), 32.3 (CH_2), 30.7 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.0 (CH_2), 24.7 (CH_2), 21.4 (CH_2); HRMS (ESI), calcd for $C_{29}H_{47}N_2O^+$ $(M+H)^+$ 439.3688, found 439.3672.

In a glove box, $LiAlH_4$ (1.0 M in THF, 160 µL, 160 µmol) was added to a solution of macrocyclic amine **84** (14.3 mg, 32.6 µmol) and THF (1.6 mL) at room temperature. The reaction vessel was removed from the glove box, stirred at room temperature for 8 h, cooled to 0 °C, and quenched with a few drops of distilled water. The resulting suspension was dried over Na_2SO_4, and filtrated. The solid was washed with Et_2O (3 mL). The resulting filtrate was then concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:19 to 1:5) to give madangamine D (**4**) (11.1 mg, 80%): a colorless oil; $[\alpha]^{25}_D$ +96.3 (*c* 0.29, $CHCl_3$); IR (film) 2925, 2855, 1460, 1443 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.47 (td, *J* = 10.9, 4.0 Hz, 1H), 5.41 (tdd, *J* = 10.9, 6.3, 1.5 Hz, 1H), 5.20 (dt, *J* = 11.5, 2.9 Hz, 1H), 3.71 (t, *J* = 3.7 Hz, 1H), 3.34 (dt, *J* = 13.5, 11.5 Hz, 1H), 3.31 (d, *J* = 11.8 Hz, 1H), 3.10 (ddt, *J* = 16.1, 12.6, 2.6 Hz, 1H), 2.84 (ddd, *J* = 13.8, 12.1, 5.8 Hz, 1H), 2.70 (d, *J* = 10.9 Hz, 1H), 2.68 (ddd, *J* = 12.6, 8.6, 3.5 Hz, 1H), 2.72–2.59 (m, 1H), 2.45 (d, *J* = 11.8 Hz, 1H), 2.39 (dt, *J* = 12.3, 3.7 Hz, 1H), 2.37–2.21 (m, 6H), 2.20 (dd, *J* = 10.9, 3.5 Hz, 1H), 1.88–1.78 (m, 2H), 1.81 (d, *J* = 10.9 Hz, 1H), 1.78–1.72 (m, 1H), 1.72–1.65 (m, 1H), 1.50–1.10 (m, 22H), 1.01 (dt, *J* = 13.5, 4.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.2 (C), 129.1 (CH), 129.0 (CH), 122.0 (CH), 61.0 (CH_2), 59.6 (CH_2), 57.4 (CH_2), 56.3 (CH_2), 54.0 (CH_2), 51.8 (CH), 38.5 (CH_2), 37.7 (CH), 37.5 (C), 36.8 (CH), 35.7 (CH_2), 32.2 (CH_2), 30.2 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 26.14 (CH_2), 26.05 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 24.6 (CH_2), 21.6 (CH_2); HRMS (ESI), calcd for $C_{29}H_{49}N_2^+$ $(M+H)^+$ 425.3896, found 425.3883.

Alcohol (62): In a glove box, sodium hexamethyldisilazide (21.1 mg, 115 µmol) was added to a mixture of phosphonium salt **61** (75.4 mg, 118 µmol) and THF (1.0 mL) at room temperature. After stirring for 5 min, a solution of aldehyde **53** (12.7 mg, 26.1 µmol) and THF (2.0 mL) was added to the mixture of the ylide. The reaction vessel was then removed from the glove box, and stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL), and extracted with EtOAc (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:5) to give pentaene, which was immediately used in the next reaction without further purification.

10-Camphorsulfonic acid (CSA, 10.6 mg, 45.8 µmol) was added to a solution of the above pentaene and MeOH (1.1 mL) at room temperature. The solution was heated to 40 °C, maintained for 1 h at 40 °C, quenched with Et_3N (13 µL, 92 µmol) at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:2) to give alcohol **62** (10.9 mg, 69% for 2 steps): a colorless oil; $[\alpha]^{23}_D$ +109 (*c* 1.00, $CHCl_3$); IR (film) 3426, 2949, 2921, 1694, 1611, 1440, 1248, 1049, 858, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.60–5.48 (m, 2H), 5.46–5.20 (m, 7H), 5.10–4.90 (m, 1H), 4.36–4.12 (m, 3H), 4.10–3.80 (m, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 3.12 (ddd, *J* = 13.8, 10.3, 9.8 Hz, 1H), 2.87 (dd, *J* = 6.3, 6.0 Hz, 2H), 2.95–2.75 (m, 4H), 2.73–2.60 (m, 1H), 2.63 (d, *J* = 13.5 Hz, 1H), 2.60–2.42 (m, 2H), 2.38 (dt, *J* = 6.9, 6.9 Hz, 2H), 2.30–2.22 (m, 1H), 2.22–1.90 (m, 7H), 1.86–1.74 (m, 1H), 1.74–1.65 (m, 1H), 1.62–1.47 (m, 2H), 1.45–1.36 (m, 1H), 1.30–1.16 (m, 1H), 1.02 (t, *J* = 8.6 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.6 (C), 156.8 (C), 137.0 (C), 130.9 (CH), 129.8 (CH), 129.2 (CH), 128.5 (CH), 128.5 (CH), 128.38 (CH), 128.0 (CH), 126.1 (CH), 125.9 (CH), 64.0 (CH_2), 62.4 (CH_2), 51.0 (CH_2), 49.2 (CH_2), 48.1 (CH), 44.4 (CH_2), 36.8 (C), 36.6 (CH), 36.2 (CH_2), 35.2 (CH), 34.4 (CH_2), 32.9 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 21.4 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{36}H_{57}N_2O_4Si^+$ $(M+H)^+$ 609.4088, found 609.4081.

Madangamine A (1): *p*-Toluenesulfonyl chloride (27.9 mg, 146 µmol) was added to a solution of alcohol **62** (44.5 mg, 73.1 µmol), Et_3N (41 µL, 290 µmol), DMAP (1.8 mg, 15 µmol) and CH_2Cl_2 (1.5 mL) at room temperature. The solution was maintained at room temperature for 15 h, and quenched with saturated aqueous NH_4Cl (1 mL). The resulting mixture was extracted with CH_2Cl_2 (2x 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:2) to give tosylate **85** (55.7 mg, 100%): a colorless oil; $[\alpha]^{27}_D$ +86.5 (*c* 1.00, $CHCl_3$); IR (film) 2951, 2921, 1693, 1627, 1439, 1361, 1248, 1176, 959, 913, 859, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 5.62–5.18 (m, 9H), 5.10–4.90 (m, 1H), 4.30–4.11 (m, 3H), 4.04 (t, *J* = 6.9 Hz, 2H), 4.07–3.94 (m, 1H), 3.94–3.76 (m, 1H), 3.12 (ddd, *J* = 14.6, 9.8,

9.2 Hz, 1H), 2.96–2.80 (m, 2H), 2.80–2.72 (m, 4H), 2.72–2.60 (m, 1H), 2.64 (d, *J* = 13.8 Hz, 1H), 2.60–2.50 (m, 3H), 2.44 (s, 3H), 2.50–2.37 (m, 1H), 2.32–2.21 (m, 1H), 2.20–1.86 (m, 7H), 1.85–1.75 (m, 1H), 1.74–1.62 (m, 1H), 1.51–1.37 (m, 2H), 1.36–1.20 (m, 2H), 1.01 (t, *J* = 8.6 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.4 (C), 156.8 (C), 144.8 (C), 137.0 (C), 134.0 (C), 131.9 (CH), 130.02 (CH), 129.95 (CH), 129.3 (CH), 128.9 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.8 (CH), 125.8 (CH), 123.6 (CH), 69.7 (CH_2), 63.9 (CH_2), 50.9 (CH_2), 49.2 (CH_2), 48.1 (CH), 44.7 (CH_2), 36.7 (C), 36.1 (CH), 36.1 (CH), 35.1 (CH), 34.4 (CH_2), 32.9 (CH_2), 30.7 (CH_2), 27.8 (CH_2), 27.5 (CH_2), 26.5 (CH_2), 25.94 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 21.7 (CH_3), 21.4 (CH_2), 18.2 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{43}H_{63}N_2O_6SiS^+$ $(M+H)^+$ 763.4176, found 763.4177.

Boron trifluoride ethyl ether complex (18 µL, 140 µmol) was added to a solution of tosylate **85** (21.4 mg, 28.0 µmol) and CH_2Cl_2 (2.8 mL) at room temperature. The solution was maintained for 30 min, and quenched with *N*,*N*-diisopropylethylamine (48 µL, 280 µmol) at room temperature. The solution was concentrated to give the corresponding amine, which was immediately used in the next step without further purification.

N,*N*-Diisopropylethylamine (24 µL, 140 µmol) was added to a solution of the above amine and MeCN (28 mL) at room temperature. The resulting solution was heated to 70 °C, maintained for 20 h at this temperature, and then concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:9 to 1:2) to give macrocyclic amine **86** (7.4 mg, 59% for 2 steps): a colorless oil; $[\alpha]^{28}_D$ +80.3 (*c* 1.00, EtOAc); IR (film) 2918, 1627, 1446, 1417, 701 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.70–5.59 (m, 1H), 5.53–5.12 (m, 8H), 4.73 (brs, 1H), 4.70 (d, *J* = 14.1 Hz, 1H), 3.26 (d, *J* = 14.1 Hz, 1H), 3.20–2.78 (m, 6H), 2.74 (d, *J* = 11.2 Hz, 1H), 2.70–2.54 (m, 1H), 2.54–1.84 (m, 13H), 1.91 (ddd, *J* = 13.2, 3.5, 3.5 Hz, 1H), 1.82–1.50 (m, 3H), 1.58 (d, *J* = 11.2 Hz, 1H), 1.50–1.20 (m, 1H), 1.20–1.14 (m, 1H), 1.10 (d, *J* = 13.2 Hz, 1H), 0.94–0.82 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.2 (C), 138.8 (C), 131.9 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.5–127.6 (CH x3), 127.2 (CH), 124.7 (CH), 60.8 (CH_2), 58.7 (CH_2), 58.4 (CH_2), 48.0 (CH), 44.6 (CH_2), 38.9 (CH), 36.8 (C), 36.1 (CH), 35.8 (CH), 35.4 (CH_2), 32.6 (CH_2), 30.8 (CH_2), 28.1 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.2 (CH_2), 23.0 (CH_2); HRMS (ESI), calcd for $C_{30}H_{43}N_2O^+$ $(M+H)^+$ 447.3375, found 447.3375.

In a glove box, $LiAlH_4$ (1.0 M in THF, 160 µL, 160 µmol) was added to a solution of macrocyclic amine **86** (14.0 mg, 31.3 µmol) and THF (1.6 mL) at room temperature. The reaction vessel was removed from the glove box, stirred at room temperature for 6 h, cooled to 0 °C, and quenched with a few drops of distilled water. The resulting suspension was dried over Na_2SO_4, and filtrated. The solid was washed with Et_2O (3 mL). The resulting filtrate was then concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:19 to 1:5) to give madangamine A (**1**) (10.3 mg, 76%): a colorless oil; $[\alpha]^{24}_D$ +142 (*c* 0.500, EtOAc); IR (film) 3005, 2912, 2873, 2853, 2792, 2758, 1459, 1440, 1128, 1091, 923, 917, 723, 675 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.58 (m, 1H), 5.45 (td, *J* = 10.9, 4.3 Hz, 1H), 5.42–5.30 (m, 6H), 5.18 (dt, *J* = 11.8, 2.9 Hz, 1H), 3.72 (t, *J* = 3.2 Hz, 1H), 3.36 (dt, *J* = 13.2, 11.2 Hz, 1H), 3.19–3.05 (m, 2H), 3.13 (d, *J* = 12.3 Hz, 1H), 3.08 (t, *J* = 16.3 Hz, 1H), 2.84 (ddd, *J* = 13.8, 11.8, 5.8 Hz, 1H), 2.73 (dd, *J* = 10.9, 0.9 Hz, 1H), 2.70–2.20 (m, 5H), 2.66 (brt, *J* = 13.4 Hz, 1H), 2.60 (m, 1H), 2.54 (ddd, *J* = 10.3, 3.2, 3.2 Hz, 1H), 2.48 (dt, *J* = 11.8, 5.2 Hz, 1H), 2.48 (d, *J* = 11.8 Hz, 1H), 2.42 (ddd, *J* = 12.4, 4.6, 3.2 Hz, 1H), 2.32 (d, *J* = 10.6 Hz, 1H), 2.24 (dd, *J*= 16.3, 7.7 Hz, 1H), 2.15 (ddd, *J* = 11.8, 5.5, 3.7 Hz, 1H), 2.11 (dd, *J* = 10.6, 3.2 Hz, 1H), 1.98–1.89 (m, 2H), 1.89–1.77 (m, 2H), 1.71 (m, 1H), 1.45 (m, 1H), 1.38 (d, *J* = 10.9 Hz, 1H), 1.29 (ddd, *J* = 12.4, 3.2, 2.6 Hz, 1H), 1.26–1.13 (m, 2H), 1.15 (m, 1H), 1.01 (dddd, *J* = 10.3, 7.5, 2.0, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.4 (C), 132.9 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.7–127.6 (CH x2), 127.5 (CH), 125.9 (CH), 121.9 (CH), 61.6 (CH_2), 59.4 (CH_2), 57.7 (CH_2), 55.7 (CH_2), 52.4 (CH_2), 51.8 (CH), 39.1 (CH), 38.4 (CH_2), 37.1 (CH), 37.0 (C), 36.1 (CH_2), 32.4 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 23.9–22.9 (CH_2, br), 22.7 (CH_2); HRMS (ESI), calcd for $C_{30}H_{45}N_2^+$ $(M+H)^+$ 433.3583, found 433.3582.

Aldehyde (64): *tert*-Butyl hydroperoxide (5.5 M in decane, 120 µL, 640 µmol) was added to a solution of aldehyde **53** (61.9 mg, 127 µmol), benzoic acid (17.1 mg, 140 µmol), TBAI (4.7 mg, 13 µmol), piperidine (1.0 M in EtOAc, 6 µL, 6 µmol) and EtOAc (13 mL). The solution was heated to 50 °C, and maintained for 16 h at this temperature. This solution was cooled to room temperature, quenched with saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to give the corresponding benzoyloxy aldehyde **63**, which was immediately used in the next step without further purification.

Sodium tetrahydroborate (24.0 mg, 635 µmol) was added to a solution of the above benzoyloxy aldehyde **63** and MeOH (2.5 mL) at room temperature. After maintaining for 1 h, potassium carbonate (87.8 mg, 635 µmol) was added to the solution. The resulting mixture was stirred for 2 h, quenched with saturated aqueous NH_4Cl (2 mL), and extracted with EtOAc (2x 2 mL). The combined organic extracts were washed with brine (2 mL), and dried over Na_2SO_4, and concentrated to give the corresponding diol, which was immediately used in the next step without further purification.

Lead tetraacetate (84.5 mg, 191 µmol) was added to a solution of the above diol and CH_2Cl_2 (2.5 mL) at room temperature. The resulting solution was maintained for 20 min, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2 to EtOAc) to give aldehyde **64** (30.2 mg, 50% for 3 steps): a colorless oil; $[\alpha]^{23}_D$ +122 (*c* 1.00, $CHCl_3$); IR (film) 2952, 2923, 1693, 1627, 1440, 1249, 859, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 9.82–9.79 (m, 1H), 5.70–5.50 (m, 1H), 5.50–5.34 (m, 1H), 5.34–5.18 (m, 1H), 5.16–4.96 (m, 1H), 4.40–4.27 (m, 1H), 4.26–4.13 (m, 2H), 4.06 (d, *J* = 13.8 Hz, 1H), 4.10–3.95 (m, 1H), 3.11 (ddd, *J* = 14.9, 10.1, 9.8 Hz, 1H), 3.06–2.95 (m, 1H), 2.95–2.83 (m, 1H), 2.87 (d, *J* = 13.8 Hz, 1H), 2.79–2.65 (m, 1H), 2.64–2.40 (m, 2H), 2.45 (d, *J* = 16.9 Hz, 1H), 2.35 (d, *J* = 16.9 Hz, 1H), 2.38–2.25 (m, 1H), 2.25–1.95 (m, 6H), 1.91–1.86 (m, 1H), 1.86–1.77 (m, 1H), 1.52–1.45 (m, 1H), 1.02 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5 (CH), 173.7 (C), 156.6 (C), 135.8 (C), 128.7 (CH), 128.0 (CH), 127.0 (CH), 64.2 (CH_2), 50.7 (CH_2), 48.8 (CH_2), 47.9 (CH), 44.9 (CH_2), 37.6 (C), 35.7 (CH), 34.5 (CH), 33.7 (CH_2), 32.7 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 27.9 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 18.0 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{26}H_{41}N_2O_4Si^+$ $(M+H)^+$ 473.2836, found 473.2842.

Aldehyde (66): Preparation of *gem*-diiodoalkane **65**: Hydrazine monohydrate (1.0 mL, 21 mmol) was added to a solution of 3-(1,3-dioxan-2-yl)propanal[36] (596 mg, 4.13 mmol) and CH_2Cl_2 (21 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature, and extracted with CH_2Cl_2 (2x 5 mL). The combined organic extracts were washed with brine (5 mL), and dried over Na_2SO_4. The solution was concentrated to give

(3-(1,3-dioxan-2-yl)propylidene)hydrazine, which was immediately used in the next step without further purification. Iodine (3.67 g, 14.5 mmol) was divided into three portions, and added to a solution of (3-(1,3-dioxan-2-yl)propylidene)-hydrazine, Et_3N (1.2 mL, 8.3 mmol), and Et_2O (21 mL) every 15 min at room temperature. The resulting mixture was stirred for 30 min, quenched with saturated aqueous $Na_2S_2O_3$ (5 mL), and extracted with EtOAc (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was filtered through a pad of silica gel (EtOAc/hexane 1:19 to 1:14) to give crude *gem*-diiodoalkane **65** (427 mg), which was immediately used in the next reaction without further purification.

In a glove box, chromium(II) chloride (75.2 mg, 612 µmol) was added to a solution of aldehyde **64** (19.3 mg, 40.8 µmol), the above *gem*-diiodoalkane **65** (245 mg) and THF (4.1 mL) at room temperature. The reaction vessel was then removed from the glove box, and stirred at room temperature for 17 h. The mixture was quenched with brine (3 mL), and extracted with Et_2O (2x 3 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:1) to give acetal **87** (18.9 mg, 79%): a colorless oil; $[\alpha]^{26}_D$ +102 (*c* 1.00, $CHCl_3$); IR (film) 2952, 2923, 2853, 1694, 1630, 1436, 1247, 1143, 1085, 859, 839 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$, 50 °C, a 4.8:1 inseparable mixture of two diastereomers) δ 5.65–5.39 (m, 3H), 5.38–5.28 (m, 1H), 5.27–5.19 (m, 1H), 5.18–4.95 (m, 1H), 4.55 (t, *J* = 4.9 Hz, 24/29H), 4.50 (t, *J* = 4.9 Hz, 5/29H), 4.25–4.07 (m, 1H), 4.17 (t, *J* = 8.0 Hz, 2H), 4.01 (dd, *J* = 11.5, 4.6 Hz, 2H), 3.96 (d, *J* = 13.2 Hz, 1H), 3.90–3.69 (m, 1H), 3.75 (dd, *J* = 12.1, 11.5 Hz, 2H), 3.40–3.05 (m, 1H), 3.01–2.83 (m, 2H), 2.82–2.73 (m, 1H), 2.72–2.58 (m, 1H), 2.56–2.36 (m, 2H), 2.34–2.00 (m, 7H), 2.00–1.68 (m, 7H), 1.64–1.52 (m, 2H), 1.50–1.37 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$, a 4.8:1 inseparable mixture of two diastereomers, signals of the major diastereomer are reported) δ 173.4 (C), 156.9 (C), 138.4 (C), 135.0 (CH), 129.5 (CH), 128.9 (CH), 126.0 (CH), 125.8 (CH), 102.2 (CH), 67.3 (CH_2), 63.9 (CH_2), 51.4 (CH_2), 49.5 (CH_2), 48.4 (CH), 45.2 (CH_2), 39.7 (CH_2), 37.7 (C), 36.6 (CH), 35.9 (CH), 35.8 (CH_2), 35.1 (CH_2), 33.4 (CH_2), 30.9 (CH_2), 28.6 (CH_2), 28.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 18.5 (CH_2), –1.2 (CH_3); HRMS (ESI), calcd for $C_{33}H_{53}N_2O_5Si^+$ $(M+H)^+$ 585.3724, found 585.3722.

Hydrochloric acid (1 M, 3.3 mL) was added to a solution of acetal **87** (18.9 mg, 32.3 µmol) and THF (3.3 mL). The mixture was heated to 60 °C, maintained for 2 h at 60 °C, quenched with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C, and extracted with EtOAc (2x 3 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:6 to 1:1) to give aldehyde **66** (15.7 mg, 92%): a colorless oil; $[\alpha]^{28}_D$ +125 (*c* 1.00, $CHCl_3$); IR (film) 2950, 2910, 1692, 1627, 1438, 1247, 859, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C, an inseparable mixture of two diastereomers, signals of the major diastereomer are reported) δ 9.75 (t, *J* = 1.7 Hz, 1H), 5.62–5.52 (m, 1H), 5.52–5.34 (m, 3H), 5.32–5.16 (m, 1H), 5.10–4.90 (m, 1H), 4.25–4.12 (m, 3H), 4.05–3.90 (m, 1H), 3.90–3.70 (m, 1H), 3.12 (ddd, *J* = 13.5, 10.3, 9.5 Hz, 1H), 3.00–2.76 (m, 2H), 2.76–2.65 (m, 1H), 2.58 (d, *J* = 13.7 Hz, 1H), 2.63–2.40 (m, 4H), 2.39–2.30 (m, 2H), 2.30–2.22 (m, 1H), 2.21–1.94 (m, 7H), 1.91 (dd, *J* = 14.3, 5.7 Hz, 1H), 1.86–1.73 (m, 1H), 1.72–1.65 (m, 1H), 1.40 (d, *J* = 13.2 Hz, 1H), 1.01 (t, *J* = 8.6 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, an inseparable mixture of two diastereomers, signals of the major diastereomer are reported) δ 202.1 (CH), 173.5 (C), 156.9 (C), 136.5 (C), 132.9 (CH), 128.6 (CH), 128.0 (CH), 126.3 (CH), 125.8 (CH), 64.0 (CH_2), 50.7 (CH_2), 48.9 (CH_2), 47.9 (CH), 44.5 (CH_2), 43.5 (CH_2), 38.9 (CH_2), 37.1 (C), 35.8 (CH), 34.7 (CH), 33.9 (CH_2), 32.8 (CH_2), 30.4 (CH_2), 28.0 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 17.9 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{30}H_{46}N_2O_4SiNa^+$ $(M+Na)^+$ 549.3125, found 549.3126.

Skipped diene ((*E*)-68): In a glove box, sodium hexamethyldisilazide (73.3 mg, 400 µmol) was added to a mixture of phosphonium salt **67** (242 mg, 405 µmol) and THF (3.0 mL) at room temperature. The reaction vessel was then removed from the glove box, and cooled to –78 °C. The solution of aldehyde **66** (15.6 mg, 29.6 µmol) and THF (3.0 mL) was added to the mixture of the ylide at –78 °C. The mixture was stirred at –78 °C for 15 min, then allowed to warm to room temperature, and stirred for 30 min. The mixture was quenched with saturated aqueous NH_4Cl (3 mL), and extracted with hexane (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19 to 1:12) to give a mixture of **(*E*)-68** and **(*Z*)-68** (18.1 mg). Two diastereomers were then separated by HPLC (PEGASIL Silica 120-5, 250×20 mm, UV 210 nm, hexane/Et_2O 1:1, 10 mL/min, **(*E*)-68**: T_R = 18.6 min, **(*Z*)-68**: T_R = 16.9 min) to afford skipped dines **(*E*)-68** (12.7 mg, 56%) and **(*Z*)-68** (2.0 mg, 8.8%). **(*E*)-68**: a colorless oil; $[\alpha]^{26}_D$ +105 (*c* 1.00, $CHCl_3$); IR (film) 2922, 2863, 1698, 1637, 1464, 1437, 1249, 1108, 1091, 860, 838, 677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.60–5.49 (m, 1H), 5.48–5.32 (m, 7H), 5.32–5.20 (m, 1H), 5.10–4.95 (m, 1H), 4.25–4.10 (m, 3H), 4.06–3.90 (m, 1H), 3.85–3.73 (m, 1H), 3.71 (t, *J* = 6.9 Hz, 2H), 3.12 (ddd, *J* = 14.6, 9.2, 8.3 Hz, 1H), 2.95–2.76 (m, 2H), 2.79 (dd, *J* = 5.5, 5.4 Hz, 2H), 2.75–2.66 (m, 1H), 2.62 (d, *J* = 14.1 Hz, 1H), 2.59–2.38 (m, 2H), 2.33 (dt, *J* = 6.6, 6.6 Hz, 2H), 2.35–2.23 (m, 1H), 2.22–1.90 (m, 12H), 1.88–1.76 (m, 1H), 1.75–1.69 (m, 1H), 1.43–1.33 (m, 1H), 1.15–1.04 (m, 21H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (C), 156.9 (C), 136.6 (C), 134.6 (CH), 129.8 (CH), 129.5 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 126.3 (CH), 126.1 (CH), 124.7 (CH), 64.0 (CH_2), 63.3 (CH_2), 50.7 (CH_2), 48.9 (CH_2), 47.9 (CH), 45.1 (CH_2), 39.0 (CH_2), 37.0 (C), 35.3 (CH), 34.8 (CH), 34.0 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 28.0 (CH_2), 27.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 18.2 (CH_3), 17.9 (CH_2), 12.1 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{45}H_{77}N_2O_4Si_2^+$ $(M+H)^+$ 765.5422, found 765.5427. **(*Z*)-68**: a colorless oil; $[\alpha]^{29}_D$ +89.4 (*c* 0.200, $CHCl_3$); IR (film) 2924, 2864, 1698, 1635, 1463, 1437, 1249, 1107, 860, 838, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.60–5.33 (m, 8H), 5.32–5.20 (m, 1H), 5.10–4.96 (m, 1H), 4.25–4.10 (m, 3H), 4.05–3.92 (m, 1H), 3.88–3.75 (m, 1H), 3.71 (t, *J* = 6.9 Hz, 2H), 3.13 (ddd, *J* = 15.5, 9.8, 8.6 Hz, 1H), 2.98–2.78 (m, 2H), 2.80 (dd, *J* = 5.4, 5.2 Hz, 2H), 2.77–2.66 (m, 1H), 2.63 (d, *J* = 13.5 Hz, 1H), 2.60–2.40 (m, 2H), 2.33 (td, *J* = 6.9, 6.3 Hz, 2H), 2.35–2.22 (m, 1H), 2.22–1.95 (m, 12H), 1.88–1.72 (m, 2H), 1.45–1.40 (m, 1H), 1.14–1.05 (m, 21H), 1.02 (t, *J* = 8.6 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7 (C), 156.9 (C), 136.7 (C), 132.8 (CH), 129.7 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 126.4 (CH), 126.0 (CH), 124.0 (CH), 64.0 (CH_2), 63.3 (CH_2), 50.7 (CH_2), 48.9 (CH_2), 47.9 (CH), 45.5 (CH_2), 39.0 (C), 37.4 (CH_2), 35.2–34.6 (CH x2), 34.1 (CH_2), 33.2 (CH_2), 31.4 (CH_2), 30.6 (CH_2), 27.9 (CH_2), 27.5 (CH_2), 27.3 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 18.2 (CH_3), 18.0 (CH_2), 12.2 (CH), –1.3 (CH_3); HRMS (ESI), calcd for $C_{45}H_{77}N_2O_4Si_2^+$ $(M+H)^+$ 765.5422, found 765.5426.

Madangamine B (2): 10-Camphorsulfonic acid (CSA, 11.0 mg, 47.6 µmol) was added to a solution of skipped dines

(*E*)-68 (18.2 mg, 23.8 μmol) and MeOH (1.2 mL) at room temperature. The solution was heated to 40 °C, maintained for 2 h at 40 °C, quenched with Et_3N (17 μL, 120 μmol) at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:1) to give alcohol **88** (14.5 mg, 100%): a colorless oil; $[\alpha]^{26}_D$ +124 (*c* 1.00, $CHCl_3$); IR (film) 3423, 2949, 2921, 1695, 1612, 1437, 1248, 1052, 860, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 5.60–5.32 (m, 8H), 5.32–5.20 (m, 1H), 5.10–4.92 (m, 1H), 4.26–4.10 (m, 3H), 4.04–3.90 (m, 1H), 3.88–3.70 (m, 1H), 3.64 (t, *J* = 6.9 Hz, 2H), 3.12 (ddd, *J* = 13.8, 9.8, 8.3 Hz, 1H), 2.95–2.77 (m, 2H), 2.82 (dd, *J* = 6.3, 5.7 Hz, 2H), 2.75–2.65 (m, 1H), 2.59 (d, *J* = 13.8 Hz, 1H), 2.63–2.40 (m, 2H), 2.36 (td, *J* = 6.9, 6.6 Hz, 2H), 2.32–2.23 (m, 1H), 2.22–1.94 (m, 11H), 1.90 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.86–1.75 (m, 1H), 1.74–1.66 (m, 1H), 1.45–1.30 (m, 1H), 1.01 (t, *J* = 8.6 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7 (C), 156.9 (C), 136.6 (C), 134.7 (CH), 131.0 (CH), 129.7 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 126.3 (CH), 125.6 (CH), 124.6 (CH), 64.0 (CH_2), 62.3 (CH_2), 50.8 (CH_2), 48.9 (CH_2), 48.0 (CH), 44.6 (CH_2), 39.1 (CH_2), 37.0 (C), 35.9 (CH), 34.8 (CH), 33.9 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 28.0 (CH_2), 27.4 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 17.9 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{36}H_{57}N_2O_4Si^+$ $(M+H)^+$ 609.4088, found 609.4086.

p-Toluenesulfonyl chloride (9.1 mg, 48 μmol) was added to a solution of alcohol **88** (14.5 mg, 23.8 μmol), Et_3N (13 μL, 95.0 μmol), DMAP (0.6 mg, 5 μmol) and CH_2Cl_2 (1.2 mL) at room temperature. The solution was maintained at room temperature for 19 h, and quenched with saturated aqueous NH_4Cl (1.0 mL). The resulting mixture was extracted with CH_2Cl_2 (2x 3 mL). The combined extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:12 to 1:1) to give tosylate **89** (15.3 mg, 84%): a colorless oil; $[\alpha]^{26}_D$ +96.7 (*c* 1.00, $CHCl_3$); IR (film) 2950, 2919, 1693, 1629, 1437, 1361, 1248, 1176, 967, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.60–5.50 (m, 1H), 5.50–5.20 (m, 8H), 5.10–4.95 (m, 1H), 4.25–4.10 (m, 3H), 4.04 (t, *J* = 6.9 Hz, 2H), 4.02–3.90 (m, 1H), 3.85–3.70 (m, 1H), 3.13 (ddd, *J* = 14.0, 9.8, 9.2 Hz, 1H), 2.95–2.77 (m, 2H), 2.72 (dd, *J* = 7.2, 7.2 Hz, 2H), 2.75–2.65 (m, 1H), 2.61 (d, *J* = 13.7 Hz, 1H), 2.65–2.49 (m, 2H), 2.44 (s, 3H), 2.43 (dt, *J* = 7.5, 6.9 Hz, 2H), 2.35–2.23 (m, 1H), 2.22–1.90 (m, 11H), 1.95 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.88–1.75 (m, 1H), 1.74–1.68 (m, 1H), 1.44–1.36 (m, 1H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (C), 156.9 (C), 144.8 (C), 136.6 (C), 134.4 (CH), 133.3 (C), 132.0 (CH), 130.0 (CH), 129.9 (CH), 128.7 (CH), 128.2–127.9 (CH x2), 127.5 (CH), 126.2 (CH), 124.8 (CH), 123.2 (CH), 69.8 (CH_2), 63.9 (CH_2), 50.7 (CH_2), 48.9 (CH_2), 47.9 (CH), 44.9 (CH_2), 39.0 (CH_2), 36.9 (C), 35.4 (CH), 34.8 (CH), 33.9 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 30.3 (CH_2), 28.0 (CH_2), 27.2–25.9 (CH_2 x2), 26.2 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 21.8 (CH_3), 17.9 (CH_2), –1.3 (CH_3); HRMS (ESI), calcd for $C_{43}H_{63}N_2O_6SiS^+$ $(M+H)^+$ 763.4176, found 763.4184.

Boron trifluoride ethyl ether complex (13 μL, 100 μmol) was added to a solution of tosylate **89** (15.3 mg, 20.0 μmol) and CH_2Cl_2 (1.0 mL) at room temperature. The solution was maintained for 30 min, and quenched with *N*,*N*-diisopropylethylamine (34 μL, 200 μmol) at room temperature. The solution was concentrated to give the corresponding secondary amine, which was immediately used in the next step without further purification.

N,*N*-Diisopropylethylamine (17 μL, 100 μmol) was added to a solution of the above secondary amine and MeCN (20 mL) at room temperature. The resulting solution was heated to 70 °C, maintained for 18 h at this temperature, and then concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:9 to 1:1) to give macrocyclic amine **90** (6.8 mg, 76% for 2 steps): a colorless oil; $[\alpha]^{31}_D$ +115 (*c* 0.680, EtOAc); IR (film) 2917, 1628, 1446 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 2.3:1 mixture of rotamers, signals of the major rotamer are reported) δ 5.72–5.60 (m, 1H), 5.56–5.04 (m, 8H), 4.75–4.68 (m, 1H), 4.62 (d, *J* = 14.3 Hz, 1H), 3.18 (d, *J* = 14.3 Hz, 1H), 3.11 (dd, *J* = 17.2, 12.3 Hz, 1H), 2.96–2.84 (m, 2H), 2.60 (d, *J* = 11.5 Hz, 1H), 2.63–2.47 (m, 2H), 2.42 (dd, *J* = 12.1, 6.1 Hz, 1H), 2.45–1.74 (m, 17H), 1.72–1.63 (m, 1H), 1.61–1.51 (m, 1H), 1.41 (dd, *J* = 12.1, 9.2 Hz, 1H), 1.30 (d, *J* = 11.5 Hz, 1H), 1.20–1.14 (m, 1H), 1.14–1.07 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.0 (C), 138.7 (C), 134.0 (CH), 129.5 (CH), 129.3 (CH), 128.9 (CH), 128.8–127.4 (CH x4), 124.9 (CH), 61.3 (CH_2), 59.2 (CH_2), 58.1 (CH_2), 48.0 (CH), 44.0 (CH_2), 39.4 (CH_2), 38.3 (CH), 36.9 (C), 36.1 (CH), 35.4 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 30.9 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 24.6 (CH_2); HRMS (ESI), calcd for $C_{30}H_{43}N_2O^+$ $(M+H)^+$ 447.3375, found 447.3372.

In a glove box, $LiAlH_4$ (1.0 M in THF, 76 μL, 76.0 μmol) was added to a solution of macrocyclic amine **90** (6.8 mg, 15.2 μmol) and THF (1.5 mL) at room temperature. The reaction vessel was removed from the glove box, stirred at room temperature for 6 h, cooled to 0 °C, and quenched with a few drops of distilled water. The resulting suspension was dried over Na_2SO_4, and filtrated. The solid was washed with Et_2O (10 mL). The resulting filtrate was then concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane 1:19 to 1:5) to give madangamine B (**2**) (5.5 mg, 83%): a colorless oil; $[\alpha]^{26}_D$ +146 (*c* 0.0670, EtOAc); IR (film) 2927, 2875, 2853, 1459, 1439, 1127, 973, 723, 498 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.53–5.36 (m, 7H), 5.25–5.17 (m, 2H), 3.72 (t, *J* = 2.9 Hz, 1H), 3.35 (dt, *J* = 13.2, 11.2 Hz, 1H), 3.15 (d, *J* = 12.3 Hz, 1H), 3.12 (dddd, *J* = 16.3, 12.0, 3.2, 2.9 Hz, 1H), 3.02 (dd, *J* = 12.4, 7.5 Hz, 1H), 3.01 (ddd, *J* = 16.4, 8.9, 8.6 Hz, 1H), 2.90 (ddd, *J* = 13.8, 12.1, 5.8 Hz, 1H), 2.71 (td, *J* = 13.8, 3.7 Hz, 1H), 2.59–2.51 (m, 2H), 2.51–2.46 (m, 2H), 2.43–2.30 (m, 2H), 2.39 (dt, *J* = 12.6, 2.9 Hz, 1H), 2.34 (brd, *J* = 10.9 Hz, 1H), 2.30–2.22 (m, 1H), 2.26 (dd, *J* = 16.3, 8.3 Hz, 1H), 2.18 (ddd, *J* = 12.0, 6.6, 3.4 Hz, 1H), 2.20–2.09 (m, 2H), 2.11 (dd, *J* = 10.9, 3.2 Hz, 1H), 2.01–1.91 (m, 3H), 1.91–1.79 (m, 2H), 1.77–1.70 (m, 1H), 1.63 (dd, *J* = 12.4, 6.9 Hz, 1H), 1.57–1.43 (m, 1H), 1.39 (d, *J* = 11.2 Hz, 1H), 1.30 (dt, *J* = 12.6, 2.9 Hz, 1H), 1.26–1.15 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.2 (C), 133.1 (CH), 129.7 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 128.4–127.7 (CH), 122.1 (CH), 61.2 (CH_2), 59.3 (CH_2), 57.7 (CH_2), 56.2 (CH_2), 53.0 (CH_2), 51.8 (CH), 40.1 (CH_2), 38.42 (CH), 38.39 (CH_2), 37.14 (C), 37.11 (CH), 32.4 (CH_2), 31.8 (CH_2), 28.9 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 25.4 (CH_2), 24.7 (CH_2), 24.1–23.5 (CH_2); HRMS (ESI), calcd for $C_{30}H_{45}N_2^+$ $(M+H)^+$ 433.3583, found 433.3588.

Cell culture: Human cell lines, lung adenocarcinoma A549, melanoma CHL-1 and SK-MEL-28, colon carcinoma HCT116, cervix adenocarcinoma HeLa, fibrosarcoma HT1080, breast carcinoma MCF-7 and MDA-MB-23, bladder carcinoma T24, and pancreatic carcinoma Panc-1, were cultured in Dulbecco's modified Eagle's medium (Nissui Pharmaceutical Co., Ltd.) including with 10% (v/v) fetal bovine serum, 100 units/mL penicillin G, 100 mg/L kanamycin, 315 mg/L L-glutamine, and 2.5 g/L $NaHCO_3$ at 37 °C in 5% CO_2. Other human cell lines, pancreatic carcinoma PK-1, prostate adenocarcinoma PC-3, and acute monocytic leukemia THP1, were cultured in Roswell park memorial institute 1640 medium (Nissui Pharmaceutical

Co., Ltd.) including with 10% (v/v) fetal bovine serum, 105 units/mL penicillin G, 105 mg/L kanamycin, 600 mg/L L-glutamine, and 2.5 g/L $NaHCO_3$ at 37 °C in 5% CO_2.

Evaluation of antiproliferative activity against human cancer cells by MTT assay: The human cancer cells were seeded in a 96-well plate (Corning Inc.) at 1.0×10^4 cells/well and incubated for 24 h at 37 °C in 5% CO_2. The medium was replaced with 200 μL of fresh medium, and 1 μL of various concentrations of each compound in MeOH solution was added, respectively. After 48 h, 20 μL of 5 mg/mL thiazolyl blue tetrazolium bromide (Merck) was added and incubated for 4 h at 37 °C in 5% CO_2. Next, the medium was removed, and the precipitation was dissolved by 150 μL of DMSO. The amounts of these products were determined by measuring absorbance at 570 nm using a microplate reader (infinite M200 PRO, Tecan Group Ltd.)[37,38]

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